

CHRONIC FATIGUE SYNDROME: A TREATMENT GUIDE, 2<sup>nd</sup> Edition  
by Erica F. Verrillo

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*Preface to the Second Edition*

When the first edition of *Chronic Fatigue Syndrome: A Treatment Guide* was completed Lauren and I were asked what we would do with the manuscript if a cure were found before the publication date. "Burn it!" we said. We weren't being naive. The late nineties were a heady time for CFS advocacy and support groups. We had a national organization, the CFIDS Association of America, which published a monthly magazine with all the latest research and treatments. *Osler's Web*, Hillary Johnson's breathtaking account of the Incline Village outbreak and the subsequent CDC coverup, hit the bookstores in 1996. And a second national organization, the National CFIDS Foundation, was formed in 1997. Ampligen trials were underway, and the initial results were encouraging, to say the least. It seemed as if a cure was just around the corner.

Fifteen years later, the cure has not been found. Those of us who contracted CFS in the eighties are now entering our third decade of illness. Researchers are still attempting to discover the cause of CFS/ME, and, despite a proliferation of studies demonstrating the many immunological and neurological mechanisms of the illness, more than a few doctors still believe it's "all in their heads." Even the much publicized discovery of XMRV was met with a "let's wait and see" attitude by the old dogs who had seen too many tricks and suffered too many disappointments. And, in spite of years of evidence proving beyond any doubt that this is an illness that can completely disable, if not kill, the medical establishment still persists in calling it by the ill-deserved name of Chronic Fatigue Syndrome.

That is the bad news.

The good news is the Internet. More than anything else, the Internet has brought our world-wide community together. People with CFS/ME talk about their symptoms, their treatments, and their doctors openly and fully online. CFS/ME doctors post their protocols, surveys of thousands of patients are taken. The evaluation of various treatments is a source of nearly constant discussion, reminding the world that we are still here, still experimenting, and still, against all odds, recovering.

It is that discussion which prompted this second edition. We have still relied on published accounts appearing in medical and scientific journals for the bulk of the information contained within its pages. But the inspiration for its expansion comes from public forums which show there is clearly a need for more accessible, more accurate, and better organized information about all aspects of CFS/ME. The purpose of this book is to provide that organization, serving as a filter for what is often an overwhelming amount of information.

I would like to thank Dr. Lucinda Bateman, Dr. Derek Enlander, Dr. Charles Lapp, Dr. Martin Pall, Dr. Jacob Teitelbaum, and Dr. Richard Van Konynenburg for their invaluable input. Any errors, of course, are my own.

Erica Verrillo

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*Preface to the First Edition*

Throughout this book we have examined the practical problems surrounding chronic fatigue and immune dysfunction syndrome (CFIDS). Rather than delve into debates concerning theoretical and political issues, we have focused on the clinical aspects of CFS/ME. We have taken great pains to present material in an objective, unbiased fashion regardless of our personal preferences.

Compiling information about an illness as complex as CFIDS can be daunting. Despite the difficulties surrounding such a project, the task has been more than worthwhile. In assembling a book that attempts to answer primary treatment questions, we have not only responded to a basic need in the CFIDS community, but have satisfied our own quest for knowledge as well. It is this knowledge, combined with the firm belief that experience is the best teacher that has enabled us to overcome some of the limitations of the illness we both have. For us this book not only represents the sum total of over fifteen years of knowledge and experience, it is the book we wish we could have had when we first became ill.

We gratefully acknowledge the input of Dr. Charles Lapp, Dr. David Bell, and Dr. Thomas Steinbach, who reviewed this book for medical accuracy. Finally, any errors remaining are our own.

Erica F. Verrillo

Lauren M. Gellman

October 1997

## INTRODUCTION: THE TREATMENT DILEMMA

*“Healing is a matter of time, but it is also sometimes a matter of opportunity.”*

—HIPPOCRATES —

CFS/ME is one of those illnesses for which receiving a diagnosis can bring as much frustration as relief. All too often a person who has spent years searching for a diagnosis expects that identification of the illness will bring with it, if not a cure, at the very least an effective treatment plan. Unfortunately, most of us who have received the diagnosis have also been told that CFS/ME has “no known cause or cure,” a phrase that invariably creates enough hopelessness to offset any relief the diagnosis may have offered.

The lack of known cause or cure, while discouraging, certainly does not imply that an illness cannot be treated, or that those who suffer from it will not recover. Throughout the ages, physicians have successfully treated diseases on the basis of their knowledge of symptoms and human physiological responses rather than on test results. And because human physiology has not changed much over the past 40,000 years, treatment approaches, for the most part, have remained remarkably consistent. For example, the Chinese medical system, which relies heavily on nutrition and the use of herbs, was codified more than 5,000 years ago. Herbal remedies, their pharmaceutical derivatives, massage and manual manipulation techniques, nutritional therapy, and stress reduction methods (meditation, yoga) are treatments that have withstood the test of time, and still form the mainstay of medical systems throughout the world.

The premise of this book is that the absence of a cure does not in any way imply that there is no treatment for CFS/ME. To make the grounds for this position clear, consider the popular concept that an illness “attacks.” Cure, in this conceptual framework, consists of killing the attacker. In CFS/ME, the attacker is unknown, unidentified, and perhaps not even a single factor; thus counterattack is impossible. The victim is left with only two choices: lie back and let nature take its course (which in CFS/ME can be agonizing), or seek alternative points of view. The alternative we suggest is to view CFS/ME as a form of systemic damage that must be gradually, methodically, and thoughtfully repaired. Or, to use an analogy, if CFS/ME is like falling into a hole, as some patients have observed, recovery is like climbing out of the hole, step by step, rung by rung.

The purpose of treatment is to provide rungs. Each treatment that relieves a symptom can serve to haul a person with CFS/ME one step farther out of the hole. And with every treatment that successfully accomplishes its purpose, the body becomes stronger and more footholds are available. People who have had CFS/ME for a long time are well aware that this approach can lead to significant improvement, enough so that return to work or recommencement of a social life is possible. Statements like: “With B12 shots I had enough stamina to go on vacation with my family” are heard frequently enough to warrant attention. If each person

measures a treatment by what it can restore to his or her life, that standard provides a basis and framework for recovery.

With that analogy in mind, we have compiled a list of treatments, therapies, and techniques that have been successfully used by people with CFS/ME. Inclusion on this list does not constitute an endorsement. None of these treatments is guaranteed. Realistically speaking, what works wonders for one person may not work at all for another. Nor are they cures. None has been shown to completely eradicate the disease. But many of these treatments may relieve the worst symptoms or decrease the severity of the illness. For people who are unable to leave their beds, have lost their jobs, or would like to resume the semblance of a normal life, a 10%, 20%, or 30% improvement is not to be lightly dismissed. The key to determining which of these treatments will be effective is knowledge.

Understanding your illness— your symptoms, your responses, your ups and downs—is the greatest favor you can do for yourself and your doctor. Dr. Patricia Salvato, a CFS/ME specialist practicing in Houston, Texas, expresses this idea quite well: "Well-informed patients simply make for better partners in health-care, and, when knowledge is shared, everybody benefits; there is an unbelievable amount of healing in just the sharing of new knowledge" (*Mass CFIDS Update*, Summer 1996).

#### HOW TO USE THIS BOOK:

This book is a reference guide – somewhat like a modified encyclopedia. It is structured to allow you to skip throughout its contents without any loss of context. With that in mind, there is a certain amount of redundancy built into the text, so that valuable information will not be missed.

The book is divided into four main parts. Part I is an overview of CFS/ME to help orient the reader. The most notable characteristics of the illness are presented, followed by a brief history of the illness, diagnosis, tests, and finally prognosis. An updated section concerning the possible causes of CFS/ME is presented at the end of Part I.

Part II deals with how CFS/ME affects the body. This is a guide to understanding the body's reaction to CFS/ME and is your resource for devising appropriate treatment strategies.

The first section deals with mechanisms. Understanding the basic mechanism of an illness is the key to devising any sort of treatment approach. For that reason, it is important to know what the illness actually does to the person who has it. The following section, Protocols, outlines protocols of prominent CFS/ME doctors and researchers based on their theories of the mechanisms of the illness.

The third section describes CFS/ME symptoms, one at a time, from the perspective of the patient. Following the description is an explanation of why the symptom occurs in CFS/ME. At the end of each symptom entry are treatment tips, recommendations for further reading, references, and resources for additional information. The "SEE" section at the end of each symptom entry provides cross-references to treatments and other relevant parts of the book.

Part III consists of a treatment dictionary, divided into three sections: 1) pharmaceuticals and prescription drugs, 2) nutritional supplements and botanicals, and 3) alternative and complementary medical and supportive therapies. It is important to remember while reading these sections that we have not included every possible treatment for CFS/ME. We are not doctors and cannot speculate as to what might or what might not constitute an appropriate treatment for this illness. Instead we have made our selection through relying on documentation found in published literature written by medical researchers, doctors and clinicians, as well as by patients themselves. The short introductions provide guidelines each person should be aware of when using these treatments, as well as essential resources.

Part IV discusses some useful coping techniques and what are commonly referred to as "lifestyle adjustments." Although this discussion comes last, we do not mean to imply that learning to cope with CFS/ME is in any way less important than treating the illness. Coping and management strategies can sometimes determine the rate of recovery a person will make, so their importance can hardly be overstated. The three areas discussed are stress (Chapter 7), the home environment (Chapter 8), and diet (Chapter 9).

Stress is one of the primary obstacles for people with CFS/ME, and some useful management tips are provided. Toxins in the home – the most important environment for people with a disabling illness – and how to keep your living area safe will be of special interest not only to people with CFS/ME, but to those with multiple chemical sensitivities (MCS), an illness in its own right and certainly a significant problem for a subset of patients with CFS/ME. The section on diet is meant to be a general guide. Making generalizations about diet is difficult when patients with CFS/ME have such varied food sensitivities. Nevertheless, the topic is important because diet can make an enormous difference in how a person with CFS/ME feels.

Chapter 10 of this book concerns children and adolescents with CFS/ME. Although children experience the same symptoms as adults with CFS/ME, their needs are fundamentally different. A child with CFS/ME cannot make treatment decisions independently, nor can a child defend him or herself against a medical or school establishment that may view symptoms as signs of "malingering." This chapter provides some special tips for parents of children with CFS/ME, who must act as advocates as well as caretakers. Included in this chapter are the personal, and often heart-rending, stories of children and adolescents with CFS/ME. At the end of the chapter are resources that respond to the specific needs of children and adolescents.

The information found in this book was gathered from a broad range of sources: medical articles, PubMed abstracts, academic publications, books about CFS/ME and related illnesses, newspaper and journal articles, research reviews, personal accounts, interviews, survey results, blogs, and websites. Although we relied on published sources for specific information concerning the mechanisms and treatment options available to people with CFS/ME, unpublished sources such as letters, telephone conversations, interviews, questionnaires, and Internet discussion

groups were invaluable in assessing the effectiveness of specific treatments and therapies. The rich and varied experience of the CFS/ME community itself forms the ballast of the book, for this is, above all, a book that reflects our own efforts to find treatment for this baffling disease.

*A Note to Our Readers . . .*

Throughout this book we have used the term Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) to refer to the illness that has been variously known as Chronic Fatigue Syndrome (CFS) and Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) in the United States and in Europe as Myalgic Encephalomyelitis (ME). We do so under duress. While the combination of CFS/ME (or ME/CFS as it is known in Europe) is currently in vogue among researchers, it is unwieldy and adds to the confusion surrounding this illness. Historically, ME has been defined as a post-viral condition that results in neurological impairment, and while CFS certainly shares many of ME's features, it is frequently contracted without a prodromic viral infection. It can also occur with an absence of pain (myalgia), which is one of the defining features of ME. Lumping the two conditions together does no good medically, and a great deal of harm politically.

The ramifications of including “fatigue” as part of the name of an illness have been enormous. That single term has generated a spate of misconceptions and often outright dismissal of what should be regarded as a serious and debilitating illness. It has led to an inexcusable lack of funding for research, and an erosion of diagnostic rigor that affects not just people with this illness, but people with any illness in which fatigue is a major presenting symptom (e.g., Parkinson's disease, cancer, multiple sclerosis, and numerous other chronic conditions). No other medical condition is named after a single symptom. In this regard, CFS – even when paired with ME – sets an unfortunate precedent.

For more than twenty years there has been widespread interest in changing the name of this illness to one that is less misleading. At this point, nearly anything that does not contain the “f” word would be acceptable. We encourage our readers to make their voices heard on this issue so that this illness can receive the appropriate recognition and attention that it deserves.

## CHAPTER 1: WHAT IS CFS/ME? AN OVERVIEW

### Distinctive Features, CFS/ME Defined: A Multisystem Disorder, Subtypes and Stages, Signs and Symptoms

#### INTRODUCTION

CFS/ME is, without a doubt, one of the most complex, multifaceted, enigmatic illnesses the medical world has encountered. World-renowned CFS/ME specialist, Dr. Paul Cheney, in an unintentional paraphrase of Sir William Osler, has remarked that if you can understand CFS/ME, you can understand any illness. To date CFS/ME has defied anyone to identify its cause, or find a cure. And even after 25 years, there is still considerable debate over how to formulate a good case definition. CFS/ME is hard to describe and even harder to diagnose because its symptoms span allergies to vertigo and can occur in every imaginable combination. Most confusing, however, is the range in severity of CFS/ME, which can manifest as a mere inconvenience to an utterly disabling disease. People with severe CFS/ME can be completely bedridden, unable to perform basic tasks without assistance, whereas those with milder illness may be able to work full time but feel nagged by a persistent feeling that their energy has waned, or their "get-up-and-go" has got up and went.

Unfortunately, no federal agency has taken the measures required to determine the true prevalence of the illness. As a consequence, no one really knows how many people have CFS/ME. According to what few epidemiological studies there are, prevalence rates swing wildly from 2 per 100,000 to 2,800 per 100,000 (Taylor). Based on a population of roughly 300 million, this means that somewhere between 6,000 and 8.4 million U.S. citizens have the illness. The reason for this huge disparity lies in sampling and definition. Doctors' reports will show a low rate, simply because most doctors don't diagnose CFS/ME. Clinic sampling tends to produce a higher rate, because everyone who goes to a clinic is ill.

Random phone calls are more accurate than either doctors' reports or clinic sampling, but phone interviews are seldom lengthy. Three or four minutes are scarcely enough to diagnose an illness that often takes a physician well over an hour of detailed questioning and multiple tests. Add to that the concept that CFS/ME can be defined by six months of fatigue and the statistics become meaningless. Everybody is tired.

An important point concerning prevalence is that CFS/ME is not restricted to any particular group. It can strike anyone at any time. It affects people of all ages, from preschoolers to the elderly. CFS/ME strikes both sexes, though women predominate (women are affected by all autoimmune diseases in higher proportions than men). Neither does CFS/ME confine itself to a particular income group.

Patients with CFS/ME range from wealthy celebrities to school custodians, from doctors to construction workers. Contrary to the media myth that CFS/ME primarily attacks white, middle-class women, CFS/ME does not discriminate by race or ethnic origin. Results of a demographic survey conducted in San Francisco

indicated a significant rate of CFS/ME among African-American and Native American populations. The study also reported that the average yearly income of patients with CFS/ME is about \$15,000. Although CFS/ME usually strikes sporadically, affecting only one member of a family or work group, it can also occur in epidemics. Since the 1930s more than 60 CFS/ME epidemics have been recorded. At no time during these epidemics was there any indication that CFS/ME was a particularly selective disease.

The enormous variation in severity and symptoms of CFS/ME, combined with a paucity of information regarding the transmissibility, prevalence, and long-term consequences of the illness, has helped contribute to the many misconceptions about CFS/ME. These misconceptions, half-truths, and errors have not only led to a certain complacency on the part of government agencies but have made it difficult for people who have the illness to recognize it in themselves, much less seek out appropriate treatment. Despite the confusion, it is possible to make some generalizations about the salient characteristics of the illness, an understanding of which will ease the task of identifying CFS/ME in patients with various "nonspecific" symptoms.

## DISTINCTIVE FEATURES

CFS/ME is often described as "the flu that never ends." Indeed, in many cases, it is preceded by a viral infection that doesn't resolve, and which, over time produces myriad other perplexing symptoms. One of the most notable characteristics of CFS/ME is that it often appears suddenly. Many patients with CFS/ME can give the precise date they first started experiencing symptoms. Often these patients describe the onset as "flu-like," with many symptoms typical of a viral infection. The sudden onset of the illness is what allows a diagnostician to distinguish CFS/ME from many of the ailments and conditions that CFS/ME can resemble, such as allergies, endocrine abnormalities, multiple sclerosis, and mood disorders, none of which develops from one day to the next.

To complicate matters for the diagnostician, and for the patient seeking a diagnosis, CFS/ME does not always come on suddenly after a flu-like illness. It can also develop with deceptive slowness, its symptoms emerging one by one until the patient's life is irrevocably changed. In these cases it may be difficult for the person experiencing the symptoms to recognize that anything is amiss until months or even years have passed, especially if that person conducts a busy, active life. In these cases there is a strong tendency to attribute the growing signs of illness to stress, overwork, or aging. It is now thought that close to half of CFS/ME cases can develop in just this manner. Needless to say, these are the hardest for a doctor to diagnose. The patient may go from doctor to doctor for years before a tentative diagnosis is reached.

The salient characteristic of CFS/ME is that symptoms wax and wane. This can help distinguish CFS/ME from progressive illnesses that may share similar symptoms, but that worsen steadily over time. Typically, someone who contracts CFS/ME will experience a period of pronounced illness for several months, followed

by shorter periods of remission, then a return of the illness. Most patients with CFS/ME refer to these as "good days" and "bad days" (keeping in mind that a "good day" for someone with severe CFS/ME may simply consist of getting out of bed).

Periods of remission and exacerbation can be entirely random, following no particular pattern, or can be cyclic, occurring at certain times of the year (fall and spring for many people). In women, they may be influenced by hormonal cycles. Sometimes, exacerbations of the illness can be attributed to a known cause, usually physical exertion, but also exposure to a toxin, stress, or injury. If the effects are short term, these exacerbations are usually referred to as "crashes" or "flares."

When the exacerbation lasts for several weeks, or longer, it is a relapse. Relapses can occur at any stage of the illness, even after the patient has experienced many years of functional recovery. Unlike short-term exacerbations, relapses may take an entirely different course from the initial illness. Relapses may also present with different symptoms (primarily autonomic and/or vascular).

## SIGNS AND SYMPTOMS

The signs and symptoms of CFS/ME are almost too numerous to list and just as daunting to categorize. Dr. Katrina Berne, a clinical psychologist who contracted CFS/ME in 1984, has compiled a list of symptoms, along with their frequency in the CFS/ME population. These percentages are based upon information reported by Drs. Bell, Cheney, Fudenberg, Goldstein, Jessop, Komaroff, Peterson, and two surveys (Kansas City and Phoenix).\*

### *General or Physical Symptoms:*

- Fatigue, often accompanied by nonrestorative sleep, generally worsened by exertion: 95-100%
- Nausea: 60-90%
- Irritable bowel syndrome (diarrhea, nausea, gas, abdominal pain): 50-90%
- Chronic sore throat: 50-90%
- Fevers/chills/sweats/feeling hot often: 60-95%
- Muscle and/or joint pain, neck pain: 65-95%
- Bladder/prostate problems, frequent urination: 20-95%
- Low blood pressure: 86%
- Recurrent illness and infections: 70-85%
- Malaise: 80%
- Heat/cold intolerance: 75-80%
- Painful and/or swollen lymph nodes: 50-80%
- Systemic yeast/fungal infections: 30-80%
- Fungal infection of skin and nails: 71%
- Weight gain: 50-70%
- Increased/severe PMS: 70%
- Swelling, fluid retention: 55-70%
- Shortness of breath: 30-70%
- Subnormal body temperature: 65%
- Severe allergies: 40-60%



- Sensitivities to medicines, inhalants, odors, and foods: 25-65%
- Difficulty swallowing: 55-60%
- Heart palpitations: 40-60%
- Sinus pain: 56%
- Rash or flushing of face: 35-45%
- Chest pain: 40%
- Hair loss: 20-35%
- Eye pain: 30%
- Pressure at the base of the skull: 30%
- Weight loss: 20-30%
- Tendency to bruise easily: 25%
- Vomiting: 20%
- Other general symptoms reported: Endometriosis; dryness of mouth, eyes; pressure sensation behind eyes; frequent canker sores; periodontal disease; pain in teeth, loose teeth, and endodontal problems; cough; TMJ syndrome; Mitral valve prolapse; Carpal tunnel syndrome; Serious cardiac rhythm disturbances; Piriform muscle syndrome, causing sciatica; Impotence; Thyroid inflammation; Hypoglycemia or hypoglycemia-like symptoms; Swelling of nasal passages

*Neurological/Central Nervous System-related Symptoms:*

- Confusion; inability to think clearly: 75-100%
- Concentration/attention deficit: 70-100%
- Sleep disorder/disturbance (insomnia, unrestorative sleep, unusual nightmares): 65-100%
- Muscle weakness: 85-95%
- Headache: 75-95% (daily headache: 50%)
- Memory problems (especially short-term memory): 80-90%
- Photosensitivity: 65-90%
- Disequilibrium, spatial disorientation, dizziness, vertigo: 60-90%
- Spaceyness, light-headedness: 75-85%
- Muscle twitching, involuntary movements: 55-80%
- Aphasia and/or dyscalculia: 75-80%
- Alcohol intolerance: 45-75%
- Seizure-like episodes: 70% (seizures: 2%)
- Coordination problems/clumsiness: 60%
- Paresthesias (numbness, tingling or other odd sensations in face and/or extremities): 25-60%
- Visual disturbance (scratchiness, blurring of vision, "floaters"): 45-55%
- Episodic hyperventilation: 40-45%
- Fainting or blackouts: 40%
- Strange taste in mouth (bitter, metallic): 25%
- Temporary paralysis after sleeping: 20%
- Earache: 20%

- Other symptoms reported: decreased libido; hallucinations; alteration of taste, smell, hearing; tinnitus

*Emotional/Psychological Symptoms:*

Anxiety: 70-90%

Mood swings, excessive irritability, overreaction: 70-90%

Depression: 65-90%

Personality change: 55-75%

Panic attacks: 30-40%

Dr. Berne notes that these figures represent a range of percentages of reported symptoms in different studies. In most cases only one-third to one-half of those reporting individual symptoms indicated that they experienced the symptom at all times. In Dr. Berne's survey of the Phoenix area group, for example, figures were compiled to indicate the average total number of symptoms experienced all of the time (11 symptoms) and the average total number of symptoms experienced by each patient some of the time (18.6 symptoms).

\*From *Running on Empty*, Excerpted with permission from Hunter House Inc, Publishers. Copyright 1995 by Katrina Berne, PhD. Although this book is no longer available for sale, there is a revised edition from 2002 entitled *Chronic Fatigue Syndrome, Fibromyalgia and Other Invisible Illnesses: The Comprehensive Guide*. This book can be ordered on amazon.com and through Hunter House (800) 266-5592, Fax (510) 865-4295, or visit their website at [www.hunterhouse.com](http://www.hunterhouse.com).

## CFS/ME DEFINED: A MULTISYSTEM DISORDER

Ultimately, CFS/ME must be defined by what it does. Because CFS/ME affects every system in the body, it should be properly classed as a "multisystem" disorder. By definition, a multisystem disorder is any illness which affects several physiological systems at once or in tandem. For example, in diabetes, the nervous system, the cardiovascular system, vision, and hearing are all affected.

Autoimmune diseases, such as lupus and Hashimoto's disease, fall into this category as well, because the immune system interacts with both the nervous system and endocrine system. Due to this interaction, autoimmune diseases frequently affect all three systems.

In CFS/ME, there is ample research demonstrating dysregulations of the immune system, endocrine system, nervous system, digestive system, reproductive system, and cardiovascular system, with multiple symptoms occurring in each category. The frequency with which symptoms occur in all of these systems, as well as their severity, proves that the underlying mechanism is something not only pervasive, but common to most cells in the body. In the end, CFS/ME may very well prove to be the mother of all multisystem disorders. As Dr. Cheney puts it, "It is larger than any of us know."

## SUBTYPES AND STAGES

Increasingly, there is a trend among researchers to view CFS/ME not as a single entity, but as a heterogeneous illness, or perhaps as many illnesses. Through genetic and other markers, subtypes are being identified, which, over time, may become distinguishable as illnesses different from one another, with different causes, different prognoses, and different treatments.

While narrowing down parameters in order to facilitate the development of effective treatment is always a welcome development, there is a certain confusion that arises from these attempts to classify CFS/ME subtypes.

The first problem with identifying subtypes is that there isn't a consensus on the case definition of CFS/ME. At this point, anyone with a long-term multi-symptom illness that isn't easily diagnosed as something else can fit into the model of CFS/ME. Moreover, people who satisfy one case definition may not satisfy another. This problem is further compounded when researchers talk about "chronic fatigue" as if it were a clinical entity. Chronic fatigue is a symptom, not a diagnosis, and it is the presenting symptom of many illnesses (e.g., post-polio syndrome, MS, anemia, Parkinson's). Should all of these illnesses be considered subtypes of Chronic Fatigue Syndrome? It may seem far-fetched, but the trend of using CFS as an umbrella term for "fatiguing illnesses" is already apparent in the absorption of ME within the general framework of "chronic fatigue."

The second problem is that every illness has subtypes. Depending on the genetic makeup of the host, even the common cold can manifest itself in a variety of ways. An autoimmune illness, such as lupus, can produce a staggering array of symptoms, of which some (or all) may manifest themselves in any given patient. Undoubtedly, each of these variations will correspond to a variation in sets of genes. Does this mean that each variant of lupus (or diabetes, or Sjögren's) should be treated as a separate illness? Given the enormous variation in severity, length, type of onset, and triggers, it would be a daunting task to determine subtypes in CFS/ME patients based on symptoms alone, especially in the presence of several disparate sets of criteria.

Finally, a number of clinicians have observed that CFS/ME, like cancer, has stages, each one of which may manifest itself in a different clinical picture. The initial stage, acute onset, may appear symptomatically as a viral illness, with flu-like symptoms (sore throat, low fever, etc.) During this stage, RNase L and sed rate will be elevated. After this stage, the patient enters into what Dr. Cheney calls autointoxication. The body becomes overloaded, particularly the liver, with toxins that are produced by excess RNase L activity, and a second set of symptoms emerges: pain, "brain fog," weakness, gut problems. RNase L levels decline, as does sed rate, which is now very low. Finally, the body enters into a third stage in which the hypothalamus, which has now been affected by autointoxication, becomes dysregulated, affecting the autonomic nervous system. This is the stage that produces dysautonomia, POTS and other problems related to loss of homeostasis. Needless to say, gene expression will reflect changes in the stage of the illness, as well as triggers and initial susceptibility.

How then, do we define subtypes – by how the illness operates at various times during its development, by sets of symptoms, by triggers, by genes, or by its as yet unknown cause? In the absence of a clear understanding of all these variables, the identification of subtypes will be a monumental and possibly fruitless task.

In spite of, or perhaps because of, these difficulties, it is apparent that there is a crying need to define what CFS/ME is clinically, to identify its cause, and to discover a biomarker. For without these, CFS/ME subtypes will never be identified, and, over time, CFS/ME will end up as “chronic fatigue” and, eventually, simply “fatigue.” This would do a great disservice to all those who have labored to unravel the mysteries of CFS/ME, as well as to those who have suffered from its depredations.

## FURTHER READING

*This is an excellent overview of CFS/ME:* <http://www.ei-resource.org/illness-information/environmental-illnesses/chronic-fatigue-syndrome-cfs-myalgic-encephalopathy-me/>

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## HISTORICAL BACKGROUND – EPIDEMICS, OUTBREAKS AND RECENT DEVELOPMENTS

One of the most perplexing questions surrounding CFS/ME is how it began. Like so many other questions about this illness, the answer remains elusive. Debate is ongoing among researchers as to whether CFS/ME is a recent phenomenon or a disease with a considerable pedigree. Some argue that CFS/ME has been around for several hundred years; others present compelling evidence that CFS/ME is a relatively new disease, arising in the last few decades at best. Those who maintain that it has been with us for centuries point to accounts of other diseases with similar symptoms, such as muscular rheumatism in the 1680s or neurasthenia, first described in the late nineteenth century. Proponents of this position maintain that CFS/ME, as it is currently described, is merely a new name for an old illness. In direct opposition to this viewpoint, many others believe that CFS/ME is a true twentieth-century disease, a product of the “cocktail effect” produced by an environment polluted by neurotoxins, new or mutated viruses, contaminated vaccines, and other factors.

The question of where the illness originated is as elusive as when. Outbreaks of CFS/ME-like diseases were reported in Northern Europe and the United States as early as the 1930s. The first documented epidemic outbreak of CFS/ME occurred in 1934 in Los Angeles County Hospital and affected 198 health care workers,

mainly doctors, nurses, and technicians. Because this outbreak followed on the heels of a poliomyelitis epidemic, it was initially diagnosed as polio. However, the diagnosis was revised when doctors noticed that, unlike polio, this new ailment did not cause paralysis or death. It also produced myriad symptoms: headache, easy fatigability (especially after exertion), loss of appetite, intestinal disturbances, sweating, chills, stiffness in the back and neck, weakness, pain, insomnia, impaired memory, and mood swings. The disease tended to strike suddenly, with an incubation period of less than a week, although insidious onset over a few weeks was also observed, producing a set of symptoms that remained intense and variable over the first six months, then becoming chronic and relatively stable. Lacking evidence to point to a new disease, a U.S. Health Bulletin simply described the illness as "atypical polio." Dr. Alexander Gilliam, the epidemiologist who chronicled the outbreak, remarked, "If the disease were not poliomyelitis, the epidemic is equally extraordinary in presenting a clinical and epidemiological picture, which, so far, is without parallel."

A second major outbreak occurred in Iceland in 1948 and 1949. Like the Los Angeles County Hospital outbreak, this epidemic also followed on the heels of a polio epidemic. An important difference was that the epidemic was not restricted to health care professionals but spread to the general population. The majority of the more than 1000 persons affected by "Iceland disease," as it came to be called, lived in three rural towns. Investigators were at first perplexed by this new disease, thinking it to be a new form of polio. However, the symptom pattern did not match their expectations of polio. In all cases, those who came down with Iceland disease had muscle pain and tenderness, numbness, and twitching, but not paralysis. Doctors also noted an unusual and troublesome persistence of cognitive and emotional problems in the recovery phases. Significantly, none of those who contracted Iceland disease came down with polio when that illness swept through the region a few years later.

A series of outbreaks occurred in the 1950s. One of the best documented was the 1955 outbreak in London at the Royal Free Hospital. Like other outbreaks, the attack rate was unusually high: 2.8% in men and 10.4% in women. Dr. Melvin Ramsay, who was in charge of the infectious diseases unit at the hospital, had the presence of mind to thoroughly document the illness. In order of frequency, the symptoms were: headache, sore throat, malaise, lassitude, vertigo, pain in the limbs, and nausea. The presence of low fever, which occurred in 89%, and swollen glands in 79% of the patients, combined with an incubation period of less than a week, led him to draw the conclusion that the disease was highly infectious. The hospital was subsequently closed for two months. A year later, a similar outbreak occurred in the same hospital. Dr. Ramsay called the illness "myalgic encephalomyelitis (ME)" which identified the primary mechanism of the illness as an inflammation in the nervous system (somewhat similar to polio).

Epidemic outbreaks also occurred in Adelaide, South Australia, from 1949 to 1951; in Kingston, New York, in 1951; in Coventry (England), Rockville, Maryland, and Denmark in 1953; in Germany, Alaska, and Liverpool in 1954; in Perth, Wales,

South Africa, and London in 1955; in Pittsfield, Massachusetts (after an ill serviceman returned home from England), Ridgefield, Connecticut, and Punta Gorda, Florida, in 1956; in Greece and again in London in 1958; in a convent in New York State in 1961; and in a factory in Kentucky in 1964. Between 1964 and 1982, an additional thirteen epidemics of “myalgic encephalomyelitis” and “neuromyasthenia” were reported from Dallas, Texas to Dunedin, New Zealand.

The most significant outbreak in recent CFS/ME history occurred in Incline Village, Nevada in late 1984. This was the outbreak that propelled the illness into the public arena, and gave it a new name that CFS/ME patients would, unfortunately, be stuck with for decades to come.

Incline Village is a small resort town located on picturesque Lake Tahoe. In the fall of 1984, two local physicians, Dr. Daniel Peterson and Dr. Paul Cheney, began to see patients who seemed to have an unusually severe and debilitating flu. What was particularly puzzling to the doctors was that these patients did not recover. Months after the initial onset of the illness, patients still reported severe symptoms, and, in many cases, there was no detectable improvement. As time went on, the doctors saw increasing numbers of patients with the same malady. Sometimes these patients were seen in clusters. In one instance, the members of a girls’ basketball team became ill, in another, it was schoolteachers in the nearby town of Truckee, Nevada. By mid-1985 the number of patients with this mysterious malady had topped one hundred.

The doctors were stymied by the illness. They had not previously encountered a disease process that so quickly reduced active, energetic individuals to bedbound invalids, with no identifiable cause. The symptoms they observed were unusual in both severity and range: exhaustion, pain, sleep disturbance, cognitive disorder, and a plethora of nervous system problems. Convinced that this was an outbreak of a new disease, the doctors contacted the Centers for Disease Control and Prevention (CDC), the government agency responsible for monitoring and controlling contagious diseases in the United States.

The CDC's response was to ignore the doctors. Not only did the CDC fail to adequately investigate the epidemic, it ultimately created an insurmountable obstacle for patients, subsequent researchers, and clinicians. Thereafter, in large part because of the CDC's casual treatment of the outbreak in Nevada, the illness became known as a figment of the overachieving young professional's imagination—the “yuppie flu,” as it was dubbed by the press.

The dismissive attitude that characterized the government's response to the outbreak did little to help control the spread of the illness. Throughout the 1980s the number of patients with severe, unrelenting flu-like symptoms increased, prompting doctors to take notice. Dr. Carol Jessop in San Francisco noted that starting in the early 1980s patients began reporting a viral-like ailment that did not resolve over time. A Harvard University physician, Dr. Anthony Komaroff, first noticed patients with similar clinical symptoms in the late 1970s, but became even more attentive to the illness when he saw increasing numbers in his Boston practice in the early part of the next decade. During this time, Dr. Richard DuBois in

Atlanta, Dr. James Jones in Denver, Dr. Irena Brus (now deceased) in New York, and Dr. Herbert Tanner in Beverly Hills all observed an increase in patients with this unique clinical picture. For these physicians the illness was indeed striking, and they puzzled individually about what was making their formerly healthy patients so ill that they were forced to leave jobs and schools, and to abandon so many of the activities previously important to them.

In 1985 another epidemic was reported, this time in a small rural community in upstate New York. Dr. David Bell, a pediatrician working in Lyndonville, began seeing young patients with recurring flu-like symptoms, abdominal pain, dizziness, fatigue, headache, joint pain, and cognitive deficits. By 1987 more than 200 people, 44 of whom were children, had contracted the illness. Like Dr. Cheney and Dr. Peterson, Dr. Bell's attempts to draw attention to the outbreak met with little success. However, he continued in his search for an explanation and eventually joined with Dr. Peterson and Dr. Cheney to research the cause of this malady.

The persistence of a few doctors who refused to dismiss the suffering of their patients, combined with press coverage, however misleading, aroused public and professional interest in the illness. Medical journals such as the *Annals of Internal Medicine* began to publish articles that described a long-term, flu-like disease with notable neurological and immunological components. At first the illness was attributed to the Epstein-Barr virus (EBV), which causes mononucleosis, because of the high titers of EBV antibodies in this group. At the time, EBV seemed to be a perfect candidate for a causative agent, because many of the symptoms the patients had were similar to those of "mono." However, this theory was soon dismissed when it was shown that EBV antibody concentrations did not correspond to the severity of the illness, nor were high titers unique to patients with the illness. Over time, it was found that people with the mysterious ailment had high antibody titers to a number of viruses in the herpesvirus family: cytomegalovirus, Coxsackie virus, and human herpesvirus 6. Nevertheless, the theory that EBV caused the new illness caught on, and the disease became popularized as "chronic Epstein-Barr" or just "Epstein-Barr."

In the late 1980s, publicity surrounding the illness began to gain momentum. Hillary Johnson, a journalist who contracted the illness, wrote an award-winning series for *Rolling Stone* magazine called "Journey Into Fear: The Growing Nightmare of Epstein-Barr Virus." The story attracted national attention. (Johnson later wrote *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic*, a compelling exposé of CFS/ME history and politics.) In 1990 *Newsweek* ran a cover story on the illness, which was the bestselling issue of the year. Stories were aired on popular television programs such as *20/20*. As a result, the CDC was flooded with calls from patients from all parts of the country who were desperately seeking information and advice. It seemed thousands more people had the illness than the agency had imagined.

From that point on, interest surged. Prodded into action by persistent patients and diligent doctors, in 1988 the CDC devised a case definition and gave the illness a name – Chronic Fatigue Syndrome (CFS). Though many clinicians and

patients considered the guidelines woefully inadequate and the name derisive, it did give physicians a uniform description and a place to begin for making a diagnosis. Patient groups were formed. The end of the decade saw the birth of the first national organization, the National CFIDS Association, based in Charlotte, North Carolina. With a national organization came advocacy, representation at the national level, fund-raising for research, organized media campaigns, public awareness programs, and patient education. Local support groups sprang up all over the United States, providing information, assistance, and validation for hundreds of thousands of patients. In April 1990, the first international symposium was held in Cambridge, England, drawing clinicians and researchers from all over the world.

It was a momentous event, providing doctors, epidemiologists, and medical investigators with the first opportunity to share their observations and knowledge about a disease that had puzzled observers for the better part of a century. Since that time, numerous international symposia have been held, with researchers gathering to present their latest research, share insights and begin fruitful collaborations with universities, private organizations, and medical “think tanks.”

Independent organizations have proven to be a boon to CFS/ME patients. Because government health agencies have dropped the ball on CFS/ME research (including diverting millions of dollars earmarked for CFS/ME research to other programs and redefining CFS/ME as a “woman's disease”), patient groups such as the CFIDS Association of America and the ME Associations of Canada and Great Britain have garnered considerable private support for CFS/ME research and put pressure on government agencies and organizations. These organizations have funded research, organized public events, and acted as steadfast advocates for patients.

Private individuals have also stepped in where government organizations have failed. In 2005 Annette and Harvey Whittemore joined with Dr. Peterson to found the Whittemore Peterson Institute for Neuro-Immune Disease (WPI). Like so many other people who have devoted their personal resources to finding a cure for CFS/ME, the Whittemores were motivated by having a family member (in this case, a daughter) with the illness. As additional support, the WPI garnered official backing from the Nevada State Legislature, which unanimously approved the WPI as a joint project between the WPI and the University of Nevada School of Medicine. The mission of the WPI is to conduct basic research on the cause of CFS/ME and other illnesses characterized by a dysregulation of the nervous and immune systems (Gulf War Illness, fibromyalgia, autism, atypical MS, and post-Lyme disease). Their ultimate goal is to find a cure. The WPI made worldwide headlines in 2009 when it announced that it had discovered the elusive virus that was the cause of CFS/ME, the XMRV retrovirus. Although the WPI's claim has not been substantiated by the wider medical research community, the efforts of the WPI have catapulted CFS/ME into a new arena.

Recently, three research institutes have been formed to investigate CFS/ME. In July 2011, Dr. Peterson established his own non-profit research foundation, the



Simarron Research Foundation. In perhaps the largest international collaboration of its kind, he joined with Bond University's Public and Neuroimmunology Unit (Australia), Queensland Health (Australia), and Stanford University to investigate the cause and further the treatment of CFS/ME. In December of the same year, the collaboration was granted \$831,000 to pursue its goals.

Also in December of 2011, renowned CFS/ME specialist, Dr. Nancy Klimas, announced that she was establishing the Institute for Neuro-Immune Medicine at Nova Southeastern University. The Institute will conduct cutting-edge research and treat patients suffering from CFS/ME/ME and Gulf War Illness (GWI). Dr. Klimas hopes that “by bringing together some of the best scientific minds in the world, the facility will act as both a think tank and a working institute for the research, and train new clinicians.”

This goal is also shared by Dr. Derek Enlander, who in another impressive international collaboration based at Mt. Sinai Hospital in New York, has joined with Dr. Kenny De Meirleir, Dr. David Bell, Dr. Eric Schadt and Dr. Miriam Merad to research the genetic, viral, and clinical aspects of CFS/ME.

While the historical questions of how, when, and where CFS/ME originated may be debatable, the question of its current status is not. Almost all reputable research institutions and clinicians agree that CFS/ME has become a serious public health problem. What is made clear from a historical review is that, over time, the incidence of epidemic outbreaks has been matched, if not superseded, by increasing numbers of sporadic cases.

Currently, most people contract CFS/ME individually, which, while as not as dramatic as an epidemic, can produce equally significant morbidity. The CDC estimates that CFS/ME has affected more than a million individuals in the United States, a conservative estimate in most clinicians' opinion. Independent prevalence studies have estimated more than double this number, with figures reaching into the millions for the United States alone. Although the definitive cause of CFS/ME remains as yet undiscovered, it is hoped that through the continuing involvement of patient groups and increased funding for both private and governmental research, some of the questions surrounding the cause of this elusive illness soon will be answered and a cure found.

## FURTHER READING

CFS Untied: <http://www.cfsuntied.com/history.html>

*Detailed historical information regarding CFS/ME outbreaks.*

National Alliance for Myalgic Encephalomyelitis: <http://www.name-us.org/ResearchPages/ResEpidemic.htm#M.E. Epidemics>

*Scroll down for a detailed list of 60 outbreaks.*

Bond University: [http://www.bond.edu.au/about-bond/news-and-events/news/BD3\\_019855](http://www.bond.edu.au/about-bond/news-and-events/news/BD3_019855)

*Mason Award Landmark Grant for CFS Research.*

“Why Royal Free Outbreak was not hysteria.” *Good review of early studies.*

[http://freespace.virgin.net/david.axford/articl02.htm#recent\\_research](http://freespace.virgin.net/david.axford/articl02.htm#recent_research)

“A Disease in Search of a Name: The History of CFS and the Efforts to Change Its Name.” Karen Lee Richards.

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*Excellent timeline of notable events in the history of CFS/ME.*

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[http://www.mereseearch.org.uk/information/keypubs/Acheson\\_AmJMed.pdf](http://www.mereseearch.org.uk/information/keypubs/Acheson_AmJMed.pdf)

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*This is an excellent article challenging the notion that the Royal Free epidemic was a case of mass hysteria.*

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## PROGNOSIS AND RECOVERY

Most people who are diagnosed with CFS/ME want to know, first and foremost, when they will recover. Will CFS/ME last a year? Two years? Ten years? Or is it a life sentence? Unfortunately, for people with CFS/ME, the answer to this question is not usually forthcoming. Doctors with little experience with the illness may tell their patients anything from: "Go home and rest and you'll be better in a few weeks" to "Nobody recovers from CFS/ME." Physicians with more experience, however, tend to be more circumspect. The reason for their caution is that there is simply too much variation from case to case and far too little epidemiological information to be able to predict outcomes.

CFS/ME is a notoriously unpredictable illness. Some people recover completely within one or two years and can return to their former lives. Others improve enough to return to work, but must make modifications of their lifestyles. The majority of those with chronic illness learn to plan every aspect of their lives within the parameters of symptoms that wax and wane. A few must adjust to long periods of illness, or "plateaus," with little or no improvement, and, at the far end of the spectrum, there are those who do not show improvement and may even decline over time.

Recovery times vary from a few months (although these short-term cases go largely unreported and therefore never make it into statistical tables) to decades. Statistics reported by physicians are highly individualized, with the more renowned CFS/ME specialists – who see the most severe cases – giving the longest recovery rates, and general and family practitioners the shortest. However, most physicians tell their patients that CFS/ME, generally speaking, is a lengthy proposition—a matter of years, not months. The prospect of a very long illness is dismal, which is why the diagnosis is often received with profoundly mixed feelings. The only bright spot in the picture is that recovery does not necessarily correlate with duration of illness. Dr. Dedra Buchwald, a physician in Seattle, concluded, after a five-year study of local patients with CFS/ME, that duration of the illness does not correlate with outcome.

Significant improvement and functional recovery are possible even after many years of illness. By functional recovery, we mean a return to normal life, with accommodations. While these patients may not return to lifestyles as active as those they enjoyed before becoming ill, they are able to work, engage in leisure activities, and fully participate in life. There are even documented cases of long-term sufferers who have recovered completely. One CFS/ME patient from North Carolina experienced full recovery after 19 years of illness. Dean Anderson, in a personal account, says he did not even begin to see an improvement until five years had passed (*CFIDS Chronicle*, Winter 1996).

While there are few reliable long-term studies of CFS/ME patients, those which have been completed are encouraging. In 2007 Matthews and Komaroff published a study in which 234 CFS/ME patients were assessed for physical and mental impairment between 1991 and 2002. This study found that physical function tended to improve for many patients over time, especially for patients between the ages of 18 and 60, and for women. Physical function did not deteriorate with time, despite the fact that they were aging. No deterioration of mental function was noted.

Although a lack of deterioration may seem cold comfort for those who are significantly disabled by the illness, for most people with CFS/ME, especially those with severe cases, the possibility of "substantial" or even "partial" recovery is cause for celebration. The Komaroff study also addresses one of the primary concerns of those with CFS/ME, which is that simply having the illness will cause long-term degeneration.

Who recovers? It is difficult to say, but those who have viral onset seem to experience the highest rate of recovery. In a study by Masuda et al, CFS/ME patients with viral onset seemed to have the best prognosis. After two years, eight out of nine viral onset patients had returned to work. Of the nine patients with non-infectious onset, only three had returned to work. All patients received the same treatments.

The best outcomes, of course, are seen in children and in those with milder cases. In a 13-year follow-up study of 35 children with CFS/ME, 80% reported full

recovery. However, 20% of those children (7) were still chronically ill, a percentage that roughly parallels chronic, severe cases in the adult population (25%).

Those with early diagnoses and who seek appropriate treatment tend to improve more quickly. Dr. Lapp, Dr. Teitelbaum, Dr. Holtorf and Dr. De Meirleir all report that 80% or more of their patients see significant improvement over time, which is to be expected in a population of patients being aggressively treated. The fact that early diagnosis and treatment seem to correlate with recovery rate, at least in some cases, should be sufficient motivation for the newly ill to seek the proper specialist. However, even those who spend years searching for a diagnosis should not lose heart. Recognition and treatment any time during the illness can bring substantial improvement, if not full recovery.

It is the fervent desire of all people with CFS/ME and those who are close to them that a cure be found. Already far too many years have been lost and far too many plans and dreams abandoned by countless children and adults affected by this illness. While we are waiting, it is important to bear in mind that, above and beyond finding a cure, a number of variables can affect the outcome of CFS/ME. Each person is different. What each has in common, though, is the need for hope.

The purpose of this book is to provide a cause for hope; that is, information that may enable you to make choices to influence the course of your illness for the better. If you are a medical practitioner or caregiver, this book may help provide much needed information and insights from various sources. In any case, we hope this book will enable its readers to "hang in there" and not lose sight of the light at the end of the long CFS/ME tunnel.

## FURTHER READING

*Kenneth Casanova's story of illness and recovery:*

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## DIAGNOSIS: CASE DEFINITIONS AND TESTS

Case definitions: Summaries: Fukuda, Canadian, Oxford, International Consensus; Objective Measurements, Specific Tests, Sources. Full Case Definitions: Fukuda, Canadian, Oxford, International Consensus.

CFS/ME is a distinct, recognizable entity that can be diagnosed relatively early in the course of the disease, providing the physician has some familiarity with the illness. Although the absence of a single test to confirm CFS/ME still makes it, in part, a diagnosis of exclusion, CFS/ME is by no means a "waste-basket diagnosis." Experience is the main stumbling block that prevents many physicians from making the diagnosis. They simply can't interpret what they are seeing. CFS/ME physicians who have attended outbreaks of the illness, or have seen hundreds (perhaps thousands) of patients have little difficulty recognizing the specific markers, indicators, and signs of the illness.

The first step in making a diagnosis is to compare the patient's history and symptoms with the case definition. This is not as simple as it appears. There have been nine case definitions, of which four are in common use. The one your doctor chooses will be a reflection of how familiar he or she is with CFS/ME.

## CASE DEFINITIONS: SUMMARIES

### *CDC/Fukuda Criteria (1994)*

The 1994 criteria were drafted by the CDC in conjunction with the International Chronic Fatigue Syndrome Study Group, an international collaboration of 20 clinicians and researchers. Dr. Keiji Fukuda was first author. As a consequence the 1994 criteria are commonly referred to as the "Fukuda" criteria. In spite of more recent updates, this is the set of criteria most frequently used by researchers and by clinicians when making a diagnosis.

The basic features of the Fukuda criteria are a minimum of six months of persisting or relapsing fatigue not substantially alleviated by rest and not the result of ongoing exertion, and that produces significant reductions in occupational, social, or personal activities. In addition, four out of eight of the following symptoms must be present:

- sore throat
- tender lymph nodes
- muscle pain
- joint pain without redness or swelling
- post-exertional malaise
- headaches of a new or different type
- impairment in short-term memory or concentration
- unrefreshing sleep

Those with any past or current diagnosis of a major depressive disorder, bipolar affective disorders, schizophrenia, delusional disorders, dementias, anorexia nervosa or bulimia are excluded.

As a diagnostic tool, the Fukuda criteria are fairly straightforward and uncomplicated, which is probably why this case definition is still in use. However, the very simplicity of the Fukuda definition, which includes no reference to severity or frequency of symptoms, has hindered its ability to accurately diagnose CFS/ME. According to a 2011 study led by Leonard Jason, the CDC "Fukuda" criteria only identified 79% of patients with CFS/ME, while the more complete Canadian

Criteria identified 87%. The CDC case definition also makes no clear distinction between fibromyalgia and CFS/ME. If your doctor uses the CDC criteria, a thorough history and in-depth examination of symptoms will be particularly important.

#### *Canadian Case Definition (2003)*

The Canadian case definition is the one used by most researchers. Like the CDC definition, it requires six months of unexplained fatigue. However, a patient must also experience all of the following:

- post-exertional malaise
- sleep dysfunction
- pain
- neurological/cognitive impairment

In addition, there must be one or more symptoms of autonomic, neuroendocrine, and immune dysfunction. The only case definition that exceeds the Canadian case definition in specifying symptoms that relate to multisystem dysfunction is the International criteria of 2011.

#### *Oxford Case Definition (1991)*

If you fall ill in England, your doctor will probably refer to the Oxford case definition. The Oxford criteria have been roundly, and justly, criticized for their lack of specificity. The only symptom which must be present is six months of unexplained fatigue, and the exclusion of any fatigue-causing medical conditions (such as anemia). The definition excludes psychiatric disorders such as schizophrenia and bipolar disorder, but allows for patients with major depression – which has skewed the results of every piece of research using the Oxford criteria. Where the criteria fail is by not including any of the neurological, immune or endocrine impairments common to CFS/ME patients. These omissions make this case definition worthless for the purposes of diagnosis or research.

#### *Myalgic Encephalomyelitis International Consensus Criteria (2011)*

To date, the most comprehensive and accurate of the case definitions is the Myalgic Encephalomyelitis International Consensus Criteria. The ME international case definition was assembled by a group of 28 physicians and researchers who have had, in some cases, decades of experience in diagnosing and treating CFS/ME. The group based its criteria on clinical presentation (supported by a study of more than 2500 patients), and on extensive research on neuroendocrine, immune system, and energy impairments.

In order to meet this case definition a patient must meet the criteria for post-exertional neuroimmune exhaustion, at least one symptom from three neurological impairment categories, at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories, and at least one symptom from energy metabolism/transport impairments. Even a brief examination at the international criteria will give doctors and patients an overall view of the basic mechanisms of CFS/ME.

## MAKING A DIAGNOSIS

Taking a careful history is essential in making a diagnosis and is just as important as comparing the patient's symptoms with a case definition. The physician should consider type of onset (acute or insidious), triggering mechanisms (exposure to chemicals, viral infection, physical trauma), and any other mitigating factors that might influence the severity or persistence of the illness. In general, symptoms that develop quickly after an initial trigger are indicative of CFS/ME.

Most specialists question their patients carefully about the type of symptoms they are experiencing. CFS/ME is a syndrome, which means that multiple symptoms must be present. Many of these symptoms are reflective of an autonomic nervous system disorder; others are indicative of a persistent viral infection. What is important to the doctor is not necessarily that you have all of the symptoms, or even a certain percentage, but that they cover a spectrum. The symptoms most doctors consider as particularly significant are relentless, persistent, or disabling fatigue, pain, sleep disorders, and cognitive problems. Other symptoms can occur in an astonishing array. Even if the patient does not have all of the symptoms, it is unlikely that a doctor will make diagnosis based strictly on fatigue.

Finally, the physician should order all the necessary tests to rule out illnesses that produce similar symptoms, and look for immune system abnormalities typical in the CFS/ME patient population. In most instances, exclusionary tests are not expensive or difficult to perform. Depending on the symptoms, the physician may wish to rule out ongoing Lyme disease, lupus, rheumatoid arthritis or other autoimmune disorders, parasitic infections, heart disease, specific neurological disorders such as multiple sclerosis, endocrine disorders such as hypothyroidism, and systemic infections and inflammatory conditions (as indicated by a high erythrocyte sedimentation rate). In general, patients with CFS/ME test negative for other conditions. However, as many physicians have noted, nothing prevents a person from having two conditions simultaneously or developing one after the other. Thus a positive test result does not necessarily rule out a diagnosis of CFS/ME.

Immune system tests can be used to confirm a diagnosis of CFS/ME. Immune system testing is specialized, so results cannot be reliably interpreted by anyone other than an immunologist or CFS/ME physician. Even among specialists, there is tremendous dissent as to what these test results actually mean. The value of having these tests done is to determine whether the patterns seen in the test results are similar to those of other people with CFS/ME. Many (but not all) people with CFS/ME have reduced numbers of natural killer cells and increased numbers of circulating cytokines (such as alpha interferon and the interleukins). Immune cell function also may be measured. Patients with CFS/ME generally have diminished T and B cell function. Reaction to pokeweed mitogen, total immunoglobulin production (IgG, IgA, IgM), and demonstrable anergy (lack of immune response) when tested with foreign proteins can help determine the effectiveness of immune cell responsiveness.

Along with immune system tests, most CFS/ME specialists look for evidence of viral reactivation. People with CFS/ME usually show evidence of reactivation of latent viruses, particularly in the herpesvirus family, such as Epstein-Barr virus,

human herpesvirus 6 (HHV-6), and cytomegalovirus. Reactivation of latent viruses (as indicated by high titers) provides further proof of immune system dysfunction, because in a healthy person these viruses are controlled.

Neurological examinations are also useful in making a diagnosis. The Romberg test, a simple test that can be performed in the doctor's office, can indicate neurological impairment. For those who can afford it, a single-photon emission computed tomography (SPECT) scan can reveal areas of the brain with reduced blood flow, also a common finding in people with CFS/ME. For patients with severe cognitive impairment, IQ tests and other neurocognitive examinations may be recommended. Exercise tests, particularly those spanning several days, can show a decreased oxygen uptake and other abnormal responses to exertion. Not all of these specialized tests are necessary to make a diagnosis, although someone applying for disability insurance may need some of them to file.

## OBJECTIVE MEASUREMENTS FOR CFS/ME

### *Initial Office Observations*

- Blood pressure: usually low (orthostatic hypotension)
- Temperature: low (97° F) or slightly elevated (<100° F) or, more commonly, both over the course of a day (excessive diurnal variation)
- Heartbeat: tachycardia (hard to detect in an office visit; Holter monitor is more efficient)
- Throat: irritated, crimson crescents
- Lymph nodes: tenderness in nodes of groin and neck, particularly on left side
- Pallor: usually present
- Positive Romberg test (tandem stance)
- Stiff, slow gait
- Nystagmus (involuntary eye movements)
- Photophobia (light sensitivity)
- Hyperreflexia (increased reflex reactions)

### *Common Findings on Routine Screening Tests*

#### Complete Blood Count with differential:

- Decreased number of white blood cells (leukopenia), also increased number of white blood cells
- Abnormal red blood cell membranes, elevated MCV (large red blood cells)
- Low concentrations of zinc and magnesium
- Low uric acid concentration (<3.5 mg/dl)
- Total cholesterol concentration slightly elevated
- Decreased potassium and sodium

#### *Other:*

- Sedimentation rate: Low (<5 mm/hr); sometimes brief periods of elevated rate (>20 mm/hr)
- Urinalysis: alkaline; mucus or blood, or both, without bacterial infection
- Positive ANA, speckled pattern
- Liver function tests: mildly elevated AST (SGOT) and ALT (SGPT)



*Exclusionary Tests*

- Autoimmune system: negative for lupus, rheumatoid arthritis, Hashimoto's disease. Note: Patients sometimes test positive on initial screening but not on more specific tests.
- Endocrine system: negative for Addison's disease, Cushing's disease, hypothyroidism, diabetes mellitus

Note: Warranted if patient demonstrates signs of hypothyroidism, such as enlarged thyroid gland (goiter). Although some patients with CFS/ME with enlarged thyroid gland test negative on standard tests, more refined tests may reveal secondary thyroid deficiencies.

- Heart: negative for mitral valve prolapse. Note: Warranted if patient reports tachycardia. Tests sometimes reveal elevated transaminase concentrations and angiotensin-converting enzyme.
- Liver: negative for hepatitis
- Neurological system: negative for multiple sclerosis (MS). *Note: Warranted if patient shows severe neurological, cognitive, and muscle dysfunction.* Although some patients with CFS/ME may test negative for MS, more specific testing (brain function) may reveal abnormalities.
- Bacterial: negative for tuberculosis, brucellosis, Lyme disease
- Cancer: negative for lymphoma
- Parasites: negative for toxoplasmosis, giardiasis, amoebiasis. Note: Patients with CFS/ME can have multiple parasitic infections as part of a prodromal illness.

**SPECIFIC TESTS THAT HELP CONFIRM DIAGNOSIS OF CFS/ME**

These tests are expensive, specialized, and, in most cases, cannot be performed locally. A diagnosis can be made without performing any of these tests, but if they are available, a positive result on two or more of these tests (especially exercise testing) would be strongly indicative of CFS/ME.

- Viral reactivation: Positive for cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 and 7, and Coxsackie virus; negative for hepatitis A or B virus
- Immune system: Low natural killer cell counts, elevated interferon alpha, tumor necrosis factor, interleukins 1 and 2; T cell activation, altered T4/T8 cell ratios, low T cell suppressor-cell (T8) count, fluctuating low and high T cell counts, low and high B cell counts, antinuclear antibodies, immunoglobulin deficiency, sometimes antithyroid antibodies
- Exercise testing: Decreased cortisol levels after exercise, decreased cerebral blood flow after exercise, inefficient glucose utilization, erratic breathing pattern. In Cardio-Pulmonary Exercise Testing with measurement of VO<sub>2</sub> max, anaerobic threshold, and maximal heart rate and respiration, patients with CFS/ME score significantly lower than controls.
- SPECT brain scan: Hypoperfusion in either right or left temporal lobe, particularly Wernicke's area, after exercise
- MRI brain scans: unexplained bright areas

- Magnetic resonance spectroscopy (MRS) brain scan: abnormally high lactic acid spikes near around the hippocampus (which indicates mitochondrial dysfunction).
- Heart function: abnormal impedance cardiography; repetitively oscillating T wave inversions and/or T wave flats during 24-hour Holter monitoring.

Although there is not yet a single test that, by itself, confirms a diagnosis of CFS/ME, the combination of exclusionary, viral, neurological, and immune system tests usually suffice for a diagnosis. However, undergoing all these tests can be both expensive and nerve-racking for the patient. A single diagnostic test would considerably lessen the financial and emotional burden of lengthy testing.

### HOPE FOR A BIOMARKER

While much of the research performed over the past 25 years has revolved around identifying the basic mechanisms and possible cause of CFS/ME, finding a biomarker has been an underfunded priority. The reason the search for a biomarker generates so few research dollars is that the main funding source (the NIH), has not designated CFS/ME as an illness worth serious investigation. (In 2011, the NIH allocated a mere \$6 million to CFS/ME research, which was exactly six million times more than it allocated in 2010.) As a consequence, the identification of a biomarker, while anxiously awaited by patients and clinicians alike, has been relegated to the efforts of a few dedicated researchers.

In 2000 Dr. Robert Suhadolnik, a professor of biochemistry and member of the Temple University Pels Institute for Cancer Research and Molecular Biology in Philadelphia, reported that people with CFS/ME possessed a novel enzyme. Dr. Suhadolnik found that people with CFS/ME have a defect in their antiviral defense system that he believes is due to a faulty version of the enzyme known as ribonuclease (RNase) L. No healthy controls tested positive for the faulty enzyme. Dr. Suhadolnik's discovery prompted a great deal of excitement in the CFS/ME community. Ultimately, the low molecular weight Rnase L did not prove to be a biomarker. However, it is still an important finding, as it confirms two of the major mechanisms that underlie CFS/ME pathology: a reduction in cellular energy and an alteration in antiviral pathways.

More recently, an international collaboration of researchers found that the cerebrospinal fluid from CFS/ME patients differed from both healthy controls and patients with Neurologic Post-Treatment Lyme disease, an illness that shares many characteristics with CFS/ME. Each medical condition exhibited a distinct set of proteins in cerebrospinal fluid, which the authors cautiously proposed would accelerate “the transition from a discovery phase of candidate biomarkers, as described in this study, to full validation [as a biomarker] for clinical application.”

There are a number of other studies which have identified anomalies in CFS/ME patients which may serve as biomarkers. In 2011 a research team from Bond University in Australia found a group of significant abnormalities in immune system function among CFS/ME patients, including a reduction of NK function, which they believed could serve as a biomarker. And in 2012, Allen et al in Great

Britain, utilized PPG (photoplethysmography) technology to assess orthostatic intolerance in CFS/ME patients. Using a tilt table test, the group was able to distinguish between CFS/ME patients and controls with 82% accuracy.

What is noteworthy about biomarker studies is that quite a few of them have successfully been able to distinguish CFS/ME patients from healthy controls, as well as from patients with depression, autoimmune disease and other overlapping illnesses. But due perhaps to their specialized nature, none of them has yet been universally adopted.

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*The National Alliance for Myalgic Encephalomyelitis keeps an excellent list of tests for CFS/ME.* [http://www.name-](http://www.name-us.org/MECFSExplainPages/TestAbnormalities.htm)

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## CDC GUIDELINES FOR THE EVALUATION AND STUDY OF CFS (1994) ("Fukuda")

- Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.
- The concurrent occurrence of four or more of the following symptoms:
  - post-exertional malaise
  - impaired memory or concentration
  - unrefreshing sleep
  - muscle pain
  - multi-joint pain without redness or swelling
  - tender cervical or axillary lymph nodes
  - sore throat
  - headache

These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

### *Conditions that Exclude a Diagnosis of CFS*

Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, and iatrogenic conditions such as side effects of medication.

1. Some diagnosable illnesses may relapse or may not have completely resolved during treatment. If the persistence of such a condition could explain the presence of chronic fatigue, and if it cannot be clearly established that the original condition has completely resolved with treatment, then such patients should not be classified as having CFS. Examples of illnesses that can present such a picture include some types of malignancies and chronic cases of hepatitis B or C virus infection.
2. Any past or current diagnosis of:
  - major depressive disorder with psychotic or melancholic features
  - bipolar affective disorders
  - schizophrenia of any subtype
  - delusional disorders of any subtype
  - dementias of any subtype
  - anorexia nervosa
  - or bulimia nervosa
3. Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards.
4. Severe obesity as defined by a body mass index [body mass index = weight in kilograms ÷ (height in meters)<sup>2</sup>] equal to or greater than 45. [Note: body mass index values vary considerably among different age groups and populations. No "normal" or "average" range of values can be suggested in a fashion that is

meaningful. The range of 45 or greater was selected because it clearly falls within the range of severe obesity.]

Any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before attempting further classification.

Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or melancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

*Conditions that do not Exclude a Diagnosis of CFS*

1. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels, or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.
2. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptoms.
3. Any isolated and unexplained physical examination finding, or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate, without additional laboratory or clinical evidence, to strongly support a diagnosis of a discrete connective tissue disorder.

CANADIAN CRITERIA (2003)

A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or

fatigue, sleep dysfunction and pain; have two or more neurological/cognitive manifestations

and one or more symptoms from two of the categories of autonomic, neuroendocrine, and

immune manifestations; and adhere to item 7.

\_\_1. Fatigue: The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.

\_\_2. Post-exertional Malaise and/or Fatigue: There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period, usually 24 hours or longer.

\_\_3. Sleep Dysfunction: \* There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.

\_\_4. Pain: \* There is a significant degree of myalgia. Pain can be experienced in the muscles, and/or joints, and is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.

\_\_5. Neurological/Cognitive Manifestations: Two or more of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances –e.g., spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory–e.g., photophobia and hypersensitivity to noise and/or emotional overload, which may lead to “crash” periods and/or anxiety.

\_\_6. At Least One Symptom from Two of the Following Categories:

\_\_a. Autonomic Manifestations: orthostatic intolerance, neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea.

\_\_b. Neuroendocrine Manifestations: loss of thermostatic stability – subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change, anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress.

\_\_c. Immune Manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.

\_\_7. The illness persists for at least six months: It usually has a distinct onset, although it may be gradual. \*\* Preliminary diagnosis may be possible earlier. Three months is appropriate for children.

To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 & 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day.

*\*There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset.*

*\*\*Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset or have more gradual or insidious onset.*

Exclusions: Exclude active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison’s

disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse.

Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if patients meet the criteria otherwise.

Co-morbid Entities: Fibromyalgia Syndrome (FMS), Myofascial Pain Syndrome (MPS), Temporomandibular Joint Syndrome (TMJ), Irritable Bowel Syndrome (IBS), Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities (MCS), Hashimoto's thyroiditis, Sicca Syndrome, etc.

Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes".

Idiopathic Chronic Fatigue: If the patient has unexplained prolonged fatigue (6 months or more) but has insufficient symptoms to meet the criteria for ME/CFS, classify it as idiopathic chronic fatigue.

#### MYALGIC ENCEPHALOMYELITIS: INTERNATIONAL CONSENSUS CRITERIA (2011)

Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus.

A patient will meet the criteria for postexertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories (C), and at least one symptom from energy metabolism/transport impairments (D).

A. Postexertional neuroimmune exhaustion (PENE pen'-e): Compulsory



A. This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions.

Characteristics are as follows:

- Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.
- Postexertional symptom exacerbation: e.g., acute flu-like symptoms, pain and worsening of other symptoms.
- Postexertional exhaustion may occur immediately after activity or be delayed by hours or days.
- Recovery period is prolonged, usually taking 24 h or longer. A relapse can last days, weeks or longer.
- Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.

Operational notes: For a diagnosis of ME, symptom severity must result in a significant reduction of a patient's premorbid activity level. Mild (an approximate 50% reduction in pre-illness activity level), moderate (mostly housebound), severe (mostly bedridden) or very severe (totally bedridden and need help with basic functions). There may be marked fluctuation of symptom severity and hierarchy from day to day or hour to hour. Consider activity, context and interactive effects.

Recovery time: e.g., Regardless of a patient's recovery time from reading for ½ hour, it will take much longer to recover from grocery shopping for ½ hour and even longer if repeated the next day – if able. Those who rest before an activity or have adjusted their activity level to their limited energy may have shorter recovery periods than those who do not pace their activities adequately. Impact: e.g., An outstanding athlete could have a 50% reduction in his/her pre-illness activity level and is still more active than a sedentary person.

## B. Neurological impairments

### 1. Neurocognitive impairments

- Difficulty processing information: slowed thought, impaired concentration e.g., confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia
- Short-term memory loss: e.g., difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory

### 2. Pain

- Headaches: e.g., chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches
- Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is noninflammatory in nature and often migrates. e.g., generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain

### 3. Sleep disturbance

- Disturbed sleep patterns: e.g., insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams/nightmares
  - Unrefreshed sleep: e.g., awoken feeling exhausted regardless of duration of sleep, day-time sleepiness
4. Neurosensory, perceptual and motor disturbances
- Neurosensory and perceptual: e.g., inability to focus vision, sensitivity to light, noise, vibration, odour, taste and touch; impaired depth perception
  - Motor: e.g., muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia

Notes: Neurocognitive impairments, reported or observed, become more pronounced with fatigue. Overload phenomena may be evident when two tasks are performed simultaneously. Abnormal accommodation responses of the pupils are common. Sleep disturbances are typically expressed by prolonged sleep, sometimes extreme, in the acute phase and often evolve into marked sleep reversal in the chronic stage. Motor disturbances may not be evident in mild or moderate cases but abnormal tandem gait and positive Romberg test may be observed in severe cases.

#### C. Immune, gastrointestinal and genitourinary Impairments

At least one symptom from three of the following five symptom categories:

- Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion. e.g., sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation
- Susceptibility to viral infections with prolonged recovery periods
- Gastro-intestinal tract: e.g., nausea, abdominal pain, bloating, irritable bowel syndrome
- Genitourinary: e.g., urinary urgency or frequency, nocturia
- Sensitivities to food, medications, odours or chemicals

Notes: Sore throat, tender lymph nodes, and flu-like symptoms obviously are not specific to ME but their activation in reaction to exertion is abnormal. The throat may feel sore, dry and scratchy. Faucial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immune activation.

#### D. Energy production/transportation impairments: At least one symptom

- Cardiovascular: e.g., inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/dizziness
- Respiratory: e.g., air hunger, laboured breathing, fatigue of chest wall muscles
- Loss of thermostatic stability: e.g., subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities
- Intolerance of extremes of temperature

Notes: Orthostatic intolerance may be delayed by several minutes. Patients who have orthostatic intolerance may exhibit mottling of extremities, extreme pallor or Raynaud's Phenomenon. In the chronic phase, moons of finger nails may recede.

### *Paediatric considerations*

Symptoms may progress more slowly in children than in teenagers or adults. In addition to postexertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances.

- Headaches: Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness.
- Neurocognitive impairments: Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes. All cognitive impairments worsen with physical or mental exertion. Young people will not be able to maintain a full school programme.
- Pain may seem erratic and migrate quickly. Joint hypermobility is common.

Notes: Fluctuation and severity hierarchy of numerous prominent symptoms tend to vary more rapidly and dramatically than in adults

### *Classification: Myalgic encephalomyelitis*

Atypical myalgic encephalomyelitis meets criteria for postexertional neuroimmune exhaustion but has a limit of two less than required of the remaining criterial symptoms. Pain or sleep disturbance may be absent in rare cases.

Exclusions: As in all diagnoses, exclusion of alternate explanatory diagnoses is achieved by the patient's history, physical examination, and laboratory/biomarker testing as indicated. It is possible to have more than one disease but it is important that each one is identified and treated. Primary psychiatric disorders, somatoform disorder and substance abuse are excluded. Paediatric: 'primary' school phobia.

Comorbid entities: Fibromyalgia, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, Raynaud's phenomenon, prolapsed mitral valve, migraines, allergies, multiple chemical sensitivities, Hashimoto's thyroiditis, Sicca syndrome, reactive depression. Migraine and irritable bowel syndrome may precede ME but then become associated with it. Fibromyalgia overlaps.

### OXFORD CRITERA (1991)

#### *Chronic fatigue syndrome (CFS)*

- (a) A syndrome characterized by fatigue as the principal symptom.
- (b) A syndrome of definite onset that is not life long.
- (c) The fatigue is severe, disabling, and affects physical and mental functioning.

(d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.

(e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance.

(f) Certain patients should be excluded from the definition. They include:

(i) Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.

(ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

#### *Post-infectious fatigue syndrome (PIFS)*

This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research).

To meet research criteria for PIFS patients must

(i) fulfill criteria for CFS as defined above, and

(ii) should also fulfill the following additional criteria: and

(a) There is definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).

(b) The syndrome is present for a minimum of 6 months after onset of infection.

(c) The infection has been corroborated by laboratory evidence.

## IN SEARCH OF A CAUSE

Although the enigmatic nature of CFS/ME has inspired thousands of scientific and popular publications, its cause remains, as yet, unidentified. The debate surrounding the pathogenesis of CFS/ME has raged for decades. Some support the idea that a virus produces the illness, while others adhere to the principal that CFS/ME is environmental, the result of exposure to a number of toxins that damage the nervous and immune systems. Each of these theories generates its own research, its own spate of tests, and its own treatment protocols – and each has merit.

CFS/ME is a complex illness, which makes the search for a cause fraught with difficulties. However, enough is known of the illness to establish some basic parameters. Any etiological model for CFS/ME must take into account the following: 1) multisystem symptoms, 2) chronic illness, and 3) outbreaks. While most researchers tend to focus on 1 and 2, they often forget the infectious aspect of CFS/ME. Ultimately, any theory purporting to explain how CFS/ME occurs in an individual must also account for why it occurs in groups.

Essentially there are three divergent schools of thought as to the etiology of CFS/ME. The first is that a single entity causes CFS/ME: a virus, a bacterium, or a toxin. The second is that multiple factors contribute to the cause, such as several pathogens, or a combination of environmental toxins and pathogens, acting in concert. The third theory centers on genetics. In this model the host has a faulty immune system (producing, or produced by, faulty gene expression), thus making the host susceptible to long term sequelae from infections and/or toxic exposure.

Single agent theories often lead to single tests and single treatments, and are therefore favored by insurance companies and funding agencies. A potential flaw with this approach is that a single pathogen can cause a number of different diseases (e.g., EBV causes mono, Burkitt's lymphoma and several types of cancer). Conversely, a single illness can be caused by a number of different pathogens (e.g., cancer, the common cold). A variation of this model is what Dr. Bell describes as the 1-2 punch. The first punch would be the cause, which can become an occult, or hidden, infection the second is the “trigger.” The first exposure to a pathogen weakens the host, the second actually makes the person ill. There is considerable support for the idea of occult infection in many disease processes, particularly in persistent viral and bacterial infections (such as Lyme).

The search for a single causal entity has been dogged, though the evidence is conflicting, and in many cases secondary. When a unique etiology remains unidentified, the argument is often made that successful treatment of the illness provides proof of cause. For example, if an illness is cured by an antibiotic, it must have been caused by a bacterium. If antivirals work, then it must have been caused by a virus. There are certain pitfalls to this *post hoc ergo propter hoc* (“after the event, therefore the cause of the event”) style of argument. If you have the flu and you take Tylenol to lower the fever, does that mean that Tylenol cures the flu? Obviously, it does not. Nonetheless, this argument has strongly influenced etiological research, and must therefore be carefully considered.

The second theoretical model is that multiple entities – environmental toxins, pesticides, radiation – exert a “cocktail effect” which damages the immune system, leaving the body open to assault from any number of pathogens. The toxins most widely investigated in this category are pesticides, as these directly damage the nervous system. Treatments following this etiological model are eclectic and will often follow an incremental strategy, as per the expression of symptoms.

The third school of thought centers on the host, particularly on genetic propensities which would leave the host susceptible to any number of pathogens or insults. According to this mode of thought, CFS/ME is caused by an endogenous deficiency; the environmental triggers are viewed as largely circumstantial. Genetic modification treatments (e.g., stem cells) to correct this deficiency are currently experimental.

Increasingly, researchers are coming to the conclusion that “all roads lead to Rome.” What were once thought to be triggers for the illness are now believed to be causes (bacterial infections, exposure to toxins, etc). This has led scientists to dig deeper into the phenomenon of CFS/ME, searching for underlying clues as to what makes some people sick for years after these exposures. Lately, researchers are proposing that CFS/ME is not one illness, but many. That is to say, while we may all end up in Rome, not all of us are Roman.

## VIRUSES

The theory that currently holds sway in the U.S. is that CFS/ME is caused by a virus. This point of view is supported by history (CFS/ME epidemics have often followed polio epidemics), incidence (correlation with a viral prodromic illness), flu-like symptoms (swollen lymph nodes, malaise, sore throat), and similarities with other ailments with viral etiologies, notably mononucleosis and post-polio syndrome.

The discovery of what appeared to be a novel enzyme in CFS/ME patients in the mid-1990s lent considerable support to a viral etiology. A research team led by Dr. Robert Suhadolnik found a novel low molecular weight enzyme (the 2-5A-dependent RNase L), which appeared to be present only in CFS/ME patients. RNase L (ribonuclease L) is an enzyme that is elevated in viral infections, which led the team to conclude that the upregulated 2-5A pathway was “consistent with an activated immune state and a role for persistent viral infection in the pathogenesis of CFS.” Subsequent research showed that CFS/ME patients have fragmented RNase L, indicating that the RNase L system is dysfunctional. While the low-molecular weight RNase L was an important discovery, it was later found that it was not universal among CFS/ME patients, which ruled it out as a biomarker. Dismissing the novel RNase L as a biomarker was an unfortunate turn of events, for while not every person with CFS/ME had the fragmented RNase L, every person with the low-weight molecule had CFS/ME. This makes it an important diagnostic marker.

A viral cause is also supported by a substantial body of primary research. In the mid-1980s, Dr. Cheney and Dr. Peterson, the two clinicians who reported the

1984 outbreak in Incline Village, Nevada, found high titers of Epstein-Barr virus (EBV) in their patients. At the time, they believed the illness was caused by chronic activation of this virus alone. However, the presence of EBV titers in most of the healthy population, as well as high titers of many other viruses in the CFS/ME population, made that theory untenable. Nevertheless, the idea that a herpesvirus was at the root of the illness has persisted, primarily because the herpesviruses are known to establish latency – that is, they are never completely eradicated by the immune system.

In order to understand the impact viruses have on the human system, it is important to understand some of the basic features of viruses. As far as viruses are concerned, size matters. The average human cell has a diameter roughly 1000 times that of a small virus (e.g., polio). To put that ratio in concrete terms, imagine that you are a small virus with a height of about 5' 3". The average cell would then have a height of one mile. If you were a very round person, with a width of 5'3", then the volume of a cell would be about a billion times greater than yours. That gives you, the virus, a lot of room to hide – and to replicate.

Herpesviruses proliferate like rabbits, and they do it everywhere. They have been shown to be present throughout the body, even in the absence of acute infection. Autopsies of people who have died of various causes have revealed that all eight human herpesviruses can be present in as many as 40 different reservoirs (nasal, neural and pharyngeal tissues, skin, cartilage, bone, bladder, thyroid, intestine, liver, and so on).

The fact that herpesviruses persist within the cells of the body makes them prime suspects for creating the havoc of CFS/ME, for not only do they inhibit normal cell functioning throughout the body, they also suppress immune function. Herpesviruses are great imitators. They can mimic components of the immune system, effectively tricking it into inactivity. For example, by imitating the anti-inflammatory cytokine IL-10, herpesviruses can effectively turn off pro-inflammatory cytokines as well as other immune cells (such as natural killer cells) that would destroy them. Aside from blocking NK cells, herpesviruses can also prevent T cells from forming. In short, no matter how efficient a person's immune system is, these viruses are too tiny, too numerous, and too clever to be completely eliminated.

Although EBV was discounted as the unique cause of CFS/ME, its role in the illness is far from irrelevant. One of the primary triggers for adolescent CFS/ME is mononucleosis. In these cases, the mono is never resolved, and the patient remains ill for years with post-mono sequelae. EBV, like other herpesviruses, remains in the body for life. It is also widespread. EBV can take up residence in the nasal mucosa, the tonsils, spleen, lymph nodes, tongue, and intestines. It can also travel through blood. Significantly, EBV can be reactivated by stress hormones (glucocorticoids). Notably, CFS/ME patients frequently experience exacerbations and flares after mental, emotional or physical stress – all of which cause an increase in circulating glucocorticoids, leading to viral reactivation.

Rather than EBV, Dr. Komaroff has proposed that HHV-6, a human herpesvirus discovered in 1986, is responsible for causing CFS/ME. Like EBV, high titers of HHV-6 have been found in CFS/ME patients. Dr. Komaroff observed that HHV-6 has been associated with many of the neurological and immunological findings in patients with CFS/ME, including seizures. Other prominent researchers have supported that view. Dr. Garth Nicolson found active HHV-6 infections in a third of CFS/ME patients, as opposed to 9% of controls. Dr. Dharam Ablashi, one of the co-discoverers of HHV-6, found reactivation of HHV-6 in over half of the CFS/ME patients he tested as well as in patients with MS, indicating a common basis for the neurological symptoms of both illnesses as well as a common pathogenesis.

Research conducted by Chapenko et al in Riga suggests that in CFS/ME patients HHV-6 may play an adjunctive role. In a study comparing CFS/ME patients with healthy blood donors, both groups were found to have latent HHV-6. However, only CFS/ME patients had both HHV-6 and HHV-7 infections simultaneously. The immune parameters of CFS/ME patients with active dual infection were characterized by significant decrease of CD3 and CD4 T helper cells (associated with reduced immune function), a significant increase of CD95 cells (associated with cell apoptosis) and a decrease of CD4/CD8 ratio (indicating a Th1/Th2 shift in the immune system). The authors concluded that “HHV-6 and HHV-7 may be involved in the pathogenesis of CFS and reactivation of both viruses may provoke changes in the phenotype of circulating lymphocytes.” Sairenji et al also found high titers of antibodies to both HHV-6 and HHV-7 as well as to EBV in the serum of patients with CFS/ME. These findings would seem to support the idea that CFS/ME is caused by at least two viruses acting either together or in tandem.

While the Chapenko study raises some serious questions concerning the immunological consequences of the interplay of different herpesviruses, the fact that these viruses are ubiquitous in the general population presents a considerable obstacle to proving that herpesviruses cause CFS/ME. If everyone has been exposed to these viruses, why is it that only some people are affected for life? Therefore, the question for many clinicians and researchers is not whether these viruses are merely present, but whether they are active, and, if so – how? The latent state of herpesvirus infection is not known to cause symptoms. And while CFS/ME patients have tested positive for latent viruses, it has been difficult to prove active infection.

In order for a virus to be considered active, it must replicate. This has been a stumbling block for researchers, as active viral replication is difficult to demonstrate in CFS/ME patients. However, viruses can damage cells in other ways.

Dr. Martin Lerner's research has shown that multiple herpesvirus strains can affect what appear to be healthy cells, altering their function. In these cases, the host cells are considered “non-permissive,” meaning they don't permit viral replication. However, what Dr. Lerner found in CFS/ME patients was evidence of cell dysregulation eventually leading to cell apoptosis (death) in non-permissive cells. In short, the damage to these healthy cells was just as profound as the damage to those destroyed by viral replication. (Dr. Richardson also observed this



phenomenon in Coxsackie virus infections, in which the function of healthy cells was altered due to nearby viral activity.) Dr. Lerner has supported his position with the evidence of successful treatment. In his practice, he has found that antiviral medications which control herpesviruses (e.g., Valcyte) also eradicate CFS/ME symptoms.

Some researchers believe that because herpesviruses are ubiquitous, they are casual rather than causal. These scientists have turned their attention to those viruses that are known to have direct effects on the immune system as well as the ability to use the host's own DNA to replicate. Retroviruses, by definition, fit into this category.

In 1986 Dr. Michael Holmes, a researcher in New Zealand, found evidence of a retrovirus in CFS/ME patients. This finding was validated by research conducted in 1990 by Dr. Elaine De Freitas of the Wistar Institute in Philadelphia. She found viral fragments of HTLV (human T-lymphotropic virus) in the mitochondria of cells from 30 patients with CFS/ME. None of the 20 controls tested positive for the virus. Dr. De Freitas concluded that her research supported an association between an HTLV-II-like virus and CFS/ME.

Dr. De Freitas' research was not replicated by the CDC, so her theory of a retroviral etiology was abandoned. However, nearly twenty years later, another retrovirus was discovered in CFS/ME patients. In 2009 the Whittemore Peterson Institute (WPI) announced that a team of researchers had found definitive proof of a retrovirus in CFS/ME patients. The researchers, who hailed from several prestigious labs, including the National Cancer Institute, the Lerner Institute, the Cleveland Clinic, and the Laboratory of Cancer Prevention, identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV) in 68 of 101 patients (67%). Only eight of 218 (3.7%) healthy controls tested positive for the virus. Their experiments also revealed that XMRV was infectious and that it could be transmitted via the plasma of infected patients. The group concluded that their findings “raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.”

The news generated a worldwide firestorm of publicity. The WPI's finding that the virus could be transmitted through blood prompted the governments of Canada, Australia, New Zealand, and the U.S. to issue bans on blood donations from individuals with CFS/ME. Great Britain followed suit, issuing its own ban in November 2010. However, XMRV was soon dismissed as the cause of CFS/ME. Independent studies conducted in Sweden, Great Britain, and the U.S. failed to find XMRV in CFS/ME patients. Initially, the results of these studies were discounted by the WPI either on the basis of cohort selection (the Oxford case definition of CFS/ME used in the British studies is notoriously vague), or methodological inconsistency. But, in the face of international consensus that the WPI findings were the result of contamination, the WPI team was finally forced to admit defeat.

In September 2011, the researchers were compelled to publish a partial retraction of the original study, which effectively put a halt to XMRV research.

While XMRV was ultimately a dead end as far as the etiology of CFS/ME is concerned, the controversy surrounding the WPI study revitalized public interest in CFS/ME. Significantly, the blood donation bans for CFS/ME patients are still in effect. And the search for an infectious agent continues.

A more prosaic family of viruses may, in fact, initiate the neuroimmune cascade of CFS/ME. The late Dr. John Richardson, a British physician who treated patients with post-viral syndromes for more than four decades, believed an enterovirus much like the one which causes polio might be at the root of the illness.

Enteroviruses are highly infectious viruses that enter the body through the gastrointestinal (GI) tract and gravitate to the central nervous system, heart and muscle tissues. They are resistant to both stomach acid and bile, which enables them to persist in the GI tract for long periods of time.

To make his case for an enteroviral etiology, Dr. Richardson pointed to the remarkable similarity and incidence of polio-related symptoms and those produced by ME. What is more important, he drew upon thousands of case histories of patients who had persistent neurological and vascular impairment for many years following enteroviral (particularly Coxsackie) infections. Many of these patients were diagnosed with ME. While it is tempting to treat acute enteroviral infections as “triggers” rather than causes, such thorough documentation of the long-term effects of this virus cannot be discounted. Indeed, subsequent autopsies of Dr. Richardson's patients revealed that even after many years had passed, the *original* enterovirus infection was still active in damaged tissues.

Dr. Peter Behan and his team of researchers in Glasgow, Scotland, have also found indications of a persistent enteroviral infection in about 60% of the CFS/ME patients they have tested. Dr. Behan speculates that the virus is a mutated form of poliovirus that attacks the brain rather than the spinal cord, causing a "cascade effect." This theory fits well with the historical evidence, as well as epidemiology.

In keeping with Dr. Behan's findings, Dr. Chia has also discovered enteroviral infections in CFS/ME patients. Stomach biopsies taken from a group of 165 CFS/ME patients showed persistent active enteroviral infections, in some cases several years after the initial infection was first noted. The degree of viral load matched symptoms to such an extent that the researchers concluded that enteroviral infections might well be causal. Dr. Chia tested his hypothesis several years later by following a group of patients who had been admitted to the hospital with acute enteroviral infections. Three of those patients went on to develop CFS/ME.

Other less well-known viruses have also been implicated. In the early 1990s, W. John Martin found evidence of atypical viral infection in the cerebrospinal fluid and brains of several patients who had previously been diagnosed with CFS/ME. The infection was thought to be due to a stealth virus, a class of neurotoxic virus that causes very little inflammation. Dr. Martin believed the stealth virus found in the brains of CFS/ME patients originally came from a mutated cytomegalovirus found in African green monkeys. (Polio vaccine was originally cultured from the

kidneys of African green monkeys.) Unfortunately, Martin's work was not continued, so the potential role of the stealth virus remains unexplored.

Recently, parvovirus B19, a virus that targets red blood cell precursors in bone marrow, has been implicated as well. Follow-up studies of patients with acute parvovirus B19 infections conducted by J.R. Kerr in Great Britain showed that a significant proportion of patients went on to develop both arthritis and CFS/ME. Kerr proposed a genetic flaw that would allow for persistent immune activation – a mechanism which has been explored by many other researchers.

While the idea of persistent viral activation is one which has dominated CFS/ME theories, until recently the precise location of the viruses has been difficult to identify – that is, until the death of Sophia Mirza, a young British woman who died of CFS/ME in 2005.

The post-autopsy analysis of Sophia's spine revealed damage to 80% of her dorsal root ganglia. (These are the bundles of nerves alongside the spine that process pain signals.) Although the doctors who examined Sophie's spine could not identify the source of the damage, Dr. Judith Shapiro has proposed that varicella-zoster, the herpesvirus that causes chickenpox, may have been the culprit.

Varicella-zoster is known to infect the dorsal root ganglia, where it causes muscle pain, numbness, vertigo, and overstimulation by sensory stimuli such as light, sound and odors. These are symptoms that tormented Sophia Mirza, and which plague many other severely ill CFS/ME patients. In addition, it is Shapiro's belief that activated varicella-zoster in autonomic nervous system ganglia is what leads to the chronic sympathetic nervous system activation that produces insomnia, dysautonomia, cardiac, and endocrine problems in CFS/ME. (Martinez-Lavin has also proposed sympathetic activation as a model for fibromyalgia.) But, it is not only the herpesvirus family that can infect the dorsal root ganglia. Polio virus, an enterovirus, also infects dorsal root ganglia, where it causes paralysis.

The disturbing reality is that many viruses may be acting in concert to produce CFS/ME. Viruses have been known to “assist” one another. For example, viral fragments left from previous infections may contribute proteins to a new virus, which increases its virulence. This is what is believed to have happened in the great flu pandemic of 1918 that killed between 50 and 100 million people. Even more problematic is the process through which bacteria may also “assist” viruses. Neurotropic bacteria, such as the *borrelia* strain that causes Lyme disease, may also take up residence in dorsal root ganglia. It is more than disturbing to imagine what happens when all of these pathogens come into contact with one another in the dorsal root ganglia of a host with a dysregulated immune system.

## BACTERIA

In a paper published in late 1999 in the prestigious *European Journal of Clinical Microbiology and Infectious Diseases*, microbiologist Garth Nicolson demonstrated that multiple species of mycoplasma were present in the blood of patients with CFS/ME (more than 60%). Mycoplasmas are tiny bacteria that lack cell walls, and thus are unaffected by most common antibiotics. Several strains of

mycoplasma have been implicated in human diseases: *Mycoplasma pneumoniae* can cause walking pneumonia, and *Mycoplasma genitalium* has been implicated in pelvic inflammatory disease. Mycoplasmas have also been found in AIDS patients and Gulf War Syndrome patients.

Using forensic polymerase chain reaction (PCR) Dr. Nicolson found *Mycoplasma fermentans*, *Mycoplasma pneumoniae*, *Mycoplasma hominis* and *Mycoplasma penetrans* in blood samples taken from patients with CFS/ME and fibromyalgia. Over half of the patients had more than one infection. A subsequent study performed in Belgium found evidence of multiple mycoplasma infections in a similar percentage of European patients diagnosed with CFS/ME. Further studies by Dr. Nicolson revealed co-infections with chlamydia (a sexually transmitted pathogenic bacterium), and HHV-6. The severity of symptoms in CFS/ME patients corresponded with the degree of infection, the greatest increases being found in fatigue and sleep problems, depression, memory loss, balance disturbances, muscle and joint pain, head and neck aches, and night sweats and fevers. Dr. Nicolson, like other doctors using *post hoc* arguments, pointed to the success of long-term antibiotics in treating CFS/ME.

Bacteria have been implicated by other physicians as well. Phillippe Bottero, a French doctor, found that all of his CFS/ME patients tested positive for bacterial infections with rickettsia. The rickettsia are a group of pathogenic tick-borne bacteria responsible for typhus and Rocky Mountain spotted fever, as well as many other diseases. Because they colonize the vascular system, and can therefore travel throughout the body, rickettsial bacteria can cause pneumonia, encephalitis, myocarditis, lesions in the liver, gastrointestinal wall and pancreas, as well as central nervous system inflammation. Dr. Bottero proposed that due to the long survival of rickettsial infection in vascular linings, the resulting vasculitis could produce many of the symptoms common in CFS/ME. An impressive 78.5% of Dr. Bottero's 98 CFS patients improved significantly after treatment with antibiotics.

Cecile Jadin, a Belgian surgeon with a practice in South Africa, also found strong correlations between rickettsial infections and patients diagnosed with CFS/ME. With a simple course of tetracycline, Dr. Jadin reversed symptoms in five hundred patients previously diagnosed with CFS/ME, as well as patients diagnosed with fibromyalgia, MS, depression, heart disease, and psychosis. To date, she has used antibiotics to successfully treat thousands of patients with underlying rickettsial infections, all of whom had been previously diagnosed with other ailments (predominantly CFS/ME, fibromyalgia, MS, and rheumatoid arthritis).

Dr. Jadin adheres to the idea that rickettsial infection is an occult disease. That is, it remains dormant until another pathogen challenges the system. (This relates to Dr. Bell's 1-2 punch theory.) At that point, the patient becomes symptomatic. This is a compelling theory for the origin of CFS/ME, as it adequately explains the wide variety of triggers as well as the multiplicity of symptoms. Significantly, another tick-borne rickettsial bacterium, *borrelia*, has been found in patients diagnosed with CFS/ME. Several species of *borrelia* are known to cause

Lyme disease, which produces central nervous system, joint, and cardiovascular symptoms, as well as fatigue.

The question that Dr. Jadin's success raises is not whether rickettsial infections cause CFS/ME, but whether people who are cured by tetracycline ever had CFS/ME. When a short course of antibiotics (weeks or months) can restore a person to health, even after years of illness, it speaks to more the laxness of diagnosticians who are apt to make an easy diagnosis of “chronic fatigue syndrome” (or various psychiatric illnesses) for patients who present with “fatigue” than it does to etiology.

## MOLD

In his book, *Mold Warriors*, Dr. Ritchie Shoemaker expresses his disdain for the diagnosis of fibromyalgia. “I used to think that the fibro term was a medical code for, 'We don't know what the Hell is wrong,'” he says. “Now I believe the diagnosis of fibromyalgia is the ultimate example of how physicians patronize patients. Fibro usually means a biotoxin illness” (p 213). According to Dr. Shoemaker, all of his referred fibromyalgia patients have mold toxicity. Dr. Shoemaker does not express the same contempt for the diagnosis of CFS/ME, but he does insist that many patients develop CFS/ME as a direct result of mold exposure. CFS/ME patients themselves have reported profound relapses and even initial symptoms after mold exposure, indicating that mold toxicity may serve to identify a subset of CFS/ME patients.

Molds are found everywhere. Their purpose is to break down organic matter so that it can be recycled into the environment for use by other living things. This is a big job, but molds are up to it. There are about 1.5 million different types of fungi, with many more yet to be identified. And they are everywhere – in your garden, in your house, and in your body. Unfortunately, while most of these species are benign, a few emit toxic substances, known as volatile organic compounds (VOCs). When certain species of molds proliferate indoors in damp environments, as occurs in “sick building syndrome,” they can exceed the body's ability to handle the toxins.

The most common molds found indoors are *Aspergillus*, *Penicillium*, *Chaetomium*, and *Acremonium*. *Stachybotrys*, the so-called “black mold,” can be found in saturated substrates (flooded basements, and so on). Once inhaled, the compounds released by these molds can cause numerous acute health problems: particularly damage to nasal passages (where they cause sinusitis), lungs (cough), and skin (rashes).

People who are chronically affected can experience fatigue, weakness, GERD, aching, unusual stabbing pains all over, light sensitivity, transient blurred vision, shortness of breath, cough, numbness, tingling, confusion, constipation and diarrhea, morning stiffness, a metallic taste in the mouth, diarrhea at night, thirst, frequent urination, static shocks, and hypothalamic problems such as mood swings, appetite swings, sweats, and trouble controlling body temperature.

Dr. Shoemaker's theory as to why some people develop chronic, widespread symptoms to mold exposure while others do not closely parallels the CFS/ME model. First there is genetic susceptibility.

People who do not recover from mold exposure have HLA DR genes which allow the toxin to evade the immune system. Because the toxin isn't "recognized" by the immune system, it isn't cleared out. Next, an alternative pathway which provokes an antigen response is turned on. This elevates the NF-kappaB gene transcription pathway which leads to production of inflammatory cytokines. The cytokines cause the release of MMP-9. Then, the release of MMP-9 in the brain causes plaques (these are UBOs, or "unidentified bright objects" on MRIs) that resemble MS, as well as joint inflammation, muscle pain, shortness of breath and coughing.

The overstimulated immune system also interferes with blood vessel dilation, which leads to cellular hypoxia, causing lower production of ATP. The ultimate result of this cascade is an overwhelmed liver (which simply dumps toxins into bile), a hyper-aroused immune system, sustained sympathetic nervous system arousal, disruption of homeostasis, exercise intolerance, and exhaustion. These symptoms are identical to those of CFS/ME.

At the 2004 American Association of Chronic Fatigue Syndrome conference, Dr. Shoemaker presented 89 patients "desperately ill" with CFS/ME. Of these patients, 79 possessed mold susceptible genotypes. These patients also showed "sky high" amounts of the complement C3a. (Complement is a part of the immune system that acts in conjunction with specific antibodies.) According to Dr. Shoemaker, C3a goes up within hours of mold exposure. Dr. Shoemaker has observed that persistent C3a elevation is often seen in patients who go on to develop CFS/ME. He noted a number of other immune system commonalities between people with mold exposure illnesses and CFS/ME. In both sets of patients, alpha interferon is increased. RNase L, the enzyme that is elevated in CFS/ME patients, is also elevated after exposure to mold.

While not embracing the idea that mold causes CFS/ME with open arms, many well-known CFS/ME physicians have acknowledged the overlap between CFS/ME and mold toxicity. Dr. Cheney has pointed out that mold has a number of strong negative effects on the body, including the creation of oxidative stress, a decrease in reduced glutathione, perforations in the blood-brain barrier, and destruction of intestinal cells.

A 2003 review of mycotoxin exposure-related health risks conducted by Anyanwu et al found that depression, psychological stress, tissue injuries, malignancies, carcinogenesis, chronic fatigue syndrome, and experimental allergic encephalomyelitis could be induced at very low physiological concentrations through mycotoxin-induced natural killer cell activity. The authors concluded that "chronic exposures to toxigenic mold could lead to abnormal NKC activity with a wide range of neurological consequences, some of which were headache, general debilitating pains, fever, cough, memory loss, depression, mood swings, sleep disturbances, anxiety, chronic fatigue, and seizures."

Moreover, Anyanwu et al observed in a later paper that patients with chronic mold exposure show vitamin B12 deficiencies, resulting in a disruption in the methylation cycle. The authors proposed that it is the interruption of B12 function that leads to neurological symptoms of mold exposure. (It is worth noting here that B12 is one of the more successful CFS/ME treatments. It is also a key element in the Methylation Block Protocol of Rich Van Konynenburg.)

Finally, in an impressive examination of what they called “mold mycotoxicosis,” Campbell et al documented no less than 38 symptoms involving the immune system, the lungs, the central and peripheral nervous systems, as well as generalized inflammatory responses after exposure to mycotoxins. The researchers reported a number of neurological symptoms, including neuropathies, cognitive deficits (visuospatial learning and memory), muscle tremors and weakness, lack of coordination, seizures, and confusion. One of their more disturbing findings was the presence of elevated autoantibodies to several neuronal antigens after exposure to molds. The titers of autoantibodies to myelin basic protein, myelin associated glycoprotein, oligodendrocyte glycoprotein, chondroitin sulfate and other substances essential to maintaining neural integrity were significantly elevated over controls, indicating that mold can cause a demyelinating process similar to MS.

There is a great deal to be said for the involvement of mold in the pathogenesis of CFS/ME. Outbreaks of CFS/ME have often occurred among people sharing the same space (barracks, hospitals, schools, and so on). This means that there is either a contagious agent involved or a mutually shared toxin (or both).

Furthermore, a block in the methylation cycle, such as the one caused by mold toxicity, has been proposed by Rich Van Konynenburg as a primary mechanism for CFS/ME. Even if mold does not prove to be the cause of CFS/ME, for some patients it may weigh in as heavy factor in its development.

## ENVIRONMENTAL CAUSES

Environmental factors have frequently been implicated as possible causes of CFS/ME, particularly in people with gradual onset. Those who contend that CFS/ME is the result of environmental contamination essentially consider CFS/ME to be the end result of the body's inability to rid itself of toxins. This is the perspective Dr. Sherri Rogers puts forth in her book, *Tired or Toxic?*

Dr. Majid Ali, another physician who believes that CFS/ME is caused by toxic overload, writes in his book, *The Canary and Chronic Fatigue*, that "chronic fatigue sufferers are human canaries—unique people who tolerate poorly the biologic stressors of the late 20th century." His point of view is that people with CFS/ME are prone to injury from environmental causes, such as pollution, chemical injuries, and unmanaged allergies, much as canaries are to underground gases. In other words, the CFS/ME population is a warning to the rest of the world that the environment is becoming dangerous.

A number of other clinicians and independent researchers have pointed out that environmental factors may play a key role in how CFS/ME develops. Joe Mangano, MPH, has put forth the theory that CFS/ME could be a radiation-related

disorder (*CFIDS Chronicle*, Winter 1994). He points out that the immunological abnormalities found in patients with CFS/ME (large numbers of cytokines such as alpha interferon and interleukins, as well as reduced number of natural killer cells) could be attributed to constant exposure to low-level ionizing radiation from atmospheric tests conducted since the 1940s.

Mangano proposes that the effect of atmospheric fallout, though not enough of a factor in itself to cause a large-scale health trend such as CFS/ME, may operate synergistically with other environmental factors, such as industrial pollution, carcinogens in consumer products, and occupational hazards to create significant health effects.

The association between exposure to radiation and CFS/ME has been noted by other researchers, though none has proposed a causal link. Dr. Martin Pall has noted that the symptoms of post-radiation syndrome are identical to those of CFS/ME. He considers the overlap to be a consequence of shared nitric oxide/peroxynitrite (NO/ONOO<sup>-</sup>) cycle-produced oxidative stress. Interestingly, Alan Cocchetto, Medical Director of the National CFIDS Foundation, has identified some unique mitochondrial characteristics in his research that implicate low level radiation as the catalyst for some patients. As Dr. Pall's NO/ONOO<sup>-</sup> model can also lead to mitochondrial defects, the two models may eventually prove to be similar, if not the same.

Pesticides are the primary focus of researchers investigating environmental causes of CFS/ME. Pesticides have long been known to cause neurological damage. Their function is to kill insects by destroying their nervous systems through a dysregulation of neurotransmitters: notably acetylcholine. Not surprisingly, people (who have the same neurotransmitters) are affected by pesticides in the same manner.

In 1994 a group of Scottish researchers proposed that fatigue syndromes might be secondary to altered sensitivity of the GABA<sub>A</sub> receptor. They believed this could be due to involvement of organochlorine and organophosphate compounds which damage cholinergic input to the dentate gyrus of the hippocampus. This is an area of the brain where cholinergic and GABAergic transmission are closely linked.

A retrospective study, also conducted in Scotland, found that sheep farmers who had been exposed to organophosphates in sheep dips showed high prevalence of chronic fatigue and that higher chronic fatigue scores were associated with higher exposure to organophosphate pesticides, indicating a dose-dependent correlation. In support of these findings, Dunstan and colleagues found that serum levels of organochlorine (a chemical found in pesticides) was higher in CFS/ME than in controls. There were no significant differences in organochlorine levels between those CFS/ME patients with a history of toxic chemical exposure, and those without. The researchers concluded that the exclusion of patients from the CDC definition of CFS/ME on the basis of a history of exposure to toxic chemicals was not valid, and that low level organochlorine bioaccumulation might lead to the development of CFS/ME.



A third group of Scottish researchers led by Dr. Faisal Khan, found a link between CFS/ME, Gulf War syndrome (GWS) and agricultural workers exposed to organophosphate pesticides. All three exhibited cholinergic abnormalities, however only the CFS/ME group showed abnormalities in the vascular system. They concluded that CFS/ME had a different etiology from either GWS or pesticide exposure, one which might involve inhibition of vascular cholinesterase.

Two later studies by the authors found that sensitivity to acetylcholine was restricted to those patients who fit descriptions for ME and post-viral fatigue syndromes, but not those for Gulf War syndrome or for those exposed to organophosphate compounds, or those with fibromyalgia. The authors were confident that the finding of increased sensitivity to acetylcholine in CFS/ME patients was “robust and unusual,” but could not conclude that pesticide exposure was causal.

Gene studies paint a somewhat different picture. In two separate studies respectively led by Kerr and Kaushik, researchers found high neuropathy target esterase (NTE) in CFS/ME patients. NTE is the primary site of action of organophosphate compounds, such as sarin, which cause neural degeneration and paralysis. Kerr et al concluded that NTE levels seen in patients with CFS/ME were consistent with organophosphate exposure, but that this pertained only to a subset of patients.

Given the extensive use of pesticides, especially in the home environment, it is not unlikely that neurotoxic pesticides play a role in the development of CFS/ME in some patients. Treatments for these patients would necessarily have to address the ongoing effects of neurotoxins, as well as the interplay between these toxins and latent pathogens.

## GENETIC THEORIES

Genetics is a field that has only recently come to the forefront in identifying risk factors for disease. While genetic diseases (those which are passed directly from parents to children, such as Parkinson's disease) have long been recognized, we have not possessed until the last decade the technology to adequately examine gene types in people who do not have these classic genetic disorders.

CFS/ME does not fall into the category of a genetic disease, for even though it can occur in family groups, it also occurs in groups whose only risk factor was being in the same place at the same time (e.g., the Royal Free outbreak). Families who contract the flu simultaneously certainly cannot be said to have a genetic disease. However, genes can still play a prominent role in determining who gets sick, and for how long.

The late Dr. John Richardson pointed out that viruses are not lethal until the host makes them so. That is to say, a “benign” virus may become deadly in a host with deficient defenses. Conversely, virulent viruses which cause severe symptoms in some people may go relatively unnoticed in others. It was a common observation among doctors in the 1950s that in families in which all members were infected with polio virus, one member would get what looked like a cold, another would be ill

for a few weeks and recover, while yet another became paralyzed. Clearly some people are better at resisting infection than others. The reason for this may lie not only in the efficiency of their immune systems, but in their genes.

The human genome, that is, the entirety of a human being's hereditary information, consists of roughly 23,000 genes. That is a lot of genes, but to put it into proper perspective, we rank only a little higher than the roundworm, which clocks in at roughly 18,500, and significantly lower than the mustard plant, which has an inheritance of 28,000 genes.

Needless to say, the fact that the human genome turned out to be not as robust as mustard was disappointing to many geneticists, who had clearly overestimated the complexity of the human being. Nonetheless, even a scant 23,000 is intimidating to someone looking for the set of genes that can lead to an illness as complex as CFS/ME. For the combinations of these 23,000 genes can result in over 3 billion base pairs. Finding a needle in a haystack is child's play in comparison to finding the set of genes that can cause a chronic illness.

Genes, while essential to our fates, do not determine it. Like light switches, they must be “turned on” via a step-wise series of complicated processes (i.e. transcription, processing, translation and post-translation modification) in order to produce an effect. Until all of this “editing” takes place, the information encoded in our genes remains unread. There are numerous pathways that can activate genes, one of which is the disease process itself, which invariably leave genetic tracks.

Twin studies have been considered the “gold standard” for determining genetic traits. Monozygotic twins share the same DNA, so when both twins develop an illness, a genetic analysis can sometimes point to underlying propensities. When one twin develops an illness and the other doesn't, environmental causes are often sought. The strongest evidence for genetic involvement comes from twins who develop the same illness, but have been separated at birth (e.g., adoption). Because the social and physical environments are different, it is assumed that genetic traits play a large contributory role.

Not many twin studies have been conducted for CFS/ME. However, those which have been performed are significant. Sabbath et al conducted a study in 2002 that revealed immune system abnormalities in discordant twins (one twin had CFS/ME, the other didn't). Significant reductions in T cell subtypes, including the expression of NK cells and total lymphocytes, were noted in CFS/ME twins. This accords with immunological findings in the general CFS/ME population. The authors were hesitant to propose a genetic factor, but suggested that this would be a fruitful area for future research.

In 2004, a study performed by Mahurin et al showed that discordant twins had much slower reaction times on all speed-related cognitive tests than healthy twins. The researchers suggested that their findings indicated a central information processing deficit in the brain. (This would be consistent with Dr. Goldstein's characterization of CFS/ME as a neuroprocessing disorder.)

A subsequent study conducted by Claypoole et al found that among discordant twins, those with CFS/ME exhibited decreases in motor functions, speed

of information processing, verbal memory, and executive functioning. Interestingly, the twins with sudden onset demonstrated slower information processing compared with those with a gradual onset of the illness.

Various non-twin genetic studies have found that the expression of genes linked to a number of CFS/ME symptoms differs sharply from those who are healthy. Changes in gene expression of lymphocytes, indicating subtle changes in the immune system, were documented in CFS/ME patients by Powell et al. And in 2007, a group of Swedish researchers led by Hanna Gräns found significantly lower messenger RNA expression levels of estrogen receptors in female patients compared with healthy controls. The researchers stated that their finding was consistent with an “immune-mediated pathogenesis” of CFS/ME.

In 2005 Whistler et al located a set of exercise-responsive genes that differed between patients and controls, adding a genetic component to the hallmark symptom of CFS/ME: exercise intolerance. Significantly, greater numbers of genes involved in ion transport and ion channel activity (two molecular functions involved in physical activity) were exaggerated after exercise in CFS/ME patients.

Also in 2005, Kaushik et al at the Imperial College in London, found 35 genes in CFS/ME patients which were different from controls. Using polymerase chain reaction (PCR) the researchers confirmed a differential expression for 16 of these genes, 15 of which were upregulated and one of which was down regulated (IL-10RA). Two of the upregulated genes suggested links with organophosphate exposure and virus infection. Significantly, a number of the genes that were identified affect the functioning of the mitochondria. This abnormal gene expression could account for many CFS/ME symptoms, including fatigue, exercise intolerance, cognitive deficits, and cardiovascular problems. The authors concluded that this profile “indicated T cell activation and perturbation of neuronal and mitochondrial function.” These findings would support immune and cellular dysfunctions consistent with a viral etiology.

More recently, an impressive group of 17 researchers in Great Britain confirmed a differential expression for 88 genes; 85 were upregulated, and 3 were down regulated in 55 CFS/ME patients. According to the researchers, the most highly represented functions were “hematological disease and function, immunological disease and function, cancer, cell death, immune response, and infection.” Of significance to clinicians, the researchers found that their data revealed clusters, or subtypes of CFS/ME, that fell into seven categories. Furthermore, these categories corresponded not only to distinct sets of symptoms, but to severity.

- Subtype 1 had the worst cognition and mental health and poor sleep, despite being associated with the least pain.
- Subtype 2, which was predominantly male, had marked postexertional malaise, muscle pain, and joint pain, but poor mental health.
- Subtype 3 was the mildest form of the illness.
- Subtype 4 had moderate neurocognitive function and cognitive defects, combined with moderate levels of bodily pain and sleep problems.

- Subtype 5, which was entirely female, had the best mental health but poor neurocognitive function, gastrointestinal complaints, and the most marked muscle weakness and postexertional malaise.
- Subtype 6 was characterized by significant fatigue
- Subtype 7, which was entirely female, had the most pain, and the most severe individual symptoms, including swollen glands, sore throat, and headaches.

Subtypes 1 and 7 were the most severe, followed by subtypes 2, 4, 5, 6, and, last of all, 3 (suggesting that mild forms of the illness are either relatively rare, or undiagnosed).

Of interest in this study was the fact that 12 of the genes associated with EBV infection were upregulated, underscoring the importance of EBV in CFS/ME. Another significant finding, especially in light of the recent studies documenting reduced white matter in the brains of people with CFS/ME, was a gene mutation associated with vanishing white matter disease.

The most extensive genetic study to date was conducted by the CDC in 2006. In this \$2 million study, 227 people in Wichita, Kansas underwent detailed clinical evaluations, which included sleep studies, cognitive functioning measurements, autonomic nervous system evaluations, extensive blood work, and genetic testing. The activity levels of 20,000 genes were assessed by multidisciplinary teams of experts in medicine, molecular biology, epidemiology, genomics, mathematics, engineering and physics. The results were published as a set of 14 articles in the April, 2006 issue of the journal *Pharmacogenomics*. On the whole, it was an impressive effort, and one which Dr. Reeves of the CDC called “groundbreaking.”

In spite of the press attention garnered by this study, the results were disappointing. After all the time and money spent on the study, the ultimate conclusion reached by the CDC was that people with CFS/ME are unable to handle stress (this is referred to as “allostatic load”). As a consequence, they are more susceptible to infections, toxins and so forth. Apart from the fact that the classification of CFS/ME as a stress-associated illness essentially relegates it to a form of anxiety, the idea that “stress” causes illness is amorphous at best. It is true that the release of catecholamines will worsen any condition, but that fact tells you nothing about causation – even if your genes can't handle the allostatic load.

The 2006 CDC study has come under considerable criticism, not just for its conclusions, but for its methodology. Patrick Sullivan, a geneticist at the University of North Carolina, Chapel Hill, voiced concern that the interpretation of the results might have been “incautious.” Dr. Kerr, who is not one to mince words, called the results “meaningless,” because PCR analysis was not employed. If it had been, he pointed out, 30% to 40% of genes would have dropped out. There were also problems in cohort selection.

The average work week of the Wichita cohort was 48 hours a week, which casts serious doubt as to the validity of the diagnosis. The majority of people with CFS/ME can barely maintain a part-time job, let alone a 48-hour work week. In addition, anxiety disorders, fibromyalgia, and primary sleep dysfunction were not

ruled out, which means that at least some of the subjects (if not all) may not have had CFS/ME. It is unfortunate that the CDC wasted so much money, time and effort on this ultimately fruitless endeavor. But considering the history of that institution's relationship with CFS/ME, the failure is sadly predictable.

Given the complexity of CFS/ME, the difficulty of determining subsets of patients, and the number of possible gene combinations, pathways and processes involved, the pursuit of a CFS/ME genome may be a pipe dream. Indeed, Dr. Patrick Sullivan feels that the endeavor is not even rational. However, anything that sheds light on the etiology of the illness, or that can help identify its pathogenesis is more than welcome in the world of CFS/ME research.

## HISTORICAL LESSONS

The fact is that illnesses do not have an infinite number of causes. Essentially, a person is either poisoned or infected – or is born with a defect that makes him or her ill (these defects are apparent very early in life, and thus do not enter into the CFS/ME model). Whether illnesses are “controversial,” enigmatic, or thought to be the result of evil spirits, too much white bread, or “psychosocial” factors, there are only two real choices: poison or pathogen (or both). CFS/ME, while producing a complex symptomatology, is not very different from any other illness in this regard. This is an important point that the CFS/ME community sometimes forgets – to its detriment. For as long as CFS/ME is considered a “one-of-a-kind” illness, it will remain *terra incognita* – the realm of “hysterical” patients and “quack” doctors.

In order to bring home the idea that CFS/ME, though complex, is not unique, it is helpful to compare it to other illnesses that share similar histories, but have advanced further along the road to medical acceptance. Multiple sclerosis (MS) is an illness that was once called “hysterical paralysis.” (Sigmund Freud himself made this diagnosis for at least one patient with MS.) For an embarrassing length of time, “hysterical paralysis” was considered a perfectly legitimate medical diagnosis. (Hysteria is now called “conversion disorder,” which makes it sound more scientific, but is equally flimsy as a diagnosis.) Of course, with the advent of MRIs, “hysterical paralysis” rapidly passed into the world of quaint diagnoses, along with “effort syndrome,” “bad blood,” and “ague.”

Multiple sclerosis is an illness which causes demyelination, the destruction of the fatty tissue that surrounds many nerves. One of the functions of the myelin sheath is to increase the speed of nervous system conduction. When the sheath is destroyed, nervous system impulses are slowed, causing tingling, numbness, weakness, paralysis, slurred speech, loss of balance and coordination, blurred vision, memory loss, cognitive impairment, and overwhelming fatigue. These, and other symptoms, may accumulate slowly, and in various combinations.

Characteristically, the symptoms occur in attacks (hence “hysterical” paralysis). The definitive test for the illness is the presence of ovoid plaques, or scar tissue, in the brain. MS is classified as an autoimmune disease, that is, it is the immune system itself which attacks the myelin, causing inflammation and,

eventually, destruction. What sets the immune system on its path of destruction has been a topic of much debate over the years, but, as with many neurological illnesses, viruses have been implicated.

This is the point at which the similarities with CFS/ME become inescapable. A strong correlation has been found between severe cases of mononucleosis in the teen years and subsequent development of MS. Studies have implicated EBV as well as HHV-6 in the pathogenesis of MS. In addition, MS can be found in epidemic form. It was unknown in the Faroe Islands until the occupation by the British in 1940, after which it occurred in epidemics. Like CFS/ME, and all autoimmune diseases, MS is an illness primarily affecting adult women. Also like CFS/ME, MS has a variety of subtypes, including a remitting, relapsing pattern. It is exacerbated by stress.

In an even more significant parallel with CFS/ME, a recent study by researchers at the University of London found that although EBV was not actively spreading in MS patients, it was releasing a chemical message into nearby areas of the brain. This chemical message was activating the body's immune system, causing inflammation. This is precisely the mechanism proposed for CFS/ME. In a twist that is nearly ironic, the London researchers proposed rituximab – the treatment that recently cured several CFS/ME patients in Norway – as a potential course of treatment for MS.

Ultimately, CFS/ME will undoubtedly follow the path laid by MS, providing yet another example of what pathogens can do to the nervous/immune system. But in the meantime, it is good to keep in mind that the “hysterical paralyses” and “yuppie flus” of yesteryear eventually become the accepted organic illnesses of tomorrow.

## RESOURCES

Online Medelian Inheritance in Man (OMIM): <http://www.ncbi.nlm.nih.gov/omim>  
*OMIM is a comprehensive, authoritative, and up-to-date compendium of over 12,000 human genes and genetic phenotypes, as well as all known genetic disorders. It is updated daily, and the entries contain many links to other genetics resources.*

## FURTHER READING

### *General*

“Anti-Immunology: Evasion of the Host Immune System by Bacterial and Viral Pathogens.”

B. Brett Finlay and Grant McFadden.

<http://immunology.wustl.edu/training/advdocs/EvasionofHost%5B5%5D.pdf>

“The Neuropsychiatric Assessment of Lyme Disease.” Robert Bransfield, M.D.

<http://www.mentalhealthandillness.com/tnaold.html>

*Though it is about the effects of Lyme disease, this article is very useful for people with CFS/ME. Dr. Bransfield does an excellent job of categorizing symptoms in terms of nervous system functions as well as to related brain structures.*

“Is Selenium Deficiency Behind Ebola, AIDS and Other Deadly Infections?” Jack Challem. [http://infonom.com.ar/task/html/selenium\\_deficiency\\_behind\\_tod.html](http://infonom.com.ar/task/html/selenium_deficiency_behind_tod.html)

#### *Viruses*

"Light on ME/CFS III: A Different Herpes Virus for CFS? - Varicella-Zoster, Shingles and ME/CFS." Cort Johnson.

<http://forums.phoenixrising.me/content.php?449-Light-on-ME-CFS-III-A-Different-Herpes-Virus-for-CFS-Varicella-Zoster-Shingles-and-ME-CFS>

*Cort Johnson's fascinating history of the CFS/ME retrovirus.*

<http://forums.phoenixrising.me/showthread.php?2857-The-First-Retrovirus-in-CFS-Part-II>

*Excellent article on Dr. Ablashi, herpesviruses and their treatment.*

<http://www.prohealth.com/library/showarticle.cfm?libid=9411>

*How viruses work:* <http://www.ncbi.nlm.nih.gov/books/NBK8181/>

*Dr. Lerner's publications:*

[http://www.treatmentcenterforcfs.com/cfs\\_publications/index.html](http://www.treatmentcenterforcfs.com/cfs_publications/index.html)

*Good critique of Dr. Lerner's research.*

<http://www.mecfsforums.com/index.php/topic,2690.msg28375.html#msg28375>

#### *RNase L*

*Phoenix Rising forum discussing RNase L as a marker.*

<http://forums.phoenixrising.me/archive/index.php/t-14165.htm%20s=b251ed9f477749d3e98faafbcd7951c8>

#### *Mold*

*Pat Sullivan's mold blog. Lots of good information here:*

<http://www.patsullivan.com/blog/mold/>

“Biotoxin Illness Conference 2011.” *Good review of Dr. Shoemaker's ideas.*

<http://betterhealthguy.com/joomla/blog/251-biotoxin-illness-conference-2011>

*CFS forum on Dr. Shoemaker:* <http://forums.phoenixrising.me/archive/index.php/t-8928.html>

*A good critique of Dr. Shoemaker by a former patient.*

<http://www.patsullivan.com/blog/2009/09/why-i-no-longer-recommend-dr-shoemaker.html>

#### *Radiation*

“National CFIDS Foundation (NCF) Announces Link between Chronic Fatigue Syndrome and Low Level Radiation Exposure.” Press Release, August 20, 2010.

<http://www.ncf-net.org/PressReleases.html>

#### *Genetics*

“Human gene number: surprising (at first) but not paradoxical.” T. Ryan Gregory.

<http://www.genomicron.evolverzzone.com/2007/05/human-gene-number-surprising-at-first/>

“Chronic Fatigue Syndrome.” *CDC press briefing on the 2006 Wichita gene study.*

<http://www.cdc.gov/media/transcripts/t060420.htm>

“CDC's Press Conference Generates Controversy.” *The CFS Report.*

<http://www.cfidsreport.com/News/06-CDC-CFS-Controversy.htm>

#### *Multiple Sclerosis*

“Influence of Viral Infection on the Etiology and Pathogenesis of Multiple Sclerosis.”

Robert Siegel, MD, PhD. March 21, 1997.

<http://www.stanford.edu/~siegelr/rnorris.html>

“Potential Viral Causes of MS.”

<http://www.msrc.co.uk/index.cfm/fuseaction/show/pageid/1680>

“Research proving link between virus and MS could point the way to treatment and prevention.” *Neuroscience*, Jan 5, 2012. <http://medicalxpress.com/news/2012-01-link-virus-ms-treatment.html>

*A new study from researchers at Queen Mary, University of London shows how EBV tricks the immune system into triggering inflammation and nerve cell damage in the brain, which is known to cause MS.*

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## CHAPTER 2: MECHANISMS AND THEORIES

Endocrine System, The Nervous System and Jay Goldstein's Limbic Hypothesis, Immune System, Vascular System and Diastolic Dysfunction, Digestive System, Oxidative Stress and Pall's NO/ONOO<sup>-</sup> Theory, Glutathione and the Methylation Block Hypothesis, Mitochondrial Failure, Channelopathies, Cause and Effect: Putting it all Together.

### INTRODUCTION: HOW DOES CFS/ME WORK?

In order to treat an illness, it is essential to understand its underlying mechanisms. In the case of many systemic illnesses, a single cause is rarely isolated, or, if known, is not deemed relevant to treatment. For example, exposure to radiation may cause cancer of the thyroid. While the link to radiation is important for avoiding future cases, this does not affect the course of treatment once the illness is under way. The same holds true for MS, diabetes, and heart disease, which can have multiple causes, but have treatments that center on the mechanisms of the illness. It is the belief of most researchers that understanding how CFS/ME works will lead, not just to identifying the nature of the illness, but to effective treatment.

The primary stumbling block to uncovering the basic mechanism of CFS/ME is that the body is not composed of discrete parts that can be taken apart and analyzed individually. Each part depends on another, which means a problem with one aspect of physiological functioning invariably has repercussions elsewhere. Nothing works in isolation. The immune system, nervous system and endocrine system are, in fact, one intricate system, each component of which is intertwined with the others. This is why researchers increasingly speak of neuroimmune, or neuroendocrine illnesses.

Unfortunately, the realities of the body are seldom reflected in medical practice, and while researchers increasingly are coming to the conclusion that CFS/ME is an illness that is multisystemic, and multiorgan, there are no “multisystemic multiorgan” doctors. (Long ago, the general practitioner used to perform that role, but, nowadays, the job of the GP is to refer patients out to specialists, who are only interested in discrete “parts.”)

The systems which have been most thoroughly investigated for their role in CFS/ME are: the immune system, the nervous system, the endocrine system, and, more recently, the vascular and digestive systems. At the cellular level – for all physiological processes are based on cellular function – the primary mechanism is mitochondrial impairment. And at the molecular level – for cellular function is dependent on molecular interactions – oxidative stress and channelopathies have been implicated. Each one of these mechanisms plays an important role in the pathogenesis of CFS/ME.

### FURTHER READING

*This is a nicely organized rundown of all the basic mechanisms involved in CFS/ME. To get a good idea of how CFS/ME works, read this first:*  
<http://www.ei-resource.org/illness-information/environmental-illnesses/chronic-fatigue-syndrome-cfs-myalgic-encephalopathy-me/>

Bassi, Nicola MD, Daniela Amital MD, Howard Amital MD, Andrea Doria MD and Yehuda Shoenfeld MD. "Chronic Fatigue Syndrome: Characteristics and Possible Causes for its Pathogenesis." *IMAJ* 2008;10:79–82. <http://www.cfids-cab.org/cfs-inform/Reviewcfs/bassi.etal08.pdf>

## ENDOCRINE SYSTEM

When clinicians describe CFS/ME as a multisystem illness, the primary systems they are referring to are the nervous system, the immune system, and the endocrine system. These are three systems which are affected in all CFS/ME patients, and which have generated the most focused research. To a great extent, the division between these three systems is artificial. The cell receptors of each of these systems are shared, which means that it is impossible to have a dysfunction in one system that does not alter the other two. The central nervous system releases neurochemicals that regulate the immune and endocrine systems; the immune system releases cytokines that regulate the nervous system; the endocrine system releases hormones that affect the nervous and immune systems, and so forth, in an endless web of interactions.

Because CFS/ME symptoms closely mirror those of endocrine disorders, research focusing on endocrine system dysfunction has generated a wealth of information, a good portion of which indicates widespread endocrine abnormalities in CFS/ME patients. These typically include mild hypocortisolism, blunted ACTH responses in challenge tests, and enhanced negative glucocorticoid feedback.

Most CFS/ME research concerning the endocrine system has centered on the main signaling organs of the endocrine system, known collectively as the hypothalamus-pituitary-adrenal (HPA) axis.

In 1991 a research team led by Dr. Mark Demitrack published a groundbreaking study demonstrating abnormalities in the HPA axis in patients with CFS/ME. The results of this study showed decreased levels of cortisol, blunted response of the pituitary gland to corticotropin releasing hormone (CRH), and enhanced sensitivity to adrenocorticotrophic hormone (ACTH). While the test results ruled out primary adrenal insufficiency (Addison's disease), they did indicate a dysregulation in the HPA axis, one which would lead to excessive fatigue, as well as many other symptoms typical of low adrenal function. The authors concluded that their test results indicated "a mild central adrenal insufficiency" in CFS/ME patients, most likely originating in the hypothalamus.

Further studies have confirmed HPA axis dysfunction in CFS/ME. In 1997 Dinan et al found that the release of ACTH (but not cortisol) was significantly blunted in response to an ipsapirone challenge. (Ipsapirone is a serotonin receptor agonist (stimulator) which increases both cortisol and ACTH.) The blunted release of ACTH means that activation of the HPA axis by serotonin is defective in

CFS/ME. (Serotonin directly stimulates the release of CRH from the hypothalamus.) The authors concluded that this defect “may be of pathophysiological significance.”

A second study conducted a year later confirmed that the release of cortisol as well as ACTH was significantly blunted in CFS/ME subjects without depression after CRH stimulation. The authors proposed that the blunted response of ACTH to CRH stimulation might be due to an abnormality in CRH levels, which would indicate a problem in the hypothalamus. Significantly, decreased levels of CRH would lead to lower adrenal output, which would produce both fatigue and exercise intolerance. In essence, these blunted responses produce a form of mild hypoadrenalism.

Hormonal irregularities indicating disruptions of the endocrine system have also been found in CFS/ME patients. In 1999 Scott et al found that levels of dehydroepiandrosterone (DHEA) and its derivative DHEA-S (dehydroepiandrosterone sulphate) were significantly lower in CFS/ME patients compared to controls. DHEA is a precursor to sex hormones, and plays a significant role in memory, anxiety, depression and sleep.

A later study by Cleare et al found that (DHEA) levels were raised in CFS/ME patients, while DHEAS was the same as controls. Higher levels of DHEA corresponded to severity in symptoms. However, in stark contrast to the Cleare findings, a study conducted by Maes et al in 2005 found low levels of DHEAS, supporting earlier research by Scott. Moreover, Maes et al found that decrease in DHEAS was highly sensitive and specific for CFS/ME. The researchers also found that DHEAS levels correlated with serum zinc and T cell activation, indicating a close relationship between immune and endocrine dysfunction.

To provide even more seemingly contradictory evidence, De Becker et al found normal DHEA levels, but a blunted response to ACTH. The authors concluded that “relative glucocorticoid deficiency might contribute to the overall clinical picture in CFS, and could explain some of the immunological disturbances observed in this syndrome.”

This study reveals one of the pitfalls of measuring absolute levels of hormones, which is that all hormones operate in concert with other hormones, and are therefore in a constant state of flux. In their study, De Becker et al correctly pointed out the importance of the responsive nature of the endocrine system, as well as the significance of the relationships between endocrine system hormones and the immune system.

Because of its widespread and profound effects on biological regulation, human growth hormone, another product of the endocrine system, has come under investigation over past few years as a treatment for a number of ailments, as well as a possible contributory factor to CFS/ME.

Research done in the late 1990s by Berwaerts et al, showed that patients with CFS/ME had low nocturnal secretion of growth hormone, as well as decreased insulin-like growth factor. A later study by the same group showed significant impairment of growth hormone response during insulin-induced hypoglycemia, as



well as a low nocturnal growth hormone secretion in CFS/ME patients. However, in this second study no decrease in insulin-like growth factor was noted.

In addition to impaired growth hormone homeostasis, the researchers found significantly increased prolactin and TSH (thyroid stimulating hormone, an indication of low thyroid function) compared to controls. While their findings may have been somewhat inconsistent, they indicate a disruption in normal pituitary function. The authors concluded that their findings gave support to the hypothesis that there is decreased dopaminergic tone in CFS/ME. (Dopamine stimulates growth hormone and inhibits prolactin.)

While endocrine disturbances are rife in CFS/ME patients, it is clear from these inconsistent research results that there is no definitive pattern that would demarcate CFS/ME patients. This does not mean that endocrine dysfunction is irrelevant – any hormonal disturbance produces widespread consequences – but that disruptions in the HPA axis and elsewhere in the endocrine system are probably a result of the illness rather than its cause. Of equal relevance is the fact that sleep disturbances, particularly insomnia, have profound effects on the endocrine system, as does immunological upregulation, both of which are prevalent in the overwhelming majority of CFS/ME patients.

Treatment protocols that address HPA axis dysfunction in CFS/ME are sparse. However, many integrative doctors make use of glandular extracts, such as Armour thyroid, to boost endocrine function. Low doses of hydrocortisone, DHEA, pregnenolone and other hormone precursors have also been used with varying rates of success. Dr. Cheney uses growth hormone with good results in some of his more severely ill patients.

SEE: Teitelbaum protocol, gynecological problems, DHEA, hormones.

## RESEARCH

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## THE NERVOUS SYSTEM AND JAY GOLDSTEIN'S LIMBIC HYPOTHESIS

Central nervous system (CNS) dysfunction is a key component of CFS/ME, producing a full spectrum of symptoms. Common CNS symptoms include neurocognitive impairments, such as difficulty processing information, slowed thought, impaired concentration, confusion, disorientation, cognitive overload, difficulty making decisions, slowed speech, dyslexia, dyscalculia, short-term memory loss, word retrieval problems, poor information recall, and impaired working memory.

There are also neurosensory and perceptual impairments, such as inability to focus vision, impaired depth perception, sensitivity to light, noise, vibration, odor, taste and touch. Motor symptoms, such as muscle weakness, twitching, poor coordination, and loss of balance are also related to CNS disturbances, as are loss of homeostasis, insomnia, headaches, and widespread pain. With this quantity of neurological symptoms, it is only logical to assume that impairment of the central nervous system plays a major role in the mechanism of CFS/ME.

In the early 1990s, Dr. Jay Goldstein, a now retired psychiatrist and psychopharmacologist, developed a theory in which he proposed that CFS/ME was the result of an insult to the limbic system, which is composed of structures relating to the hypothalamus, such as the hippocampus, amygdala, cingulate gyrus, and dentate gyrus. The limbic system is an area located deep in the brain just above the brainstem, and is involved with memory, emotion, and regulation of the autonomic nervous system. This last function is of critical importance to maintaining homeostasis in the body, as the autonomic nervous system regulates appetite, body temperature, blood pressure, blood sugar, sleep, wakefulness, heart rate, digestion – in short, nearly every physiological function necessary for maintaining life.

Dr. Goldstein's theory, as laid out in his book, *Betrayal by the Brain*, was that CFS/ME is essentially a communication problem between the limbic system and the rest of the nervous system. His "limbic hypothesis" essentially states that no matter what the underlying cause of CFS/ME, the result is an injury (encephalopathy) to the limbic system, which subsequently causes widespread neuroimmune dysfunction. He identified CFS/ME as a "neurosomatic" illness, that is, a disorder of central nervous system processing. Dr. Goldstein based his theory on what he knew of the brain, which was substantial, as well as what he had

observed of his patients' reactions to various psychotropic medications. In one sense, Dr. Goldstein was old-fashioned; he followed a time-honored scientific practice – observation. Recent studies, however, have shown that Dr. Goldstein was actually far ahead of his time, if not prescient.

Currently, there seems to be no doubt of central nervous system (CNS) involvement in CFS/ME, and a variety of approaches have been used to measure its extent. Typically, psychologists have employed cognitive tests to measure the overall performance of patients, while neurologists have used brain scans: MRIs to locate structural damage, functional MRIs to measure brain activation, SPECT scans to measure blood flow, PET scans to measure glucose uptake, and MR Spectroscopy to measure biochemicals associated with inflammation inside the brain.

Cognitive deficits, because they among the most frequently reported causes of disability in CFS/ME patients, have received a considerable amount of attention from researchers. Dozens of studies have been performed in an effort to categorize the nature of these deficits, quantify them, and distinguish these cognitive deficits from those produced by other disorders (in most cases, depression). In general, the studies have revealed that patients with CFS/ME do, in fact, suffer from the very problems they report – slow processing of information, lack of concentration, and so forth. Researchers have found that people with CFS/ME have problems processing auditory information, experience mental fatigue quickly, and cannot multitask. These results are buttressed by studies such as those by Majer et al and Marcel et al, which show that cognitive impairment in people with CFS/ME is independent of depression, a disorder with which CFS/ME is often confused.

The most informative cognitive studies are those which have measured brain function during the performance of tasks requiring mental effort. Tanaka et al, in 2006, used functional magnetic resonance imaging (fMRI) to demonstrate distractibility in CFS/ME patients. In this study, subjects were given a visual task to perform while listening to intermittent noise. Over the course of the task, people with CFS/ME showed reduced responsiveness in the areas of the brain associated with task performance, demonstrating an inability to focus on a task while receiving simultaneous input from competing stimuli. A previous study by de Lange et al showed that given a visual and simultaneous motor task, patients with CFS/ME solved the motor imagery task by using additional cerebral regions supporting visual processes. The authors suggested that CFS/ME patients might rely on visual imagery to compensate for dysfunctional motor planning.

Tests of working memory also show impairments. Caseras et al conducted an fMRI study to objectively compare brain activity in 17 CFS/ME patients with 12 controls during a test of working memory. The study revealed significant differences in brain activation between the two groups. CFS/ME patients showed greater activation than control subjects in areas associated with working memory (prefrontal regions). Under more challenging conditions, patients, but not controls, showed a significantly activated large cluster in the right inferior/medial temporal cortex (an area associated with working memory and attention). These findings are

consistent with earlier studies demonstrating that patients with CFS/ME could perform as well as controls, but that the effort involved greater brain activity.

A subsequent functional MRI study conducted by Cook et al confirmed that several areas of the brain are activated to a greater extent in CFS/ME patients compared to controls during challenging cognitive tasks. During a task that required no mental effort (finger tapping), neither patients nor controls showed significant differences in activation or fatigue. However, when presented with a complex mental task involving attention, working memory, and executive function, patient perceptions of fatigue correlated with brain activation: the greater the brain activity, the greater the fatigue.

Given that fatigue is the result of work of any kind, whether physical or mental, the conclusion that CFS/ME patients are more easily fatigued by mental effort than healthy people seems obvious. However, most cognitive studies are based on the assumption that people with CFS/ME merely “feel” fatigued. There is a lingering suspicion that the mental exhaustion experienced by people with CFS/ME may be form of neurosis unless physiological correlates can be identified.

In this regard, brain scans have been of enormous interest to the CFS/ME community because they provide concrete proof of neurological impairment. Dr. Ismael Mena and Dr. Jay Goldstein pioneered the use of SPECT (Single-photon Emission Computed Tomography) to document brain abnormalities in CFS/ME patients. SPECT scans measure blood flow in the brain, as opposed to MRIs, which show structure. Studies in the 1990s by Mena, Goldstein, Richardson, and Costa showed brainstem hypoperfusion (low blood flow) in a high percentage of CFS/ME patients.

In 1998 the late John Richardson conducted SPECT scans on some of his patients suffering from ME. The scans showed hypoperfusion in 90% of the patients in several areas. These included the brainstem (62%), the caudate nuclei in the basal ganglia (51%), temporal lobes (62%), parietal lobes (31%), and frontal lobes (23%).

A group of Australian researchers led by R. Casse also found a deficit in regional cerebral blood flow in similar areas: the brainstem, left medial temporal lobe, right medial temporal lobe, frontal lobe, and anterior cingulate gyrus. These are the areas of the brain responsible for auditory processing, attention, autonomic nervous system regulation, memory, sleep and pain.

The most recent studies to show brain hypoperfusion in CFS/ME have not used SPECT scans, but a xenon-CT. This type of scan measures the uptake of xenon gas by the brain. (When the gas is inhaled, it is distributed through the brain via the bloodstream.) Using this technique, Yoshiuchi et al found that patients with CFS/ME have reduced absolute cortical blood flow in broad areas when compared with healthy controls. Non-depressed patients with CFS/ME had reduced cortical blood flow in both right and left middle cerebral arteries. The authors concluded that their data supported earlier findings that CFS/ME patients without depression are the group most at risk for having symptoms due to brain dysfunction. In a 2011 study by Biswal et al, 9 of 11 patients with CFS/ME showed broad decreases in

cerebral blood flow compared to healthy controls. While these are small studies, they are significant in that they used a different tool to confirm hypoperfusion.

Small lesions, called “unidentified bright objects” (UBOs), often appear on the MRIs of CFS/ME patients. UBOs are often ignored by radiologists unless they are profuse and accompanied by signs of MS or other neurological injury, such as stroke. However, CFS/ME researchers have repeatedly stressed the significance of UBOs, which have appeared on the MRIs of CFS/ME patients since the first scans were performed in the 1980s.

Coincidentally, the first MRI scanner in Reno, Nevada was being set up by Dr. Royce Biddle just as the Lake Tahoe outbreak occurred. From 1985 to 1988 Dr. Biddle performed hundreds of MRI scans on patients seen by Dr. Peterson and Dr. Cheney. In conjunction with Dr. Buchwald, and Drs. Komaroff and Jolesz of Harvard, scans of 142 patients were analyzed. UBOs were found in 79% of the scans. While Dr. Biddle could not definitively state that the UBOs were pathological, he theorized that the disease might involve edema in perivascular spaces.

As far as brain structure in CFS/ME is concerned, the most dramatic studies have been those showing loss of brain matter. In 2004 Okada et al found that patients with CFS/ME had reduced gray matter volume in the bilateral prefrontal cortex. Furthermore, the volume reduction in the right prefrontal cortex paralleled the severity of the fatigue of the subjects (the lower the volume, the more fatigued the subject). The researchers concluded that the fatigue experienced by people with CFS/ME was central, that is, the difficulty in the initiation of and the ability to sustain voluntary activities was generated in the brain.

In 2006 a group of researchers in Holland led by de Lange, mapped structural brain structure and volume in two cohorts of CFS patients (28 patients total) and 28 healthy controls with high-resolution structural magnetic resonance images using voxel-based morphometry, a form of statistical analysis that measures the shape, size and position of brain structures. The de Lange study found “substantial and consistent” reductions in gray matter volume in two groups of CFS/ME patients as compared with controls.

A subsequent study in 2011 by Barnden et al found reductions in both white and gray matter. In the midbrain, white matter volume was decreased, while vascular abnormalities were observed in the brainstem, midbrain gray matter, deep prefrontal white matter, caudal basal pons, and hypothalamus. According to the authors, their findings were consistent with an injury to the midbrain at the onset of the illness, which could affect many feedback control loops, resulting in suppressed CNS motor and cognitive activity and a disruption of homeostasis.

Significantly, this type of injury would include resetting some elements of the autonomic nervous system, which might account for why people with CFS/ME experience increased sympathetic nervous system arousal. In line with the findings of this study, Claypoole et al found that sudden onset was predictive of cognitive impairment, particularly reduced speed in processing information.

In the same year, Puri et al conducted a large voxel-based morphometry study comparing 26 CFS/ME patients with 26 healthy volunteers matched for age and gender. Reduced gray matter volume in the CFS/ME group was noted in the occipital lobes (right and left occipital poles; left lateral occipital cortex, superior division; and left supracalcrine cortex), the right angular gyrus and the posterior division of the left parahippocampal gyrus. Reduced white matter volume in the CFS/ME group was also noted in the left occipital lobe. The authors concluded that their data supported the hypothesis that “significant neuroanatomical changes occur in CFS, and are consistent with the complaint of impaired memory that is common in this illness.” Their data also indicated that “subtle abnormalities in visual processing, and discrepancies between intended actions and consequent movements, may occur in CFS/ME.”

These various cognitive, fMRI, SPECT and voxel-based morphometry studies bring us right back to Jay Goldstein, for most of the problems are precisely where he predicted them – in the midbrain.

Aside from the experimental work done by Dr. Goldstein, not many physicians have attempted to reset midbrain functions in people with CFS/ME. That being said, Dr. Goldstein left a considerable corpus of information on treating the brain, which he describes in great detail in his book, *Betrayal by the Brain*. Of course, many doctors use psychotropic medications for treating CFS/ME patients, such as antidepressants, anticonvulsants, and benzodiazepines, but these are used primarily for symptomatic relief.

SEE: Cognitive and Emotional Symptoms; Antidepressants, Anticonvulsants, Benzodiazepines, Pentoxifylline; Herbs (Ginkgo), Piracetam

## RESOURCES

List of brain scan research studies: <http://www.cfids-cab.org/cfs-inform/Brainscans/brainscans.html>

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## IMMUNE DYSFUNCTION

One of the earliest theories proposed as the fundamental underlying mechanism of CFS/ME was that the illness was perpetuated by an underlying defect in the host's immune system. This is, in fact, a good explanation for any chronic illness, as the word “chronic” implies that the immune system is not functioning properly. Basically, the CFS/ME argument is that after an initial event, such as an infection or exposure to a toxin, the immune system does not recover, but keeps fighting the infection long after it has passed. The ensuing chronic immune system upregulation is responsible for the malaise, flu-like symptoms and inflammation that are characteristic of the illness. There is much to be said for this theory, for immune system activation causes most of the symptoms we associate with illness.

Among the first, and most significant, observations made by Drs. Peterson and Cheney, was that the patients in the Lake Tahoe outbreak appeared to have high titers of EBV (Epstein-Barr virus). However, when it turned out that EBV was ubiquitous in the general population, researchers turned to the immune system. The reasoning was that if everyone has the virus in latent form, there must be something amiss in the immune systems of people who can't keep it under control.

As early as 1987, a research team headed by Dr. Caligiuri at the Dana Farber Institute discovered that NK (natural killer) cells did not work properly in CFS/ME patients. (NK cells are responsible for destroying viruses.) The NK cells of CFS/ME patients consistently demonstrated low killing power, that is, their NK cells could not destroy Epstein-Barr virus-infected B cells. In 1994 Barker et al found that NK cell dysfunction was a “common manifestation of CFS.” Further studies led by Ogawa, and Ojo Amaize confirmed that NK cells were not properly activated, and, when they were, had low cytotoxicity. Ojo Amaize et al concluded that low cytotoxicity of NK cells was consistent with flu-like symptoms, and, perhaps, the reactivation of viruses.

The case for altered NK cell function was quite convincing, but soon researchers noted additional immune system abnormalities in CFS/ME patients, particularly in the ratios of T cells. T cells are a class of lymphocytes (white blood cells) that are involved in cell-mediated immunity, that aspect of the immune system that helps fight viruses. There are many different types of T cells (also known as CD cells), but of note are T helper cells, which activate other immune system cells, and T suppressor cells, which shut down immune responses once the job has been completed. A reduction in T cells, particularly a disproportion in the ratio of T helper to T suppressor cells, has been documented by a number of researchers.

One of the first studies to find a reduction in T cells was published in 1989 by Lloyd et al. Lloyd's group found that in patients with CFS/ME, a significant reduction was found in the absolute number of total T helper cells (CD4) as well as

T suppressor cells (CD8) subsets (“CD” stands for “cluster differentiation”). A significant reduction also was found in T cell function. In addition, reduced immunoglobulin (Ig) levels were common (56% of patients). Other studies have found a chronic activation of T cells, indicating an upregulated immune system.

The most frequently mentioned immunological abnormality among CFS/ME patients is what is referred to as the Th1/Th2 shift. This represents a shift from cellular, or Th1, immunity (in which immune defenses combat invaders within the cells), to humoral, or Th2, immunity (in which the immune system concentrates on pathogens in the bloodstream). The evidence for a Th1/Th2 shift lies in the presence (or absence) of different sets of cytokines.

Cytokines are immune system messengers which, among their other functions, can either provoke inflammation or stem it. Research on cytokines indicates that many “sickness behaviors” – decreased activity, reduced intake of food and water, sleep disturbances and cognitive impairment – are linked to pro-inflammatory cytokines, particularly to the interleukins. IL-1B, IL-6 and TNF-alpha (tumor necrosis factor). Th1 cells mainly secrete the cytokines IFN- $\gamma$ , IL-2, IL-12, IL-18, and TNF- $\beta$ , while Th2 cells secrete primarily IL-4 (which regulates allergic responses via mast cells), IL-5, IL-6, IL-10, IL13, and TGF- $\beta$ . The Th1/Th2 shift is not limited to CFS/ME patients. Indeed, this shift is the predominant immune system change seen in aging. The shift is also a feature of HIV infection, chronic mycobacterial infections, and allergies. In CFS/ME, this shift is believed to be responsible for the reactivation of latent viruses, which reside within cells.

In 2008 Torres-Harding et al found concrete evidence for the Th1/Th2 shift. The research team measured the percentage of Th1 and Th2 memory cells using cell surface flow cytometry in 114 patients with CFS/ME. The researchers then compared the ratio of Th1 and Th2 memory cells with various illness parameters, including symptom severity, psychiatric functioning, neurocognitive functioning, salivary cortisol levels, and chronic pain status. The results indicated that those who exhibited a more extreme shift towards a Th2 immune response also had poorer sleep and high levels of basal salivary cortisol. (High cortisol levels will interfere with sleep.)

Increased pro-inflammatory cytokines are commonly found in CFS/ME patients, particularly IL-1B and IL-6, the cytokine associated with unrefreshing sleep. In 2001 Hanson, Gause and Natelson found that a number of cytokines were selectively activated in CFS/ME patients, but that all of them interacted with IL-4. (IL-4 promotes inflammatory allergic responses resulting from activation of mast cells triggered during the Th2 response.) The authors concluded that the involvement of IL-4 provided solid evidence for a Th2 shift.

In 2010 Broderick et al found that IL-5, IL-6 and IL-1a were significantly elevated in at least one subset of CFS/ME patients, suggesting the inflammation typical of Th2 immunity. In this broad study of cytokine networks, the researchers proposed that the cytokine expression patterns observed in their study were consistent with some of the disruptive effects of chronic viral infection.

The most recent effort to investigate immune system abnormalities in CFS/ME patients was published in early 2012 by Maes et al. In this study, inflammatory cytokines and immune markers were not only found to be elevated, but were associated with specific symptoms. Elevated IL-1 and TNF alpha were associated with fatigue, sadness, autonomic symptoms, and a flu-like malaise. Neopterin, a marker of Th1 activation, correlated with fatigue, autonomic symptoms, and a flu-like malaise. Another marker of inflammation, polymorphonuclear (PMN) elastase, was associated with concentration difficulties, failing memory, and a subjective experience of infection.

Aside from direct testing of immune system components, which is problematic due to the highly responsive nature of the immune system, support for chronic immune dysregulation in CFS/ME can also be garnered from indirect sources. Onset of new allergies, which would indicate a Th1/Th2 shift, is a common problem for CFS/ME patients. Comorbidities with inflammatory conditions, such as interstitial cystitis, migraines, IBS, rhinitis, lupus, asthma, tinnitus, rheumatoid arthritis, rosacea, and certain types of cancer also point to chronic immune activation. Finally, the presence of autoimmunity in a high percentage of CFS/ME patients confirms immune system dysregulation.

Over half of CFS/ME patients test positive for anti-nuclear antibodies (ANA), a non-specific test indicating the presence of an autoimmune process. In 2003 Tanaka et al found that in a group of 60 CFS/ME patients there was a significant increase in antibodies to muscarinic cholinergic receptor 1 (an acetylcholine receptor) and that these increases were reflected symptomatically in a “feeling of muscle weakness.” (Acetylcholine is the neurotransmitter that activates muscles.) Antibodies to serotonin, phospholipids (the substance that makes up cell walls), and gangliosides (found in the nervous system) have also been found in a significant percentage of CFS/ME patients.

Perhaps most important of all, antibodies against cardiolipin were found by Hokama et al in 95% of the blood samples taken from CFS/ME patients. Cardiolipin is found almost exclusively in the inner mitochondrial membrane where it is essential for the function of the enzymes that are involved in mitochondrial energy metabolism. Anticardiolipin antibodies (ACA) are found in autoimmune diseases such as lupus, rheumatoid arthritis, autoimmune hepatitis, and scleroderma. It was the striking prevalence of ACA in CFS/ME patients that led Hokama et al to suggest reclassifying CFS/ME as an autoimmune disease. Given the recent successful treatment of CFS/ME patients in Norway with rituximab, an agent that normalizes high ACA titers of patients with autoimmune disease, there is good reason to take this suggestion seriously.

The one thing that is apparent over the past 25 years of research is that the immune systems of CFS/ME patients are difficult to assess. In 2002 Benjamin Natelson undertook the arduous task of reviewing 239 papers concerning immune system dysfunction in CFS/ME papers. (Of these, only 72 fulfilled Dr. Natelson's criteria for inclusion.) The only consistent findings were low NK cell function, a higher percentage of patients with ANA (indicating autoimmunity), and a higher

percentage of CD4 and CD45RA cell surface markers. (The latter finding is significant because CD45RA expression allows T cells to recognize EBV-infected cells long after the initial infection.) All other findings were either inconsistent or contradictory.

The fact that most immune system evidence is inconsistent does not mean it is “controversial.” No one denies immune system involvement in CFS/ME. Rather the inconsistency points to the difficulties surrounding any examination of the immune system. The immune system is enormously complex. It is designed to respond to everything the body comes into contact with, therefore it changes by the minute.

In addition, there are relationships between the nervous system and endocrine system that affect which aspects of the immune system come into play and when. Cytokines, for example, follow diurnal rhythms, peaking at certain times of day. Chronic insomnia, as experienced by the majority of people with CFS/ME, will reverse those patterns. This will undoubtedly affect the outcome of any study comparing CFS/ME patients with controls. One group may be experiencing a peak in cytokines, while the other is experiencing a trough. Stress hormones released by the endocrine system, which has been shown to be affected by CFS/ME, also have a strong effect on the immune system, both suppressing and activating it.

Given that there are also variations within the CFS/ME community – those with abrupt as opposed to gradual onset, differing lengths of illness, and severity of symptoms, for example – and that many types of pathogens may be involved, it is a formidable, and possibly unproductive, task to try and pin down static markers in a system that is inherently dynamic. That being said, the overall picture of immune system function in CFS/ME patients does point to chronic immune activation.

Immunotherapy treatments which push the immune system towards a Th1 response (thus aiding in the control of latent or persistent viruses) are Ampligen (which promotes the production of TNF, interferons and other lymphokines), gamma globulin, Imunovir (aka isoprinosine/inosine), *mycobacterium vaccae* vaccine (See Rook below), and *staphylococcal* vaccine. Rituximab and GcMAF, two anti-cancer medications, have shown some promise in treating CFS/ME. Rituximab lowers B cell activity (thus reducing inflammation), and GcMAF stimulates macrophages.

SEE: Ampligen, Inosine/Isoprinosine, GcMAF, Rituximab.

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## VASCULAR SYSTEM AND DIASTOLIC DYSFUNCTION

In a normal person, the heart pumps out roughly seven liters per minute when lying down, and five liters per minute when standing. This amount is sufficient to maintain blood pressure, provide oxygen to the organs, and sustain muscles. When the amount that the heart pumps is reduced, the entire body is affected. Blood pressure drops, weakness ensues, and, if the reduction is severe enough, the heart fails. Even if the heart does not come to a stop, even a mild impairment in cardiac output can lead to pronounced symptoms. In people with CFS/ME, the impairment is often significant; in severe cases cardiac output can be less than half of that of a normal person.

Reduced cardiac function has come to the fore as a major contributor to the pathology of CFS/ME due, in large part, to a 2003 study by Peckerman et al which documented cardiac impairment in CFS/ME patients. The team tested 38 patients with CFS/ME for heart function using impedance cardiograms to provide measures of cardiac output. Heart rate was measured via an electrocardiograph. The team also assessed severity of illness. Test results showed that patients with severe CFS/ME had "significantly lower stroke volume and cardiac output than the controls and less ill patients." The authors proposed that in patients with CFS/ME, "blood pressure is maintained at the cost of restricted flow, possibly resulting in a low flow circulatory state. Thus, there might be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes in at least some vascular compartments."

Dr. Cheney has proposed that this impairment in diastolic function is what lies at the heart of the majority of CFS/ME symptoms. In a three-hour lecture given to the Dallas/Ft. Worth CFS/ME support group, Dr. Cheney described the hypothetical results of low diastolic function in detail. The first is that a person would develop orthostatic intolerance. If the cardiac output is low to begin with, standing up would reduce it to levels so low that a person would experience dizziness, black-outs, and even fainting. Once cardiac output is sufficiently reduced, all other systems would decline as well. The body, in an effort to supply blood to the heart, would restrict blood flow to other organ systems, such as the gut. As a consequence, digestion would be impaired, with resultant dysbiosis, malabsorption, and a host of GI problems.

Blood flow to the brain would also decline, leading to cognitive problems, depression and anxiety, and impairment of hypothalamic function. With reduced blood flow, the immune system, which depends on the vascular system for transport, could not function efficiently; latent viruses and secondary infections would proliferate. The liver, an organ which relies heavily on blood flow, could not

detox the body sufficiently, leading to a buildup of toxins. Needless to say, under these conditions, exercise would not only strain the system, it could be dangerous.

In sum, not only does cardiac impairment explain the mechanisms of CFS/ME, it accounts for its hallmark symptom – exercise intolerance. The response to exercise in people with CFS/ME is not just fatigue, it is an exacerbation of *all* symptoms. The only logical explanation for why mowing the lawn can produce several days of malaise, flu-like symptoms, digestive disturbances, insomnia, brain fog, dizziness, and so on, is that blood flow to every part of the body has been impeded.

While the treatments for heart failure, including beta blockers, are routinely given to patients with cardiac dysfunction, these have not proven to be particularly effective for patients with CFS/ME. According to Dr. Cheney, the cause of cardiac impairment in CFS/ME is a reduction in cellular energy. Diastolic function, that is the blood flow back into the heart, requires large amounts of ATP. Once ATP is reduced, even by 10%, the heart cannot pump as well. The treatments for this type of cardiac problem center on mitochondrial support: CoQ10, D-Ribose, B12, magnesium and acetyl L-carnitine. Anticoagulants and blood thinners, such as Piracetam, Coumadin and vitamin E, have also been used, though not frequently, to increase blood delivery.

SEE: Cardiac and Cardiovascular Symptoms/Dysautonomia: Amino Acids (Carnitine), CoQ10, D-Ribose, Minerals (Magnesium), Piracetam, Vitamins (B12, E)

## RESEARCH

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## DIGESTIVE SYSTEM

### *Edo ergo sum*

In his book, *America Exhausted*, Dr. Edward J. Conley pronounced the gut, “the most important organ in the body.” Dr. Conley was not exaggerating. The heart and the brain are certainly more dramatic than the lowly bowel, but the gut is responsible for the intake and utilization of nutrients, without which we could not survive for long. We are, like all other living organisms, first and foremost, eating machines.

Gastrointestinal symptoms have been like the black sheep of CFS/ME symptomatology. Always present, but rarely mentioned, they comprise the dubious relatives of the more illustrious members of the physiological family. Aside from nutritionists, osteopaths, and manufacturers of nutritional supplements, the role of the digestive system in CFS/ME pathology has received scant attention, especially when compared to the nervous, immune, endocrine, and vascular systems. Dr. Kenny De Meirleir, has taken a different view entirely, tying the gut not just to a wide array of symptoms, but to the same systems that have been implicated in all the other proposed pathogeneses for the illness.

Molecular biologist Michael Gershon, in his book, *The Second Brain*, has described the enteric nervous system as a separate branch of the autonomic nervous system. The gut contains 100 million neurons, more than in either the spinal cord or the peripheral nervous system. Neurotransmitters such as serotonin, which were formerly thought to be produced exclusively in the central nervous system, have been found in abundance in the intestines – 90% of the serotonin in the body is produced in the gut. The gut also produces 400 times more melatonin than the brain. Dopamine, glutamate, norepinephrine and nitric oxide are also found in the gut, as well as a wealth of endorphins.

Given the sheer quantity of neurotransmitters in the gut, it is not a stretch to associate neurological and psychiatric symptoms with abnormal gut flora. In their exhaustive review of gut-brain interactions, Grenham et al cited numerous studies confirming active and constant communication between the gastrointestinal tract and the brain. This communication is regulated at neural, hormonal, and immunological levels, and influences not just the functions of the GI tract, but brain function as well. Put simply, your gut feelings can be taken literally. In their review, the authors cite studies in which disruptions of normal gut flora produced

alterations in the amygdala and hippocampus, leading to anxiety and memory dysfunction. Specific strains of intestinal flora can also directly influence the nervous system. *B. infantis* 35624, for example, elevates plasma tryptophan levels (a precursor to serotonin), which is a key neurotransmitter involved in sleep regulation and mood.

Not only does the gut contain greater amounts of neurotransmitters than the brain, it is our first line of defense against invaders. Given the fact that the GI tract is in constant contact with the outside world, it is only logical that it also performs our most active immune functions. Alpha interferon, the cytokine that inhibits viral replication, is produced in the mouth, and IgA antibodies are contained in gut mucosa. In the small intestines, Peyer's patches produce macrophages, dendritic cells, B cells, and T cells. Kupffer cells in the liver represent the main cellular system for removing microbes from the circulatory system. Finally, in the large intestine, trillions of helpful bacteria (flora) destroy foreign microbes, rendering them harmless.

When the gut does not perform its dual roles as provider of nutrients and protector from pathogens, the entire body is at risk. This is precisely Dr. De Meirleir's argument. Expanding upon earlier work by H. L. Butt in Australia, in which aberrant intestinal flora was associated with neurological and cognitive impairment, fatigue, and muscular pain, Dr. De Meirleir has proposed that the translocation of intestinal flora into the bloodstream is what causes the chronic immune activation of CFS/ME. The mechanism through which intestinal bacteria enter the bloodstream is known as "leaky gut" (intestinal permeability), a condition that compromises the protective barrier of the intestinal wall, allowing large molecules and bacteria that would otherwise be trapped in the intestines to pass through.

There are strong correlations between immune (IgA) responses to the lipopolysaccharides produced by bacteria, and the symptoms typical of CFS/ME patients, particularly cognitive impairment, pain, dysautonomia, and flu-like symptoms. Studies have shown that patients with an abnormally high IgA response show increased serum IL-1, TNF $\alpha$  and neopterin levels (neopterin is produced by macrophages, and is an indication of immune activation). The same patients also have a higher rate of irritable bowel syndrome (IBS) than people with a normal IgA response.

In 2012 Dr. Maes et al measured responses to intestinal flora in blood samples from 128 patients with CFS/ME. The researchers found higher levels of IL-1, TNF $\alpha$ , neopterin and elastase (an enzyme that destroys bacterial proteins) than in controls, indicating an immune response to bacteria in the bloodstream. Furthermore, IL-1, TNF $\alpha$  and neopterin were significantly related to fatigue, flu-like malaise, autonomic symptoms, neurocognitive disorders, sadness and irritability. The authors concluded that "increased translocation of commensal bacteria may be responsible for the disease activity in some ME/CFS patients."

Not only do translocated intestinal flora activate the immune system, their by-products, particularly hydrogen sulfide (the gas that produces the "rotten egg"

smell), can exert profound effects on the endocrine system, including a decrease in core body temperature, sleep apnea, reduced heart and respiration rates, and a severe metabolic drop. Excess hydrogen sulfide also can also inhibit mitochondrial oxygen utilization.

Marian Dix Lemle has proposed that the production of excess hydrogen sulfide is responsible for the mitochondrial dysfunction that lies at the base of CFS/ME symptomatology. Between these three researchers, the primary features that comprise gut pathogenesis have been established: Marian Lemle has identified the chemical component. Dr. De Meirleir has explained the cause for its increase in the gut, and Dr. Maes has identified the mechanism through which it causes symptoms—translocation.

Taken as a whole, this is a compelling argument for the pathogenesis of CFS/ME, especially when considered in conjunction with Dr. Richardson's and Dr. Chia's work on persistent enteroviral infections in CFS/ME patients. Moreover, the Gut-Immune Axis theory can lead to a well-established, easily tested, and possibly quite effective line of treatment.

SEE: Digestive Disturbances; Antibiotics, Enzymes, Probiotics.

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### OXIDATIVE STRESS AND PALL'S NO/ONOO<sup>-</sup> ("No! Oh, no!") HYPOTHESIS

In recent years there has been a virtual explosion of research into the mechanisms of oxidative stress. Literally thousands of articles have been published, most regarding the contribution of oxidative stress to the processes of aging and disease. Oxidative stress has been associated with diabetes, sickle cell anemia, heart failure, atherosclerosis, cataracts, Parkinson's disease, Alzheimer's disease, pre-eclampsia, persistent pulmonary hypertension, schizophrenia, bipolar disorder, and a host of other ailments. There is, at this point, overwhelming evidence that CFS/ME fits into the category of oxidative stress diseases as well, and that the damage due to oxidative stress is both systemic and pervasive.

Oxygen, which some biologists call "the first pollutant," has a powerful effect on everything it comes into contact with. It makes iron rust, turns apples brown, and "makes your whites whiter." Oxygen is also responsible for nearly every process that involves generating energy (e.g., combustion) and is the driving mechanism behind cell respiration. This dynamic chemical combination of oxygen with a chemical compound is referred to as oxidation.

Essentially, oxidative stress is the term used to describe an imbalance between the substances that cause oxidation (referred to as reactive oxygen species – ROS – or free radicals), and antioxidants, those substances that keep it in check. In simple terms, if you want to make supper, a stove (oxidation) is a good idea – a house fire (oxidative stress) is not. Oxidative stress is caused by having either too many free radicals (which have lost an electron) or too few antioxidants. This does not mean that free radicals are "bad guys" and antioxidants are the "good guys." In fact, free radicals are important components of the immune system. They are as destructive as Molotov Cocktails when it comes to warding off invading pathogens.

When a bacterium comes within range of a free radical (so named for its unpaired electron), the free radical draws off an electron from its opponent's molecules, thus destabilizing, and eventually destroying it. This is how hydrogen peroxide and other disinfectants work. However, once their destructive capacity has been unleashed, the free radicals need to be turned off, because their bombs are still ticking. This is accomplished by means of an antioxidant, which is a molecule that



donates an electron to a free radical, stabilizing it, and preventing it from damaging healthy tissue.

When there are too few antioxidants to control the free radicals, the damage to neighboring cells can be extensive, causing ATP depletion, cell damage and death. (You may be wondering what happens to the antioxidants that have donated their electrons – they become free radicals, which then require more antioxidants in order to be neutralized.) While it is well known that unchecked free radicals can cause tissue damage, the real problem may lie, not in the free radicals themselves, but in their by-products, which can cause far more damage than some of the original oxidizing agents. Peroxynitrite ( $\text{ONOO}^-$ ) is one such by-product.

In 2000 Dr. Martin Pall set forth a plausible explanation for previously “unexplained” illnesses, such as fibromyalgia, multiple chemical sensitivities, Gulf War Syndrome, and CFS/ME. He called it the NO/ $\text{ONOO}^-$  (“No! Oh, No!”) theory. In broad terms, the NO/ $\text{ONOO}^-$  theory proposes that these illnesses are the result of runaway oxidative stress. Dr. Pall has proposed that nitric oxide (NO) is the driving force behind these illnesses. NO is a free radical involved in many physiological processes (e.g., vasodilation, memory). It is also produced in response to stressors, such as a bacterial or viral infection, carbon monoxide poisoning, exposure to radiation, and physical trauma, via NMDA (*N*-methyl-*D*-aspartate) receptors. NMDA is a cell receptor that responds to excitatory amino acids, such as glutamate. When NMDA receptors are stimulated, NO is produced, and cells become hypersensitive, which can lead to pain and neurotoxicity.

Nitric oxide has short-term effects, but its metabolites, peroxynitrite ( $\text{ONOO}^-$ ) and superoxide, are more far-reaching. These powerful free radicals can, if unchecked by antioxidants, cause significant damage. For example, they may damage the cell wall, which is composed of a bi-layer of lipids. This damage is known as peroxidation. Once the lipids are peroxidized, the cell becomes “leaky” and eventually dies. Peroxynitrite may also interfere with the cell's mitochondria, leading to ATP depletion. Once ATP is depleted, NMDA (*N*-methyl-*D*-aspartate) receptor activity is increased, which contributes to the vicious cycle.

NO also leads to activation of NF- $\kappa$ B, a protein that transcribes genes responsible for activating cellular immune responses (B cells). Once these genes are “switched on,” inflammatory cytokines are released. These can travel throughout the bloodstream, initiating inflammatory responses throughout the body.

All of these responses, when well-timed, are necessary to maintain life. Inflammation is a key function of the immune system, and oxidation is required to produce cellular energy and destroy pathogens. The problem, as Martin Pall sees it, is that in CFS/ME this cascade of effects becomes self-perpetuating. Rather than mounting a well-coordinated attack against an invader, the NO/ $\text{ONOO}^-$  cycle becomes trapped in a positive feedback loop that continues to produce inflammatory cytokines and cell damage even in the absence of an infection. In the end, our defense mechanisms are turned against our own bodies.

There is an ample body of research to support Dr. Pall's theory. In 2005 Kennedy et al found that isoprostanes (peroxidized lipids), which are strong

indicators of oxidative stress, were significantly increased in CFS/ME patients. Isoprostanes have powerful vascular effects which may lead to symptoms such as orthostatic intolerance and a worsening of symptoms after exercise. In 1999 Fulle et al found evidence of oxidative damage in muscles, leading to pain and post-exertional malaise.

This finding was supported by several studies conducted by Jammes et al which also found oxidative damage in muscles of CFS/ME patients. Studies by Maes, Richards, and Smirnova found markers of oxidative stress in the sera of CFS/ME patients (peroxynitrite, methemoglobin and protein carbonyls). There is even evidence for oxidative stress in the brain.

A study published in 2012 by Shungu et al at Cornell University found increased levels of lactate in the cerebrospinal fluid of CFS/ME patients. Elevated lactate in cerebrospinal fluid is associated with cerebral inflammation. The authors concluded that the results of the study “support a pathophysiological model of CFS in which increased oxidative stress may play a key role in CFS etiopathophysiology.”

Antioxidant status is also affected by CFS/ME. Vitamin E, an important antioxidant, is low in CFS/ME patients. In a 2010 study, Miwa and Fujita discovered that vitamin E levels were significantly lower in patients than in controls, but that these levels were normalized during remissions. The authors attributed the fluctuating levels to increased oxidative stress during exacerbations. These findings, as well as supportive evidence of oxidative stress in CFS/ME-associated symptoms (such as migraines, early cataracts, and leaky gut) confirm that oxidative stress may well be the molecular mechanism behind CFS/ME.

Oxidative stress can affect any part of the body, but its inhibition of mitochondrial activity has profound implications for the heart, an organ which relies heavily on the production of ATP.

In 2000 a team of Japanese researchers led by Tetsuya Tatsumi found that nitric oxide (NO) can directly inhibit aerobic energy metabolism and impair cell function. The research group examined the effects of the inflammatory cytokine, IL-1 $\beta$ , on cardiac muscle cells. When treated with IL-1 $\beta$ , cardiac muscle cells showed a significant increase in glucose consumption, a marked increase in lactate production, and a significant decrease in cellular ATP. The authors concluded that IL-1 $\beta$ -induced NO production in cardiac tissue lowers energy production and myocardial contractility through a direct attack on the mitochondria. This important study provides the link between the mitochondrial dysfunction and cardiac dysfunction theories, both of which appear to be produced by oxidative stress.

Even with such overwhelming evidence, there still remains an important question: What drives the vicious cycle of oxidative stress?

In 2011 a team led by L.A. Jason at DePaul University proposed that “kindling,” a phenomenon in which hypersensitivity and spontaneous seizure-like activity is produced by sustained arousal of the HPA axis, might be responsible for the widespread oxidative stress experienced by people with CFS/ME. The model that Jason's team proposed was that among patients with CFS/ME, chronically

repeated low-intensity stimulation due to an infectious illness might cause kindling of the limbic-hypothalamic-pituitary axis. (Kindling also occurs after high-intensity stimulation, such as brain trauma.)

Once this system is charged, or kindled, it can sustain a high level of arousal with little or no external stimulus, eventually leading to hypocortisolism. Hypocortisolism, or “adrenal exhaustion,” is a common finding in CFS/ME patients. The authors concluded that kindling “may also be responsible for high levels of oxidative stress, which has been found in patients with ME/CFS.”

There are a number of treatments that act to lower oxidative stress, primarily antioxidants. Taurine, which is a major component of bile, is a powerful anti-inflammatory and antioxidant. Omega-3 fatty acids found in fish oil and flaxseed oil have been proven to reduce the harmful effects of peroxidation. Bilberry, ginger, green tea, licorice, and many other bioflavonoids have antioxidant properties. Alpha lipoic acid, vitamin E, vitamin C and B12 are also powerful inhibitors of free radical damage. Dr. Pall has discussed these supplements, and more, in his protocol, which is well worth reading not only for people with CFS/ME, but for anyone with a chronic illness.

SEE: Pall Protocol; Amino Acids (Taurine), Antioxidants, Bioflavonoids, Vitamins, Minerals

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## GLUTATHIONE DEPLETION – METHYLATION CYCLE BLOCK HYPOTHESIS

Closely related to Dr. Pall's theory is the methylation block theory proposed by Rich Van Konynenburg.

Methylation is a chemical process in which a methyl group (CH<sub>3</sub>) is added to a compound. Methylation occurs in all cells of the body, and has profound effects. It produces molecules vital to cell metabolism, such as CoQ10 and carnitine. Methylation also controls the expression of genes, which are responsible for protein synthesis, which, in turn, creates the neurotransmitters, enzymes, hormones and immune system molecules that run every system in our bodies. Methylation is also necessary for the production of myelin, which allows the nervous system to function.

Significantly, methylation also determines the rate of glutathione synthesis, our body's most powerful antioxidant. It is the disruption of glutathione synthesis that forms the basis for Rich Van Konynenburg's theory.

Rich Van Konynenburg's hypothesis for ME/CFS includes several elements: (1) a genetic predisposition that decreases the ability to maintain a normal level of glutathione, (2) a combination of a variety of stressors (physical, chemical, biological and/or psychological/emotional) that deplete glutathione (the particular combination differing from one case to another), raising oxidative stress and the level of peroxynitrite, a highly damaging free radical, (3) a functional deficiency in vitamin B12, caused by depletion of glutathione, (4) a partial block of the enzyme methionine synthase, caused by the functional B12 deficiency, lowering the methylation capacity and disrupting the folate metabolism, and (5) depletion of the various forms of folate.

Rich Van Konynenburg suggests that this combination depletes sulfur metabolism – which further inhibits the formation of glutathione – producing a vicious circle mechanism that makes ME/CFS a chronic condition. Essentially, all other aspects of ME/CFS, including abnormalities in lab testing, as well as clinical signs and symptoms, stem from this vicious circle mechanism. He further proposes that this hypothesis describes the pathophysiology that is common to all cases of ME/CFS, but that the causes leading to this mechanism in different cases can vary because of differing genetic and environmental factors. He suggests that the manifestations of this vicious circle mechanism, in terms of symptoms, can also vary from one case to another, because of differing genetic factors and differing exposures to pathogens and toxins, both before and after onset of the illness.

Evidence to support this theory comes from research focusing on metabolic abnormalities of CFS/ME patients. Metabolic studies by Bralley and Eaton have shown that methionine levels are low in CFS/ME patients. Low methionine can be caused by methylation cycle blocks. Substances that aid the methylation cycle, such as CoQ10, carnitine, and B12, are either low, or have been shown to be of benefit in treating CFS/ME. And, of course, there is a great deal of evidence for the presence of oxidative stress, which can affect the methylation cycle.

While it is likely there is lowered methylation cycle activity in CFS/ME patients, the question is whether it is the chicken or the egg. Dr. Pall believes the methylation block is caused by oxidative stress (not the other way around). Nitric oxide and peroxynitrite both inhibit the methylation cycle enzyme methionine synthase. It is possible that the lowering of energy metabolism through oxidative stress is the cause of the partial methylation block.

Regardless of which of these mechanisms causes the other, Rich Van Konynenburg's protocol is worth examining, as it addresses a fundamental mechanism of CFS/ME at the molecular level.

SEE: Van Konynenburg/Yasko Methylation Protocol

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## MITOCHONDRIAL FAILURE

The mitochondria are small structures within cells that produce adenosine triphosphate (ATP), the molecule that generates cellular energy. ATP is essential for every function in the body, which means that when the powerhouses of energy production, the mitochondria, are damaged and levels of ATP decline, the body literally runs out of energy. If low levels of ATP are sustained, there can be lasting damage to the heart, which is highly dependent on ATP. Mitochondrial dysfunction has also been linked to diabetes, Alzheimer's disease, Huntington's disease, cancer, and liver disease, all of which produce profound fatigue.

Because mitochondria are found in every cell (with the exception of red blood cells and certain cells in the eye), and can number in the thousands per cell, it is difficult to imagine how a small reduction in mitochondrial function can produce such profound effects on the body's essential functions. The answer to that question is simple: life is expensive – and its currency is ATP.

The ATP molecule is composed of a central sugar (ribose), adenine, and three phosphates. When a phosphate bond is broken, over 7,300 calories of energy are released. The average human body produces more than two hundred trillion trillion molecules of ATP each day, which means there are more than six hundred trillion trillion phosphate bonds. Multiply that number by 7,300 and you will get an idea of how much energy ATP generates.

It may seem that with so many molecules of ATP generating such an unimaginable amount of calories, there is some leeway to allow for mitochondrial damage. Unfortunately, there is not. Six hundred trillion trillion times 7,300 is how many calories your body needs to breathe. If you want your body to mow the lawn, you will need more. If you get sick, and your body needs to recover, you will need much more. And if your illness is caused by a virus that impairs mitochondrial function . . . you can see how difficult recovery may be.

The first doctor to suggest mitochondrial damage in people with CFS/ME was Dr. Melvin Ramsay, the physician who documented the Royal Free Hospital outbreak of “epidemic neuromyasthenia” in the 1930s. In an article written in 1978, Dr. Melvin Ramsay proposed that “abnormal muscular fatigability is the dominant clinical feature and it is suggested that mitochondrial damage may provide an explanation for this phenomenon.” (Two decades later, in validation of Dr. Ramsay's proposal, Dr. Lane's group would find a significantly lower proportion of mitochondria-rich muscle fibers in CFS/ME patients.)

Not long after Dr. Ramsay's observation, the Drs. Behan found concrete evidence of damaged mitochondria in muscle biopsies of patients with post-viral syndrome. Out of 50 samples, mitochondrial degeneration was obvious in 40 of the biopsies. The Behans noted swelling, vacuolation, myelin figures and secondary lysosomes in CFS/ME patients, as opposed to the mitochondria of controls, where even mild changes were rarely detected.

Significantly, they also noted the presence of “ragged red mitochondria,” a sign of mitochondrial disease. The authors concluded that their findings provided the first evidence that post-viral syndrome “may be due to a mitochondrial disorder precipitated by a virus infection.” (A later study by Plioplys and Plioplys did not find similar structural damage to the mitochondria, however, they did find evidence of mitochondrial dysfunction.)

Since that time, CFS/ME clinicians and researchers have accepted the fact that CFS/ME produces mitochondrial damage. Dr. Cheney has long held that CFS/ME is a mitochondrial disease, a position strongly supported by research showing mitochondrial dysfunction in the muscles of CFS/ME patients – as indicated by the production of excess lactate. Until recently, however, not much attention has been paid to non-muscle portions of the body.

According to Dr. Sarah Myhill, mitochondrial dysfunction is the central cause of CFS/ME. Her explanation of mitochondrial damage is that when the body is stressed, the demands placed on ATP production can exceed the supply. In people with CFS/ME, the body is continually stressed by an overworked immune system and secondary infections, resulting in a depletion of overall ATP, which damaged mitochondria cannot regenerate. Once stores are low, the cells begin to convert glucose into lactic acid, which is the reason why CFS/ME patients so quickly switch to anaerobic metabolism during exercise. The net result is exhaustion, at the metabolic level.

In a study conducted in 2009 by Dr. Myhill and two colleagues, Dr. Myhill measured the levels of five biomarkers indicative of mitochondrial function in the



sera of CFS/ME patients. The results of the study indicated that when analyzed together, these markers were predictive of illness severity in CFS/ME patients. The researchers concluded that their findings strongly implicated mitochondrial dysfunction as the immediate cause of CFS/ME symptoms. However, they could not determine whether the damage to mitochondrial function was a primary effect, or an effect secondary to cellular hypoxia or oxidative stress – including, as they stated, excessive peroxynitrite.

Mitochondrial dysfunction and oxidative stress pose the proverbial chicken-and-egg dilemma, as their relationship is reciprocal. Oxidative stress is both the product and the cause of mitochondrial dysfunction. That being said, there is also ample evidence that viruses can directly cause extensive damage to mitochondria. The herpes simplex virus causes massive damage to mitochondrial DNA, contributing to cell death and tissue damage. Viruses can also hijack mitochondrial proteins (for their own nefarious purposes), induce cell apoptosis (death), and increase the production of free radicals.

In short, whether mitochondrial dysfunction is primary or secondary, it is certainly reasonable to entertain the notion that the dysfunction is strongly correlated with all CFS/ME symptoms, and that it may be initiated by viral activity. Indeed, in a study by Hickie et al that followed 253 patients with Epstein-Barr infections, *Coxiella burnetii* (Q fever), and Ross River virus, twelve percent of participants still had prolonged illness – including neurocognitive problems, mood changes, musculoskeletal pain, and disabling fatigue – a year later. Eleven percent of the study's participants met the CDC diagnostic criteria for CFS/ME.

Perhaps predictably, mitochondrial disease bears a striking resemblance to CFS/ME. Without delving into the complexities of mutant genes (most mitochondrial diseases appear to be genetic), both illnesses share similar markers – evidence of oxidative stress, high lactate levels, low acyl-carnitine, and low glutathione levels (which has been proposed as a marker for mitochondrial diseases) are common lab findings in both mitochondrial disease and CFS/ME. Both illnesses are heterogeneous, manifesting in different organs and at different rates of severity. Both are difficult to diagnose. And finally, exercise intolerance is a hallmark characteristic of both illnesses, a feature which no doubt led Dr. Ramsay to conclude that ME was a mitochondrial disease. Given the overlap in lab results, symptoms, and treatment, there is no reason not to consider CFS/ME as a secondary, or acquired, mitochondrial disease.

There are a variety of approaches for treating mitochondrial dysfunction. Quercetin, a bioflavonoid, has been shown in animal studies to increase the biogenesis of mitochondria in both skeletal muscle and brain cells, in the absence of exercise. Mitochondrial supports such as CoQ10, D-Ribose, carnitine, and magnesium are also helpful (these are known as the “mito cocktail”). While direct administration of glutathione is problematic, supplementation with precursors, such as cysteine, and undenatured whey has been beneficial for some patients. SEE: Van Konynenburg/Yasko Methylation Protocol; Amino Acids (Carnitine), CoQ10, D-Ribose, Minerals (Magnesium).

## FURTHER READING

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The Central Cause: Mitochondrial Failure](http://www.drmyhill.co.uk/wiki/CFS_-_The_Central_Cause:_Mitochondrial_Failure)

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## CHANNELOPATHIES

The cells that form our bodies are both highly structured and permeable, which allows them to function both as discrete units and as conduits for the elements that enable our bodies to work. The primary means by which cells perform this second function is through electrical charges which are generated by ions, particularly calcium, potassium, and sodium. When the charges of a particular ion outside the cell are sufficiently high, a channel opens in the cell, allowing some of that ion to pass through, thus equalizing the charge. Opening and closing the channels is a complex and intricately timed process, and one which is essential for maintaining water balance, transmitting nervous system impulses, and a host of other functions.

When one or more of these ion channels is disrupted, it is called a channelopathy. Because cellular activity depends in part on the ion levels in cells, a channelopathy can impair normal cellular activity. If the channelopathy is extensive, then dysfunctions in any organ or physiological system can occur. The low tolerance to alcohol and drugs which affect ion channels (such as anesthesia) supports the idea of a channelopathy in CFS/ME, as does the cardiac impairment observed in CFS/ME patients.

In 2000, Chaudhuri, Watson, Pearn and Behan proposed that the pathogenesis of CFS/ME was due to abnormal ion channels in the cell membrane.

They based this hypothesis on three observations 1) CFS/ME and Syndrome X (an ion channel disorder that produces chest pain) share clinical symptoms, 2) CFS/ME can begin after exposure to certain toxins which are known to cause a disruption in sodium ion channels (e.g., ciguatera poisoning), and 3) CFS/ME patients exhibit increased resting energy expenditure, a phenomenon that is produced by abnormal ion channel transport. Since roughly 25% of the energy used during resting goes to maintaining ion gradients, the authors concluded that the increased energy expenditure was the result of an ion channel dysfunction. The authors proposed that CFS/ME could be the result of an acquired abnormality of ion channels and that this alteration “could affect normal receptor sensitivity to neurochemicals and neurohormones such as acetylcholine, serotonin or other monoamines, accounting for the neuroendocrine abnormalities previously documented in CFS.”

The evidence supporting channelopathies in CFS/ME is accumulating. In 2003 Nijs et al evaluated CFS/ME patients for whole body potassium content, as well as RNase L ratio, serum electrolytes (sodium, calcium and potassium), immune cells, blood cell count and sed rate. More than fifty percent of the patients showed abnormal whole body potassium content. Eight patients had increased, while six had depleted potassium content. However, as the authors pointed out, whole body potassium content does not indicate where or how the potassium is distributed. But, because the ratio of serum potassium to whole body potassium was higher than expected, they concluded that a channelopathy involving intracellular potassium loss occurs in about half of CFS/ME patients. This would certainly account for muscle weakness.

Of even greater significance was the finding that NK cell activity was associated with decreases in serum calcium levels as well as increases in the RNase L ratio. According to the authors, this suggests a channelopathy in a subset of CFS/ME patients (those with reduced NK cell activity), as well as a strong interaction between immune and ion channel function.

Ion channel dysfunction has also been implicated in exercise intolerance, the hallmark symptom of CFS/ME. Whistler et al examined gene expression in patients with CFS/ME before and after exercise. Differences between controls and patients with CFS/ME were pronounced – both before and after exercise. Furthermore, the authors found that genes related to ion channel activity could be used to differentiate cases from controls, and that exercise intensified these differences. The authors noted that several other conditions in which fluctuating fatigue occurs are caused by abnormal ion channels.

Several known CFS/ME triggers have been associated with channelopathies. Toxic exposure to organophosphates and heavy metals can alter ion channel activity. Herpesviruses, which are strongly associated with CFS/ME, can alter ion channel functioning as well. It is Dr. Kenny De Meirleir's position that the fragmentation of RNase L indicative of viral reactivation in CFS/ME patients is what leads to ion channel disruptions.

In a study analyzing ion transporter dysfunctions in CFS/ME, Dr. De Meirleir and his colleagues noted that transporter dysfunctions could account for

night sweats, sarcoidosis, chemical hypersensitivities, macrophage dysfunction, immune deficiency, altered monoamine transport, increased pain sensitivity, Th2 dominance, central nervous system abnormalities, vision problems, potassium losses in muscles, transient hypoglycemia, and depression. This list comprises immune system, nervous system, and endocrine system disturbances, the holy trinity of CFS/ME mechanisms.

#### FURTHER READING

*Good discussion of channelopathy studies in CFS/ME.*

[http://www.alfredblasi.net/documentacio/es\\_eng\\_Channelopathy1.pdf](http://www.alfredblasi.net/documentacio/es_eng_Channelopathy1.pdf)

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#### CAUSE AND EFFECT: PUTTING IT ALL TOGETHER

It is difficult to separate causes from mechanisms in CFS/ME. Once an illness becomes chronic, as Dr. David Bell has pointed out, the mechanism takes over, and

the cause becomes irrelevant. Nonetheless, it's comforting to have a “bad guy,” and a virus can always fit the bill. This is not to say that heavy metal exposure, bacteria (which can also do considerable damage), mold, and numerous other toxins can't produce the same end result.

Dr. Bell, in his elegant monograph, *Cellular Hypoxia and Neuro-Immune Fatigue*, proposes that we consider CFS/ME as a slow, chronic form of septic shock. The sequence of events in septic shock is: 1) a serious infection, 2) production of cytokines, 3) increased nitric oxide, and 4) interference with the production of cellular energy. In septic shock, the loss of cellular energy is so profound that it can be fatal.

Dr. Bell suggests that a similar sequence takes place in CFS/ME, but more gradually. The CFS/ME sequence is: 1) there is an initiating infection or toxic exposure, 2) this leads to immune activation, increasing the production of cytokines, 3) the increase in cytokines leads to the production of increased nitric oxide (NO), 4) NO increases peroxynitrite and superoxide, which leads oxidative stress, and interferes with mitochondrial function, 5) the cell becomes hypoxic (oxygen-starved), and 6) vasculopathies, neuropathies, and autoimmune processes develop. On the whole, this explanation provides a neat, concise model which draws together all the possible causes, triggers and mechanisms of CFS/ME.

But the model still doesn't explain why some people get CFS/ME and others don't after the same exposures. Why was the attack rate in the Royal Free outbreak 6% and not 100%? Why do only 8% of people with mono go on to develop CFS/ME? The consistent reply to that question is “genes.” Some people have more efficient immune systems than others – in other words, better genes. That answer is reasonable enough, but somehow, it is disappointing. If faulty genes are responsible for the CFS/ME epidemic, why now? Why not earlier? Regardless of claims to ancient Egyptian ancestry, CFS/ME seems to be very much a product of the 20<sup>th</sup> century, or at least of the industrial era.

Rather than put genes at the beginning of this sequence of events, as most theoreticians do, it makes better sense to put them at the end. Our active genetic makeup is, at least in part, the result of environmental influences. As a species, we develop resistance to pathogens. Plagues come and go, because resistance manifests itself in our genes. It could very well be that CFS/ME, like sickle cell anemia, is an adaptation that allows us to survive, albeit poorly, in the face of plagues that have already swept – or are still sweeping – the planet. To complete Dr. Bell's model, step number 7 should be “genetic modification” – the inevitable end result of pathogens which disable, but do not kill en masse.

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## PROTOCOLS

### INTRODUCTION

Protocols are based on theories, which is probably why there are so many of them. As Dr. Cheney has pointed out, there are nearly as many protocols as there are doctors. While Dr. Cheney was being somewhat facetious with this comment, it is probably true. Protocols range from a single treatment to hundreds. Some are strictly pharmaceutical, others strictly complementary, depending on the theory and philosophical orientation of the practitioner. A conventional doctor, who views CFS/ME as an agglomeration of individual symptoms, will approach each symptom with palliative care – analgesics for pain, hypnotics for sleep, and stimulants for energy. A nutritionist will evaluate nutritional deficiencies and prescribe supplements. A CFS/ME specialist will, in most cases, address the underlying mechanisms of the illness and offer treatments that increase the efficiency of cellular energy in addition to palliative care.

The reason for this astonishing array of treatment approaches is not that “nothing really works,” as is said so often, but that everything works – albeit not for everyone. The reason so many treatments work (or don't work, as the case might be) is that in spite of thousands of studies, and decades of research into the subtle workings of chronic illnesses, long-term illnesses are only understood in theory – not in practice.

Clinicians have a basic theoretical understanding of how the body works, in keeping with their cultures and times. Our current theory holds that the body is like a car. If a part breaks, you replace it. A great many physicians, and nearly all surgeons think this way. Those who deal with systems, such as the nervous system, or the digestive system, tend to look at the way all of the components fit together within a single system – somewhat like a transmission. Yet, there is little understanding of what occurs outside each individual system. A more recent perspective (or perhaps a very old one) is that every system in the body affects every other system in the body. Therefore, the nervous system, the immune system, the endocrine system, the vascular system, the digestive system, are all intertwined, each one assisting, or, in the case of illness, impeding the other. For a multisystem illness such as CFS/ME, this is the only sensible approach to take.

Unfortunately, we still don't know precisely how all these systems interact, which makes developing treatment protocols for multisystem illnesses a monumental task. Nevertheless, some brave researchers and physicians (and here I am not being facetious; to hang out a shingle as “CFS/ME specialist” takes courage) have attempted to do just that.

Treatment approaches maintain an intimate relationship with theories concerning the mechanisms of the illness. Taking that into account, we have chosen a representative sample of protocols based on their contribution as to how CFS/ME should, theoretically, be treated. Not every protocol that has been developed is included. Treatment protocols based on a single treatment are discussed in the appropriate treatment sections. Many interesting protocols which have been

developed abroad have been omitted, simply because our access to information about them is limited.

#### SITES THAT LIST AND/OR COMPARE PROTOCOLS

Ken Lassen's *comparison of 24 different protocols*:

<http://www.lassen.com/cfids/protocols.htm>

ProHealth.com: [http://www.immunesupport.com/chronic-fatigue-syndrome-treatment.htm#chronic fatigue syndrome conventional](http://www.immunesupport.com/chronic-fatigue-syndrome-treatment.htm#chronic%20fatigue%20syndrome%20conventional)

*Links to articles about five leading protocols.*

CFS/MS Recovery Path: <http://www.cfsrecoverypath.com/tools/a-summary-of-leading-cfsme-protocols-part-1-tool/>

*Excellent page on protocols. Provides a summary, methods, publications, and success rates.*

Phoenix Rising: <http://aboutmecfs.org.violet.arvixe.com/Trt/TrtDocProts.aspx>

*Cort Johnson's excellent page on protocols (with links): Dr. Cheney, Dr. Enlander, Ashok Gupta, Dr. Holtorf, Rich Van Konynenburg, Dr. Myhill, Dr. Lapp, Dr. Lerner, Martin Pall, Dr. Perrin, Dr. Shoemaker, Dr. Stratton, and Dr. Teitelbaum.*

ME/CFS Assist. <http://www.mecfsassist.org/mecfs-supplement-protocols.html>

*Detailed information about four protocols: Dr. Cheney, Dr. Myhill, Dr. Teitelbaum, Dr. Yasko.*

*The CureTogether.com ratings of CFS treatments and protocols:*

<http://curetogether.com/chronic-fatigue-syndrome/treatments/>

#### PATIENT DISCUSSIONS OF PROTOCOLS

*Excellent Phoenix Rising forum discussion of B12:*

<http://forums.phoenixrising.me/showthread.php?11522-Active-B12-Protocol-Basics/>

*Phoenix Rising thread on Dr. De Meirleir's protocol.*

<http://forums.phoenixrising.me/archive/index.php/t-241.html>

#### ADDITIONAL PROTOCOLS

“Michael E. Rosenbaum, M.D., on Treating Chronic Fatigue Syndrome and Fibromyalgia.” *ProHealth.com*. March 14, 2003

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*Michael E. Rosenbaum, M.D. is a pioneer in Nutritional Medicine. This enlightening interview covers his nutritional protocols.*

“Treating Chronic Fatigue Syndrome and Fibromyalgia: Interview with David Moskowitz, M.D.” *ProHealth.com* October 3, 2003

[http://www.prohealth.com/library/showarticle.cfm?id=5007&t=CFS/ME\\_FM](http://www.prohealth.com/library/showarticle.cfm?id=5007&t=CFS/ME_FM)

*David Moskowitz, M.D. graduated from Harvard Medical School in 1980. This article discusses Fibromyalgia and Chronic Fatigue Syndrome as autoimmune diseases.*



Kent Holtorf, M.D. on Effective Treatment of Chronic Fatigue Syndrome and Fibromyalgia. ProHealth.com. February 21, 2003

[http://www.prohealth.com/library/showarticle.cfm?id=4320&t=CFS/ME\\_FM](http://www.prohealth.com/library/showarticle.cfm?id=4320&t=CFS/ME_FM)

*Kent Holtorf, M.D. is director of several CFS/ME clinics located throughout the country. He focuses on the role of hormones in creating HPA axis dysfunction.*

“Highlights from Dr. Klimas' presentation to the Connecticut CFS/ME & FM Association – An Update on Chronic Fatigue Syndrome & Fibromyalgia - From Research to Management.” R. Sanderson. June 2009.

<http://www.masscfids.org/resource-library/3/192>

*Dr. Klimas is one of the country's leading CFS/ME researchers and clinicians. This article is an excellent summary of a talk given by Dr. Klimas in Connecticut. She discusses her theories, and gives a good overview of specific treatments and therapies she uses in her practice.*

CFS and Fibromyalgia Self Help. “Fred Friedberg's Seven-Step Protocol for Treating CFS and FM.” Bruce Campbell.

<http://www.cfidsselfhelp.org/library/fred-friedberg%E2%80%99s-seven-step-protocol-treating-cfs-fm>

*Fred Friedberg is a psychologist specializing in CFS and FM. His protocol is based on lifestyle changes and management strategies.*

Life Extension:

[http://www.lef.org/protocols/immune\\_connective\\_joint/chronic\\_fatigue\\_01.htm](http://www.lef.org/protocols/immune_connective_joint/chronic_fatigue_01.htm)

*Life Extension has assembled a complete CFS/ME nutritional protocol. While LE recommends consulting with a physician before embarking on a supplement regime, their information is sound and their recommendations are backed up by medical literature.*

#### DR. CHENEY'S PROTOCOLS

*Dr. Cheney's website provides information about Dr. Cheney as well as various treatments he has used. Dr. Cheney charges a fee for access to most of his research:* <http://www.cheneyresearch.com/>

*A complete list of Dr. Cheney's protocols, theories, and papers gathered by Cort Johnson:* <http://aboutmecfs.org.violet.arvixe.com/Trt/Cheneyfiles.aspx>

*The Dallas/Fort Worth's list of talks and papers by Dr. Cheney.*

<http://www.dfwcfids.org/medical/cheney.html>

*Dr. Cheney's treatments in 1995, with explanatory notes.*

<http://www.immunesupport.com/news/95sum003.htm>

“The Cheney Papers.” *Based on talks given in 1995, these are very comprehensive and well worth reading.*

<http://homepage.mac.com/doctormark/Medical/CFS/CFSpapers/cheneylecturescfs.html>

*A list of treatments used by Dr. Cheney in 1998, with explanatory notes.*

<http://www.dfwcfids.org/medical/basc2002.html>

“New Insights Into the Pathophysiology and Treatment OF CFS.” *Dr. Cheney lecture (2001).* <http://www.me-cfs.info/cheneyII3.pdf>

“Dr. Cheney's Basic Treatment Plan for Chronic Fatigue Syndrome.” Carol Sieverling. *ProHealth.com* October 19, 2001.

<http://www.prohealth.com/library/showarticle.cfm?libid=8023>

*Dr. Cheney's 8-Step Protocol of 2003.*

<http://www.dfwcfids.org/medical/basc2003.html>

“The Heart of the Matter: CFS and Cardiac Issues.” *Carol Sieverling's articles on Dr. Cheney's views on cardiac insufficiency in CFS/ME.*

<http://www.dfwcfids.org/medical/cheney/heart04.part2b.htm>

*Interesting patient board on Dr. Cheney's use of growth hormone.*

<http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=262313>

*Highlights from Dr. Cheney's 2009 seminar. Scroll down for oxygen toxicity and cell signaling factors:* <http://www.cfsnova.com/sp-Cheney.html>

*Video of a 3-hour presentation on cardiac insufficiency in CFS/ME by Dr. Cheney.*

*This is long, but well-worth watching:* [http://www.cfids-cab.org/MESA/CFS\\_Dist.htm](http://www.cfids-cab.org/MESA/CFS_Dist.htm)

## BATEMAN PROTOCOL

Dr. Lucinda Bateman is an internist specializing in the treatment of CFS/ME. She has served on the boards of the International Association of Chronic Fatigue Syndrome (IACFS/ME) and the CFIDS Association of America. Dr. Bateman is also the co-founder and a board member of OFFER (the Organization for Fatigue and Fibromyalgia Education and Research). Dr. Bateman opened her Fatigue Consultation Clinic in 2000, and since that time has evaluated more than 1000 patients.

Dr. Bateman employs a fairly conventional pharmaceutical-based approach to treatment. She starts by treating comorbid or secondary infections, and then moves on to symptomatic treatment. The following is taken from her website, and from a seminar transcript which first appeared in the Vol. 19, no 3 edition of *The Lifeline, A Quarterly Newsletter of the Wisconsin Chronic Fatigue Syndrome Association, Inc.*

- If primary or secondary viral or bacterial infection or known immune dysfunction (including allergies and asthma) can be identified, treating the condition might reduce CFS symptoms.
- If orthostatic intolerance is prominent, it may respond partially to standard interventions such as oral fluids (2 liters of water daily), sodium (2–4 gms per day) and electrolyte supplementation, fludrocortisone (Florinef) 0.1-0.2 mg daily, a trial of midodrine 2.5-10 mg 3 to 4 times a day while up and active (i.e. not while sleeping or resting). Physical deconditioning can worsen OI.
- Replacing identifiable hormone deficiencies can be useful in modulating symptoms, but should be monitored carefully due to the known potential side effects associated with each hormone.
- Stimulants and Provigil or Nuvigil are occasionally helpful, but should be used cautiously because of impact on sleep, anxiety, and the tendency to over-exert instead of pace appropriately.

- Antidepressant, anti-anxiety and anticonvulsant medications can be helpful for some aspects of the syndrome, including pain and sleep modulation independent of effect on mood.
  - Sleep disorders can also be treated with Ambien (5-10mg), Sonata (5-10 mg), Lunesta (1-3 mg), Restoril (15-30 mg), Rozarem (8 mg), and Melatonin.
  - Topamax and Zonegran, two anticonvulsants, are Dr. Bateman's favorite medications for pain if weight gain has been problematic while taking others.
  - Dr. Bateman encourages people to do movement exercises lying down and seated and in very small increments, maybe 30 seconds to 5 minutes, depending on conditioning. "You shouldn't do very much without a rest, and you should start with ridiculously small amounts. The key is to do the activity regularly, but not daily. When you start, every other day is good."
- Dr. Bateman states that "the most effective intervention for chronic fatigue syndrome is pacing, better than every intervention any doctor has ever prescribed."

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 Website: <http://www.fcclinic.com/Dr.Bateman.htm>

#### MORE INFORMATION

"CFS Treatment Tips"

<http://www.youtube.com/watch?v=UWUz-yjDlo>.

*This presentation was made for health care providers during the OFFER 2007 Conference. Dr. Bateman is a clear speaker, and makes several interesting points about treatment in this talk.*

Dr. Lucinda Bateman: Fighting the Fight Against Pain and Fatigue"

<http://www.everydayhealth.com/chronic-fatigue-syndrome/spotlight-lucinda-bateman-chronic-fatigue-syndrome.aspx>

*This is an excellent article about Dr. Bateman's background and motivations for treating CFS/ME.*

OFFER's Website

<http://www.offerutah.org/aboutoffer.htm>

*OFFER has a very well organized website, with concise information about CFS/ME, support groups, events, and much more.*

#### ENLANDER PROTOCOL

Dr. Derek Enlander is a native Irishman from Belfast. He came to New York as Assistant Professor of Medicine at Columbia University and then became Associate Director of Nuclear Medicine at New York University. Dr. Enlander is on the faculty of Mount Sinai Medical School and is an attending physician at Mount Sinai Medical Center in New York.

Dr. Enlander's protocol is based on treating the immune system dysfunction that underlies CFS/ME. He has an active research program, including Ampligen and GcMAF, in which his patients are invited to participate. Dr. Enlander is the founder of the ME/CFS Center, an international collaboration which includes virologist Illa Singh, geneticist Eric Schadt, immunologist Dr. Miriam Merad, Dr. Kenny De Meirleir and Dr. David Bell. Videos of the 2011 Mount Sinai ME/CFS conference are posted here: <http://blip.tv/mecfscenter>

The following are current treatments used by Dr. Enlander (taken from his website).

*Hepapressin Injection:* Hepapressin is an amino acid complex similar to Kutapressin, derived from Argentinian bovine liver. Like Kutapressin, it is an immune system adjuvant. As Hepapressin on its own is rarely effective, Dr. Enlander combines the injection with his own specialized formula to produce a more efficient complex.

*Immune Resist* is an amino acid food additive. It is an oral capsule taken once daily. It is thought to be involved in the immune system and may diminish fatigue and "brain fog," and assist in concentration and short-term memory. It can be purchased online at: <http://immunoprop.com/>

*IMMUNOPlus:* Immunoplus is given as an adjunct to Immune Resist. It contains folic acid, along with other amino acids and other components in the methylation cycle. Dr. *Enlander* believes that the methylation cycle is part of the CFS/ ME dysfunction. It can be purchased online at: <http://immunoprop.com/>

*Catapult* contains phosphatidyl serine and cat's claw. It is a non-prescription OTC supplement used to diminish "brain fog." Dr. Enlander reports quite good results with it. It can be purchased online at: <http://immunoprop.com/>

*Neurontin:* Neurontin is a prescription drug used as an anti-epileptic in grand mal seizures. In CFS and fibromyalgia the abnormal impulses that come from the brain are thought to be suppressed by Neurontin, allowing muscle fibers to be less fatigued. The daily dose can be up to 2400 mg per day.

#### *Experimental Treatments*

*Low Dose Naltrexone (LDN):* Opiate receptors are activated by naltrexone, which in low dose produces a cytokine reaction. This is thought to be helpful in CFS. Dr. Enlander states that it is too early to determine the effects.

*LECTROLYTE* or *RECUP* (a Spanish Electrolyte mixture) has been successful in fortifying muscles. *LECTROLYTE* may also reduce muscle pain. It contains 450 mg sodium, 125 mg potassium, 15 mg each of calcium and magnesium. *LECTROLYTE* does not contain sucrose or fructose (*RECUP* does contain these sugars). It can be purchased online at: <http://immunoprop.com/>

*Valcyte:* Valcyte is a prescription antiviral medicine that Dr. Montoya at Stanford University has shown to be effective against the HHV-6 virus. Dr. Enlander collaborated in a study of Valcyte under the auspices of the HHV-6 Foundation. Patients interested in this treatment are encouraged to contact Dr. Enlander's office.

*Ampligen:* Dr. *Enlander* is cooperating with Hemispherx Corporation in a study of Ampligen in the treatment of Chronic Fatigue Syndrome.

*GcMAF:* GcMAF is a naturally occurring substance in the human body which destroys pathogens by activating macrophages. Several CFS physicians, including Dr. Cheney, Dr. De Meirleir, and Dr. Elson (Northampton, MA), have begun using GcMAF for patients who test high in nagalase, the enzyme that destroys naturally occurring GcMAF in the body.

*EECP Treatment:* EECP (enhanced external counter pulsation) therapy is an outpatient treatment used to improve blood circulation and increase cardiac output. It is normally used for angina and heart failure. In ME/CFS the treatment sessions are 30-45 minutes and are given once a week. During the treatment, the patient lies on a comfortable treatment table with large blood pressure-like cuffs wrapped around the legs and buttocks. These cuffs inflate and deflate continuously at specific times between heartbeats, a continuous electrocardiogram (EKG) set the timing so the cuffs inflate while the heart is at rest, in diastole, when it normally gets its supply of blood and oxygen. The cuffs deflate at the end of that rest period, just before the next heartbeat, systole. When timed correctly, this will decrease the afterload that the heart has to pump against, and increase the preload that fills the heart, increasing the cardiac output.

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*Dr. Enlander accepts Medicare (not HMO), Medicaid (NOT) managed care, GHI-HealthNet- HMO – POS, PHCS, United Health, Cigna, JJ Newman, Oxford freedom Plan.*

*The office does not accept Blue Cross BC/BS.*

*Initial Visit (including comprehensive physical history and examination) ... \$750. This includes: Comprehensive history, full examination, phlebotomy (blood is drawn to rule out diseases with overlapping symptoms), EKG to rule out heart conditions, impedance cardiogram to determine Cardiac output (a new updated tilt table test),*

*spirometry to rule out respiratory disease, test dose heparin complex to rule out allergic reaction, urinalysis.*

*XMRV virus blood test will be drawn on request.*

*Office visit follow-up ... \$150*

*If you cancel 24 hours or more prior to your appointment, there is no charge.*

*Canceling with less than 24 hours notice will result in a \$25 cancellation fee.*

## HUNTER-HOPKINS PROTOCOL

Dr. Charles Lapp is the director of the Hunter-Hopkins Center (HHC), a nationally recognized clinic specializing in the treatment of CFS/ME and fibromyalgia.

Dr. Lapp has had considerable experience in treating CFS/ME. In 1987 Dr. Lapp began a collaboration with Dr. Paul Cheney after an outbreak of CFS/ME in the Raleigh area. From 1992 to 1995 Dr. Lapp acted as Medical Director of the Cheney Clinic in Charlotte, North Carolina. In addition to his long and distinguished practice as a CFS/ME physician, Dr. Lapp has been a board member of the International Association for CFS/ME (IACFS), and advisor to the American Fibromyalgia Syndrome Association, ProHealth Incorporated, the CFIDS Association of America and the National Fibromyalgia Association. He has co-authored numerous training programs, websites, webinars, and publications for the CDC, the Chronic Fatigue Syndrome Association, and the pharmaceutical industry. Dr. Lapp's major interests are fibropain, sleep, and orthostatic (autonomic) disorders.

Dr. Laura Black has worked with Dr. Lapp for over a decade. In addition to her experience with CFS and FM, she has special interests in complementary and alternative therapies, sleep disorders, pain, and acupuncture.

In addition to an active research program, HHC strives to evaluate all treatment modalities in order to provide patients with the most advanced therapy possible. The Charlotte office offers tilt testing, cardio-pulmonary exercise testing, and neuropsychiatric screening on site. There is also a Raleigh office for easy access to patients residing in Eastern North Carolina, Virginia, and Georgia.

HHC pioneered the "Stepwise Approach," a protocol designed to help the patient heal naturally through proper nutrition, low level graded activities, medical management of symptoms and supportive therapies. The Stepwise Approach is outlined below (from the HHC website, [drlapp.com](http://drlapp.com) and [Treat CFSFM.org](http://TreatCFSFM.org)):

### I Treatment of Symptoms

*Sleep:* Dr. Lapp considers sleep the most important symptom to treat. Dr. Lapp uses Klonopin (clonazepam) and doxepin as the cornerstones of his therapy, followed by trazadone and hypnotics, such as Ambien. Lapp has had some success with using low doses of melatonin at night and bright-light therapy in the morning.

*Pain:* This is the next most important symptom to address. Non-pharmacological methods (increased water and salt intake, hot or cold packs, liniments, tub soaks, massage, chiropractic, acupuncture, etc.) are emphasized, but many patients require pharmacological therapy with neuron transmitting altering medications such as doxepin or desipramine, anti-epileptics (such as gabapentin and pregabalin), NSRIs (duloxetine or milnacipran), and even investigational therapies such as pamiprexole or low dose naltrexone.

*Fatigue:* A small dose of Prozac or Zoloft may help some patients with daytime fatigue. Dr. Lapp has also found some success with drugs that raise the body's dopamine levels, such as Wellbutrin and others.

*Headaches:* Dr. Lapp uses Diamox and calcium channel blockers, which are thought to increase cerebral blood flow. For vascular type headaches (migraines), he uses Midrin and triptans (e.g., Imitrex, Axert, Relpax, Maxalt, Zomig, and others).

*Orthostatic Intolerance:* Many Persons with CFS (PWCs) experience increased heart rate (tachycardia), very low blood pressure, or even fainting (syncope) with standing or prolonged sitting. Therapy begins with increase water and salt intake followed by a variety of medications depending on the results of passive head-up tilt table testing.

*Investigational Therapies:* HHC was the first medical office to receive approval from the FDA to provide the experimental treatment, Ampligen (rintatolimod), on a cost-recovery basis, and has been treating patients with this medication continuously since 1997.

## II Supplements

Dr. Lapp advises that people try only one new supplement at a time, which allows the patient to evaluate it for effectiveness. He also suggests taking yearly supplement holidays, that is, not taking the supplement for several weeks to test whether it is still effective. The following are on Dr. Lapp's "Top Ten" list of supplements:

1) *Multi-vitamin:* To optimize overall health, he recommends using a multi-vitamin that includes B complex, folate, vitamin D, calcium and magnesium.

2) *B12 injections:* Dr. Lapp reports that up to 80% of his patients experience a 10% to 15% energy boost with B12 injections.

3) *Vitamin D3:* Dr. Lapp recommends 2,000 IU per day to reduce pain and morning stiffness.

4) *Calcium and Magnesium:* People often take these two together in a calcium-magnesium tablet. The ratio is 1000-1500 mg of calcium to 500 – 750 mg magnesium daily. He cautions that magnesium is inappropriate for those with kidney disease and may cause diarrhea.

5) *D-Ribose:* D-Ribose is a sugar that helps increase ATP. Dr. Lapp recommends 5000 mg three times once daily for two weeks, then 5000 mg twice daily. Results are usually seen within three weeks.

6) *NADH*: This is another substance used to help increase ATP. Dr. Lapp recommends a dosage of 10 - 20 mg per day. He uses NADH with his most severely ill patients and those with the worst cognitive impairment. It takes three to six months to see a response.

7) *Acetyl-carnitine*: Dr. Lapp recommends a dosage of 1,000 mg twice a day. He often uses this supplement to improve cognition, or in conjunction with NADH to increase energy production.

8) *DHEA*: Dr. Lapp recommends 25 to 50 mg daily for women and 50 to 100 mg for men. It is not needed if a person is already taking estrogen and/or testosterone via hormone replacement therapy. Side effects may include oily skin, acne and excessive hair growth.

9) *Lysine*: The recommended dosage of lysine is 1,000 to 2,000 mg per day. This supplement can be used to reduce the frequency and severity of herpetic mouth ulcers (mouth sores).

10) *Fish Oil*: The recommended dosage is 3000-4000 mg a day. This supplement is used to treat pain and to lower cholesterol. Dr. Lapp recommends using the enteric-coated version [Fisol] to reduce regurgitation.

### III Diet

Dr. Lapp recommends a prudent diet with an emphasis on fresh fruits, vegetables, and light meats (e.g., chicken and fish). “We’ve always told patients to minimize sugar, caffeine, alcohol, neurotoxins (e.g., aspartame, MSG), and tobacco,” says Lapp. “Many of our patients with irritable bowel syndrome have been found to be sensitive to dairy and wheat, so these may be withheld from the diet to see if it makes a difference.”

### IV Activity

Dr. Lapp has been working with physical and occupational therapists to put together a rehabilitation program to help get patients on their feet and moving up the treatment ladder. The following are key components of his program:

*Stretching*: Dr. Lapp suggests that patients routinely stretch their muscles throughout the day. If possible, consult a physical therapist about gentle stretches that you can do, including ones that can be done while sitting in a chair or supine.

*Deep breathing*: Dr. Lapp notes that most patients breathe using the muscles in the upper part of the chest. This aggravates neck and shoulder pain, and increases the odds of postural muscles wearing out before noon. To ease tension on muscles that are already under stress from CFS/FMS, Lapp recommends deep breathing through the lower part of your diaphragm. “This type of breathing,” says Dr. Lapp, “tends to relieve things like chest tightness, shortness of breath as well as spasms in the postural muscles.”

*Low-Level Interval Exercise*: Cardio-pulmonary Exercise Testing is frequently obtained in order to prescribe a precise exercise routine. Such routines might include range of motion or floor exercises, or aerobic activities limited by 3-10 minute intervals, a maximum heart rate, or the number of steps taken per day.



## V Complementary Therapies

*Massage and Acupuncture:* Dr. Lapp reports that massage and acupuncture have been extremely helpful in some of his patients. Other techniques like transcutaneous electrical nerve stimulation (TENS) and ultrasound may provide some relief, but Dr. Lapp hasn't found them as beneficial as the other methods mentioned.

*Hydrotherapy:* Dr. Lapp has patients float in tepid pool water or even a tub at home. You only need to be in the water for 15 minutes and the water should be around 85-90 degrees. Hydrotherapy helps patients in two ways:

1. The cool water tends to down regulate the immune system, so patients feel less fatigued and less flu-like.
2. The water pressure squeezes out fluid in the legs and trunk tissues where it tends to accumulate, and pushes it back into circulation where it is more helpful.

## VI Coping and Management

*Comorbid factors:* Allergies, chronic infections (including yeast problems), and chemical sensitivities (odors, fumes and smokes) also need to be treated when present. While specific medical treatments may be helpful for allergies and infections, Dr. Lapp finds that teaching avoidance is the best way for patients to deal with chemical sensitivities.

*Stress:* Chronic illness can create additional stressors, financial pressures, and problems at work. It can also cause family dysfunction. Dr. Lapp does not aggressively treat these problems himself, but he does refer patients to a counselor skilled in helping people with chronic illnesses.

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*Hunter Hopkins does not participate in insurance or accept assignment of insurance benefits. The clinic does not accept Medicare, Medicaid, or Workman's Compensation.*

### MORE INFORMATION

Hunter-Hopkins Center: <http://drlapp.com/>  
"Dr Lapp's Recommendations on Supplements." Bruce Campbell. *CFIDS and Fibromyalgia Self-Help*. <http://www.cfidselfhelp.org/library/dr-lapp's-recommedations-supplements>

*or*

<http://www.prohealth.com/library/showarticle.cfm?libid=16109>

ProHealth: <http://www.prohealth.com/library/showarticle.cfm?libid=8801>

*This is a good interview with Dr. Lapp, in which he discusses the “Stepwise Approach.”*

“Dr. Lapp's Stepwise Approach to Managing Fibromyalgia and Chronic Fatigue Syndrome.” Charles W Lapp, MD July 12, 2002.

[http://www.prohealth.com/library/showarticle.cfm?id=3714&t=CFIDS\\_FM](http://www.prohealth.com/library/showarticle.cfm?id=3714&t=CFIDS_FM)

*This is a useful one-page summary of the Stepwise Approach.*

## PALL PROTOCOL

Dr. Martin Pall's NO/ONOO<sup>-</sup> (“No! Oh, no!”) hypothesis is probably the most comprehensive explanation of cellular dysregulation in CFS and other oxidative stress illnesses to date. Essentially, the model proposes that the chronic stage of CFS is driven by a vicious cycle of oxidative stress, in which the basic mechanisms that are meant to control pathogens don't turn off. The result is oxidants run amok, creating havoc in the cell's energy cycles, and increasing inflammation.

The protocol described here was originally put together by Dr. Pall and by Dr. Grace Ziem. and is based on antioxidant treatments which break the vicious cycle of oxidative stress as well as other agents that act to lower other parts of the cycle, such as lowering inflammatory responses, improving mitochondrial function and lowering excessive NMDA activity. However, a word of caution: taking large quantities of antioxidants can actually increase oxidative stress. Once antioxidants such as tocopherols (vitamin E), vitamin C, and flavonoids react with free radicals, these antioxidants are themselves converted into free radicals. Other antioxidants are then needed to neutralize those newly formed free radicals. Therefore, a wide variety of antioxidants may be optimal.

*PLEASE NOTE: Dr. Pall emphasizes that he is a Ph.D., not an M.D., and none of this should be viewed as medical advice.*

Below is a simple version of Dr. Pall's “best guess” therapy (aka The Pall/Ziem protocol). More detailed information follows.

1. Nebulized reduced glutathione
2. Nebulized inhaled hydroxocobalamin
3. Mixed natural tocopherols
4. Buffered C
5. Magnesium, as malate
6. Four flavonoids: ginkgo, cranberry extract, silymarin and bilberry
7. Selenium, as selenium-grown yeast
8. CoQ10
9. Folic acid
10. Carotenoids including lycopene, lutein and B carotene
11. Alpha lipoic acid

12. Zinc (modest dose), manganese (low dose), copper (low dose)
13. Vitamin B6, as pyridoxal phosphate
14. Riboflavin 5'-phosphate
15. Betaine (trimethylglycine)
16. Acetyl-carnitine
17. Taurine
- 18.

*Detailed antioxidant protocol:*

*Vitamin C.* Pall did not suggest mega-doses of vitamin C in his book, but has more recently reconsidered this issue. He believes that doses on the order of 500 to 1000 mg/day, taken several times per day may be beneficial. Vitamin C can act to regenerate tetrahydrobiopterin (BH4) and, therefore, may act to lower NOS uncoupling, and high doses of vitamin C can be useful in scavenging peroxynitrite (ONOO<sup>-</sup>), the most central element in his NO/ONOO<sup>-</sup> cycle hypothesis.

*CoQ10.* CoQ10 has been used in a number of diseases to improve mitochondrial function. It scavenges free radicals, protects against loss of mitochondrial respiratory function, increases energy metabolism, and down regulates NMDA activity. Take early in the day.

*Magnesium.* This mineral lowers NMDA activity, reducing excitotoxicity. Dr. Pall believes that “magnesium is one of the most promising agents for treatment of multisystem diseases, but, like other such agents, it produces modest responses and may best be used in a complex, combination therapy.”

*Selenium.* Selenium is considered an antioxidant because certain proteins that contain selenium have antioxidant properties. Selenium occurs in glutathione peroxidases, enzymes that eliminate peroxide in cells. Selenium is also essential in making T3, the most active form of thyroid hormone. The best form of selenium is selenomethionine, which is a selenium-grown yeast. (For those who are yeast-sensitive, there are non-yeast forms.)

*Carotenoids.* These are plant pigments which are quite active in scavenging free radicals. Lycopene is more active than beta-carotene as a peroxynitrite scavenger. Lutein and zeaxanthin, two carotenoids, may also have special roles as antioxidants because of the way they insert into biological membranes.

*Flavonoids.* Anthocyanidins, which are found in purple plants, lower inflammatory activity, act as potent chain-breaking antioxidants, and regenerate other chain-breaking antioxidants after they have been converted to free radicals.

Flavonoids also act as chelators for free iron, protecting cells from oxidative damage. Many flavonoids are soluble in both water and lipids. Flavonoids from green tea, citrus, grape seed extract, ginkgo, soy, olive, hawthorn, blueberry, and purple rice are effective antioxidants. Silymarin scavenges peroxynitrite, and increases the synthesis of SOD (superoxide dismutase), which makes it especially important. Flavonoids are rapidly absorbed in foods, and are quickly excreted through the kidneys, so they need to be eaten (or taken) throughout the day.

*Acetyl-L-carnitine.* Carnitine transports fatty acids into mitochondria, and is therefore essential for providing cellular energy. Acetyl-L-carnitine is more effective than L-carnitine because most oral L-carnitine ends up being excreted by the kidneys before it can be transported through the blood-brain barrier. Acetyl-L-carnitine is transported more efficiently. Recently, it has been shown that acetyl-L-carnitine lowers excessive NMDA activity and this may well be more important than the effects on mitochondrial function for lowering the NO/ONOO<sup>-</sup> cycle.

*Reductive Stress Agents.* Reductive stress causes oxidative stress. Methyl groups – SAME, betaine, and carnitine – act as protective agents. Dr. Pall's preference for a methylated compound is betaine (TMG.) It is cheaper and more stable than SAME.

*Hydroxocobalamin form of B12.* B12 is a potent nitric oxide scavenger, but it is difficult to absorb. Oral absorption of B12 is limited by intrinsic factor. [Independent of intrinsic factor, the absorption rate of B12 is less than 1% of the total amount ingested.] Hydroxocobalamin taken as a nasal spray or injection is more effective.

*Folate (folic acid).* Reduced folate decreases uncoupling of NOS activity. Reduced folate in the form of 5-methyltetrahydrofolate (5-MTHF) is a potent scavenger of peroxynitrite and may well turn out to be among the most useful agents for lowering the NO/ONOO<sup>-</sup> cycle. Optimal dosage may well vary among different individuals but, in general, it should be taken along with quite a bit of vitamin C (at least 500 mg and preferably perhaps twice this amount). The reaction between peroxynitrite and 5-MTHF is important not only because it can be used to lower peroxynitrite levels. It is also important because in NO/ONOO<sup>-</sup> diseases, elevated peroxynitrite will act to lower the levels of 5-MTHF, lowering methylation cycle activity, and will also act to lower all reduced folates in the body. In this way, lowered methylation activity may be caused by the NO/ONOO<sup>-</sup> cycle.

*B6, as P5P.* B6 minimizes neurotoxicity. The best form is pyridoxine phosphate (P5P).

*Riboflavin.* Riboflavin is important for the production of reduced glutathione. It is also useful in the treatment of migraine.

*Alpha Lipoic Acid (ALA)* scavenges free radicals. As an added benefit, it can regenerate other antioxidants by reducing oxidized and free radical forms of glutathione, tocopherols, vitamin C and flavonoids. It can maintain glutathione pools by turning oxidized glutathione into its active form, reduced glutathione. ALA can cross the blood-brain barrier, making it an effective tool for reducing damage due to oxidative stress in the brain.

*Zinc, Manganese and Copper.* These minerals are components of superoxide dismutases (SOD), the enzymes that convert the oxidant superoxide into hydrogen peroxide and oxygen. Zinc, copper and manganese deficiencies can produce oxidative stress, part of which may be due to the lowered ability to produce SODs. Doses of these metals can be tricky. Excessive levels of copper

and manganese can themselves produce oxidative stress. Excessive zinc lowers copper levels. Dr. Pall suggests “modest levels.”

*Taurine* is an unusual amino acid, because it is an antioxidant as well as a neurotransmitter. Taurine acts to stimulate the synthesis of GABA, and is transported easily across the blood-brain barrier, allowing it to work in the brain. Taurine stimulates several inhibitory receptors, leading to lowered NMDA activity. It also acts to lower intracellular calcium levels, thus lowering NO synthesis.

*Long-chain omega 3 fatty acids.* Poly-unsaturated fatty acids (PUFAs) are more susceptible to lipid peroxidation than are other fatty acids, and consequently they tend to be depleted whenever there is oxidative stress. Fish oil, borage oil and flaxseed oil are sources of long-chain omega 3 fatty acids.

*Curcumin, honokiol* (from *magnolia*), *cat's claw*, *vinpocetine* and *feverfew* all reduce inflammation by lowering NF-kappaB activity, as do a number of conventional pharmaceuticals.

*Vitamin E* should *not* be taken as synthetic alpha-tocopherol, which is the most commonly taken form, Pall argues. Rather, it should be taken as relatively high doses of gamma-tocopherol and tocotrienols with modest amounts of natural alpha-tocopherol. These other forms of vitamin E have important functions, such as lowering inflammation, scavenging an important breakdown product of peroxynitrite, lowering excessive NMDA activity and improving mitochondrial function, all important for lowering NO/ONOO<sup>-</sup> cycle diseases.

*Algal supplements.* Both chlorella and blue-green algae are rich in antioxidants. Blue-green algae contain phycocyanin, which is a potent free radical scavenger.

SEE: Mechanisms: Oxidative Stress for an explanation of oxidative stress and a more in-depth discussion of Dr. Pall's theories.

## FURTHER READING

Pall, Martin. *Explaining “Unexplained Illnesses”:* Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others. New York: Harrington Park Press, trade division of Haworth Press, Inc. 2007.

*This book is technical, but well worth reading. Dr. Pall has made a remarkable contribution to the study of “unexplained illnesses.”*

“How Can We Cure NO/ONOO<sup>-</sup> Cycle Diseases? Approaches to Curing Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, Fibromyalgia, Multiple Chemical Sensitivity, Gulf War Syndrome and Possibly Many Others.” Martin Pall. *Townsend Letter*. Feb/March 2010.

<http://www.townsendletter.com/febMarch2010/cureNO0210.html>

*Excellent paper by Martin Pall on agents that lower parts of the NO/ONOO<sup>-</sup> cycle. Contains detailed information on protocols and potential therapeutic agents.*

*Interview with Martin Pall (2009):*

<http://www.chronicfatiguetreatments.com/wordpress/category/dr-martin-pall/>

*Martin Pall discusses his NO/ONOO<sup>-</sup> theory, B12, methylation, and the medical community.*

European Society for ME Research & Knowledge: <http://esme.eu.com/supplements/supplements-in-me-cfs-by-prof-martin-pall-article276-139.html>

*Nicely organized table of supplements recommended by Dr. Pall, along with mechanisms and comments.*

Allergy Research Group

<http://www.allergyresearchgroup.com/proddesc/discuss/MartinPallAntioxidantSugguestions.pdf>

*Allergy Research Group, one of the nation's top supplement manufacturers, cooperated with Dr. Pall to devise a set of nutritional supplements based on his protocol. This page gives dosage, ingredients, and contact information.*

Tenth Paradigm Society Yahoo Group

*This Yahoo group has 560 members. This is a good place to find out more about the Pall protocol from people who have tried it.*

## TEITELBAUM PROTOCOL

Dr. Jacob Teitelbaum is a board-certified internist and Medical Director of the national Fibromyalgia and Fatigue Centers and Optimized Health and Wellness. He is an advocate of integrative medicine, which combines complementary modalities, such as supplements and acupuncture, with conventional medicine (pharmaceuticals).

While Dr. Teitelbaum's protocol encompasses the full spectrum of medical treatments, and can thus appear overwhelming, they are organized according to what Dr. Teitelbaum calls the "SHINE" protocol. SHINE is an acronym for: **S**leep (which is necessary for proper immune system functioning), **H**ormones (deficiencies can contribute to FM and CFS), **I**nfections (yeast, viral and bacterial infections can contribute to CFS symptoms), **N**utritional **S**upplements (many nutrients can become depleted as a result of CFS), and **E**xercise. These are the building blocks of Dr. Teitelbaum's approach.

The following is a list of the more common treatments Dr. Teitelbaum uses for treating CFIDS.

*You can begin to slowly taper off most treatments when you feel well for 6 months. On average, it takes 3 months to start feeling better. Stop things one at a time (e.g., one every 1 to 3 weeks) so you can see if you still need it.*

### Sleep

1. Ambien (zolpidem) - 10 mg- ½ to 1 tablet at bedtime. If you tend to wake during the night, leave an extra ½ tablet at bedside, and you can take it as needed to help you sleep through the night. Bite the ½ pill between your front teeth and put under your tongue so it will work within a few minutes

2. Desyrel (trazodone) - 50 mg – ½ - 2 tablets at bedtime. Also helpful for anxiety
3. Passion flower (Passiflora) -100 to 200mg at night. This is also good for anxiety during the day. A mix of 6 herbs, Valerian, passion flower, wild lettuce, Jamaican dogwood, hops and theanine is especially effective to improve sleep. It is available as the Revitalizing Sleep Formula by Enzymatic Therapy.
4. Klonopin (clonazepam) – ½ mg - begin slowly and work your way up as sedation allows. Take ½ tablet at bedtime increasing up to 2 tablets at bedtime as needed. Can be effective for sleep, pain and Restless Legs.
5. Melatonin- 3/10 mg -1 mg at bedtime (available at health food stores). Don't use a higher dose, unless you find it to be more effective (3/10 mg is usually as effective as 5 mg, and may be safer).
6. Doxylamine (Unisom For Sleep) -25 mg at night (this is an antihistamine).
7. Flexeril (cyclobenzaprine) -10 mg- 1/3-1 tab at bedtime. Muscle relaxant – can cause dry mouth. Just taking 1/3 tab can give the benefits without the side effects
8. Neurontin (Gabapentin) 100-600 mg at bedtime. Also helps pain and Restless Leg Syndrome.
9. Elavil (amitriptyline) -10 mg- ½ to 5 tablets at bedtime. May cause weight gain or dry mouth.

Hormones: *(dosage as indicated by your doctor)*

1. Thyroid – Synthroid, Cytomel, Armour
2. Adrenals – Cortef, DHEA

*Take vitamin C 500mg twice a day for adrenal support. Panax ginseng 100mg twice a day (taken in “6 week on and 2 week off” cycles) can also help your adrenals to heal. After 9 months, you can try to wean off the Cortef (decrease by ½ tablet a day each 2 weeks) if you feel OK (or no worse) without it*

Infections: *NOTE: Most important is to treat the Candida with Nystatin, Diflucan, and probiotics, and to avoid sugar.*

### *Candida*

1. Avoid sweets - this includes sucrose, glucose, fructose, corn syrup, or any other sweets until the doctor says that it is OK to include them in your diet again. Having 1-2 fruits a day (the whole fruit as opposed to the juice) is OK.
2. Acidophilus or other milk bacteria. 1 Pearls Elite a day.
3. Garlic -1 clove 1 to 3 times a day with meals.
4. Nystatin -500,000 units- 2 tablets 3 x a day. Begin with 1 a day and increase by 1 tablet a day until you are up to the total dose. Your symptoms may initially flare as the yeast die off. If this occurs, decrease the dose and then increase the Nystatin more slowly or stop for a while until symptoms decrease. Nystatin is usually taken for 5 to 8 months. If nausea occurs take 2 twice a day and/or switch to the Nystatin powder in capsules or mixed in

water. Repeat Nystatin for 4 to 6 weeks anytime you take an antibiotic or have recurrent bowel symptoms.

5. Diflucan –200mg a day for 6 weeks. Begin taking the Diflucan 4 weeks after beginning the Nystatin. If the symptoms have improved and then worsen when you stop the antifungal, refill the prescription for another 6 weeks. If your symptoms flared when you began the Nystatin, begin with ¼ to ½ the above dose for the 1st week.

### *Viral Infections*

1. Valcyte 900 mg 2x day is given for 3 weeks, then 900 mg 1x day is given for 23 weeks. Only used if there is an inadequate response to SHINE and if the blood tests for old CMV or HHV-6 viral infection (called an IgG antibody ) is very high (over 4 or 1:640 or higher).
2. Monolaurin -Use the Lauricidin form, 1/4 to 1 scoop 2-3 times daily with or after meals.
3. Olive leaf- 500mg -2 capsules 3 times a day for 10 to 14 days for respiratory infections.

### *Nutritional Supplements*

- *A multiple vitamin*- Dr. Teitelbaum recommends a good vitamin powder, where 1 drink replaces over 35 pills. Get one which also includes at least a high dose B complex, zinc 15 mg, Magnesium 150-200 mg, malic acid, Vit C&D, and amino acids.
- *Ribose* 5000 mg (5 gm) 3 x day for 6 weeks, then twice a day. In a recent study, ribose increased energy by an average of 61% after 3 weeks in people with FMS.
- *Lipoic acid* - 300 mg twice a day if nerve pain is present.
- *B12* - If your B12 blood test is under 540, ask your doctor for Vitamin B-12 - 1 I.M. injection (1 cc = 3000 mcg) 3 to 5 times weekly for 15 doses, then as needed (e.g., 1 to 12 times a month). This needs to be made by a compounding pharmacy.
- *NAC* (N-Acetyl-L-Cysteine) - 500mg a day for 9 months -then as needed. OR glutathione 200 to 250mg a day
- *Iron* - 30 mg in a tablet with at least 100 mg of Vitamin C a day if your ferritin blood test is under 60. Do not take within 6 hours of thyroid hormone preparations or Cipro (antibiotic), as this can prevent their absorption. Take on an empty stomach (i.e., take between 2 and 6PM on an empty stomach). It is OK to miss up to 3 doses a week. Stop in 4 to 6 months or when your Ferritin blood test is over 60. This can help Restless Leg Syndrome as well.
- *Fish oil*. Dry eyes, mouth and hair suggest a need for this supplement. 3-4 servings of fish a week, 8 fish oil caps or 1 tablet of Vectomega a day.

*Use the following for 9 months. Then drop the dose to the lowest dose that maintains the effect (or stop it if no benefit).*

- Acetyl-L-Carnitine - 500 mg - 2 capsules twice a day for 3 months. Then 250 to 500 mg/day or stop it. Although important in CFS/FMS, it is even more important to take this if you also have Mitral Valve Prolapse and/or elevated



blood triglycerides. Take less or L-Carnitine can be substituted if the cost is prohibitive.

- Coenzyme Q10 -100-200 mg -1 x a day. Especially important if taking cholesterol lowering prescriptions (e.g., Lipitor, which Dr. Teitelbaum avoids using in FMS unless the person has known heart disease). Take it with a meal that has fat, oil supplements or in an oil based form to improve absorption.

**Exercise:** *Exercise as able. After 10 weeks on the 4 steps above, you will be able to slowly increase your exercise-without being wiped out the next day.*

### **CONTACT:**

Jacob Teitelbaum, M.D.

Medical Director of the Fibromyalgia and Fatigue Centers (FFC's), a national network of medical offices that specialize in treating patients with CFS/FM.

For a local FFC Center please see:

Website: <http://www.fibroandfatigue.com>

Dr. Teitelbaum gives consultations by phone and in person. His website also has a free online program which can analyze your symptoms and lab tests (if available), and create a treatment regimen tailored to your case. Dr. Teitelbaum's website: [www.EndFatigue.com](http://www.EndFatigue.com). Phone: 800-333-5287.

Dr. Teitelbaum's assistant, Cheryl Alberto, is available for protocol counseling (\$45 per half-hour). Having counseled Dr. Teitelbaum's patients for over a decade, Cheryl has the clinical experience and knowledge to help you organize and effectively utilize your protocol for maximum results. You can call Cheryl at (410) 573-5389 or email at [Consulting@endfatigue.com](mailto:Consulting@endfatigue.com).

### **MORE INFORMATION**

Teitelbaum, Jacob. *From Fatigued to Fantastic*. New York: Avery, 2007.

*Dr. Teitelbaum's website:* <http://www.endfatigue.com/>

“Dr. Jacob Teitelbaum's Treatment Protocol for Chronic Fatigue Syndrome & Fibromyalgia.” <http://www.immunesupport.com/chronic-fatigue-syndrome-teitelbaum.htm>

“An overview of CFS/Fibromyalgia, and effective therapies - Highly Effective Treatments for Pain and Fatigue.” From *Townsend Letter for Doctors and Patients*, 2/1/04 by Jacob Teitelbaum: [http://66.197.58.78/flexeril\\_article\\_7.htm](http://66.197.58.78/flexeril_article_7.htm)  
*In this article Dr. Teitelbaum discusses the integrative approach to treating CFIDS.*

### **VAN KONYNENBURG/YASKO METHYLATION PROTOCOL**

Dr. Richard Van Konynenburg is an independent researcher with a background in the physical sciences. He worked for roughly thirty years in research and development in the fields of chemistry, physics, and engineering before he turned his investigations to ME/CFS in 1996. Richvank, as he is referred to on the

Internet, is a member of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and the Orthomolecular Health-Medicine Society.

Dr. Van Konynenburg's theory is that ineffective methylation is the major cause of fatigue in CFS/ME patients. Methylation is a chemical process in which a methyl group (derived from methane) is added to another compound. As a chemical process it is fairly simple, but as a biological process methylation has profound effects. It produces molecules vital to cell metabolism, such as CoQ10 and carnitine. Methylation is also necessary to activate genes which are responsible for protein synthesis, and which, in turn, create the neurotransmitters, enzymes, hormones and immune complexes that run every system in our bodies. Methylation is also necessary for the production of myelin, which allows the nervous system to function. Significantly, methylation also determines the rate of glutathione synthesis. Glutathione is the kingpin of detox systems, and is a powerful antioxidant. (Low levels of glutathione are characteristic of many oxidative stress diseases.)

Dr. Van Konynenburg has suggested a protocol that addresses the vicious circle mechanism he has hypothesized. He emphasizes that it does not directly address the initial causes of this vicious circle, which vary from case to case, nor does it directly address the various pathogens and toxins that may accumulate after onset of ME/CFS. He suggests that these factors will usually require additional treatments.

The “simplified” protocol Dr. Van Konynenburg has suggested was extracted from the full treatment program developed by Dr. Amy Yasko, used primarily in treating autism. This simplified protocol focuses on lifting the hypothesized partial block of methionine synthase. Based on the autism research of Dr. S. Jill James et al, Dr. Van Konynenburg has found this protocol to be the key to lifting the partial methylation block in ME/CFS, as was found in autism.

This protocol has undergone several modifications since it was first proposed in January 2007, but its essence remains the same. A version of it was used in a clinical study conducted by Dr. Neil Nathan, M.D., together with Dr. Van Konynenburg, which was reported in 2009.

*PLEASE NOTE: Richard Van Konynenburg is a Ph.D., not an M.D., and none of this should be viewed as medical advice. Dr. Van Konynenburg states that anyone using this protocol must be under the care of a licensed physician.*

The most recent version of the protocol is shown below.

*Simplified Treatment Approach For Lifting The Partial Methylation Cycle Block In Chronic Fatigue Syndrome—March 30, 2011 Revision (extracted from the full treatment program of Dr. Amy Yasko)*

1. General Vitamin Neurological Health Formula: Start with ¼ tablet and increase dosage as tolerated to 2 tablets daily. General Vitamin Neurological Health Formula is formulated and supplied by Holistic Health Consultants LLC.

2. Hydroxy B12 Mega Drops: 2 drops under the tongue daily. Hydroxy B12 Mega Drops is a liquid form of hydroxocobalamin (B12), supplied by Holistic Health Consultants. Two drops is a dosage of 2,000 mcg.
3. MethylMate B: 3 drops under the tongue daily. MethylMate B is a liquid form of (6s)-methyltetrahydrofolate supplied by Holistic Health Consultants, based on Extrafolate S, a trademark of Gnosis S.P.A. Three drops is a dosage of 210 mcg.
4. Folinic acid: ¼ capsule daily. Folinic acid is 5-formyltetrahydrofolate. ¼ capsule is a dosage of 200 mcg.
5. Phosphatidyl Serine Complex: 1 softgel capsule daily. Phosphatidyl Serine Complex is a product of Vitamin Discount Center. One softgel is a dosage of 500 mg.

All these supplements can be obtained from <http://www.holisticheal.com>. Some of them, or their equivalents, can also be obtained from other sources. Folinic acid comes in capsules that contain 800 mcg. It will be necessary to open the capsules, dump the powder onto a flat surface, and separate it into quarters using a knife to obtain the daily dose. The powder can be taken orally with water, with or without food. Some people prefer to split tablets, such as Source Naturals Megafolinic, rather than to deal with powder.

These supplements can make some patients sleepy, so in those cases they take them at bedtime. In general, they can be taken at any time of day, with or without food.

Phosphatidyl serine can lower cortisol levels. Patients who already have low evening cortisol levels may wish to substitute lecithin, which is a combination of phospholipids without phosphatidylserine. One softgel daily will replace the phosphatidyl serine above. (One softgel is a dosage of 1,200 mg.) Lecithin is also available from <http://www.holisticheal.com>. For those allergic to soy, lecithin from other sources is available.

GO SLOWLY. As the methylation cycle block is lifted, glutathione may initially be lowered further, toxins may be mobilized and processed by the body, and a greater need for potassium may develop, and these can lead to an exacerbation of symptoms. If this happens, try smaller doses, every other day. *Slowly* work up to the full dosages.

Monitor blood potassium levels periodically, and supplement with potassium if necessary.

The appropriate dosages appear to vary from one person to another. While this protocol does address what Dr. Van Konynenburg believes is the core of the pathophysiology of ME/CFS, it has not been completely optimized. It is likely that the protocol could be improved by systematic clinical testing, which has not yet been done.

*Although this treatment approach consists only of nonprescription nutritional supplements, a few patients have reported adverse effects while on it. Therefore, it is necessary that patients be supervised by physicians while receiving this treatment.*

**PATIENT REPORTS:** In their clinical study, Dr. Nathan and Dr. Van Konynenburg reported that over half of the 30 patients reported an initial worsening of symptoms, beginning within three or four days, but in some cases beginning at up to two weeks. The most common side effects were gastrointestinal problems (pain, cramps, constipation or diarrhea), increased fatigue, decreased appetite, poor sleep, weak legs, flu-like symptoms, and an increase in anxiety and depression. According to the report, improvement on the protocol began at an average of five or six weeks, with a range from immediate improvement (which was rare) to as long as eight weeks before improvement was experienced. After 6 months of treatment, over two-thirds of the patients reported improvement in their symptoms.

In an informal poll conducted on the Phoenix Rising forums about half of those who had tried the methylation protocol reported improvement, with 22% reporting significant improvement. Roughly 20% reported that they were unable to continue with the protocol.

On the Curetogether.com website, methylation treatments recently ranked in the top 10% out of a total of more than 200 treatments and lifestyle changes informally rated for average effectiveness by CFS patients.

#### MORE INFORMATION

Yasko, Amy. *Autism: Pathways to Recovery*. Neurological Research Institute, 2009. Available from <http://www.holisticheal.com> or Amazon.

*Detailed information about testing for methylation blocks:*

<http://www.mecfsforums.com/index.php?topic=290.0>

*Ken Lassesen's treatment protocol database:* <http://www.cfs-healing.info/treatment-protocols.htm>

*This page contains Rich Van K's full protocol, in detail.*

Nutritional Healing: <http://www.nutritional-healing.com.au/content/articles-content.php?heading=Major%20Mental%20Illness%20Biochemical%20Subtypes>

*This is the mother of all methylation sites. The chart is so complete, it's mind-boggling.*

“Methyl donors for more energy and mood.” Ray Sahelian.

<http://www.raysahelian.com/methyl.html>

*Dr. Ray Sahelian discusses different methyl donors, and gives helpful recommendations.*

*Phoenix Rising's poll on the methylation protocol.*

<http://forums.phoenixrising.me/showthread.php?4528-Rich-Vank-s-Simplified-Methylation-Protocol-Poll>

*This is a very informative page on responses to the methylation protocol. Rich Van K's comments are well worth reading.*

*Phoenix Rising's poll results on the methylation protocol.*

<http://forums.phoenixrising.me/index.php?threads/rich-vanks-simplified-methylation-protocol-poll.3579/>

*The CureTogether.com ratings of CFS treatments:* <http://curetogether.com/chronic-fatigue-syndrome/treatments/>

“Dr. Myhill - CFS - The Methylation Cycle.” [http://drmyhill.co.uk/wiki/CFS -  
The Methylation Cycle](http://drmyhill.co.uk/wiki/CFS_-_The_Methylation_Cycle)

*Dr. Myhill's explanation of the methylation cycle is, as always, clear and concise. She gives supplement recommendations.*

"Treatment Study of Methylation Cycle Support in Patients with Chronic Fatigue Syndrome and Fibromyalgia." Neil Nathan, MD and Richard A. Van Konynenburg, PhD.: <http://www.mecfs-vic.org.au/sites/www.mecfs-vic.org.au/files/Article-2009VanKonynenburg-TrtMethylStudy.pdf>

“A Simplified Treatment Approach Based on the Glutathione Depletion - Methylation Cycle Block Pathogenesis Hypothesis for Chronic Fatigue Syndrome (CFS).” Rich Van Konynenburg, Ph.D.: <http://www.ei-resource.org/articles/chronic-fatigue-syndrome-articles/simple-methylation-treatment-protocol-for-chronic-fatigue-syndrome/>

*This is an older version of the simplified protocol, but it contains valuable explanations of how the supplements work.*

*Rich Van Konynenburg's July, 2007 article (two parts), after the first six months of experience with the simplified protocol:* <http://phoenixrising.me/cfs-chronic-fatigue-syndrome-me/treating-chronic-fatigue-syndrome-mecfs-glutathione-and-the-methylation-cycle/a-simplified-treatment-approach-based-on-the-glutathione-depletion-methylation-cycle-block-pathogenesis-hypothesis-for-chronic-fatigue-syndrome-cfs-by-rich-van-konynenburg-ph-d>  
<http://phoenixrising.me/cfs-chronic-fatigue-syndrome-me/treating-chronic-fatigue-syndrome-mecfs-glutathione-and-the-methylation-cycle/simplified-treatment-approach-based-on-the-glutathione-depletion-methylation-cycle-block-pathogenesis-hypothesis-for-chronic-fatigue-syndrome-cfs-by-rich-van-konynenburg-ph-d>

"Treatment Study of Methylation Cycle Support in Patients with Chronic Fatigue Syndrome and Fibromyalgia." Neil Nathan, MD and Richard A. Van Konynenburg, PhD.: <http://www.mecfs-vic.org.au/sites/www.mecfs-vic.org.au/files/Article-2009VanKonynenburg-TrtMethylStudy.pdf>

*The 2009 paper by Dr. Neil Nathan and Rich Van K about their clinical study (A shortened and modified version was published in the December 2011 issue of the Townsend Letter)*

"A Simplified Methylation Protocol is Effective for the Treatment of Chronic Fatigue Syndrome and Fibromyalgia." Dr. Neil Nathan. *ProHealth*, May11, 2011. <http://www.prohealth.com/library/showarticle.cfm?libid=16138>

*A 2011 article by Dr. Neil Nathan on the simplified methylation protocol.*

## LABORATORY TESTING

Health Diagnostics and Research Institute

540 Bordentown Avenue, Suite 4930

South Amboy, NJ 08879

USA

Phone: (732) 721-1234

Fax: (732) 525-3288

*Methylation panel test, including two forms of glutathione (reduced and oxidized), adenosine, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), and seven folic acid derivatives.*

## CHAPTER 3: SYMPTOMS

### INTRODUCTION: HOW TO ASSESS AND MONITOR YOUR SYMPTOMS

One of the hallmarks of CFS/ME is wide-ranging symptoms that wax and wane. Because symptoms vary so much, and because some symptoms eventually fall into patterns, it is important to keep track of them. Keeping a good symptom record not only helps identify patterns as an aid to treatment, but can help distinguish CFS/ME symptoms from secondary problems (infections, for example). An additional benefit of keeping a written record of your symptoms is that office visits to clinicians go more smoothly. You don't have to keep all your symptoms in your head, or worry about how well you can express them that day.

To keep track of symptoms, you need a method. First, either purchase a calendar, or make one. (A regular notebook will work.) Each day, write down information useful to you and your doctor: your temperature, to track fever and low temperature fluctuations; basal temperature, to indicate thyroid problems; your weight, to track sudden gain or loss; blood pressure (if you have a monitor); for women, day in menstrual cycle (day 1 is the first day of your period; many symptoms worsen in the last 10 days of the cycle); and weather conditions, which sometimes can exacerbate symptoms.

Next write down your primary symptoms. You may experience many symptoms over the course of a day, but usually two or three will predominate. Rating symptoms with a rating scale (mild, moderate, severe) can prove quite important. If symptoms worsen over time, your doctor may want to order tests for other systemic disorders such as thyroiditis, anemia, or diabetes.

Secondary or new symptoms should also be noted. If secondary symptoms are consistently severe or worsen out of pace with primary symptoms, you should see your doctor. An added benefit of tracking symptoms is that it is easier to identify some of the things that exacerbate symptoms. It is also easier to prove to yourself that you are, indeed, recovering if you keep good track of symptoms over an extended period. The following list will help you identify your primary and secondary symptoms:

### CFS/ME SIGNS AND SYMPTOMS CHECKLIST

- Fatigue, usually made worse by physical exercise
- Flu-like malaise, feeling "sick all over"
- Sore throat
- Low-grade fever or feeling hot often
- Low body temperature
- Muscle and joint aches with or without "trigger points"
- Sleep disturbance
- Headache
- Changes in vision
- Seizures
- Numb or tingling sensations

- Loss of balance, dizziness
- Feeling "spaced out" or "cloudy," "brain fog"
- Frequent, unusual nightmares
- Depression
- Anxiety, panic attacks
- Personality changes
- Mood swings
- Difficulty moving the tongue to speak
- Tinnitus (ringing in the ears)
- Paralysis
- Severe muscle weakness
- Blackouts
- Photophobia (light sensitivity)
- Alcohol intolerance
- Changes in taste, smell, hearing
- Decreased libido
- Muscle twitches
- Cognitive function problems
- Attention deficit disorder (inability to concentrate)
- Calculation difficulties
- Memory loss
- Spatial disorientation
- Word searching or saying the wrong word
- Severe premenstrual syndrome (PMS) or exacerbation of symptoms before and during period
- Weight changes, usually loss followed by gain
- Painful, swollen lymph nodes, especially on the neck and underarms
- Abdominal pain, diarrhea, nausea, gas, irritable bowel
- Severe new allergic reactions to medicines, food, and other substances
- Night sweats
- Heart palpitations
- Uncomfortable or frequent urination
- Rash of herpes simplex or shingles
- Flushing, rash
- Hair loss
- Chest pain
- Dry eyes and mouth (sicca)
- Impotence
- Cough
- Temporomandibular joint (TMJ) dysfunction
- Canker sores
- Cold hands and feet
- Carpal tunnel syndrome
- Sciatica



- Gum disease
- Shortness of breath
- Temperature and weather sensitivity
- Symptoms worsen when standing up

Keep a separate list of medications, treatments, and supplements you are using, along with your dosage and reactions.

In the beginning you may want to keep records daily. Later, during recovery, you may make an entry only when trying new therapies, during exacerbations, or only occasionally, just to keep a record of your progress. Remember, having CFS/ME does not exempt you from other illnesses. If you notice new or unusual symptoms, especially after the illness has been stable for a while, make sure you bring these to the attention of your doctor.

In addition to rating your symptoms, you may want to rate your illness overall. Many people with CFS/ME rate their illness on a scale of 1 to 10. The following list will help you gauge your overall symptoms and energy level. For example, if you rate your condition at 8, you can do 80% of your normal workload, and it will take you perhaps 20% longer; at 5 you can plan on being able to do about 50% of what you would normally expect of yourself, and it will take you twice as long; at 2, you can do 20% of what you could do formerly, and it will take you five times longer; at 1, you can't do anything without help.

When setting tasks for yourself, this rating scale will help you to be realistic and make allowances for your limitations. By making allowances for your limitations, you will accomplish more and with less frustration than if you set out with previous expectations in mind.

You can also use this scale to help evaluate treatments. Doctors often observe that people who are moderately to mildly ill respond much better to various treatments, whereas those who are severely ill have fewer options.

- 0 (Severe, Hospitalized) I feel like I am dying. I can't get out of bed. I need help for the simplest tasks, such as brushing my hair. I can't care for myself.
- 1 (Severe) I am in bed all day. Getting up for more than 10 minutes makes me feel awful. My symptoms are incapacitating. I don't leave the house except for trips to the doctor.
- 2 (Severe) I can get up for about an hour, but I still can't move around much. I don't leave the house except for medical appointments and emergencies. I need help for household chores. I am always sick.
- 3 (Severe) I have a "window" of time, maybe 2 or 3 hours, when I don't feel ill, but I usually still have to rest during that time. If I do too much, my symptoms get considerably worse. I can do some light housekeeping chores. Symptoms are always with me, though sometimes some of them lighten up. I can go out briefly to shop, provided I am not on my feet for too long.
- 4 (Severe-Moderate) I can get up for 2 or 3 hours at a stretch, but I absolutely must rest for as much time as I am up. I can prepare simple meals and do light housekeeping. I can drive short distances, but prefer to have others do the

- driving. I can cope with my symptoms. I no longer feel ill, though I don't have nearly the stamina I used to have.
- 5 (Moderate) I can get through the day, but I need to take rests or a nap. I can do nearly all my housekeeping chores. Symptoms are tolerable, though with flares they can sometimes become severe. I can get out during the day to run errands or visit with friends if I rest afterward. I can take walks or go for a swim, provided I don't overdo it.
- 6 (Moderate) If I take short, recuperative rests, I can get through the day. Sometimes I need to nap. By dinnertime, I am often quite tired, and I need to get to bed by 9:00 PM. I can work a little. Sometimes symptoms seem to vanish altogether. I can go on hikes, go swimming, go on a picnic.
- 7 (Moderate-Mild) I can get through the day without having to lie down, but I need more sleep than I used to. I can work part-time, preferably on a flexible schedule, and allowing for flares. I have longer periods of feeling almost normal.
- 8 (Mild) I can get through the day with no problem, provided I don't skimp on sleep or overdo it. I can work full-time, although I don't have much energy for anything else. Flares are usually brief, and with adequate rest I recover well.
- 9 (Mild) My stamina is much improved. I can hold a full-time job. And provided I get enough rest and watch myself, I don't have flares. I can go out in the evening without "paying for it later," although I'm still more tired than usual the next day. Symptoms are few and far between.
- 10 I am completely recovered. I have lots of energy, with no sign of symptoms. I am back to climbing mountains on weekends.

Obviously, the above criteria are not ironclad. Many people who rate their illness at a 5 or 6 still manage to force themselves to go to work. Others, because of their particular array of symptoms, may be able to get out more or perform more physical work. Children, for example, may have greater energy levels than adults with the same degree of illness, and some men may recover physical stamina faster than women, which allows them to work even when other symptoms are debilitating.

Becoming familiar with your symptoms and understanding their causes is one of the biggest challenges of CFS/ME. Nevertheless, it is a challenge that, if met, can help open the way to choosing treatments and coping strategies that will be most effective for you.

#### FURTHER READING

*A comprehensive list of symptoms compiled by Jodi Bassett:* [http://tnq-support-group.net/Symptoms\\_ME\\_CFS-FNQ.html](http://tnq-support-group.net/Symptoms_ME_CFS-FNQ.html)

Katrina Berne's list of symptoms from her book: *Running on Empty, along with their frequency in the CFS/ME population:* <http://wwcoco.com/cfids/bernesx.html>

## ALLERGIES

Airborne: Pollen, Mold, Animal Dander, Fur and Feathers, Dust, Food, Chemical Sensitivities: Indoor Chemical Air Contaminants, Outdoor Chemical Air Contaminants, Drugs and Medications, Clothing and Personal Care Products.

New onset of allergies or worsening of existing allergies is a widespread problem among patients with CFS/ME. According to Dr. James Jones, 75% of people with CFS/ME have allergies, compared with 25% in the general population. Dr. Jones noted that because CFS/ME and allergies produce the same inflammatory cytokines, allergens may contribute to CFS/ME symptoms. Significantly, a group of researchers at the University of Rome (Italy) found that *whether or not* CFS/ME patients tested positive on a RAST test, they all showed eosinophil (an allergy mediator) activation. Based on their results, the researchers posited that either eosinophil activation had a causative role in CFS/ME, or that a common immunological background might exist for both allergy and CFS/ME.

Allergies can be triggered by airborne agents, chemicals, or foods. The most frequent airborne allergies in CFS/ME are to molds, dust, and pollens. Chemical odors (perfumes, hairspray, gasoline, household cleaners, plastic outgassing) can also produce allergic reactions. Food allergies and sensitivities are quite common and comprise the full spectrum of anything that can be ingested.

Allergy can be described as an over-response of the immune system in which immune cells mistakenly identify an innocuous substance as a potentially harmful one. The immune response involves the production of histamine, a chemical that causes inflammation by increasing cell permeability and localized blood flow (histamine is a vasodilator). Normally, inflammation fulfills a positive role in combating infection. It serves to isolate a wounded area and draw fluid to it, thereby enabling white blood cells to identify and kill invading microorganisms. The increased permeability of cell membranes allows for the release of heparin and zinc, which are needed for connective tissue repair after injury. If the mucous membranes are involved, the resulting inflammation produces cold-like symptoms (runny nose, sneezing), stomach pain, and diarrhea. If the skin is affected, the inflammation produces itching or rash. When the allergic response is systemic, the inflammation can occur in any soft tissue (throat, joint area, gums, brain), producing an astonishingly wide array of symptoms:

- *Skin:* Pallor, itching, burning, tingling, flushing, warmth or coldness, sweating behind the neck, hives, blisters, blotches, red spots, pimples, dermatitis, eczema
- *Eyes:* Blurred vision, itching, pain, watering, eyelid twitching, redness of inner angle of lower lid, drooping or swollen eyelids
- *Ears:* Earache, recurring ear infections, dizziness, tinnitus, imbalance
- *Nose:* Nasal congestion or discharge, sneezing
- *Mouth:* Dry mouth, increased salivation, stinging tongue, itchy palate, toothache

- *Throat*: Tickling or clearing, difficulty in swallowing
- *Lungs*: Shortness of breath, air hunger, wheezing, cough, mucus or recurrent bronchial infections
- *Heart*: Chest tightness, pounding or skipped heartbeats
- *Gastrointestinal tract*: Burping, heartburn, indigestion, nausea, vomiting, abdominal pain, gas, cramping, diarrhea, constipation, mucus in stool; frequent, urgent, or painful urination, bedwetting (in children)
- *Muscular system*: Muscle fatigue, weakness, pain, stiffness, soreness
- *Central nervous system*: Headache, migraine, vertigo, drowsiness, sluggishness, giddiness
- *Cognition*: Lack of concentration, feeling of "separateness," forgetting words or names, anxiety, tension, panic, overactivity, restlessness, jitteriness, depression, premenstrual syndrome (PMS)

It is not surprising, given the tremendous overlap between allergic reactions and CFS/ME symptoms, that some allergists have mistaken CFS/ME for allergy. The difference is that CFS/ME is prolonged, whereas normal allergies are short-lived after provocation. Nor are allergies disabling. To confound matters, many clinicians have noticed that although people with CFS/ME demonstrate clear evidence of allergic reactions on standard tests, their allergies seem to fluctuate with the severity of the illness. This has led a number of clinicians and researchers to propose that many of the allergic reactions experienced by people with CFS/ME should better be classified as sensitivities. Despite this distinction, there are some significant commonalities between the two phenomena.

The immune system hyper-response brought about by CFS/ME uses the same mechanism as an allergy; it is mediated through the action of inflammatory chemicals. Lucy Duchene, Ph.D., has proposed that histamine overproduction can substantially contribute to the development of CFS/ME's most significant effects (*CFIDS Chronicle*, Summer 1993).

Chief among these are increased excretion of electrolytes, leading to dehydration and alteration in cell function; binding to acetylcholine receptors, causing insufficient nervous system responses in muscle and brain function; increased delta waves, leading to daytime lethargy and disturbed sleep; stimulation of the vagus nerve, contributing to activation of the parasympathetic nervous system and general metabolic slowing; irregularities in heart rate; gastrointestinal disturbances from histamine-induced release of gastric juices, leading to acid stomach and other gastrointestinal problems; release of adrenal hormones, leading to activation of the sympathetic nervous system, speeding up of heart rate, increased glucose metabolism, and, when prolonged, eventual adrenal exhaustion and hypoglycemia; changes in gonadotrophin and prolactin levels, causing hormone imbalance; changes in immune system function; and last, but not least, both stimulation and depression of certain parts of the hypothalamus.

As the brain appears to be one of the main sources of the syndrome's many myriad effects, the ability of histamine to cross the blood-brain barrier, where it affects the metabolism of serotonin and acetylcholine, and ultimately alters

functioning of the hypothalamus makes it a prime culprit for causing CFS/ME symptoms.

## AIRBORNE ALLERGENS

When most people think of allergies, what comes to mind are the sneezing, wheezing, itching eyes, sinus headaches, and runny nose that are the typical responses to airborne allergens.

### *Pollen*

The strongly scented, bright-colored flowers typical of heavy-pollen plants do not usually cause problems for people with hay fever because they are generally cross-pollinated by insects. The plants that create problems for allergic individuals are those that produce light, abundant, widely wind-distributed pollen. When these small, light pollens are inhaled, the grains pass into the bronchi, where they can cause the wheezing of an allergic response. To complicate the picture, some pollens contain as many as 15 allergenic compounds, which can stimulate a variety of other systemic reactions. You should suspect an allergy to pollens if you have the following symptoms during spring and fall:

- Your eyes itch and you have a thin, watery nasal discharge.
- You feel worse outdoors between 8:00 am and noon, when most plants release pollens.
- You feel worse on clear, windy days.
- Your symptoms improve after a heavy rainstorm, when pollens are washed out of the air.
- Your symptoms improve after the first frost in fall.

### *Mold*

The principal activity of mold is to break down organic matter to make it available for other life. As nature's greatest recycling force, molds can hardly be avoided. They can be found on farms, in houses, at work, in factories, outdoors and indoors, in showers, refrigerators, food, under rugs, and any place it is warm and humid. They can contaminate the air with spores and VOCs (volatile organic compounds).

Molds can also colonize the body, as in systemic or local *Candida* overgrowth, athlete's foot, ringworm, and various other fungal infections. Molds cause special problems because the overgrowth of *Candida* frequently experienced by people with CFS/ME can produce an allergy to all molds (see *Candida*). But even without *Candida* overgrowth, people with CFS/ME seem to be particularly vulnerable to mold allergies. In her book, *When I Cry Wolf: A Society Lost to CFS and Mold*, Dr. Sharon Kirk describes her long struggle with CFS/ME and her eventual undoing by mold. After ten years of successfully managing CFS/ME, Dr. Kirk unwittingly moved into a house contaminated by mold. Daily contact with this powerful allergen caused a relapse which left her disabled.

According to Dr. Richie Shoemaker, the reason biotoxins from molds affect us so severely is that they produce systemic, as opposed to localized, effects. Once a person is exposed, biotoxins set off a cascade of inflammatory responses that, left unchecked, can produce damage to any part of the body.

Those who are constantly exposed to mold by living or working in structures that have been water-damaged are particularly at risk, and may develop “sick building syndrome.” Symptoms of sick building syndrome are wide-ranging: nausea, headaches, dizziness, fatigue, diarrhea, sore throat, dry cough, blurry vision, congestion, muscle and joint pain, cognitive impairment, and shortness of breath.

The most common types of mold found indoors are *Cladosporium*, *Penicillium*, *Alternaria*, and *Aspergillus*. *Stachybotrys*, also known as “black mold,” is one of the primary molds responsible for sick building syndrome and is considered an environmental hazard. *Stachybotrys* is found in areas that are impregnated with water, such as flooded cellars. (The black growth you may see on the surface of bathroom tiles is not *Stachybotrys*.)

In contrast to pollen and food allergies, mold symptoms do not usually include itchy eyes. The most common symptoms are profound fatigue, dizziness, vertigo, chills, rashes, depression, pulmonary symptoms, and cognitive problems. Suspect an allergy to molds if you have the following symptoms:

- You feel worse in humid weather.
- You feel worse outdoors between 5:00 and 9:00 PM.
- You feel worse when mowing or raking leaves.
- You feel much worse from August to the first heavy frost.
- You feel worse in damp places, basements, and bathrooms.
- You feel worse after eating mushrooms, seaweed, fermented products, aged cheeses, beer, tofu, pickles, or vinegar.

Erik Johnson, one of the first CFS/ME patients treated by Dr. Peterson and Dr. Cheney during the Incline Village outbreak, identified mold exposure as the primary cause of his symptoms. Through a program of rigorous avoidance he managed to control and overcome his symptoms. Read his story at: <http://www.cfsuntied.com/toxicmold.html#avoidance>.

Dr. Ritchie Shoemaker has devised a mold treatment protocol based on cholestyramine (Questran). Read an interview with him at: <http://articles.mercola.com/sites/articles/archive/2012/07/22/mold-and-other-chronic-diseases.aspx>.

*Animal Dander, Fur, and Feathers.* Many people are sensitive to animal hair and react to fur coats and trimmings, feather pillows, stuffed toys, wool clothing, yarn, felting, carpets, and wigs. Allergies to animal dander can also produce an allergic reaction to serum from those same animals. For example, to avoid an allergic response, people with horse dander allergies need to be careful about receiving horse antiserum (tetanus shots). Suspect allergies to animal dander if you feel worse when you are exposed to animals or animal hairs in items such as bedding or clothing.

*Dust.* Dust is a complex mixture composed of breakdown products of airborne allergies plus inorganic matter from synthetics, smoke, soot, cellulose, dead skin cells, and mite or other insect droppings. You can be allergic to any component of dust, and it is impossible to pinpoint exactly what causes symptoms without testing. If you feel worse indoors after dusting or vacuuming, or first thing in the morning, you may have an allergy to dust.

#### MANAGEMENT TIPS FOR ALLERGIES

- Dust with a damp sponge to avoid spreading dust.
- Avoid vacuuming or emptying vacuum bags (which harbor molds as well as dust).
- Eliminate under-the-bed storage.
- Use easy-to-wash curtains, bed covers, pillows, rugs, and clothing.
- Empty and clean drawers. Use drawers only for storing clean clothes.
- Avoid keeping knickknacks, books, or dust-catching clutter in your room.
- Do not allow pets in the bedroom.
- Replace furnace and air-conditioning filters often; check for mold.
- Use an air filter in your room; high-efficiency particle arresting (HEPA) filters are best.
- Use antihistamines or steroidal nasal sprays (Nasalcrom) for symptom relief.
- Take natural antihistamines (quercetin, bromelain) and vitamin C for nutritional support.
- Avoid eating moldy or mold-laden foods, inhaling old dust (such as in attics and used-book shops), and make sure bathrooms and kitchens are free of mold and mildew. (Soap kills mold.)

#### FOOD

Allergies and intolerance to various foods are common in people with CFS/ME. Dr. Robert Loblay, lecturer in immunology and Director of Allergy Service at the Royal Prince Alfred Hospital in Sydney, Australia, estimates that food intolerance is a "significant factor in 20% to 30%, and may be the principal trigger in perhaps 5% to 10%" of the CFS/ME population. In some of these individuals, allergies to other substances, such as pollen and dust, may have predated the onset of CFS/ME; in others, food sensitivities are a new problem brought on by CFS/ME itself. (See Food and Diet for a more in-depth discussion of food intolerance).

The distinction most clinicians make between food allergy and food intolerance is subtle. Currently, most allergists agree that food allergies are mediated by immunoglobulin E (IgE), an antibody that attaches itself to histamine-releasing mast cells. Allergens, because they produce antibodies, provoke an immune response even in the tiniest amounts. They often occur in groups, for example, citrus fruits, fungi, or milk products. The most common food allergens are corn, eggs, milk, soy, sugar, wheat, and yeast. Allergies can be tested for with a radioallergosorbent test (RAST), which measures the amount of IgE antibodies a person produces in response to specific substances.

Intolerance to certain foods, on the other hand, is not IgE mediated and cannot be measured with the RAST. It often results from increased permeability of the small intestine lining ("leaky gut"), a problem that can arise after infections from viruses or *Candida* as well as treatments with certain drugs (e.g., antiparasitic agents, antibiotics, chemotherapy). When the intestinal wall is compromised, molecules derived from food digestion pass through the membrane before they are completely broken down. The oversized molecules now circulating in the bloodstream provoke an immune response, although this may be delayed by several hours or even days. In the case of food intolerance, the less you eat of a food the less likely it is to bother you. And whereas true allergies usually last throughout life (the immune system "remembers" the offending protein), sensitivities are often transient.

The conditions that lead to food sensitivities are multifold. An initial viral trigger can affect the gut mucosa, making the intestinal wall more permeable. Bacterial infections and parasites can produce the same result. In addition, negative responses to certain foods could be a result of low amounts of T suppressor cells, the immune system cells that modulate immune responses to food molecules. Parasites, *Candida*, and alterations in intestinal flora after antibiotic intake are also possible factors contributing to food sensitivities. Needless to say, people with CFS/ME can experience all these conditions so it should not be surprising that food sensitivities are so common in the CFS/ME population.

Reactions to food allergies and sensitivities are fairly similar. Suspect food sensitivities if you have the following symptoms:

- You feel excessively thirsty after eating.
- You experience bloating within 20 minutes after eating.
- You experience bowel problems, dizziness, heart palpitations, fatigue, insomnia, depression, or anxiety after eating certain foods.
- You have any symptoms after eating citrus fruits, milk products, wheat, solanaceous foods (nightshade family, such as potato, tomato, eggplant, peppers), or artificial colorings or preservatives.

*Note: all of these symptoms can be delayed.*

## TREATMENT TIPS

For food allergies and sensitivities, the first order of business is to identify and avoid the offending foods. A record should be kept of symptoms that arise, such as heartburn, increased heart rate, bloating, headache, or diarrhea after eating certain foods, and those foods should be avoided. Note whether symptoms decrease after a few days. (In some cases, however, symptoms can increase for a few days until the offending item passes from the GI tract.) Foods should be separated as much as possible. Don't mix too many suspect foods at a single meal to better judge their aftereffects.

Second, diet should be rotated. In the rotation diet, no food is eaten more than once within four days. Not only does this diet allow you to identify foods that may be causing trouble, it helps prevent the formation of allergic responses from



overexposure. Because people with CFS/ME have a strong tendency to develop allergies, this last point is crucial. Of course, many people with food reactions find that they eat too few foods to rotate them. In that case, alternate as best you can.

When reactions occur, the best immediate course of action is as follows:

- Drink a glass of water into which you have mixed a half-teaspoon of baking soda or trisodium compound (Tri-Salts) to increase alkalinity (allergic reactions are acidic).
- Take buffered (nonacid) vitamin C or Alka Seltzer Gold.
- Take over-the-counter antihistamines if the reaction is severe.
- Drink plenty of water.

An interesting new approach to food sensitivities is Histame. Histame is a naturally occurring enzyme that breaks down histamine in the intestines. It does not prevent true allergic reactions (IgE), but in many cases it can forestall GI symptoms caused by foods high in histamine. (Basically, everything that tastes good is high in histamine – aged and fermented foods, sausage, eggplant, ketchup, canned fish, as well as bananas, tomatoes, strawberries, pineapple, nuts, peanuts, shellfish, spinach, egg white, and chocolate). Gastrocrom (cromolyn sodium), which works by inhibiting mast cell production, is a pharmaceutical means of managing food reactions. Quercetin, a natural supplement, also inhibits mast cell production.

GLA (evening primrose oil) and Cytotec, a synthetic prostaglandin, are helpful in treating food sensitivities due to leaky gut. (For information on how to heal leaky gut, the source of most food sensitivities, see Digestive Disturbances.) Zinc deficiency can lead to excess histamine production; thus increased dietary zinc, especially in the form of zinc carnosine, may help control food sensitivities.

In severe cases, judicious use of systemic anti-inflammatory agents (hydrocortisone, cortisol) can be lifesaving. Cortisol is the body's most powerful anti-inflammatory chemical and can stop inflammation in its tracks. However, it also depresses the immune system and, over time, can depress adrenal function. It should be used sparingly and only in cases in which immune system hyper-reactivity threatens to create malnutrition.

## CHEMICAL SENSITIVITIES

Sensitivities to synthetic chemicals are fairly common among people with CFS/ME, although many may not be aware that their symptoms are due to chemical exposure. People who experience fatigue, dizziness, flushing, anxiety, or other symptoms after shopping in furniture or dry goods stores, sitting in a new car, strolling through a mall, or filling the tank at a gas station are probably chemically sensitive.

Chemical sensitivities were first described in 1951 by Dr. Theron Randolph, the pioneering physician who discovered that people who demonstrated allergies to fruits (all fruits in this case, not just specific types of fruit) were actually reacting to the pesticide residues left on them. Dr. Randolph observed that even in small doses, chemicals can cause severe reactions in sensitive individuals. In 1962 Dr. Randolph published a landmark book, *Human Ecology and Susceptibility to the Chemical*

*Environment*, in which he identified the chemicals responsible for a wide range of human ailments.

Chemical sensitivity usually develops over a long period of time. Small amounts of chemicals that continually enter the body through the skin, nasal passages, or digestive tract can eventually induce sensitivities, with symptoms that for all intents and purposes are identical to those of common allergic reactions. IgE-mediated chemical reactions include hives, rashes, and skin eruptions. Delayed responses can include any of the symptoms common to other allergies, such as confusion, respiratory problems, fatigue, diarrhea, excessive thirst, tinnitus, runny nose, cramps, and itching.

Chemical sensitivities can also surface as the result of massive exposure to a contaminant, such as a chemical spill or fire, pesticide spray, or general anesthesia. In these cases, the massive exposure overwhelms the body's normal detoxification mechanisms or damages the regulatory systems in the brain that normally direct endocrine and immune functions.

*Indoor Chemical Air Contaminants.* Building materials, carpeting, glues, paints, plastics, deodorants, tobacco, insecticides, and disinfectants are common sources of indoor pollution found in most homes. Of particular concern is the outgassing of contaminants such as formaldehyde from sources such as pressboard, found in most recently built homes. Low-level exposures, even though they can induce symptoms, originate from sources that are not easily detected and thus remain hidden. Other common sources of indoor pollution are copy machine inks, correction fluid, carbon paper, solvents used in the workplace, and gas leakage from stoves and heaters.

*Outdoor Chemical Air Contaminants.* Traffic exhaust, smog, paving and resurfacing of roads, industrial fumes, and the indiscriminate spraying of lawns are the most common sources of outdoor pollution. Of these, exposure to gasoline and diesel fumes presents the biggest problem for the chemically sensitive because they are ubiquitous and virtually unavoidable.

*Drugs and Medications.* People with chemical sensitivities frequently develop sensitivities to pharmaceuticals. Many drugs are synthetic, that is, they are derived from petroleum, a common source of sensitivity for many people. In addition, the excipients, preservatives, colorings, and inactive ingredients found in many medications may provoke reactions. Many people with drug sensitivities are unable to tolerate antibiotics or local anesthetics. Because the majority of people with CFS/ME have allergies/sensitivities as well as hyper-responsiveness to histamine, anesthesiologist Patrick Glass recommends that CFS/ME patients avoid anesthetics containing histamine releasers, such as sodium pentothal, during surgery.

*Clothing and Personal Care Products.* Synthetic fabrics, as well as the detergents, finishers (such as formaldehyde), sizing, dyes, and plastic residues found on many natural fabrics, can provoke topical or systemic reactions in many people. The harsh

chemicals often included in body lotions, skin cleaners, cosmetics, and deodorants are also common sources of irritation for the chemically sensitive.

### TREATMENT ADVICE FROM PEOPLE WITH CFS/ME

In a 1995 survey conducted by a DePaul University research team, 305 patients with multiple chemical sensitivities (MCS) were asked to rate treatments on the basis of personal experience. Of these patients, 93% rated "adopting a practice of avoiding exposures to chemicals which could cause MCS reactions" as a "major" or "enormous help" (*CFIDS Chronicle*, Winter 1996). It is clear from this report and from testimonies of numerous people with chemical sensitivities that effective control of chemical reactions hinges on avoidance. Clean, filtered water and air, and organic foods help cut down the chemical load and remove all sources of contamination from the home. (See *Cleaning Up* for more information on alternatives to toxic household chemicals.)

Nutritional support can also be of help, particularly those nutrients that help mediate allergic symptoms and provide support for the liver and kidneys. Vitamins C and B12 are especially important. Alpha ketoglutarate and glutathione are two of nature's most potent natural detoxifiers, as are all antioxidants.

SEE: Digestive Disturbances: Antihistamines, Cytotec, Hydrocortisone: Alpha Ketoglutarate, Amino Acids (glutathione), Bioflavonoids, Minerals (zinc), Vitamins: Chapter 8: *Cleaning Up*.

### MORE INFORMATION

American Academy of Allergy and Immunology: <http://www.aaaai.org/home.aspx>

Asthma and Allergy Foundation of America:

<http://www.aafa.org/display.cfm?id=10&sub=26&cont=463>

Food Allergy Network: <http://www.foodallergy.org/>

Human Ecology Action League: <http://www.healnatl.org/>

*Online suppliers of allergy products* (HEPA filters, bedding, etc.):

National Allergy Supply: <http://www.natlallergy.com/>

Allergy Store: <http://www.allergystore.com/>

Achoo Allergy: <http://www.achooallergy.com/iqairpurifiers.asp>

Allergy Buyer's Club: <http://www.allergybuyersclub.com/>

### FURTHER READING

*Mold exposure standards and testing for buildings. Includes state, national and international guidelines:*

[http://inspectapedia.com/sickhouse/Mold\\_Standards.htm](http://inspectapedia.com/sickhouse/Mold_Standards.htm)

*Excellent information about food allergies:* <http://www.allergy-clinic.co.uk/food-allergy/food-allergy-guide/>

“Allergies To Foods, Plants May Predict Chronic Fatigue Syndrome.” (Jones study)

<http://www.sciencedaily.com/releases/1999/01/990119104557.htm>

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- Loblay, Robert H, and Swain, Anne R. "The Role of Food Intolerance in Chronic Fatigue Syndrome." In Hyde, Byron M, ed. *The Clinical and Scientific Basis of ME/CFS*. Ottawa, Ontario: Nightingale Research Foundation, 1992.
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*If you are thinking of buying a home and have mold allergies, this book will be invaluable. The author, a home inspector, explains everything you need to know about mold contamination and remediation. Includes a good chapter about health effects.*

## RESEARCH

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## CANDIDA

*Candida albicans* is a yeast-like fungus found in the moist mucous lining of the intestines, genital tract, mouth, and throat. A certain level of *Candida* in the body is normal; some conditions, however, can cause rampant overgrowth. The overgrowth, manifested in easily observed "yeast" infections of the vagina and mouth ("thrush"), as well as less apparent intestinal infections, can lead to serious health problems.

The most common cause of *Candida* overgrowth is the administration of antibiotics. Antibiotics have been a mainstay of medical practice for decades and have saved millions of lives, but they exact a price. Antibiotics, particularly broad spectrum antibiotics, destroy not only infection-causing bacteria, but the normal, "friendly" bacteria that inhabit the gut and are responsible for enabling us to digest food. Once the friendly flora is destroyed, fungal microbes, which are not affected by antibiotics, no longer have a check on their proliferation. As a consequence, many of the side effects experienced by people taking antibiotics are comprised of digestive problems, not only because their friendly flora has been eliminated, but because the yeast that normally inhabits the gut can grow unimpeded.

A number of common digestive problems are believed to be caused or exacerbated by this yeast overgrowth. Yeast can adhere to the intestinal walls, causing loss of integrity of the mucous lining. This damage results in greater

permeability of the lining, allowing undigested food particles to pass through (“leaky gut”). When these undigested food molecules reach the bloodstream, many systemic allergic reactions can occur. Bloating, gas, diarrhea, and food, drug, and chemical sensitivities owe their origins, in many cases, to this problem. In addition to symptoms related to increased intestinal permeability, people with yeast overgrowth experience fatigue, headaches, cognitive problems, and endocrine imbalances (hypothyroidism and hypoglycemia).

There are a number of doctors who believe that chronic overgrowth of *Candida* may actually cause CFS/ME. In his book, *Chronic Fatigue Syndrome and the Yeast Connection*, Dr. William Crook squarely laid the blame for most CFS/ME symptoms on *Candida* overgrowth. His theory was based not only on observations of patients, but on research indicating that *Candida* has a profound effect on the immune system. Several years after Dr. Crook's book was published, Dr. R. Cater proposed that chronic intestinal candidiasis might lead to immune suppression. In his article, Dr. Cater pointed to the fact that the reduction of natural killer cell activity caused by candidiasis could result in an inability to control latent viruses, such as Epstein-Barr, cytomegalovirus and other herpesviruses. Based on the reactivation of latent viruses found in CFS/ME patients, he proposed intestinal candidiasis as the causal factor in developing CFS/ME.

While proponents of the antibiotic/*Candida* overgrowth theory have been routinely dismissed by conventional doctors, research has shown that upsets in gut flora by antibiotics can have profound systemic consequences. Because *Candida albicans* can secrete prostaglandin-like (pro-inflammatory) immune modulators, any organ can be affected.

A study conducted in 2004 by Noverr et al found that *Candida* overgrowth contributed to asthma and allergic airway disease. The researchers discovered that disruption in the gut mucosa subsequent to antibiotic administration played an important role in regulating immune responses in the lungs. More ominously, a ten-year review of over 78,000 biopsies and 783 autopsies conducted in Spain revealed that over 60% of the fungus infection cases were caused by *Candida*, with systemic fungal infections having a 91% percent fatality rate.

People with compromised immune systems, such as AIDS, often have both topical and systemic infections. The stubborn, recurring local infections such as athlete's foot, vaginal yeast infections, and thrush are indications that the immune system is simply too weak to combat the proliferation of yeast throughout the body. When the immune system is compromised, *Candida* can spread from the mucous linings of the mouth and intestines to other organ systems, as well as the bloodstream, causing a systemic infection.

Many researchers believe that a combination of immuno-suppressive factors contributes to the likelihood of developing yeast infections. Dr. Carol Jessop, an internist in California who treated yeast infection in thousands of patients with CFS/ME, noted that 84% of her patients had undergone repeated and prolonged antibiotic treatment, 70% had taken oral contraceptives, and 10% had taken

prescribed steroid drugs (*CFIDS Chronicle*, Spring 1991). All of these drugs can be immune system inhibitors and may be linked to Candida overgrowth.

Dr. Jorge Flechas has also addressed the problem of Candida overgrowth as it is related to immune system dysregulation in patients with CFS/ME. Dr. Flechas proposed that Candida overgrowth may be linked to a specific immune defect (*CFIDS Chronicle*, Summer/Fall 1989). He observed that patients with CFS/ME commonly demonstrate T cell abnormalities, such as T suppressor cell depletion and reduced number of natural killer cells. Because T cells are largely responsible for controlling viral and fungal infections, a defect in the system may allow reactivation of latent viruses and fungal overgrowth.

This theory seems to be borne out by a Swedish study conducted in 2007 (*Scandinavian Journal of Gastroenterology*, 2007, Vol. 42, No. 12 : pages 1514-1515), in which high levels of *Candida albicans* were found in fecal matter of CFS/ME patients during the acute stage of illness. The researchers could not determine whether the overgrowth was a cause or effect of the illness, but, either way, the consequences of Candida overgrowth need to be addressed.

## DIAGNOSIS

To make a diagnosis of Candida overgrowth, a careful medical history must be taken, with particular attention to courses of antibiotics, steroid therapy, or oral contraceptives taken in the past. In addition, the presence of certain symptoms may be highly suggestive of candidiasis.

Suspect Candida if you have:

- Oral thrush
- Recurrent vaginitis
- Topical fungal infections, such as athlete's foot and seborrheic dermatitis (dandruff and flaky patches on the skin caused by an inflammatory reaction to the yeast *Malassezia*).
- Chemical and food sensitivities
- Gastrointestinal problems (bloating, gas, diarrhea, constipation)
- Chronic sinusitis
- Itching in the ears
- Sugar craving

If a patient has the above signs and symptoms, laboratory testing (usually a stool test) for Candida may be recommended. Blood tests for IgG and IgA antibodies may also be ordered. (Genova Diagnostics performs all these tests.)

While few physicians believe that Candida overgrowth is the underlying cause of CFS/ME, most agree that yeast overgrowth can greatly exacerbate symptoms. As Dr. Flechas states, "[Candida] can take a bad situation and make it worse." And, as many people with CFS/ME have found, the reduction in yeast overgrowth can lessen the general overload on the body, allowing for greater overall improvement.

## TREATMENTS

In a study conducted in 1997, a team of scientists led by Dr. Gerald Fink found that the key to Candida's infectiousness lay in its ability to switch from a rounded form to filamentous forms. The group discovered that the switch could be inactivated through two genetic pathways, rendering Candida harmless. This discovery led to further research on substances that could inhibit the filamentous form of Candida.

The following year a group of Japanese researchers found that lactoferrin, a substance found in colostrum (breast milk), has the ability to inhibit the growth of Candida by preventing it from forming filaments. The basic mechanism involved the disruption of iron uptake by Candida. Research is currently underway to find an effective means of preventing Candida from switching into filamentous forms, but in the meantime there are many steps that can be taken to control the spread of infection.

*First step: Eliminate sugar.*

Most physicians recommend dietary modifications to help control the infection. Yeast thrives on sugar, so a mainstay of the diet is to avoid sweets. Alcohol, refined carbohydrates, milk (because of lactose), and fruits may also be eliminated in the early stages of treatment. People with Candida overgrowth have a “sweet tooth,” so cutting sweets from the diet can come as a hard blow. Fortunately, there are other sweeteners that don't encourage the proliferation of yeast. Dr. Teitelbaum recommends stevia, which is a natural sweetener. (Start with a small amount; stevia causes diarrhea in some people.)

*Second step: Avoid foods containing yeast*

Specialists also recommend avoiding fermented products (soy sauce, aged cheeses) and pickled products because these contain yeast and mold. Although Candida does not need molds to grow, Candida overgrowth often creates allergies to all mold and fungus. As a consequence, eating moldy foods, (blue cheese is a prime example), will provoke allergic symptoms. Another high source of mold is fruit, especially the peel. A good rule of thumb is to emphasize whole grains, high-quality proteins, and lots of vegetables. Foods should be purchased fresh and without additives, hormones, or antibiotics, which exacerbate the condition.

*Third step: Replace healthy gut flora.*

Taking probiotics, such as acidophilus and bifidus bacteria, is essential for controlling Candida overgrowth. Health food stores generally carry a wide array of different strains and combinations. Many people prefer the enteric-coated varieties (such as Pearls) because they are not affected by stomach acid. If you need to take antibiotics for any reason, it is wise to supplement with acidophilus or bifidus bacteria (taken at least two hours before or after the antibiotic) to replace helpful bacteria that have been destroyed. These friendly bacteria will keep the yeast under control during treatment.

#### *Fourth Step: Antifungal Treatments*

Prescription antifungal medications are normally recommended for intestinal Candida overgrowth. The most commonly prescribed drugs are nystatin and Diflucan. Nizoral, while effective, is used less often because of the potential for liver toxicity. Sporanox, another antifungal agent, is also used. Your doctor may recommend a 3- to 6-week trial to help determine which of your symptoms are yeast related.

Effective nonprescription antifungal agents include garlic (liquid, capsule, or fresh), olive leaf, caprylic acid, pau d'arco, and tea tree oil. These can be applied topically or taken orally (except for tea tree oil, which can only be applied topically). Grapefruit seed extract is also a potent antimicrobial agent, but is extremely caustic and should not be used by anyone with a sensitive stomach or esophagus. It can be purchased in health food stores and from nutritionists and some chiropractors. Monolaurin is effective against yeast, as well as bacteria and viruses.

Vaginal yeast infections should be treated with pharmaceuticals when they occur. Over-the-counter antifungal creams for vaginal infections can now be purchased, but many women still prefer prescription drugs for insurance reimbursement. The main problem that may arise from using vaginal creams, however, is allergic reaction (characterized by burning and itching). You may want to discuss some of the single-treatment options (such as Vagistat) with your gynecologist or other doctor if this is a problem.

Throat infections (thrush) can be treated with an oral nystatin preparation and with an adjunct of any kind of acid gargle (vinegar, lemon), because molds and fungus will not grow in an acid environment. If you can tolerate yogurt, a yogurt "swish" (around the mouth and down the throat) also helps.

#### *Fifth step: Supporting the immune system.*

The reason people with CFS/ME contract Candida overgrowth is because their immune systems are dysregulated. Some supplements have anti-inflammatory and immuno-regulatory effects. For people with Candida, the supplements most commonly recommended for this purpose include vitamin C, zinc, vitamin B complex, essential fatty acids (evening primrose oil, borage seed oil), and fish oil.

SEE: Antifungals; Essential Fatty Acids, Herbs, Minerals, Monolaurin, Probiotics, Vitamins.

#### MORE INFORMATION

*Very large Candida forum (36,000 members) which covers all topics related to*

*Candida.* [http://www.candidayeastthrushforum.com/view\\_forum.php?id=1](http://www.candidayeastthrushforum.com/view_forum.php?id=1)

*Patient threads discussing Candida:* <http://curezone.com/forums/f.asp?f=100041>

#### LABORATORY TESTS FOR CANDIDA

Genova Diagnostics

63 Zillkicia Street



Asheville, NC 28801  
USA  
Telephone: (800) 522-4762  
Local phone: (828) 253-0621  
Website: <http://www.gdx.net/>

### *Europe*

Genova Diagnostics  
Parkgate House  
356 West Barnes Lane  
New Malden  
Surrey  
KT3 6NB  
U.K.  
Phone: +44 (0)20 8336 7750  
Fax: +44 (0)20 8336 7751

### FURTHER READING

“Biological Treatments for Autism.”

<http://www.greatplainslaboratory.com/book/bk6sect2.html>

*This page contains extensive information about treating candidiasis.*

“Discovery of Genetic Pathways May Provide New Ways to Combat Candida Infections.” [http://www.wi.mit.edu/news/archives/1997/gf\\_0905.html](http://www.wi.mit.edu/news/archives/1997/gf_0905.html)

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## CARDIAC AND CARDIOVASCULAR SYMPTOMS/DYSAUTONOMIA

Blood Circulation; Dysautonomia, Orthostatic Intolerance, POTS, NMH, Shortness of Breath/Air Hunger

Because of the serious nature of heart problems, cardiac-related symptoms are among the most worrisome for patients with CFS/ME. Many patients with CFS/ME have chest pain, blood pressure fluctuations, and periodic increases in heart rate. Dr. Byron Hyde has noted that among his patients, and in many of the epidemic outbreaks of CFS/ME, cardiovascular problems tend to appear early in the illness—in the first month—and disappear by the third to twelfth month. In some cases, however, heart problems will either resurface or even appear for the first time after several years have passed.

Abnormalities such as premature atrial and ventricular contractions, increased tendency for mitral valve prolapse (especially in children), pericarditis, myocarditis, palpitations (skipped heart beats), tachycardia (rapid heartbeat), various arrhythmias, ectopic heart beats, edema (swelling in the hands and feet), nasal stuffiness (not due to allergies), and unusual readings from electrocardiography (ECG) or Holter monitoring are not unusual in the CFS/ME population. However, unlike many other CFS/ME symptoms, which are difficult to quantify, cardiac problems can be measured using standard tests.

In a revealing study conducted in 2002, a research team headed by cardiologist Dr. Arnold Peckerman found that people with CFS/ME have reduced cardiac output. The team tested 38 patients with CFS/ME for heart function using impedance cardiograms to provide measures of stroke volume and prejection period (the period between ventricular contraction and the opening of the semilunar valves, allowing blood flow into the aorta to begin). Heart rate was measured via an electrocardiograph.

The team also assessed severity of illness. Test results showed that patients with severe CFS/ME had significantly lower stroke volume and cardiac output than the controls and less ill patients. The authors proposed that in patients with

CFS/ME, “blood pressure is maintained at the cost of restricted flow, possibly resulting in a low flow circulatory state. Thus, there might be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes in at least some vascular compartments.”

The results of this study provide evidence of reduced cardiac output in people with CFS/ME. Reduced cardiac output would explain post-exertional fatigue, orthostatic intolerance, and a host of other CFS/ME symptoms. Periodic restrictions in blood flow would also account for the waxing and waning of symptoms that is typical of CFS/ME. The researchers concluded that their findings indicated that some cases of CFS/ME might be explained, and treated, as low circulation problems.

Dr. Cheney considers the Peckerman study to be “the best, most important publication in 20 years”—and with reason. For not only does the Peckerman study identify the source of fatigue, it provides an objective means of measuring illness severity. To a certain degree, the Peckerman study also accounts for the predominance of women in CFS/ME. Women have smaller blood vessels than men, which is why women also predominate in other microcirculatory disorders.

A second study by Peckerman et al pinpointed the source of low cardiac output and, in the process, explained the hallmark symptom of CFS/ME—exercise intolerance. The researchers measured the volumes of blood in the left ventricle (the heart’s main chamber) at the end of relaxation and at the end of contraction periods. (This is called the ejection fraction, or EF.) Normally the heart pumps more blood during exercise. When a group of 16 CFS/ME patients was compared to healthy controls before and after exercise, the researchers found that the hearts of 13 out of 16 CFS/ME patients actually pumped out *less* blood during and after exercise.

It is Dr. Cheney's firm belief that heart problems are fundamentally an energy problem, that is, they stem from decreased ATP production. Among CFS/ME patients, systolic function (the contraction required to pump blood out) is usually normal. However, the heart's ability to fill back up after blood is released (diastolic function) is reduced. Diastolic function is important, because in order to pump the blood out of the heart, there has to be blood to pump.

The cause of diastolic dysfunction is cellular energy impairment. Diastolic function requires significantly more ATP than systolic function, so when ATP is reduced the heart's ability to fill is reduced as well. Once the heart does not fill properly, a cascade of events is set into motion. Adrenaline is released, leading to sympathetic nervous system arousal, which leads to tachycardia, NMH, POTS, anxiety, and other autonomic symptoms. Eventually, the supply of adrenaline runs short, at which point the body attempts to compensate by tapping the digestive system for extra blood. This, in turn, leads to leaky gut, cognitive impairment, malaise, exhaustion, and the numerous other symptoms that comprise CFS/ME.

The incidence of heart-related problems is difficult to assess because there are no agencies collecting morbidity data on people diagnosed with CFS/ME. Dr. John Richardson, in his book, *Enteroviral and Toxin Mediated Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Other Organ Pathologies*, noted

that among his 1,783 patients with postviral syndromes (including CFS/ME), 20% went on to develop significant cardiac problems. Polio, as Dr. Richardson points out, produces a similar statistic. While the incidence of heart problems in CFS/ME may be hard to calculate, it is worth noting that mortality due to heart attacks in CFS/ME occurs much earlier than in the general population.

According to a 2006 mortality study conducted by Jason et al at DePaul University, the average age of heart failure among CFS/ME patients is 58.7 years. The national average is 83.1 years.

## BLOOD CIRCULATION

An important factor affecting the cardiovascular system is the composition of the blood itself. In 1996 Dr. Leslie O. Simpson, a New Zealand pathologist, discovered that the blood of people with CFS/ME tends to have a higher proportion of cup-shaped red blood cells. Cup-shaped cells are more difficult to squeeze through small capillaries than disc-shaped cells, making it harder for blood to oxygenate capillary-dependent tissues. Dr. Simpson observed that blood cell shapes can vary from minute to minute, and can be affected by many factors, including even small muscle activity, which might account for some of the highly localized variability of CFS/ME symptoms.

A later study conducted in 2000 by Richards et al found further red blood cell abnormalities in CFS/ME patients, notably an increase in methemoglobin (pronounced “met-hemoglobin”). Methemoglobin is a form of hemoglobin in which the iron has been altered, resulting in blood that cannot release oxygen. Unlike the characteristic bright red of hemoglobin, methemoglobin is a bluish brown in color. Normally, only one to two percent of hemoglobin is composed of methemoglobin; a higher percentage can cause significant health problems. When methemoglobin comprises 10% of the blood, a person exhibits cyanosis, a bluish tinge to the skin. Higher levels (20%) can cause shortness of breath, anxiety, and headache. Once the levels reach 70%, death ensues.

In the Richards study, methemoglobin was found to be the major component associated with variation in symptom expression in CFS/ME patients, including fatigue, musculoskeletal symptoms, pain and sleep disturbance. Variation in levels of malondialdehyde and 2,3-diphosphoglycerate, which are both indicators of oxidative stress in the blood, were associated with cognitive symptoms and sleep disturbance. Though the authors were not able to determine whether these abnormalities were the cause or simply an effect of CFS/ME, there can be no doubt that these abnormalities, or the underlying mechanism that causes them, are closely linked to CFS/ME symptoms.

In related research, Berg et al found that the blood of CFS/ME and FM patients had increased viscosity. When a person is infected with viral or bacterial pathogens (e.g., HHV-6, CMV, rickettsia) the membranes of healthy cells are damaged. This exposes phosphatidyl serine, a lipid on the inner layer of the cell membrane. The exposure of phosphatidyl serine activates immune system antibodies, which increase blood coagulability.

Under normal circumstances, this process is self-regulating, but in some people a hypercoagulable state persists, and the blood remains in a highly viscous state, reducing blood flow through capillaries and decreasing oxygen supply to tissues. Berg et al proposed that the pathogenesis of CFS/ME is a persistent hypercoagulable state, due perhaps to a genetic deficiency. Much like the mechanisms proposed by Simpson and Richards, the resulting hypoxia could produce all the symptoms typical of CFS/ME.

Hypercoagulability of the blood has been proposed as a primary CFS/ME mechanism for a subset of patients. Ken Lassen, an employee of Microsoft who contracted CFS/ME in 1999, has explored the possibility that CFS/ME, for at least some patients, is actually a variation of Hughes Syndrome, or Antiphospholipid Antibody Syndrome, an illness which causes abnormal blood clotting. The symptoms of Hughes Syndrome bear a striking resemblance to those of CFS/ME: headache or migraines, memory impairment, GI disorders, visual disturbances, MS-like symptoms, cardiac problems. All of these, of course, can be explained by low oxygenation due to poor circulation.

Throughout history, a plethora of conditions has been attributed to poor circulation. In a truly fascinating meeting of East and West, Kenneth Jones has linked CFS/ME to the Japanese blood disorder known as “Oketsu Syndrome.” Oketsu is a traditional concept in Asian medicine, often described as “sluggish” or “stagnant” blood.

Oketsu produces a broad array of symptoms, including allergies, vision problems, insomnia, sensitivities, psychological disturbances, reproductive disorders, skin and nail problems, neck stiffness, back and shoulder pain, headache, thirst and dry mouth, gastritis, GI problems and weakness.

Japanese researchers have long attempted to find a correlation in Western medicine to Oketsu, the closest match being a vascular clotting problem (somewhat similar to Hughes Syndrome). Significantly, Oketsu has been associated with an upregulation of the sympathetic nervous system, which is a persistent finding in CFS/ME patients.

Herbal combinations used to treat Oketsu are designed to increase blood flow, but they have several other functions. In a study by Shimada et al, Keishibukuryo-gan, an Oketsu treatment, inhibited nitric oxide-generated neuronal damage induced by brain ischemia (hypoxia).

Given the overlap in symptomatology, Jones has suggested that Oketsu treatments might be useful for treating CFS/ME. Oketsu treatments would involve herbs with blood thinning and neuroprotective properties (e.g., cinnamon, *Fu-ling*, peony, *prunus persica*). It is important to note that many CFS/ME patients have reported an improvement of symptoms after taking blood thinners.

#### FURTHER READING

“Cardiac Insufficiency.” <http://www.medicalinsider.com/cardiac1.html>

*This page contains everything you ever wanted to know about cardiac insufficiency in CFS/ME, including drawings, links to research, discussion of the*

*different types of cardiac insufficiency, and commentary. Dr. Cheney's views are discussed in detail.*

“Tissue Oxygenation and CFS.”

<http://www.medicalinsider.com/cardiac2.html#hypocapnia>

*More on blood flow and oxygenation from the Medical Insider.*

“Tricky Heart May Cause ME/CFS.” Daniel DeNoon, reviewed By Michael Smith, MD.: <http://www.cfids-cab.org/MESA/cardiac.html>

*Good article explaining Dr. Peckerman's research.*

“In Some Patients With Chronic Fatigue Syndrome (CFS), Left Ventricular Function May Be At The Heart Of The Matter.” Press release. *American Physiological Society*. April 9, 2003:

<http://www.prohealth.com/library/showarticle.cfm?libid=9624>

*Three-hour presentation by Dr. Cheney given in Dallas, Texas, in which he discusses cardiac problems at length:* [http://www.cfids-](http://www.cfids-cab.org/MESA/CFS_Dist.htm)

[cab.org/MESA/CFS\\_Dist.htm](http://www.cfids-cab.org/MESA/CFS_Dist.htm)

*This video is a must-watch for understanding heart problems in CFS/ME.*

“CFS is Heart Failure Secondary to Mitochondrial Malfunction.” Dr. Sarah Myhill

<http://www.cfids-cab.org/MESA/DrMyhill-373.pdf>

“Research on Red Blood Cell Shape & CFS.”

<http://www.anapsid.org/cnd/diagnosis/redcells.html>

*This is a good summary of L.O. Simpson's research.*

*How blood circulation works in the body.*

[http://www.tutorvista.com/content/biology/biology-](http://www.tutorvista.com/content/biology/biology-ii/transportation/circulation.php#hepatic-portal)

[ii/transportation/circulation.php#hepatic-portal](http://www.tutorvista.com/content/biology/biology-ii/transportation/circulation.php#hepatic-portal)

*General information about Hughes Syndrome:* [http://www.hughes-](http://www.hughes-syndrome.org/symptoms.htm)

[syndrome.org/symptoms.htm](http://www.hughes-syndrome.org/symptoms.htm)

*Ken Lassesen on Hughes Syndrome, hypercoagulation and CFS/ME.*

<http://lassesen.com/cfids/familyhistory.htm>

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## DYSAUTONOMIA

What causes cardiac symptoms? As with many other simple questions regarding CFS/ME, there is a complicated answer. In the case of most cardiovascular symptoms, signs point to dysautonomia, which is an umbrella term covering a number of neurologically related conditions, including postural orthostatic tachycardia syndrome (POTS), vasovagal syncope, neurally mediated hypotension (NMH), orthostatic intolerance (OI), pure autonomic failure (PAF), multiple systems atrophy (MSA), and Ehlers-Danlos syndrome. In CFS/ME, the

most common forms of dysautonomia are orthostatic intolerance and neurally mediated hypotension (NMH).

In simple terms, dysautonomia is a dysregulation of the autonomic nervous system. This dysregulation can be caused by direct interference with autonomic regulation in the hypothalamus by toxins, oxidative stress, illness, or injury, or indirectly, by the cascade of catecholamines triggered by diastolic insufficiency. In either case, the cardiovascular system will be affected.

The autonomic nervous system is comprised of the sympathetic and parasympathetic nervous systems, which, because they have opposing effects, must be coordinated in order for the body to function properly. The sympathetic nervous system, which is stimulated by norepinephrine (noradrenaline), controls “fight or flight” responses. These responses include increased heart rate, sweating, increased blood flow to the large muscle groups (in preparation for running), and rapid breathing (to increase oxygen).

The parasympathetic system, which is regulated by acetylcholine, controls the basic resting functions of the body: digestion, elimination, procreation. Normally, the two systems complement one another. For example, after the sympathetic nervous system increases heart rate, the parasympathetic system slows it down. When the two systems are not balanced, the autonomic nervous system either sends mixed signals, or too much of one type of signal.

Typical symptoms produced by dysautonomia are: tachycardia (fast heart rate), shortness of breath, anxiety, migraines, chest pain, bradycardia (slow heart rate), low blood pressure, orthostatic intolerance (inability to remain upright), nausea, insomnia, dizziness, blood pressure swings, frequent urination, thirst, visual blurring, GI problems, exercise intolerance, and fatigue.

Considering the fact that nearly all CFS/ME patients demonstrate some form of orthostatic intolerance (96% by some estimates), it is reasonable to assume that a dysregulation of the autonomic nervous system lies behind most cardiovascular symptoms in CFS/ME. The symptoms of dysautonomia are so prevalent in CFS/ME patients that some researchers have proposed that CFS/ME patients possess their own form of dysautonomia which may be diagnostic of the illness. In fact, there may be, at this point, sufficient cumulative evidence to support the idea that CFS/ME actually *is* a form of dysautonomia.

In 2002 a group of Israeli scientists developed a method for distinguishing CFS/ME from other similar or overlapping illnesses on the basis of dysautonomia alone. They used the tilt table test to assess blood pressure and heart rate, which they then computed, using a set of 52 variables, into a “haemodynamic instability score (HIS)”. Using this score the researchers were able to distinguish between patients with fibromyalgia, non-CFS/ME chronic fatigue, syncope, familial Mediterranean fever (which causes dysautonomia), hypertension, anxiety disorders and healthy controls. Their results suggested that a definable autonomic dysfunction characteristic of CFS/ME may exist. The group concluded that “the presence of this distinctive dysautonomia in CFS, which is not usually observed in



other fatigue syndromes, lends support to the concept that CFS is a separate entity among illnesses characterized by fatigue.”

Dr. Luis Leon-Sotomayor, the cardiologist who documented the 1965 CFS/ME epidemic in Galveston, Texas, described a type of neurological dysfunction that he called a "sensory storm." These storms produced sweating, pallor or flushing, elevated blood pressure, slowed respiratory rate, tachycardia, dizziness, and the feeling that one was about to lose consciousness. After the experience, a person would feel lingering tiredness or malaise.

Dr. Leon-Sotomayor's "sensory storm" bears a striking resemblance to the autonomic crisis, or "autonomic storm" experienced by children with familial dysautonomia, an inherited condition characterized by overwhelming sympathetic nervous system arousal. The symptoms of the autonomic crises of this genetic condition are, in fact, identical to the CFS/ME "sensory storm": sweating, pallor or flushing, hypertension, tachycardia, retching, vomiting, anxiety, and a general overwhelming feeling of discomfort.

At the time that Dr. Leon-Sotomayor documented the 1965 CFS/ME epidemic, research on dysautonomia was, charitably speaking, scant. If there had been more available published research, he may have recognized the similarity between the two disorders, which would have undoubtedly advanced our understanding of CFS/ME by several decades. As it is, we must give credit where credit is due, and acknowledge the importance of Dr. Leon-Sotomayor's contribution.

## MORE INFORMATION

National Dysautonomia Research Foundation.

Website: <http://www.ndrf.org/>

*The NDRF maintains an excellent website with detailed information on various disorders of the autonomic nervous system, as well as research, reference materials, forums, and a list of doctors who treat problems related to dysautonomia.*

Dysautonomia Information Network

Website: <http://www.dinet.org/>

*DINET provides a wealth of information about different forms of dysautonomia. An excellent resource.*

*List of doctors who treat OI: <http://www.ndrf.org/physicia.htm>*

*Resource page for OI and chronic illnesses. Includes research, list of doctors, articles, and much more. <http://www.chronic-illness.org/blog/postural-tachycardia-syndrome-pots>*

## FURTHER READING

“Tilt-Test Formula: A Diagnostic Marker for CFS?” *CFIDS Chronicle* Spring 2003.

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*This is a good overview of the research conducted by Naschitz et al. Includes an interview.*

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<http://www.ncbi.nlm.nih.gov/pubmed/12528078> (Abstract)

## ORTHOSTATIC INTOLERANCE

Orthostatic intolerance (OI) is a broad classification within dysautonomia that refers to exaggerated blood pressure and/or heart rate responses that occur when standing up. When a healthy person stands up, the effects of gravity cause about 10-15% of the blood to settle (pool) in the abdomen, legs, and arms. To make up for the lower amount of blood returning to the heart, the body releases adrenaline and noradrenaline (epinephrine and norepinephrine), which cause the heart to beat a little faster and blood vessels to constrict. This can be measured as an increase in heart rate of 10 to 15 beats per minute, accompanied by an increase in diastolic pressure (resting pressure, the lower number) of 10 mmHg, and a very slight change in systolic pressure (pumping pressure, the upper number). This slight change, which is enough to guarantee that the heart has filled properly, triggers a complementary response from the parasympathetic nervous system, returning the body to normal parameters. Altogether, it takes roughly a minute for the body to stabilize.

People with OI have reversed responses to changes in position. When people with OI stand up, they pool a larger amount of blood in regions below the heart. Moreover, the longer they remain upright, the more blood pools in their abdomen and legs. The adrenal glands respond by releasing more adrenaline and noradrenaline in an attempt to cause constriction of the blood vessels and boost cardiac output. However, the blood vessels do not constrict enough to ensure increased back flow into the heart, and, due to the effects of adrenaline (combined

with inadequate filling), the heart races. This, in turn, leads to a lower blood volume (hypovolemia) which exacerbates the problem and perpetuates the cycle. The ill effects produced by this loop—fatigue, nausea, light-headedness, heart palpitations, sweating, and sometimes fainting (syncope)—are the net result of a combination of excess adrenaline and low cardiac output.

There appears to be a genetic component to OI. This is not to say that the condition itself is inherited, but that when a certain gene is activated, the condition may develop. The gene in question is a mutation of the gene encoding the norepinephrine transporter (SLC6A2; 163970).

In a study published in the *New England Journal of Medicine* in 2000, a group of researchers at Vanderbilt University's Autonomic Dysfunction Center examined a patient with orthostatic intolerance (along with her family) and compared her to controls. They found that a mutation in exon 9 (encoding a change from guanine to cytosine at position 237) resulted in more than a 98 percent loss of function. The abnormal gene caused an inability to clear norepinephrine from the system, resulting in excessive sympathetic activation in response to physiological stimuli. As chronic sympathetic activation is characteristic among patients with CFS/ME, it may very well turn out that this mutant gene is one of the “movers and shakers” of this illness.

The simplest means of measuring OI is to simply take blood pressure and heart rate measurements while a person is sitting (or lying), and then again after he or she stands up at periodic intervals over the course of an hour (or for as long as the patient can tolerate standing still). This is easy to do, and requires no fancy equipment, but most doctors are unwilling to spend the time required to do a long test. (A nurse could take the measurements, but staff is usually too busy as well.) In addition, there are no set standards for how long to wait before taking measurements, or how many measurements to take.

The most commonly used test for OI is the head-upright tilt (HUT) test. During the HUT test, the patient is strapped to a flat table. Then, after a period of rest, the table is tilted up at roughly 60-70° from the horizontal position for 10-45 minutes. (The reason the table does not come completely upright is that some people, especially adolescents, without OI will faint.) This mimics the act of standing, while keeping the patient still long enough to take various measurements. At present, this is the “gold standard” for OI testing.

Research concerning OI in CFS/ME patients has been mixed, with some studies finding a pronounced degree of orthostatic intolerance among CFS/ME patients, and others finding no significant differences between patients and controls. However, even those studies finding no appreciable difference in heart rate or blood pressure tend to find other related conditions.

A 2007 investigation headed by Dr. Benjamin Natelson was one such study. Dr. Natelson's group found no cardiac differences between controls and CFS/ME patients that would be indicative of OI. What is noteworthy about this study is not what they what they did not find, but what they did. Over 20% of the 75 CFS/ME patients had hypocapnia (low plasma levels of CO<sub>2</sub>) compared to 2.9% of the

controls. Moreover, plasma CO<sub>2</sub> levels were sustained and progressive upon standing. Dr. Natelson's group had only two explanations for this unusual finding, either the patients were hyperventilating, or the venous return to the right side of the heart was inadequate. The group concluded that the increase in CO<sub>2</sub> was due to hyperventilation, but was confused as to why. They came up with a working hypothesis that hypocapnia in CFS/ME was due to a complex interaction between the baroreflex, chemoreceptors, and thoracic blood volume.

Dr. Natelson's findings did not make a big splash in the CFS/ME community, perhaps because the researchers themselves were somewhat perplexed. However, the study results are, in fact, significant. The symptoms of hypocapnia – dizziness, shortness of breath, chest pain, heartbeat irregularities, anxiety, pins and needles in the face and hands, numbness in hands and feet, and fainting – can be disabling in CFS/ME patients. Natelson's group provides an explanation for these symptoms, which, as the researchers point out, are susceptible to treatment.

#### FURTHER READING

“General Information Brochure on Orthostatic Intolerance and its Treatment.”

Chronic Fatigue Clinic Johns Hopkins Children’s Center, June 2010:

<http://www.cfids.org/webinar/cfsinfo2010.pdf>

*This is clearly presented information about OI, with definitions, clinical parameters, and mechanisms.*

“Orthostatic Intolerance.” Julian M Stewart, MD, PhD:

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*Very thorough article on all forms of OI, including testing, diagnosis, and different varieties of OI.*

“Diagnosis: Orthostatic Intolerance (OI).” <http://www.cfids.org/about-cfids/orthostatic-intolerance.asp>

*A concise description of different types of OI in CFS/ME patients from the CFIDS Association of America.*

"The Outs and Ins of OI." <http://www.research1st.com/2011/06/19/the-outs-and-ins-of-oi/>

*Excellent article by Kimberly McCleary on orthostatic intolerance in CFS/ME patients.*

“Orthostatic Intolerance (OI) Test Results.” David Bell. *Lyndonville News*. May 2000 Volume 2 Issue 3 <http://www.oiresource.com/tresults.htm>

*This is Dr. Bell's concise discussion of OI disorders. Includes a research review.*

“The Perils of Standing: Treating Orthostatic Intolerance in Chronic Fatigue Syndrome (ME/CFS).”

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*Cort Johnson's article on OI in CFS/ME patients.*

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*A continuation of the previous article, in which Cort Johnson organizes the different subtypes of OI as they relate to CFS/ME. Includes a thorough discussion of symptoms and causes.*

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*An excellent summary of the role of hypovolemia in CFS/ME.*

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*A summary of Dr. Cheney's thoughts on how to increase blood volume.*

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## POTS/TACHYCARDIA

Postural tachycardia syndrome (POTS) is an exaggerated increase in heart rate (tachycardia) upon standing. Healthy people have a slight increase in heart rate (roughly 10-15 beats per minute) within the first ten minutes of standing. When there is a rise in heart rate of 30 beats per minute (bpm), or if the heart rate exceeds 120 beats per minute, a diagnosis of POTS can be made.

Heart rate increases can occur at random or follow fairly regular patterns. Tachycardia appears to be greatest in the morning after blood has pooled during the night. Surges in heart rate can also occur after exercise, lifting, and, in the severely ill, even sitting up or changing position in bed can cause an increase in heart rate.

According to Dr. Julian Stewart, director of the Center for Hypotension at the New York Medical College, "orthostatic intolerance in most adolescents (and many adults) with CFS appears to be POTS." Dr. Stewart has found that his CFS/ME patients exhibit more signs and symptoms of POTS than all other forms of orthostatic intolerance, including NMH (which Dr. Stewart believes is actually a form of POTS). However, as Dr. Stewart points out, the subclassifications of orthostatic intolerance are fuzzy at best, as they all share the same essential characteristics.

Symptoms of POTS include fatigue, palpitations, exercise intolerance, dizziness, headache, nausea, loss of concentration, light-headedness, and sometimes fainting. Anxiety, caused by the release of adrenaline, is a prominent symptom and often leads to a misdiagnosis of generalized anxiety disorder. Reactive hypoglycemia is a common problem for POTS patients, which can often delay the diagnosis, as the symptoms of hypoglycemia are virtually indistinguishable from symptoms induced by heart rate and blood pressure alterations.

Coldness and numbness in the hands and feet are common symptoms of POTS. It is not unusual for people with POTS to wake up with completely numb legs, arms or hands. Patients report sporadic itchiness, and burning and tingling sensations all over the body, especially at night. Some patients may experience reduced sweating. In the Mayo Clinic review of 157 patients with POTS, half of the patients had abnormalities in sweat gland responses (as measured by thermoregulatory sweat tests).

POTS is an abnormality in the regulation of heart rate; the heart itself is usually normal. Studies by the Center for Hypotension of New York Medical College seem to confirm that theory that POTS is caused by an inadequate cardiac venous return during orthostasis. In other words, not enough blood flows back into the heart when a person with POTS stands up, causing the heart to beat faster. Some patients with increased heart rate but normal blood pressure in the first ten minutes of upright standing (or tilt table testing) will go on to develop a drop in blood pressure (NMH) if the test is continued; the two conditions often are found together, and they are not mutually exclusive diagnoses.

Hypovolemia plays a significant role in POTS. Studies by the Center for Hypotension of New York Medical College seems to confirm that POTS is related to inadequate cardiac venous return during orthostasis. This lowered blood return could theoretically be caused by low blood volume. However, the Mayo Clinic found that low blood volume, which is often associated with POTS, was not causative but was likely compensatory (or exacerbating). It turns out that the cholinergic responses to reduced back flow to the heart (increased adrenaline), are also responsible for producing or perpetuating low blood volume, which, in turn, exacerbates POTS.

As with many cardiovascular problems, there are different types of POTS. The primary form of POTS is “partial dysautonomia” (PD), or neuropathic POTS, which is thought to be a problem of the peripheral nervous system. People with this form of POTS experience a much greater than normal degree of blood pooling in the legs, lower arms, and abdomen while upright. PD usually comes on abruptly after a viral illness, surgery, pregnancy or trauma. There is a roughly a five to one female to male ratio in this form of POTS.

A second form of POTS, hyperadrenergic POTS, is caused by centrally mediated increases in norepinephrine or a decrease in uptake. Typical symptoms include tremor, anxiety, cold sweaty extremities when upright, increase in urinary output and migraine headaches. Like other forms of OI, dizziness and faintness predominate. A study conducted by Kanjwal et al at the University of Toledo Medical Center in Toledo Ohio, reported digestive disturbances in 30% of their hyperadrenergic POTS patients, including diarrhea, nausea and bloating. This form of POTS comes on gradually, and is difficult to treat. Most people with CFS/ME will fall into this subgroup.

In addition to these subgroups, there are also three types of POTS that can be characterized by peripheral blood flow. These are the low-flow, normal-flow and high-flow forms of POTS. Low-flow POTS is characterized by mild hypovolemia and general decreased regional blood flows in the limbs and skin. This is due to a reduced release of nitric oxide. (Nitric oxide is a vasodilator). Symptoms are pallor, cool skin, and resting tachycardia. High-flow POTS is characterized by normal blood volume and peripheral vasodilation, causing a flushed appearance and warm skin. This form of POTS is primarily associated with post-viral peripheral neuropathy.

Normal-flow POTS is characterized by normal blood volume, normal resting heart rate, but abnormal pooling in the abdomen when upright. This type of POTS is associated with patients who fulfill the criteria for the Ehlers-Danlos Syndrome. Most people with CFS/ME fall into the first grouping: low-flow POTS.

There appears to be immune involvement in many cases of POTS. Some patients with POTS have episodic flushing, typically in the face and hands. In about half of these cases there is an associated mast cell activation disorder. Mast cell activation results in the release of histamine and prostaglandin 2, which are a vasodilators. (People with CFS/ME have been shown to experience histamine intolerance, and prostaglandin 2 has been implicated in fibromyalgia pain.) Mast cell activation can be diagnosed by collecting urine from 2-4 hour voids following a

severe flushing spell for determination of methylhistamines. A review of 152 patients treated at the Mayo Clinic for POTS found that there was a neuropathic basis for at least half the cases of POTS, and that a substantial percentage of cases may have been autoimmune.

Finally, as with all ailments, there is a genetic component to POTS. Garland et al, at Vanderbilt's renowned Autonomic Dysfunction Center in Nashville Tennessee, found that a genetic polymorphisms affecting enzyme activity, particularly nitric oxide-mediated (NO) functions, may increase the risk of developing POTS. The researchers developed their hypothesis based on evidence that these genetic polymorphisms have been associated with a number of cardiovascular diseases. Patients with these gene abnormalities experienced the largest changes in heart rate and plasma norepinephrine upon standing. The team concluded that "NO may influence the development of POTS and the severity of POTS symptoms."

Research suggests that POTS is underdiagnosed in people with CFS/ME. In a 2008 study conducted by Hoad et al in Great Britain, 27% of the group with CFS/ME had POTS, as compared with 9% of the control population. The Center for Hypotension of New York Medical College found that POTS was the basis for orthostatic intolerance in a large majority of adolescents with CFS/ME. The implication of these findings is that POTS may serve as a basic mechanism for a significant subgroup of the CFS/ME population, especially adolescents.

#### MORE INFORMATION

*Wikipedia-style website that allows you to jump to detailed information on causes, treatments, symptoms, and related disorders. Very useful:*

[http://www.bean.dreab.com/p-Postural\\_orthostatic\\_tachycardia\\_syndrome](http://www.bean.dreab.com/p-Postural_orthostatic_tachycardia_syndrome)

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*This is an excellent summary. Start here.*

"Postural tachycardia syndrome (POTS)."

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*Good general description of POTS.*

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## ORTHOSTATIC HYPOTENSION/NMH

Abrupt decreases in blood pressure, occasionally manifested as "blackouts" or periods of sudden faintness, are quite common in patients with CFS/ME. Dr. Luis

Leon-Sotomayor, the cardiologist who recorded the 1965 CFS/ME epidemic in Galveston, Texas, observed that hypotension was common in his patients with CFS/ME, particularly after activity or upon standing. (Normally, blood pressure rises after standing.) The apparent dysregulation of blood pressure in CFS/ME is not, as it would appear, directly connected to cardiac problems but is the result of hypothalamic dysfunction. The hypothalamus, among its many other functions, is responsible for maintaining arterial pressure.

Studies performed at Johns Hopkins University have confirmed Dr. Leon-Sotomayor's observations. The Johns Hopkins researchers concluded that some patients with CFS/ME have a condition known as neurally mediated hypotension (NMH) (*Lancet*, 1995). The condition is characterized by light-headedness, and fainting (syncope). NMH represents a flaw in neuroendocrine coordination. Normally when blood pressure falls, the brain sends a signal for the adrenal glands to release adrenaline (epinephrine). The adrenaline signals the heart to beat more vigorously, raising blood pressure. Once the heart rate increases and blood pressure is restored, the nerves within the left ventricle send a message to the brain that blood pressure is too high and the brain, in turn, sends a signal to lower blood pressure.

In people with NMH, this well-coordinated system for maintaining blood pressure goes awry. People with NMH have low blood pressure, causing blood to settle, or pool, in the lower extremities. When the heart starts to beat more vigorously to compensate, the nerves in the left ventricle send the erroneous message that pressure is already too high, forcing blood pressure to drop even farther. The result is feeling light-headed. In people with NMH, any sudden release of adrenaline can produce the same result, which is why they may feel faint at the sight of blood or after receiving bad news.

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## SHORTNESS OF BREATH/AIR HUNGER

Shortness of breath, particularly after exertion, is common in patients with CFS/ME, although many people experience the phenomenon of "air hunger" even if they are not moving; it is not uncommon to wake up with it. In CFS/ME, this phenomenon is directly related to cardiovascular problems. When people with CFS/ME exercise, the heart does not speed up quickly enough to meet the extra demands placed on it. Although the body's need for oxygen is increased, the heart fails to deliver. The result is chest pain and shortness of breath. In severe illness, even getting out of bed too quickly can produce this effect.

Air hunger is a characteristic symptom of the cardiac problems caused by dysautonomia. Reduced blood flow means reduced oxygen, which the body attempts to compensate for by chest breathing. While this is a good means of increasing oxygen supply rapidly, it can lead to hyperventilation. The reduction in CO<sub>2</sub> levels in the blood, known as hypocapnia, can cause reduced oxygenation in the brain. Symptoms of hyperventilation include tingling in the fingers or the face, palpitations, hot or cold sensations, light-headedness, and dizziness.

In 2006 Naschitz et al found that an upright position was enough to produce hyperventilation in CFS/ME patients. In fact, even while lying down, fourteen patients showed signs of hypocapnia. The researchers found that sustained hypocapnia lasting 10 minutes or more, in the absence of hypotension or POTS, was most frequent in CFS patients. While the authors did not conclude that hypocapnia was a causative factor, the remarkable correlation between sustained hypocapnia and CFS/ME would seem to support studies that indicate brain hypoperfusion.

While a number of people have suggested that diaphragmic breathing can correct this problem, in point of fact, chest breathing in this case is not under voluntary control. It is a compensatory response to insufficient oxygen. Attempts to regulate it by altering breathing patterns are not usually successful. In most cases, reclining if you are upright, or, if you are already lying down, shifting to the right side will help alleviate symptoms. Bag breathing (breathing into a paper bag) can provide short-term alleviation, especially if symptoms include anxiety or panic. Rebreathing exhaled CO<sub>2</sub> helps restore the proper pH balance in the blood.

Anyone with a history of heart problems needs to be conscientious about following up on cardiac symptoms, including shortness of breath. If symptoms are severe or persistent, wearing a Holter monitor for a day or having a test for mitral valve prolapse may be recommended. Inasmuch as many of the symptoms produced by mitral valve prolapse (breathlessness, fatigue, edema) are commonly found in CFS/ME, your doctor may wish to investigate the possibility of mitral valve prolapse just to be on the safe side.

## FURTHER READING

*Informative patient thread on air hunger:*

<http://forums.phoenixrising.me/index.php?threads/shallow-infrequent-breathing.15808/page-2>

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## TREATMENTS

The first-line treatment for OI is to increase fluid intake along with salt intake, which has the effect of increasing blood volume. Four or more grams of salt a day are recommended. (That's a little over half a teaspoon.) For those who find it difficult to increase dietary salt, Thermotabs, which are composed of sodium and potassium chloride, or regular salt tablets should be taken. These can be hard on the stomach, so take them with a little food. (Too many Thermotabs can cause dehydration, so use in moderation.)

Isotonic fluids (electrolytes) are more effective than water for increasing blood volume. In fact, drinking excessive amounts of water will only exacerbate hypovolemia, as too much water will wash electrolytes out of your system.

Electrolyte solutions, such as E-Lyte, can be purchased online or at sports stores. (Gatorade and other commercial sports drinks usually contain large quantities of sugar, which is not recommended for CFS/ME patients.) An equivalent home brew can be made by mixing ¼ tsp of table salt and ¼ tsp of salt substitute (potassium chloride) into two cups of water. Dr. Cheney recommends adding ¼ tsp of buffered vitamin C (which contains magnesium carbonate, calcium carbonate, and potassium carbonate). Drink 4-6 cups early in the day.

Because cortisol and aldosterone, which are important for fluid retention, drop over the course of the day, your ability to hold fluids drops as well. (In other words, if you drink this “home brew” late in the day, you'll be going to the bathroom all night.) To increase blood volume, it is best to “guzzle.” Doctors recommend rapidly drinking two 8-oz glasses of water to expand plasma volume. This can increase standing systolic pressure by more than 20 mmHg for two hours. (This is an excellent technique to use before shopping.)

As a stop-gap measure for severe cases, IV saline drips can be used to raise blood volume quickly. A saline drip needs to be administered by medical personnel,

so a doctor must order it. Dr. Bell, who was the first CFS/ME doctor to seriously investigate orthostatic intolerance, used saline drips quite successfully in his practice. In the November 1, 2006 issue of the *Lyndonville News*, Dr. Bell unequivocally states that IV saline is “the most effective treatment for severe ME/CFS that I have found in my 21 years of looking.” To be most effective, a liter of saline should be administered over the course of an hour or two. Not all patients respond.

Compression stockings are usually recommended for treating OI. These prevent pooling in the legs by literally squeezing the blood back up into the torso. Unlike regular pantyhose, the pressure in compression stockings is graded. The highest pressure is at the ankles, and the lowest pressure is at the top. To be effective, the stockings must at least reach the groin. Thigh-high and waist-high stockings, which doctors recommend, can be purchased at medical supply stores and, more inexpensively, online. For people with severe OI, waist high compression stockings (which not only compress the legs but the lower abdomen as well) are a necessity.

Doctors recommend firm compression (30-40 mmHg weight) stockings, although many patients find these a chore to put on. Starting with lower weight thigh-high stockings (20-30 mmHg), or even regular support hose, may be the best way to ease into higher weights. Good brands are Jobst, Sigvaris, Juzo, and Mediven. Compression hose can be expensive (\$30-\$45 a pair), but they will last a long time if properly cared for. (You cannot throw them in the washing machine.) In an interesting study published in 2000, Dr. Bell and Dr. Streeten discovered that military antishock trousers (45 mmHg) restored all orthostatic measurements to normal within ten minutes in CFS/ME patients with orthostatic intolerance – of any type.

Very mild exercise, such as walking, or even flexing the leg muscles while in bed, can help increase blood volume. In his 2006 lecture in Dallas, Dr. Cheney pointed out that while lying down can increase cardiac output by 33%, so can simply shifting from foot to foot while standing. Keep in mind that physicians universally recommend restricting vigorous aerobic exercise for patients with all forms of cardiac problems until symptoms abate.

Three nutritional supports noted for strengthening and improving heart function are CoQ10 (or ubiquinol), acetyl-L-carnitine and omega-3 essential fatty acids. Each one of these has powerful antioxidant and energy-promoting effects; they will help increase the amount of ATP available to heart muscle. D-Ribose can also help increase ATP production. Vitamin B12 increases disc-shaped red blood cells, which will help microcirculation. The antioxidant alpha lipoic acid reduces oxidative stress in both blood and tissues, which can help reduce the amount of methemoglobin produced in the bloodstream. Magnesium is enormously helpful for all forms of cardiovascular problems.

Herbs that have been shown to have a beneficial effect on cardiovascular problems are licorice, hawthorn and butcher's broom. Licorice extract has been shown to increase fluid retention in a manner similar to cortisol. It can be taken in

lieu of Florinef – with the same precautions. Butcher's broom (*ruscus aculeatus*) has vasoconstrictive and venotonic properties which make it well suited to treat pooling in the limbs and low blood pressure characteristic of NMH.

Hawthorn is a traditional herbal remedy, similar in chemical makeup to digoxin (digitalis). Hawthorn increases the pumping function of the heart, resulting in improved filling. Because hawthorn is already in wide use, there have been numerous studies on its effectiveness. Recently, the Cochrane Collaboration analyzed 14 of these studies for scientific rigor and concluded that “there is a significant benefit in symptom control and physiologic outcomes from hawthorn extract as an adjunctive treatment for chronic heart failure.”

Pharmaceutical treatment for OI revolves around drugs that either regulate heart rate (beta blockers: propranolol, atenolol, metoprolol) or that increase blood volume (Florinef). Due to potential serious side effects, beta blockers are given in low doses. While some patients have improved with Florinef, it has fared no better than placebo in randomized trials.

Midodrine (an alpha-1 agonist), which one study has shown to be an effective treatment, may be prescribed for NMH. However, as it is an anti-hypotensive drug midodrine is not recommended for patients with normal or high blood pressure. Calcium channel blockers are sometimes prescribed as well.

Pyridostigmine, an acetylcholinesterase inhibitor, can help stabilize heart rate by increasing the amount of synaptic acetylcholine. (Acetylcholine is the primary neurotransmitter associated with parasympathetic activity; it slows the heart.) Pyridostigmine increases bowel motility, so it is not well tolerated among patients prone to diarrhea. Clonidine, an alpha-2 agonist, also acts to decrease sympathetic nervous system activity. Predictably, common side effects are drowsiness, fatigue and brain fog.

Erythropoietin (marketed as Epogen), the hormone that regulates red blood cell production, is sometimes prescribed when other drug treatments have failed. In addition to stimulating red blood cell production, Epogen has a direct vasoconstrictive effect, possibly through enhanced nitric oxide scavenging by red blood cells. The high doses of Epogen that have been prescribed for patients with kidney disease have resulted in an increase in heart attack and stroke. As a consequence, the FDA has recommended that only the smallest doses of Epogen be used.

“Sensory storms,” or autonomic crises, constitute a profound problem for CFS/ME patients during acute onset and during relapses. Pharmaceuticals that have been used traditionally to treat autonomic crises are CNS depressants, such as benzodiazepines (e.g., clonazepam). These have the effect of down regulating the entire nervous system. More recently, a study has shown that the anticonvulsant pregabalin (trade name, Lyrica), is effective for treating autonomic crises. Lyrica is one of the few drugs that has been formally approved by the FDA for treating fibromyalgia.

There are significant potential side effects associated with all drugs prescribed for cardiovascular problems, which means it is essential that patients taking pharmaceuticals for cardiac problems be closely monitored by a physician.

SEE: Anticonvulsants, Beta Blockers, Calcium Channel Blockers, Florinef: Alpha Lipoic Acid, CoQ10, Essential Fatty Acids, Herbs (Licorice), Minerals (magnesium).

#### MORE INFORMATION

*List of doctors who treat OI:* <http://www.ndrf.org/physicia.htm>

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*The Cochrane Collaboration's meta-analysis of hawthorn extract (2009)*

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## COGNITIVE AND EMOTIONAL SYMPTOMS

Loss of Concentration, Short-Term Memory Impairment, Multitasking and Sequencing, Linguistic Reversals, Word Searching, Math Problems, Emotional Problems

Cognitive, emotional, and perceptual problems affect nearly every person with CFS/ME at one time or another during the course of the illness. These symptoms are, in fact, so prevalent that many doctors consider them to be as great an identifying feature of the illness as fatigue. In some cases these problems are evident at onset; in others they develop after a few weeks or even months have passed. Although not, perhaps, as obvious to the casual observer as some of the more overt symptoms, cognitive and emotional problems can be just as disabling. Indeed, in some cases cognitive problems form the nexus of disability, making it impossible for the more severely affected to hold a job, read a book, or even carry on a coherent conversation. The cumulative effect of these symptoms – most notably, slowness and lack of concentration combined with short-term memory loss – results in what most people with CFS/ME call "brain fog."



Researchers agree that many cognitive, emotional, and perceptual changes that arise as a result of the illness are organic; that is, they are due to alterations in normal brain function rather than to secondary psychological factors, such as being distressed about having CFS/ME. Many people with CFS/ME have observed that distortions in emotional and mental states seem to correlate with the degree of severity of their other symptoms, usually, but not always, fatigue. This seems to point to a similar, if not the same, origin for both.

Dr. Jay Goldstein, Dr. Ismael Mena, and others have suggested that physiological symptoms, such as muscle weakness, temperature fluctuation, and decreased blood pressure, as well as emotional and cognitive symptoms, can all be caused by abnormalities in an area of the brain that roughly corresponds to the limbic system and adjacent regions of the temporal lobe.

The limbic system is a ring of structures located at the center of the brain. It is composed of a number of small but vitally important components that affect nearly every aspect of physical and psychological function, the most important of which is the hypothalamus.

The hypothalamus, a thumb-sized assembly of about twenty nuclei located just below the thalamus (the brain's sensory processor), is responsible for regulating the autonomic nervous system, that part of the nervous system that controls physiological mechanisms that are largely unconscious (e.g., digestion, sleep, etc.).

The autonomic nervous system is composed of two main branches, sympathetic and parasympathetic. While the parasympathetic nervous system controls resting functions, such as sleep, digestion and reproduction, the sympathetic controls arousal, particularly the so-called “fight or flight” responses. When hypothalamic function is altered the disruption is profound, resulting in sleep disturbances (insomnia, hypersomnia), loss of homeostasis (the body's ability to maintain itself within constant parameters of temperature, blood pressure, and so on), eating disorders (anorexia, gorging), and mood disturbances (panic, rage, anxiety).

Alterations in hypothalamic function can also cause disturbances in distant areas of the brain that rely on communications from the nerve fibers passing through the hypothalamus, such as the endocrine system (via the pituitary gland). In addition to these vital functions, the hypothalamus has a central role in mediating immune system responses and is a virtual thoroughfare for fibers connecting the higher cortical centers governing thought with structures in the midbrain and limbic system that regulate motor activities, the senses, memory, and emotion.

It is well known that sympathetic hyperactivity, indicating an alteration in hypothalamic function, is common in CFS/ME patients. There is evidence that increases in sympathetic tone may be a major contributory factor to mental fatigue. In 2011 a group of Japanese researchers measured mental fatigue in healthy volunteers after a prolonged cognitive task (8 hours). They found that sympathetic hyperactivity was induced by prolonged cognitive load. This, in turn, was associated with mental fatigue. While to a certain extent this finding was predictable, it does a

lot to explain why people with CFS/ME are so easily overwhelmed. If the demands of a work day can produce sympathetic hyperactivity in healthy individuals, it is logical that people who start the day with upregulated sympathetic tone will be exhausted by any cognitive task.

Other structures in the limbic system can produce both cognitive and muscular impairment. If the basal ganglia are impaired, motor function will be affected. Tremors and difficulty sequencing complex motor coordination (such as speech) may result. The amygdala and hippocampus, two closely related limbic structures embedded in the temporal lobe, play an important part in learning and processing short-term memory. Damage to these sensitive structures results in learning and information retention problems, as well as difficulty with visual and aural comprehension.

Given the wide range of neurological symptoms experienced by people with CFS/ME, it is not surprising that radiological examinations, such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI), of the brains of patients with CFS/ME have revealed low blood flow (hypoperfusion), small lesions, and lowered glucose absorption in the areas of the brain around the hypothalamus. The juncture between the temporal and parietal lobes (roughly above and slightly behind the ear) is also an area frequently found to be deficient in adequate blood supply. This area corresponds to the part of the brain responsible for correlating complex sensory information. Deficiencies and abnormalities have also been noted in the motor cortex and frontal lobe, as well as the limbic system. Impairments of these areas of the brain produce a wide range of cognitive, emotional, and perceptual problems in people with CFS/ME.

In some interesting corollary research, Dr. Kenny De Meirleir, noted Belgian CFS/ME specialist, has found that gut dysbiosis correlates with cognitive dysfunction in people with CFS/ME. Dr. De Meirleir discovered that in people with CFS/ME there are high levels of bacteria not normally found in gut flora, notably gram positive lactic acid bacteria. Gram positive bacteria interfere with normal digestive processes in the gut, leading to a condition in which D-lactic acid accumulates. Excess D-lactic acid (D-lactic acidosis) can produce a number of neurological symptoms, including weakness, confusion, poor balance, slurred speech, a feeling of being “drunk,” and loss of memory. While it would seem that the gut is a long way from the brain, it should be pointed out that the vast majority of several important neurotransmitters (e.g., serotonin and melatonin) are produced in the gut.

## LOSS OF CONCENTRATION

Loss of concentration is one of the most common—and most serious—cognitive problems affecting people with CFS/ME. Problems in this area can significantly affect work performance. One source of concentration problems is a loss of comprehension of either aural or visual information. The brain lags behind input and either processes new information slowly or misses it entirely. When the

input is aural, there seems to be loss of the initial orienting information. The person may be listening, but the information simply does not register; as a consequence, the person cannot focus or make sense of what follows. Sometimes a delay in processing results in longer pauses than usual before a verbal response is made. Processing delays can also produce a mistiming of conversational turn-taking resulting in interruptions and apparent non sequiturs. Often, information must be repeated several times before it registers.

Visual processing can also be significantly delayed. Material may have to be read many times before it is absorbed, and sometimes words in a sentence do not make sense, especially if the syntax is complicated or the meaning ambiguous. Reaction times may also be slowed. People may run red lights or disobey other traffic signs because the information does not register as fast as is required to act on it.

Dr. Byron Hyde believes the loss of comprehension associated with CFS/ME is due to a dysfunction in the area of the angular gyrus in the region of the left posterior (rear) parietal lobe, an area of the brain that processes and interprets both visual and aural information. However, dysfunction in the posterior temporal lobe also has been noted with some frequency.

#### SHORT-TERM MEMORY IMPAIRMENT

The loss of short-term memory (also known as working memory) can present serious difficulties for people with CFS/ME. Those who forget why they came into a room may also forget where they are driving. People simply forget what they were doing and why. The problem can become so severe for some people that they cannot finish a sentence. Memory loss can also manifest itself in loss of the ability to remember people's names or faces (facial agnosia). People with these problems may find it hard to identify friends, relatives, students, or coworkers, especially if they are called upon to come up with an identification quickly. In those circumstances even familiar people and places can suddenly seem strange. Problems with memory and learning are traditionally associated with dysfunction of the hippocampus, though a number of other structures are also involved.

In 2008 Neary et al conducted a study examining the effects of exercise on cerebral blood flow in CFS/ME patients. The researchers compared cerebral oxygenation in the brains of six CFS/ME subjects and eight healthy controls before and after exercising using a stationary bicycle. The CFS/ME group showed decreased blood flow in the prefrontal cortex, the area of the brain believed to be primarily responsible for working and short-term memory. The fact that short-term memory loss can be associated with exercise is an indication that exercise intolerance may be due to central nervous system damage, rather than to muscle impairment.

A 2011 study in which high-resolution MRIs were used to compare CFS/ME patients with healthy controls revealed reductions in gray and white matter volume in the occipital lobes, right angular gyrus and left parahippocampal gyrus of CFS/ME patients. The parahippocampal gyrus plays an important role in memory

encoding and retrieval. The researchers concluded that their data supported the hypothesis that “significant neuroanatomical changes occur in CFS, and are consistent with the complaint of impaired memory that is common in this illness.”

### MULTITASKING AND SEQUENCING

Multiple-task sequencing is related to word sequencing. As with short-term memory, sequencing of complex tasks involves the lateral prefrontal cortex, an area of the brain which has been implicated in the profound central fatigue of CFS/ME as well as memory impairment.

People who experience difficulties with multitasking may find it hard to follow step-by-step instructions, prepare food from a recipe, or perform tasks that require a series of separate actions. Decision making is also affected. Putting away objects held simultaneously (for example, a saltshaker and a stick of butter), may present a major challenge if the impairment is severe. People may also lose the ability to look up numbers in a telephone book or words in a dictionary.

Children with CFS/ME are particularly shy of doing academic tasks, forgetting alphabet order easily and finding it difficult to remember numbers in sequence. Younger children may experience significant problems in school as a result. Adults may also experience a similar decrease in learning ability, particularly if the information is complex.

Those with multitasking and simultaneous processing problems need to keep input at a minimum when performing necessary tasks. They should not listen to the radio while driving. They should avoid conference telephone calls or meetings with several people. If crowds, malls, big events, and parties trigger symptoms, these environments should be avoided, or a small area should be created in which the person can remain stationary while others circulate.

### LINGUISTIC REVERSALS (PSEUDODYSLLEXIA)

People with CFS/ME routinely structure linguistic elements backwards. They reverse word order, letter order when typing or writing, initial sound order when speaking, and even sentence order in a paragraph, resulting in a series of seemingly disconnected digressions rather than a logical flow of ideas. Any of these problems can stem from disruptions in the final stage of linguistic output, which are thought to occur in the supplemental motor area of the brain. This area, located deep within the central fold separating the two hemispheres, acts as a kind of holding area for final linguistic assembly. Problems there result in word, letter, and short-term ordering problems. Dysfunctions in the left temporal lobe (roughly above the left ear) also cause significant problems in linguistic production. True dyslexia and aphasia are the result of permanent damage to this area, which is why the temporary problems arising from CFS/ME are prefixed with "pseudo."

### WORD SEARCHING (PSEUDOAPHASIA)

Another common linguistic problem for CFS/ME patients is word searching. Commonly used words are hard to retrieve and, when they finally are uttered, may

sound or even be wrong. Often a similar sounding word is substituted incorrectly for the "missing" word, making the response completely inappropriate. The person speaking may not catch these errors, in some cases resulting in significant loss of communicative ability. Most of these retrieval problems are related to lack of blood flow to the left temporal lobe, the part of the brain responsible for most language-oriented tasks.

### MATH PROBLEMS (DISCALCULIA)

Problems with math are rife in the area of cognitive dysfunction. People have difficulty balancing checkbooks, following timetables, adding columns of figures, and, especially, subtracting. As a consequence, work that requires a lot of calculating, such as preparing taxes, can become so stressful that it can induce an exacerbation. People with CFS/ME frequently wobble or fall during the Romberg test if they are required to simultaneously subtract by sevens from 100. Dyscalculia is associated with dysfunction in the temporal lobe.

### TREATMENTS

A number of approaches can be taken to improve cognitive symptoms. Drugs can be taken that act directly on neurotransmitters and the central nervous system (e.g., Klonopin, naphazoline, antidepressants). Another approach is to remedy the mechanical problem of low blood flow to the brain by increasing circulation. Drugs used for this purpose are primarily vasodilators, calcium channel blockers, and the beta blockers (nitroglycerin, nimodipine, atenolol).

Pentoxifylline (Trental), a drug used to lower blood viscosity, can also increase blood flow to the brain, and reputedly helps alleviate short-term memory loss. Anticoagulants have been used for this purpose by some patients with CFS/ME. In some milder cases of CFS/ME, central nervous system stimulants such as Ritalin can be helpful, as can Prozac or Wellbutrin.

CFS/ME patients report cognitive improvements with low doses (50 mg) of piracetam, one of the so-called "smart drugs." Piracetam lowers blood viscosity (which increases blood circulation) enhances mitochondrial function, and protects limbic structures from toxicity. Given the numerous cognitive problems associated with hypoperfusion in the brain, as well as the susceptibility of limbic structures to low blood flow, this drug has good potential as an overall CFS/ME treatment.

Herbs that increase blood flow, such as ginkgo, gotu kola, and bilberry, have also been used to enhance cognitive capacity. An important nutritional support for brain function is CoQ10. Vitamin E also helps increase blood flow by lowering viscosity. All antioxidants, especially taurine, which crosses the blood-brain barrier easily, should have a positive effect on cognitive symptoms.

An alternative approach involves enhancing brain function through cognitive rehabilitation. The brain's neurons are remarkably capable of regenerating dendrites. In other words, when individual cells are destroyed, others can take over their function, given the proper stimulus. Working with new or different learning techniques can restore much of the cognitive function lost in the acute stage of

CFS/ME. Biofeedback and meditation techniques are also reported to be effective in alleviating cognitive dysfunction.

SEE: Ampligen, Beta Blockers, Calcium Channel Blockers, Central Nervous System Stimulants, Pentoxifylline; CoQ10, Herbs (Gingko), NADH, Vitamins; Biofeedback, Meditation.

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#### EMOTIONAL PROBLEMS

CFS/ME patients are composed, by and large, of people who had been enjoying relative health before falling ill. Colds and flus, pregnancies, broken bones, and minor procedures are things we can all cope with. These events are bumps in the road of life, detours that have well defined beginnings and endings. CFS/ME comes as a shock, not just to the body, but to the mind.

Even for those who have had exposure to chronic illnesses through close friends and family members – diabetes, heart conditions, perhaps cancer – there is nothing within our framework of reference to prepare us for an illness that has no predictable course, no established treatment protocol, and no associated medical specialty. CFS/ME forces us to completely re-evaluate who we are within the context of something we simply can't understand.

What's worse is that our doctors usually don't understand it either, and so begins a long journey into loss, disappointment, despair – a journey that challenges all of our notions of how our bodies should work, how the medical establishment should work, and for those who try to obtain disability, how society should work.

It is impossible to go through such a profoundly disturbing event without all the emotions that usually accompany long-term illness – anxiety, fear, depression. These are the normal and expected responses to a long-term illness. However, the profound emotional lability characteristic of CFS/ME is brought about, not by the experience of CFS/ME, but by the mechanisms of the illness itself. For people with CFS/ME, these emotional phenomena can be just as unsettling as physical symptoms, and are equally disturbing for the people witnessing them.

In the acute stage of CFS/ME, strong, sometimes overwhelming, feelings can seemingly appear out of nowhere. Most people find these intense emotions highly disturbing, particularly when they are accompanied by severe physical and cognitive symptoms. In many cases, the emotions that accompany exacerbations, or “flares,” of the illness are complicated by sensory and perceptual alterations, such as changes in vision and hearing, which may lend an air of unreality to what used to be familiar environments. Some people even report feelings of dissociation, or a sense that they are watching themselves, as if in a movie.

When patients report these symptoms, it is all too common for the attending physician to recommend that the patient see a therapist or psychiatrist. Because people with CFS/ME are already struggling with a disease that has just barely gained acceptance in the medical community, they are often offended by the suggestion. They may feel stigmatized or blame themselves for “creating” their illness. Many find that sessions with therapists are not particularly helpful, unless the sessions are conducted by a therapist who is knowledgeable about CFS/ME. In some cases, a therapist inexperienced with the illness may make an incorrect diagnosis of major depression or bipolar disorder. The reason therapy often fails is that the emotional roller coaster produced by the onset of CFS/ME is as organic as the fever, swollen glands, low blood pressure, or any other observable physiological sign or symptom. Contrary to popular notions that “negative” emotions produce illness, CFS/ME proves the reverse.

The intense emotions characteristic of acute CFS/ME—rage, terror, overwhelming grief, anxiety, depression, and guilt—are the result of the same mechanism that produces cognitive difficulties; that is, alterations in the normal functioning of the limbic system and related structures. It should not come as a surprise that the areas of the brain most affected by alterations in neurotransmitter activity are located in the limbic system, which functions, in part, as a processor of emotions, and the temporal lobe, in which emotion is joined to experience to facilitate memory formation. These are two of the areas of the brain most commonly affected by CFS/ME.

It has long been known by neuroscientists that stimulation of one part of the hypothalamus produces rage, and electrical stimulation of the other side produces profound calm. This experiment was the impetus for Dr. Herbert Benson's landmark treatise, *The Relaxation Response*, a book that provides the foundation for many of the stress management techniques currently recommended by psychologists.

The brain is not limited to these two rather primitive responses, however. Changes in neurotransmitter activity can cause depression (low serotonin levels), irritability (low followed by high serotonin levels), euphoria (high norepinephrine levels), and jitters or acute anxiety (excitatory neurotransmitters, such as dopamine and glutamate). The amygdala, a particularly sensitive structure located in the midbrain, produces fear. High levels of vasopressin (a hormone produced by the hypothalamus) have been associated with the continual review of unpleasant experiences or memories typical of depression.

That many of these emotional states can be generated directly by alterations in neurochemicals does not indicate that all these emotions are necessarily caused by neurological dysfunction. Disturbances in the endocrine system can lead to hypothyroidism, which produces severe depression and lethargy. Hypoglycemia caused by hypothalamus-pituitary-adrenal (HPA) axis dysfunction can cause weepy depression as well. (Indeed, Dr. Ramsay observed spontaneous weeping with no apparent cause during the Royal Free outbreak.) HPA axis dysfunction leading to adrenal disturbances can cause panic and extreme anxiety. Irritation is often produced by the hormonal imbalances that accompany premenstrual syndrome (PMS), as are uncontrollable outbursts of rage and grief. Some cases of panic disorder may be caused by an autoimmune disorder in which serotonin is targeted. This is entirely possible in CFS/ME, which has a high rate of autoimmune comorbidity and produces demonstrable serotonin antibodies.

All of the above are good candidates for the emotional disturbances experienced by people with CFS/ME. And accompanying these physiological causes are the inevitable emotional upsets and frustrations that result from not having a functioning mind or body, losing a career or family, worrying about loss of income, and the threat of mortality. These may result in secondary, or reactive, depression, a mood disturbance due to a traumatic life event. Secondary depression can be just as devastating as primary (physiological) depression and should be treated with the same seriousness.

Although it is important to remember that emotional states can be generated by purely organic disturbances, it is equally important to keep in mind that the line between physiological and psychological disturbance is a fine one. In reality, the two are intertwined, each feeding into, supporting, and providing the basis for the other. Both need to be attended to in order to maintain a sense of emotional equilibrium.

## TREATMENTS

There are a variety of treatments for depression. Usually, drug treatments for depression center on antidepressants. Unfortunately, because of CNS disturbances, many patients with CFS/ME are unable to tolerate this class of drugs. However, some people find very low doses of antidepressants useful for alleviating depression. Low doses of fluoxetine have been used to treat the depression that accompanies PMS (as well as hypersomnia). Anxiety states are usually treated with very low doses of a benzodiazepine (Klonopin or Valium) or other anxiolytic agents, always taking care to monitor for depression, as anxiolytics lower CNS activity.



In an interesting study published in 2007 by Boiko et al, piracetam, a drug used for focal brain damage, was found to alleviate depression in CFS/ME patients when combined with an antihistamine. This drug increases blood flow to the brain, as well as acting on cholinergic receptors, which can act as a mild brain stimulant.

Herbal treatments include skullcap for anxiety and jitters, and valerian for anxiety. St. John's Wort has antidepressant effects, and is used widely in Europe as a treatment for depression. SAMe (S-Adenosyl methionine) has been proven to be effective for treating depression. The first studies confirming its use for depression were conducted in the 1970s. Since that time, numerous studies have confirmed that SAMe is both safe and effective.

An important supplement for emotional stability is vitamin B complex. Patients with CFS/ME have reported that vitamin B complex helps stabilize their mood, enabling them to handle stressful situations.

The trace mineral, selenium, has mood-enhancing effects. Maes et al found that glutathione levels were low in depressives, and suggested that a combination of selenium, NAC and glutathione might be helpful.

The amino acid arginine, sometimes recommended as a mood enhancer, should not be used to treat CFS/ME because herpesviruses replicate through arginine.

Choline and inositol are two compounds related to B complex vitamins that have been shown to decrease both depression and anxiety. Other remedies that have been effective for people with CFS/ME are controlled hyperventilation (deep breathing exercises to assuage panic), meditation, autohypnosis, Bach remedies, and biofeedback.

Acupuncture is a very effective treatment for anxiety. Acupuncture works to alleviate stress by releasing endorphins, natural pain-killing chemicals in the brain. Acupuncture improves circulation of blood throughout the body, which oxygenates the tissues and cycles and helps clear the body of excess cortisol, a chemical that can lead to depression and anxiety. Because acupuncture balances and calms the entire body, it can act to decrease heart rate, lower blood pressure and relax the muscles, all of which are beneficial in controlling anxiety states.

For the many fears, anxieties, and doubts that accompany the loss of income, relationships, and good health, a counselor can be of benefit. Someone who has had experience working with people with CFS/ME will be much more helpful than someone who has not. Psychologists who are unfamiliar with the illness will sometimes attribute the strong emotions produced by neuroendocrine disturbances to suppressed childhood events, such as abuse, neglect, or other stressful life experiences, and insist on psychotherapy. While these problems may occur coincidentally with CFS/ME, it is important to remember that they are not the cause of the illness.

That being said, during periods of acute or ongoing illness, advice on how to cope with the illness from an experienced counselor can be invaluable. Support groups, whether in the flesh or online, are equally as important. Talking to people who share your experience can alleviate much of the feeling of isolation that

accompanies the illness, and has the added benefit of perhaps leading to finding an understanding physician.

Last, but not least, avoiding upsetting or stressful situations is a good strategy to use whenever possible, especially in acute stages of the illness. Unplug your phone, cancel your newspaper subscription, and turn off your TV.

Support from other people who have had CFS/ME is invaluable for learning to cope with emotional swings and upsets. Once we begin to share our experiences with others, most of us find that we are not alone in what we are experiencing. That, in itself, is one of the best therapies of all.

SEE: Antidepressants, Antihistamines, Benzodiazepines; Amino Acids, Butyric Acid, Choline, Herbs, Inositol, Minerals (Selenium), Piracetam, Vitamins; Acupuncture, Aroma Therapy, Bach Remedies, Biofeedback, Hypnosis, Meditation; Stress Reduction and Elimination.

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Phoenix Rising forum: <http://forums.phoenixrising.me/showthread.php?7653-Non-Standard-Anti-Anxiety-Treatment>

*Interesting patient thread about anxiety remedies. Includes how to make your own magnesium cream.*

Phoenix Rising forum: <http://forums.phoenixrising.me/showthread.php?2018-Anxiety-Ammonia-and-the-NMDA-Receptor>

*Patient thread on anxiety symptoms, feeling "tired and wired" and a discussion of the role of ammonia.*

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## DIGESTIVE DISTURBANCES

Esophagus: Spasm, Difficulty Swallowing, Loss of Appetite, Reflux/Heartburn;  
Stomach: Nausea, Small Intestine: Permeable Intestine (Leaky Gut), SIBO, Large Intestine: IBS, Gas, Diarrhea, Constipation; Rectum/Proctalgia Fugax, Tenesmus; Gallbladder; Liver

The gastrointestinal tract is composed of a series of organs that include the esophagus, stomach, gallbladder, liver, pancreas, and small and large intestines. For the most part, the actions of these organs are regulated by the enteric nervous system, although the central nervous system and endocrine system also play active roles.

The main function of the digestive system is processing food, which it accomplishes largely independently from the brain's direction. The nervous system of the gut is so extensive that molecular biologist Michael Gershon, in his eloquent and enlightening book, *The Second Brain*, has described the enteric nervous system as a separate branch of the autonomic nervous system. For instance, neurotransmitters such as serotonin, which were formerly thought to be produced exclusively in the central nervous system, have been found in abundance in the intestines. In fact, 90% of the serotonin in the body is produced in the gut.

The action of these neurotransmitters, along with peptides, neurohormones and other secretory substances, regulates the peristaltic action of the digestive organs, organizes the timing of the opening and closing of inter-organ valves, determines the strength and frequency of muscle contractions, and controls the release of digestive juices. Because the network of nerves found on the inside of mucous membranes throughout the digestive tract is responsible for the smooth functioning of these organs, any problem in the enteric nervous system will lead to a host of disturbances—from the esophagus all the way to the rectum.

It is likely that many of the gastrointestinal difficulties manifested in people with CFS/ME stem from an autonomic nervous system dysregulation which either interferes directly with the functioning of the digestive system, or limits its ability to function through secondary means. Because the stomach and pyloric sphincter (which orchestrates the release of partially digested food into the intestines) rely on the subtle interaction of the parasympathetic (mediated by the vagus nerve and the action of acetylcholine) and sympathetic (mediated by noradrenaline) nervous systems, any imbalance in these systems will inevitably result in faulty digestion. The vagus nerve, while not essential for the functioning of the intestines, relays information from the gut back to the brain, which can affect mood, cognitive function and HPA axis regulation.

Unfortunately, people with CFS/ME seem to have both poor vagus nerve tone as well as an upregulated sympathetic nervous system, which may well contribute to a cascade of neurally-mediated digestive system problems.

The primary result of an upregulated sympathetic nervous system is insomnia. Many people observe that when they have poor sleep for several nights they get GI symptoms. This is because the “gut clock” has been altered. About 400 times more melatonin, the so-called “sleep hormone,” is produced in the gut than in

the brain. The reason for this enormous production of melatonin is that digestion is regulated by circadian rhythms. Bile flow increases at night, as do other digestive secretions. Melatonin functions not only to set the circadian rhythms of the digestive system, but to harmonize them with immune and endocrine functions.

When these rhythms are disrupted, digestive disturbances result. It is known that people with chronic insomnia are more prone to irritable bowel syndrome (IBS), peptic ulcers, fatty liver, GERD, and dyspepsia. The chronic insomnia experienced by people with CFS/ME is undoubtedly a contributory factor to multiple digestive disorders.

The digestive problems in CFS/ME are further complicated by a simple lack of blood flow into the digestive organs. Recent studies by Peckerman et al have shown that people with CFS/ME have reduced cardiac output stemming from reduced diastolic function. What this means is that less blood is flowing back into the heart. As a consequence, the heart must pump faster and harder to get blood circulating through the system. When there is too little blood to maintain heart function effectively, the body simply squeezes blood from other organ systems, primarily the blood-rich digestive system. This, in turn, results in hypovolemia (low blood volume), which further exacerbates diastolic dysfunction. The net result, as far as the digestive tract is concerned, is that it becomes very difficult to digest food; leaky gut ensues, food allergies and sensitivities develop and soon there is very little that you can eat.

Given the predominance of both dysautonomia and reduced cardiac output it is not surprising that gastrointestinal symptoms plague more than 60% of the CFS/ME population. Indeed, there are some researchers who believe that the gut is, if not the ultimate cause of CFS/ME, at least the central locus of ongoing symptomatology.

#### FURTHER READING

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*This is a must-read for anyone interested in how the digestive system works.*

*Gershon writes about the digestive system in a clear, engaging style that is equally informative and entertaining.*

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*This site contains everything you ever wanted to know about digestion.*

<http://www.medicalinsider.com/digestion.html>

*Colorado State's very informative website about digestion. Includes average transit times.*

<http://www.vivo.colostate.edu/hbooks/pathphys/digestion/basics/transit.html>

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## ESOPHAGUS

The esophagus is an 8- to 9-inch long tube that extends from the base of the throat, just below the Adam's apple, to the stomach. Its function is to transport food from the throat to the stomach by means of peristaltic action. The upper third of the esophagus consists of striated muscle, and the lower two-thirds consist of smooth muscle. The two valves at the upper and lower ends of the esophagus – the upper and lower esophageal sphincters, respectively – allow food to pass first into the esophagus, then into the stomach. The lower valve also prevents reflux of corrosive stomach acid into the esophagus and throat. Problems with the esophagus can arise from faulty operation of the lower valve (lower esophageal sphincter) or from the muscles responsible for peristalsis.

One of the more painful experiences in CFS/ME is the esophageal spasm. Because the spasm usually occurs in the center of the chest, the pain is frequently mistaken for a heart attack. An esophageal spasm can feel like a tight, squeezing pain that sometimes radiates to the stomach or mid-back. Unlike cardiac pain, however, the pain does not radiate down the arms or increase after exertion. Esophageal spasms in the striated muscle portion of the esophagus produce a cramp so excruciating that it can send you straight to the emergency room.

Spasms in the lower portion of the esophagus are painless but the blips, pops and twitches are nonetheless disturbing. Spasms in this area are generally thought to be caused by an exaggerated motor response to peristalsis; that is, the esophagus contracts too much. Repeated spasms of this nature are referred to as diffuse esophageal spasms and are not uncommon in people with CFS/ME.

## TREATMENTS

Treatment of esophageal spasms is somewhat limited because the problem is usually not chronic. Muscle relaxants may help diminish the force of the spasm in those who experience spasms in the upper esophagus. Swallowing something that coats the esophagus (like kefir) can ease the cramp.

Avoiding foods that irritate the stomach also helps. Spasms in the lower part of the esophagus are sometimes caused by reflux. Carbonated drinks, acid foods,

foods that are too hot or too cold, or indeed any food to which there is sensitivity may cause esophageal spasms. Even sudden changes in temperature, (for example, a hot shower) can trigger esophageal spasms in the sensitive individual. Emotional upset and stress can exacerbate this problem. Avoidance of esophageal stressors, treatment of reflux, and general stress management can help reduce the frequency and severity of esophageal spasms.

### DIFFICULTY SWALLOWING (DYSPHAGIA)

Dysphagia is often experienced in the acute stage of CFS/ME and during severe relapses. Basically, dysphagia refers to any difficulty in swallowing. Food may become stuck in the esophagus or, in severe cases, may not even make it past the mouth. Most problems with swallowing can be attributed to sympathetic nervous system dysregulation (dysautonomia).

The peristaltic action of the esophagus is governed by the central nervous system, specifically the parasympathetic nervous system, which acts in response to the release of acetylcholine through vagus nerve endings in the esophageal muscle. This results in the regular muscle contractions (peristalsis) involved in swallowing. When the sympathetic nervous system, which is mediated by the adrenal hormone noradrenaline (norepinephrine), is overactive, it reduces parasympathetic control, inhibiting the peristaltic action of the esophagus.

Most people are aware that a sudden rush of adrenaline, caused by fear or intense excitement, makes it nearly impossible to swallow. This is because the release of large amounts of adrenal hormones causes sympathetic nervous system arousal, inhibiting peristalsis. People with CFS/ME have a well-known sensitivity to stress hormones, which means a rush of adrenaline can inhibit the ability to swallow for extended periods of time. Those who experience profound dysautonomia may have persistent difficulty with swallowing food, pills, and even liquids.

### TREATMENT TIPS

People who have difficulty swallowing can benefit from any treatment that calms the sympathetic nervous system. Sometimes an antispasmodic or mild tranquilizer (e.g., benzodiazepines) can help if the problem is severe. A calming tea, such as skullcap or valerian, can be used if tranquilizers are not tolerated. CFS/ME specialist and gastroenterologist, Dr. Thomas Steinbach (now retired), used to recommend drinking 2 oz. of warm water mixed with 1 teaspoon of apple cider vinegar to ease dysphagia caused by esophageal spasms. Coincidentally, this is also a popular home remedy for heartburn, which means the spasms, in this instance, are probably caused by acid reflux.

SEE: Cardiac and Cardiovascular Problems (Dysautonomia); Anticonvulsants, Benzodiazepines; Herbs

### LOSS OF APPETITE

Loss of appetite, like many upper GI problems, is most common during acute phases of the illness. The inability to eat, although sometimes misdiagnosed as "anorexia," is not due to an aversion to food but, in most cases, can be attributed to sympathetic nervous system arousal. Norepinephrine, which is released during sympathetic activity, suppresses the appetite. This is, in fact, how most appetite-suppressing medications work. It is very difficult to eat when one has no appetite, so during phases of sympathetic arousal, weight loss is very common.

## TREATMENT TIPS

Calming the sympathetic nervous system can be accomplished with time and patience. Biofeedback is a useful method for down regulating the sympathetic nervous system, as are meditation and stress reduction techniques. Acupuncture and acupressure are both useful for increasing appetite. The acupressure point for appetite is located in the depression between the bones of your forearm about 2 1/2 finger widths below your wrist crease.

Central nervous system depressants, such as benzodiazepines, are quite effective at inhibiting the release of norepinephrine. Herbs, such as kava, valerian, and skullcap, have a calming effect and can be drunk as teas throughout the day. Magnesium is a potent down regulator of sympathetic arousal and has a long track record as a CFS/ME treatment. The amino acid taurine is neuroinhibitory, and can act to stabilize the autonomic nervous system.

Acetyl-L-carnitine is probably the most effective supplement for increasing appetite. It has been marketed as a weight-reduction supplement, but when taken during acute stages of CFS/ME, it has the reverse effect due to carnitine's important role in energy metabolism. Once energy is increased, appetite improves.

Medicinal marijuana, although used to stimulate appetite in cancer patients, is not recommended. Patients report that it increases sympathetic arousal, worsening all related symptoms.

SEE: Benzodiazepines; Amino Acids (Carnitine, Taurine), Herbs (Kava, Valerian, Skullcap); Acupuncture, Acupressure, Biofeedback, Meditation; Stress Reduction and Elimination.

## REFLUX/HEARTBURN

Reflux is caused by a lax lower esophageal sphincter (LES), which allows partially digested food and stomach acid to wash back up into the esophagus, causing the burning pain of heartburn. Normally, the LES remains in a closed position. When food enters the esophagus, its rhythmic contractions signal the LES to open, allowing food to pass through. Once the food has passed, the LES closes. In this simple but well-timed process, food is deposited into the seething vat of hydrochloric acid produced by the stomach, without subjecting the esophagus to its depredations.

However, when the LES remains open for too long, the acid-laced food can come back up the esophagus, causing burning pain. Once the esophagus is irritated,



a chain of symptoms, including nausea, retching, faintness, anxiety, and difficulty breathing is set into motion, transforming a simple case of reflux into a monster. It is no wonder that antacids are among the top-selling drugs in the U.S. In 2009, Nexium alone racked up a mind-boggling \$6.3 billion.

In CFS/ME nothing is straightforward, and when acid reflux is present it is rarely a case of having eaten too much fried chicken. The LES is controlled by the central nervous system, which is a major player in most CFS/ME symptoms. When the CNS sends signals that are uncoordinated, the LES remains open. This is particularly true of patients who have orthostatic intolerance (e.g., POTS, and NMH). In these forms of dysautonomia, sympathetic activity is increased, which inhibits peristalsis. When peristalsis is slowed, the LES loses its fine sense of timing. In addition to nervous system dysregulation, any alteration in stomach acid – either too much or too little – can result in reflux.

### TREATMENT TIPS

Reflux can be somewhat mitigated by mechanical means. An extra pillow placed under the upper back while lying down tilts the stomach downward, preventing its contents from sloshing against the sphincter. Sitting up straight or bending slightly backward accomplishes the same function. Bending over or forward should be avoided when the stomach is full. If reflux is severe at night, raising the head of the bed by nine inches can help decrease reflux. Place supports under the bed frame, not the mattress.

Foods that relax sphincter pressure and smooth muscles, including alcohol, tobacco, coffee (even decaffeinated), peppermint, chocolate, garlic, and onions, should be eliminated. Spicy, acid, and excessively sweet or salty foods can also irritate the esophagus and should be avoided. Fatty meals delay gastric emptying, which can lead to heartburn. Large meals can also aggravate the condition. A bland diet consisting of easily digested, nonacidic, cooked foods, is recommended.

Certain drugs and medications may exacerbate heartburn. Among these are progesterone-containing oral contraceptives, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and beta blockers. Proton pump inhibitors, such as Prilosec, often worsen heartburn in CFS/ME patients.

There are a multitude of home remedies for heartburn: drinking ½ tsp of baking soda dissolved in a glass of water is quite effective. Drinking alkaline potato water leftover from boiling potatoes, warm honey, as well as anything that coats the esophagus, such as kefir or slippery elm can help soothe the irritated tissue.

Chewing gum is also very good for reflux. It releases saliva, which is alkaline, and stimulates peristalsis. Some people report that royal jelly helps, presumably because it contains acetylcholine, the neurotransmitter associated with parasympathetic activity.

Several acupressure points located on the abdomen, wrists, and shin can help improve digestion and relieve heartburn. Massaging any of the following pressure points for about two minutes can help relieve heartburn:

- The point CV12 is on the midline of the body, halfway between the base of the breastbone and the belly button.
- P6 is located in the depression between the bones of your forearm about 2 1/2 finger widths below your wrist crease.
- St36 is located four finger widths down from the knee cap and one finger width away from the shin bone.

Over-the-counter remedies for excess acid include Tums (which will offer temporary relief), and H2 blockers such as Zantac and Tagamet (which will offer longer relief). The H2 blockers work by inhibiting the release of histamine in the stomach, thereby limiting gastric acid and pepsin secretion. The drawback of long-term ingestion of over-the-counter acid suppressors is that there is a rebound effect. Once the cells in the lining of the stomach perceive that there is too little acid, they merely produce more.

Conversely, heartburn symptoms can also be caused by too little stomach acid. Dr. James Balch, in his book, *Prescription for Nutritional Healing*, notes that a number of people with chronic heartburn problems have found that taking a small amount of apple cider vinegar diluted in a little water (this is Dr. Steinbach's remedy for the esophageal spasm) actually helps relieve symptoms. If antacids do nothing to relieve symptoms or if they worsen them, a little diluted apple cider vinegar might be helpful.

A derivative of licorice, DGL (available in health food stores), has been shown to be effective in healing stomach ulcers and can help with heartburn as well. Control of allergies can often help if excess acid production is due to allergies (histamine promotes gastric secretion).

Chronic heartburn is referred to as gastro-esophageal reflux disease (GERD). GERD is basically caused by a lower esophageal sphincter (LES) that never closes properly. The LES is controlled directly by the brain, so the disorder is most likely mediated by the CNS. It should be mentioned that GERD is one of the common symptoms of dysautonomia, which, in many people's minds, is virtually synonymous with CFS/ME.

Interestingly, a recent study done in Brazil demonstrated that melatonin combined with L-tryptophan, vitamin B6, folic acid, vitamin B12, methionine and betaine was 100% effective in treating GERD, as opposed to 66% of the omeprazole group. In a later study, Werbach showed that melatonin was key to preventing a return of GERD symptoms. Considering the fact that the GI tract produces 400 times more melatonin than the pineal gland, it should not come as a surprise that melatonin plays an important role in GI function.

If you have chronic heartburn, especially if it is accompanied by gastritis, it is well worth being tested for *H. pylori*. Back in the dark ages (before 1986), ulcers, like so many other gastrointestinal maladies, were considered a manifestation of neurosis. Now we know better. To avoid even the remote possibility of developing ulcers, it's worth getting tested. Symptoms of *H. pylori* infection include: stomach pain, acid reflux, a gnawing feeling in the stomach, heartburn, belching, bloating, nausea, diarrhea, bad breath, anxiety, pain between the shoulder blades,

palpitations, headache, chest pain, sleep problems, sinus problems, skin problems (rosacea, urticaria), depression, and fatigue.

SEE: Antihistamines, H2 Blockers; Melatonin, Vitamins; Acupressure, Acupuncture

#### FURTHER READING

“Acid Stomach – CFS and FMS patients listen up.”

<http://iseektruth.wordpress.com/2009/07/14/acid-stomach-or-not-enough-stomach-acid-the-symptoms-are-similar-but-for-cfs-and-fms-patients-i/>

*This is Daniel B's informative blog entry on low stomach acid and CFS/ME. Includes treatment suggestions.*

Acupressure points for GERD, including photos:

<http://www.livestrong.com/article/191417-acupressure-point-for-gerd/>

“The Symptoms Of H Pylori Your Doctor May Not Tell You About.” <http://h-pylori-symptoms.com/h-pylori-symptoms/>

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Wallace, John L. "Prostaglandins, NSAIDs, and Gastric Mucosal Protection: Why Doesn't the Stomach Digest Itself?" Inflammation Research Network, University of Calgary, Calgary, Alberta, Canada. *Physiol Rev* October 2008 vol. 88 no. 4 1547-1565 <http://physrev.physiology.org/content/88/4/1547.full> (*For those who are interested in the research that has been done on the subject of mucosal protection this is an excellent review article.*)

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#### NAUSEA

Many people with CFS/ME feel continually nauseous for months, regardless of what they eat and in the total absence of any identifiable infection. Although nausea can arise spontaneously from factors associated with improper digestion, other causes should also be considered. Antibiotics, which radically alter intestinal flora, can produce severe nausea, as can antimicrobial agents (e.g., metronidazole), beta blockers, and other drugs commonly prescribed to treat CFS/ME. Vertigo, carsickness, eye strain, migraine headaches, and Candida overgrowth also can produce nausea.

Disruption of neurotransmitter levels can lead to nausea as well. Serotonin, the most widely distributed neurotransmitter in the gut, controls the emesis reflex

(vomiting). Any disruption in normal serotonin levels can lead to nausea. Dopamine, an excitatory neurotransmitter, has also been implicated in nausea, especially the nausea associated with migraine.

There is some evidence that cerebral hypoperfusion can lead to nausea. In an interesting study performed in 2005, healthy subjects were spun in a centrifuge and monitored for vascular changes. Those who developed motion sickness experienced reductions in blood flow to the brain just prior to developing nausea. Given the fact that cerebral hypoperfusion is a frequent finding in CFS/ME patients, this has interesting implications. Low blood flow could conceivably affect not just neurotransmitter levels but vagus nerve stimulation, which could lead to nausea, syncope (fainting) and GI problems.

Research conducted by Burton and Chatterton in 2004 suggests that people with CFS/ME suffer from gastroparesis, or slow stomach motility. Gastroparesis—a condition which produces nausea, vomiting, bloating, early satiety, abdominal pain, and weight loss—is strongly associated with dysautonomia, particularly POTS (postural orthostatic tachycardia syndrome). Normally, the stomach, like the rest of the GI system undergoes rhythmic contractions – roughly three contractions a minute. These contractions knead and pulverize solid food until it becomes a liquid, which is referred to as *chyme*. Once the chyme is ready for further breakdown in the intestines, the pyloric sphincter (which protects the intestines from the acidic juices of the stomach) opens, allowing the chyme to pass through.

The process takes two to four hours, during which the stomach contracts at regular intervals, while the pyloric sphincter spits small amounts of chyme into the duodenum. If the stomach does not contract at these regularly timed intervals, there is delayed emptying, which causes nausea and, in some cases, vomiting.

Conversely, “dumping,” a syndrome in which the stomach empties too rapidly, forcing food that has not been adequately broken down into the intestine, produces nausea as well.

There are two types of dumping, “early” dumping begins soon after a meal, especially a meal that contains fats. The symptoms include nausea, vomiting, bloating, cramping, diarrhea, and dizziness. “Late” dumping, which is associated with difficulty digesting carbohydrates, occurs between one and three hours after eating. Symptoms of late dumping include weakness, sweating, and dizziness. Many people have both types. Dumping can also cause hypoglycemia, as the rapid passage of food stimulates the pancreas to excrete too much insulin. Dr. Cheney has noted that many patients with CFS/ME experience dumping.

Hypochloridia, or low stomach acid, can also lead to nausea. Hypochloridia is a well-documented condition among the elderly and in patients with gastric bypass surgery. When the stomach contents are not sufficiently acid, chyme that is too alkaline, and has not been adequately broken down passes into the duodenum. This leads, among other things, to dumping syndrome, as well as insufficient release of pancreatic enzymes and bile, all of which can produce nausea and vomiting.

While the CNS is implicated in gastric problems in the upper GI tract (dysphagia, esophageal spasms, reflux), it is not likely that the CNS plays an

integral role in hypochloridia. Certain vitamin and mineral deficiencies (zinc, vitamin B12, B6) can lead to low production of stomach acid. However, it is more probable that in CFS/ME the cause is insufficient cellular energy. The stomach utilizes an immense amount of ATP to produce hydrochloric acid, which means the mitochondrial dysfunction typical of CFS/ME patients will inevitably lead to hypochloridia.

## TREATMENTS

Eating small meals reduces the workload of the stomach. Smaller amounts of food, eaten more frequently, are easier for the stomach to handle and will decrease its energy requirements.

For quick relief of nausea, acupuncture is sometimes helpful. The P6 point is used by acupuncturists to both increase appetite and control nausea. To find it, place three fingers across the inside of the wrist, with the top finger placed just below the crease where the hand joins the arm. The pressure point is at the middle of the arm, on the line where the bottom finger rests. Sometimes holding a thumb there for a minute can relieve nausea. (This is the same point used for dizziness.)

Ginger is renowned for its effectiveness in treating nausea. Ginger stimulates stomach juices and aids in digestion, which, in turn, reduces nausea. Studies have shown that ginger reduces nausea caused by surgery, chemotherapy, pregnancy, and motion sickness. (Like the P6 point, ginger also relieves dizziness.) A tiny piece can be chewed raw or in candied form, held under the tongue, or taken as a tea. Powdered ginger taken in capsule form should be avoided as it may cause heartburn. The herb lemon grass, taken in a tea, is also excellent for calming the stomach and relieving nausea.

Acidophilus may help relieve nausea related to Candida infection or intestinal flora imbalance. In these cases, intestinal symptoms, such as gas and bloating will also be present. When nausea is accompanied by upset stomach, activated charcoal tablets can sometimes help – though these should be taken judiciously because they slow the absorption of nutrients from the intestines.

If nausea is preceded by reflux, antacids and acid-reducing remedies can be used. Dramamine and other motion sickness remedies are useful if the nausea is accompanied by dizziness. The antihistamine Antivert is also effective for treating nausea.

Betaine hydrochloride (Betaine HCl) is often recommended to increase stomach acid in patients with hypochloridia. The supplement HCl is a salt derived from hydrochloric acid, which, once dissolved in the stomach, produces weak hydrochloric acid. Betaine is a methyl donor, and is important in liver function. So, with this supplement you get the benefit of two important digestive aids. (Three, if the supplement also contains pepsin.) Apple cider vinegar or lemon juice can also be taken with a meal to slightly increase the acidity of the stomach. Salt also helps contribute to the production of stomach acid. Very little liquid should be taken with meals so that stomach acid is not diluted.

For those with early dumping, including fiber with meals will slow the rapid transit of food through the stomach. When both forms of dumping are present, or if there is an overgrowth of bacteria in the small intestines, a hypoallergenic brand of cellulose can be taken in very small doses to gradually increase fiber content.

The most frequently prescribed medication for nausea is Zofran. Zofran works by blocking 5-HT<sub>3</sub> serotonin receptors, which effectively stops smooth muscle contractions. (Smooth muscle is found in the lower two-thirds of the esophagus and in the stomach.) In most cases, this is a quick, effective way of alleviating nausea. However, it will not correct the underlying cause.

The antibiotic, erythromycin, also reduces nausea by stimulating gastric emptying. Azithromycin, an antibiotic often prescribed for *H. pylori* infections, also promotes gastric emptying. (Please note that neither of these would be appropriate for dumping syndrome.)

Supplements that increase the amount of ATP available to the digestive system are an important adjunct to any mode of therapy. These include D-Ribose, ubiquinol, and all antioxidants.

SEE: Candida; Antibiotics, Antihistamines, Antioxidants; Herbs, Minerals, Probiotics, Vitamins

#### FURTHER READING

*This is a concise article about the anatomy and function of the stomach.*

[http://biology.about.com/od/humananatomybiology/ss/anatomy-of-the-stomach\\_3.htm](http://biology.about.com/od/humananatomybiology/ss/anatomy-of-the-stomach_3.htm)

*Johns Hopkins' recommendations on the treatment of gastroparesis*

[http://www.hopkins-gi.org/GDL\\_Disease.aspx?CurrentUDV=31&GDL\\_Cat\\_ID=AF793A59-B736-42CB-9E1F-E79D2B9FC358&GDL\\_Disease\\_ID=dbfa1f93-0401-48c3-a6e0-8a0bedd710ad](http://www.hopkins-gi.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59-B736-42CB-9E1F-E79D2B9FC358&GDL_Disease_ID=dbfa1f93-0401-48c3-a6e0-8a0bedd710ad)

“Hypochloridia - lack of stomach acid - can cause lots of problems.” Dr. Myhill's informative article on low stomach acid.

[http://drmyhill.co.uk/wiki/Hypochlorhydria\\_-\\_lack\\_of\\_stomach\\_acid\\_-\\_can\\_cause\\_lots\\_of\\_problems](http://drmyhill.co.uk/wiki/Hypochlorhydria_-_lack_of_stomach_acid_-_can_cause_lots_of_problems)

*Dr. Cheney's views on hypochloridia and betaine HCl supplementation*

[http://www.prohealth.com/library/showarticle.cfm?id=3171&t=CFS/ME\\_FM](http://www.prohealth.com/library/showarticle.cfm?id=3171&t=CFS/ME_FM)

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[www.ncbi.nlm.nih.gov/pmc/articles/PMC2792728/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2792728/)

Wallace, John L. "Prostaglandins, NSAIDs, and Gastric Mucosal Protection: Why Doesn't the Stomach Digest Itself?" *Inflammation Research Network*. University of Calgary, Calgary, Alberta, Canada. *Physiol Rev* October 2008 vol. 88 no. 4 1547-1565 <http://physrev.physiology.org/content/88/4/1547.full> (*This is an excellent review article.*)

Waseem, Shamaila, Baharak Moshiree, and Peter V Draganov. "Gastroparesis: Current diagnostic challenges and management considerations." *World J Gastroenterol*. 2009 January 7; 15(1): 25–37. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653292/>

## GALLBLADDER

The gallbladder is a small organ that hangs like a partially filled balloon between the liver and duodenum. It acts as a receiving station for bile produced by the liver. Its main function is to release the bile into the duodenum so that fats may be digested. Problems with gallbladder function, such as obstructive stones, result in faulty processing of fats and the ensuing symptoms of nausea, belching, and intense pain in the upper right quadrant of the abdomen that radiates outward toward the right side and back.

People with CFS/ME, although not more prone to gallstone development than the general population, frequently experience classic gallbladder pain. However, standard tests (e.g., ultrasounds, HIDA scans) seldom show any mechanical or structural problem, even when attacks are severe. In some cases hyperkinesia is diagnosed, indicating that the gallbladder is producing spasms. (Gallbladder contractions are ultimately regulated by the autonomic nervous system, which in CFS/ME patients goes awry.)

Inflammation can also cause persistent gallbladder pain. It is interesting to note that in several cases of gallbladder attacks in people with CFS/ME in the Lake Tahoe epidemic, human herpesvirus 6 was found in gallbladder biopsy specimens.

Bacterial overgrowth in the small intestine (SIBO) can also lead to inflammation and subsequent irritation of the gallbladder. Hypothyroidism, because it leads to slow motility, can also lead to gallbladder problems.

## TREATMENTS

To a certain degree, gallbladder attacks can be prevented by avoiding foods that stimulate the gallbladder, such as fatty meals and cold drinks. (Finicky gallbladders react strongly to eggs.) Pain can be alleviated by applying moist heat in the form of compresses or a hot water bottle to the affected area. Because most gallbladder attacks occur at night – usually between 11PM and 1AM – it is wise to have a hot pad at the ready by your bed. Some drugs can help regulate gallbladder spasms as well.

Apple cider and olive oil flushes, two home remedies for gallstones, usually worsen the condition in people with CFS/ME, although eating apples seems to help. In the case of severe or persistent symptoms, consultation with a gastroenterologist to rule out gallstones is highly recommended.

## MORE INFORMATION

*This is a very informative site about the gallbladder, including what ails it, and what helps it: <http://www.gallbladderattack.com/>*

## LIVER

The liver is a large organ that spans the region from the right inner ribs to the side of the rib cage, reaching nearly down to the waist. It produces bile, which breaks down fats, carbohydrates, and proteins; stores glycogen for the body's immediate energy needs; metabolizes toxins, drugs, and metabolic waste products such as ammonia; and aids in immune system function, in part by acting as a cleanup crew for marauding pathogens.

Immune system complexes that have been engaged in battling invading viruses are transported through the bloodstream to the liver. In the liver, macrophages devour what is left of the invaders, helping to escort immune-activating proteins from the body. In this way the liver serves two functions: It cleans out debris and helps the immune system regulate itself.

Because of its intimate involvement in all facets of digestion, toxin elimination, and immune system function, the liver frequently suffers from strain in CFS/ME (although liver function tests usually yield normal results). Many people who experience pain or tenderness over the area of the liver (upper right quadrant) notice that a number of substances tend to aggravate it, including fats, alcohol, chocolate, allergens, and many pharmaceutical agents.

Symptoms associated with a malfunctioning or overwhelmed liver are: nausea, a reversal of sleep patterns (awake at night, asleep during the day), lethargy, itching (due to bile deposited in the skin), excessive thirst, pale stools, loss of appetite, and pain and tenderness over the entire area of the liver. Some patients report that their liver feels swollen. In addition to pain or discomfort over the liver area, many people experience a distinct malaise often described as feeling "poisoned." Even at its mildest, most people find this sensation intensely uncomfortable.

In CFS/ME, the poisoned feeling may be closely related to an overtaxed liver. Metabolic waste products, such as ammonia and carbon dioxide produced as a result of muscle use, are normally removed through the circulatory system. When circulation is impaired, as it usually is in CFS/ME, toxins build up and irritate nerve endings. The result is a tingling, uncomfortable sensation much like the "pins and needles" one feels when circulation is restored to an area that has been temporarily cut off from normal blood flow.

It has been proposed by Dr. Paul Cheney, Dr. Scott Rigden, and other clinicians that people with CFS/ME generate greater quantities of metabolic waste products because of faulty carbohydrate metabolism (*CFIDS Chronicle*, Summer 1995). To compound the problem, elimination of these extra waste products proceeds slowly in people with sluggish liver function, leading to a state of general auto-intoxication, or self-poisoning.



A second complicating factor leading to problems in liver function is low blood flow. The majority of blood that flows into the liver comes directly from the stomach and intestines. (Only 25% comes from the heart.) This allows the liver to filter toxins before they enter the bloodstream. As an added precaution, the liver performs this function twice. When blood flow is low, the liver can be literally overwhelmed by toxins that are too concentrated, much in the way a drought can concentrate bacteria in water. Hypovolemia (low blood volume) is quite common in the CFS/ME population, resulting in a state of perpetual circulatory drought and ensuing overload in the liver.

## TREATMENTS

Milk thistle (or Silymarin) is an herb that possesses the unique ability to stimulate liver regeneration. A number of people with CFS/ME report taking this herb to both protect the liver and enhance sluggish liver function. Dandelion root tea, a mild diuretic, can also be taken as a liver tonic.

Sufficient intake of water is also recommended to flush toxins from the liver. Keeping the liver warm (warm baths or a hot water bottle) helps the liver function with greater efficiency. (As in all bodily functions, heat speeds metabolic processes.)

Antioxidants (e.g., vitamin C, vitamin A, superoxide dismutase) and glutathione also help to reduce free-radical damage to liver tissue.

In an interesting study conducted by Abdelmalek et al in 2001, betaine, a metabolite of choline, was found to reduce fatty liver injury in non-alcoholics. Given the frequency with which people report improved digestion with betaine supplements, this supplement holds some promise for liver protection.

Resting definitely helps alleviate the "poisoned feeling." Lying down increases cardiac output, which, in turn, eases the effects of hypovolemia. Drinking electrolytes helps not only to flush the liver, but to increase blood volume. Avoiding liver irritants is a must (alcohol, fatty foods, pharmaceuticals which are processed through the liver). Activated charcoal can be taken to absorb toxins.

Remedies for leaky gut (e.g., butyric acid, enzymes, Cytotec) are useful, as they decrease the total load on the liver. Alpha ketoglutarate, the citric acid cycle metabolite that aids in removing ammonia from the system, can help reduce symptoms caused by an overwhelmed liver.

SEE: Cytotec; Antioxidants, Alpha ketoglutarate, Butyric Acid, Herbs (Silymarin), Vitamins; Bed Rest

## FURTHER READING

*The Medical Insider's detailed page on liver toxicity in CFS/ME. Contains a great deal of useful information on treatments:*

<http://www.medicalinsider.com/toxicity1.html>

Abdelmalek, Manal F, Paul Angulo, Roberta A Jorgensen, Pamela B Sylvestre, and Keith D Lindor. "Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study." *The American Journal of*

*Gastroenterology* (2001) 96, 2711–2717.

<http://www.nature.com/ajg/journal/v96/n9/full/ajg2001671a.html>

## INTESTINES

The intestinal tract (“the gut”) is where the hard work of digestion actually takes place. What was begun in the stomach ends in this long, hollow tract of multilayered tissue, where it will stay for two days or more while the gut employs every means at its disposal to turn food into nutrients. It is here that the chyme released by the stomach is broken down into its molecular constituents.

In the small intestines, fat is broken down by bile. Carbohydrates, proteins and fats are further broken down by pancreatic enzymes. Once the slew of liquid nutrients is broken down into its constituent units, the small intestine absorbs the molecules and allows them to pass through its cellular membrane where the nutrients can be used by the body. But the work of the gut does not end here. As the liquid slurry passes into the large intestine, gut flora go to work, generating vitamin K, biotin, thiamine and riboflavin from the waste products left by the small intestine.

The gut flora also help regulate the enteric immune system, producing antibodies which help control pathogens that may have entered the digestive tract. As waste passes through the large intestine, bile is reabsorbed and water is removed, which compacts the waste, turning it from liquid to solid. This last function is very important. Approximately two gallons of water pass through the large intestine every day. If this water were not reabsorbed, death from dehydration would rapidly ensue.

Dr. Kenny De Meirleir, professor of physiology, pathophysiology and internal medicine at Vrije Universiteit, Brussels, believes that many CFS/ME symptoms originate in the gut. Dr. De Meirleir has seen over 12,000 CFS/ME patients and, along with his research team, has performed over 4,000 *in vitro* experiments and published more than 80 professional papers. He has observed that among his patients, 80%-90% have gastrointestinal symptoms. Patients show delayed gastric emptying, inflammation of the stomach mucosa, imbalanced intestinal flora, malabsorption, lactose intolerance, small intestine bacterial overgrowth, bloating, diarrhea and constipation. Dr. De Meirleir has also observed that there is a direct correlation between cognitive dysfunction and gut problems in his CFS/ME patients; the higher the degree of digestive impairment, the greater the cognitive dysfunction.

Gut problems can arise from a variety of sources. Any alteration in GI motility (including upstream problems in the stomach), will produce intestinal symptoms. Ongoing, chronic viral infections from enteroviruses as well as other viruses that invade the intestinal tract will also lead to numerous problems in the gut, and may contribute to the immune dysregulation typical of CFS/ME patients.

In a study published in 2009 (Frémont et al), Dr. De Meirleir's team found active parvovirus B19 infections in the GI tracts of 40% of CFS/ME patients, as well as EBV and herpesvirus 6 in lesser amounts. Interestingly, while De Meirleir's

group found that parvovirus B19 persisted in the gut, there was no detectable viral DNA in the blood samples isolated from the same patients. The researchers' statement that "the gastro-intestinal tract appears as an important reservoir of infection for several potentially pathogenic viruses" indicates that the gut may well be a first-line area of treatment for CFS/ME patients.

#### FURTHER READING

*Dr. De Meirleir's views on gut dysbiosis; includes treatments.*

<http://www.prohealth.com/library/showarticle.cfm?libid=13306>

"Healing Your Gut." <http://www.beatcfsandfms.org/html/HealYourGut.html>

*This is a very informative page about gut problems, testing and treatment.*

"Gut Bacteria, the H2S Test & Mitochondrial Dysfunction in ME/CFS - Dr. Myhill Puts It All Together Simply and Suggests Things to Try."

<http://www.prohealth.com/library/showarticle.cfm?libid=14757>

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Frémont M, Metzger K, Rady H, Hulstaert J, De Meirleir K. "Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients." *In Vivo*. 2009 Mar-Apr;23(2):209-13.

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#### SMALL INTESTINE

After leaving the stomach, chyme enters the small intestine where it will stay for the next five or six hours. The small intestine, which is approximately 22 feet long, attaches to the stomach at one end and the large intestine at the other. It is composed of three main segments: the duodenum, jejunum, and ileum.

Bile from the liver and pancreatic enzymes enter the duodenum through their respective ducts, assisting in the breakdown of food that stomach processes have begun. The jejunum, which is about eight feet long, is the most important part of the small intestine as far as nutrient absorption is concerned. This is where the breakdown products of carbohydrates, fats, and protein are absorbed. Vitamin A, vitamin D, water-soluble vitamins, water, minerals, and other nutrients are absorbed into the bloodstream through the jejunum.

The last part of the small intestine is the ileum, which is about 12 feet long. Bile salts and the all-important vitamin B12 are absorbed through the ileum. The ileum terminates at the ileocecal valve, which serves to separate the small from the large intestine. This is an important function, as the large intestine contains huge amounts of bacteria, which would wreak havoc in the relatively sterile environment of the small intestine. The distal portion of the small intestine ends at the cecum, in the lower right quadrant of the abdomen.

#### GUT FERMENTATION AND SMALL INTESTINE BACTERIAL OVERGROWTH (SIBO)

The fermentation of non-soluble sugars by intestinal flora is a normal function of the colon. However, it is not a normal function of the small intestine. When abnormal fermentation takes place in the small intestine, it can lead to fatigue, malaise, irritable bowel, bladder function disorders, depression, and pulmonary problems. More problematically, it can lead to dysbiosis.

A study performed in 2004 in Great Britain by Eaton et al found that patients with abnormal gut fermentation had resulting B vitamin, zinc, and magnesium deficiencies. People with gut fermentation problems have an intolerance to alcohol, and typically crave carbohydrates and sweets, usually chocolates, cookies and bread. These foods, according to the study, “are often consumed in a ‘binge’, followed by a brief period of abstention.”

This disorder has a long history in medical literature. In the early 20<sup>th</sup> century, it was called “germ carbohydrate fermentation,” and in the 1930s, it was described as “intestinal carbohydrate dyspepsia.” It was clear, even then, that the problem originated in the faulty digestion of carbohydrates. In more recent years, the condition has been referred to as small intestinal bacterial overgrowth (SIBO).

Small intestinal bacterial overgrowth (SIBO) is a common problem in CFS/ME, and is closely related to leaky gut and Irritable Bowel Syndrome (IBS), and probably to GERD as well. At one point, Dr. Cheney estimated that the majority of his patients with GI symptoms had SIBO.

The gastrointestinal tract is inhabited by trillions of organisms, primarily bacteria. For the most part, these are “friendly” organisms; in fact we could not live without them. Without these friendly bacteria, known as gut flora, humans would be unable to break down carbohydrates, which would lead to starvation. Intestinal flora are responsible for producing vitamin B12, vitamin K, short-chain fatty acids, and biotin as well as many other nutrients. In addition, gut flora are integral in protecting the gut from pathogens. They regulate immune activity, and maintain the structural integrity of the lining of the gut, preventing toxins and pathogens from entering the bloodstream.

The vast majority of intestinal flora reside in the large intestine, where they perform their essential tasks competently and then, once finished, are flushed out with the feces. (The bulk of feces consists of bacteria.) However, a smaller number of bacteria (approx 1000/ml to 10,000/ml) reside in the small intestine. Among the most important of these are the lactobacilli, which are anaerobic bacteria that convert lactose and other sugars to lactic acid. The lactobacilli are known for their ability to suppress infections, including listeria, Candida, and *H. pylori*, as well as mitigating antibiotic-induced diarrhea. The most familiar strain of lactobacilli, *L. acidophilus*, is found in yogurt and many fermented foods.

The beneficial effects of these bacteria are eradicated when large numbers of foreign bacteria – chiefly those which are found in the large intestine – begin to grow in the small intestine. Once the small intestine is colonized by these strains, there is a multitude of consequences.

The orderly process of digestion is now undermined by bacteria that deconjugate bile before it can be used, leading to an inability to digest fats and

producing nausea and cholecystitis-like symptoms. Carbohydrates, which are normally broken down in the large intestine, are now fermented in the jejunum, leading to bloating, distension and gas. Moreover, the action of these bacteria on proteins leads to excess ammonia production, which, in essence, acts like a poison if not adequately cleared from the system.

Once digestion is impaired (dysbiosis), deficiencies of fat soluble vitamins (A,D,E), as well as deficiencies of B12, thiamine (B1), and nicotinamide (an amine of B3 involved in cognitive function) will result. Most deleterious of all is the resultant inflammation of the lining of the intestine, which leads to malabsorption, leaky gut, immune system upregulation and numerous food allergies and sensitivities.

Because SIBO affects every aspect of small intestine digestive function, it produces a wide range of GI symptoms: diarrhea, weight loss, GI pain, anemia, heartburn, GERD, and constipation.

As might be imagined, SIBO can lead to dysfunctions elsewhere in the GI tract – and beyond. There appears to be a strong association of SIBO with IBS (irritable bowel syndrome). In a 2003 study by Pimental et al, fully 84% of IBS patients tested positive for SIBO. A significant reduction in IBS symptoms was achieved after treatment for SIBO.

SIBO has also been linked to the inflammatory skin condition, rosacea. Several studies have shown that once SIBO is treated, rosacea disappears. Joint pain related to inflammation also improves dramatically when SIBO is treated. Interestingly, treatment of SIBO improves cognitive symptoms in CFS/ME patients, providing further evidence of the link between the gut and the brain.

The most common cause of SIBO is antibiotic treatment. Intestinal bacteria live in a symbiotic relationship with one another. Once several strains of beneficial flora have been selectively removed, others may proliferate unchecked. In addition, the use of broad-spectrum antibiotics, which effectively remove all bacteria, can pave the way for pathogens, such as *Candida* and harmful bacteria.

Slow motility can also lead to SIBO. Normally the steady peristalsis of the small intestine flushes any excess bacteria out into the large intestine, where it can be effectively neutralized. When peristalsis is slowed, bacteria have a greater chance to multiply, and, although the ileocecal valve is designed to prevent a backwash of bacteria from the large intestine, some of the billions of bacteria per milliliter found in the colon may invade the small intestine.

A third major contributory factor in the development of SIBO is the use of antacids, and subsequent hypochloridia. Low stomach acid not only allows for the passage of bacteria which might otherwise have been destroyed in the stomach, it reduces the secretion of pancreatic enzymes which are, in part, stimulated by the acid chyme passing into the duodenum. Once digestion is impaired by a reduction in enzymes, there is additional substrate for bacterial overgrowth.

Diagnosis of SIBO is made by the Lactulose Breath Test (also known as the Hydrogen Breath Test), a simple, non-invasive breath test that you can do yourself. The breath test measures the amount of hydrogen and methane, two gases which

are only produced by bacteria, after the ingestion of lactulose, a non-digestible sugar used to treat mild constipation.

The test can be ordered from Genova Diagnostics in Asheville, NC (800-522-4762) and costs \$130. It is very important that no antibiotics be taken for two weeks prior to the test. It is also important for an accurate result to follow a restricted diet for three days prior to the test in order to “starve” the bacteria. The bacteria particularly like to feed on sugar, complex carbohydrates, and milk. Genova provides a complete set of instructions to accompany the kit.

## TREATMENTS

Ironically, the first-line treatment for SIBO is a hair of the dog that bit you. Antibiotics, often several kinds, are prescribed to reduce the overgrowth. Bacteria quickly develop resistance (and, indeed, if you contracted SIBO as a result of antibiotics, they probably already have), so several rounds are needed to control the overgrowth.

Commonly used antibiotics are Flagyl and doxycycline. Xifaxan (rifaximin), a newer antibiotic that acts solely in the gut, has been successfully used to eradicate not only SIBO but rosacea, indicating a clear link between the two conditions. Because Xifaxan is a non-systemic antibiotic, it is currently the drug of choice for treating SIBO. Generally, antibiotic treatments are given for one week once a month until the infection has cleared.

The second line of treatment, often given simultaneously and/or immediately after treatment with antibiotics, is probiotics. In milder cases of SIBO, antibiotics may be skipped altogether in favor of a probiotic course of treatment. Probiotics of varying strains have been used for treating SIBO, but the more successful varieties have been *Acidophilus GG* (marketed as Culturelle), and *Bifidobacterium infantis* (marketed as Align).

Follow a low-carbohydrate diet. The main role of bacteria in the colon is to break down carbohydrates. If you lower your consumption of carbohydrates, you will give them less to feed on. The list of food to avoid on the lactulose breath test kit basically includes everything bacteria enjoy: milk products, sugar, beans, legumes, soybeans, whole grains, corn, cornmeal, basmati and brown rice, pasta, dried fruit, nuts and seeds, and most vegetables. While avoiding all of these foods would be difficult, one would be well advised to avoid milk and sugar at the very least.

Enteric-coated peppermint oil has been shown to be lethal to bacteria. In one case study, only ten days of treatment with enteric-coated peppermint oil resulted in not only a significant reduction in hydrogen production in the hydrogen breath test, but a reduction in bloating, pain, and belching. It is important to note that the peppermint oil must be enteric coated in order to avoid heartburn.

Increase stomach acid. Hypochloridia is so common in CFS/ME patients that low stomach acid is among the most likely culprits of SIBO. Fortunately, increasing stomach acid is fairly easy. Supplementation with Betaine Hydrochloride (HCl) will increase stomach acid and aid the production of pancreatic enzymes. Start with one tablet with a meal. If you get heartburn, stop and try again in a week or so. (Don't

take the supplement before or after the meal, but during.) Stomach acid can also be aided by taking vitamin C with a meal, or by sipping a dilution of apple cider vinegar (1-2 TBS to 4 oz water.)

Pancreatic enzymes are important adjuncts in SIBO treatments. Enzymes are frequently under-utilized in people with SIBO, due to hypochloridia and bacterial deconjugation of bile. Supplementation with Ultrazyme or another broad spectrum enzyme will aid the process of digestion and limit the substrate available to harmful bacteria.

SEE: Antihistamines, Cytotec, Tagamet and Zantac; Alpha Ketoglutarate, Amino Acids, Antioxidants, Butyric Acid, Digestive Enzymes, Herbs (milk thistle), Vitamins; Acupressure, Acupuncture, Aroma Therapy, Bed Rest.

#### FURTHER READING

DiBaise, John K., MD. "Nutritional Consequences of Small Intestinal Bacterial Overgrowth." *Nutrition Issues in Gastroenterology, Series #69*. 2008.  
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## PERMEABLE INTESTINE (“LEAKY GUT”)

The intestine, unlike the stomach, has a permeable mucous lining that serves as both a screen for unwanted material, notably toxins, and as a sieve for acceptable nutrients. If the mucosa becomes inflamed as a result of damage from bacterial or viral infection, allergic reactions, parasitic infections such as *Giardia lamblia*,



chemotherapy, radiation, or environmental insults, the membrane becomes too permeable, allowing larger molecules to pass through. These larger molecules in turn excite the immune system, creating an allergic-like response to what would normally have been innocuous food by-products. Indeed, many researchers believe that leaky gut is responsible for most food allergies.

According to Dr. Paul Cheney, the vast majority of his patients with gastrointestinal symptoms have leaky gut as the primary underlying problem. While a number of insults can cause leaky gut, Dr. Cheney attributes leaky gut in CFS/ME to low cardiac output, which is common in CFS/ME patients, particularly those with cardiac-related symptoms such as orthostatic intolerance, fainting, tachycardia and low blood pressure (see Cardiac and Cardiovascular Symptoms).

As cardiac output diminishes, other areas of high blood flow are tapped to supply additional blood. More often than not, the blood-rich vessels of the gut are tapped. This is a boon to the heart, but when the blood supply to the gut is diminished, the cells lining the gut become oxygen-starved (hypoxic). The lack of oxygen, in turn, causes the cells to secrete vascular endothelial growth factor (VEGF), which causes capillaries to leak. Once the gut is leaky, bacteria from the gut can enter the bloodstream, causing widespread symptoms, including cognitive impairment. The liver can also become overwhelmed with self-generated toxins. As Dr. Cheney puts it, “You will feel poisoned; in fact you are poisoned. You're poisoned by your own GI tract.”

Small intestine bacterial overgrowth (SIBO) is a major component in the development of leaky gut. An overgrowth of colonic bacteria can be disastrous in the small intestine, leading to a host of GI symptoms, as well as inflammation and subsequent hypersensitivities and immune system dysregulation. As the two conditions often march hand-in-hand (along with IBS), it is worth being tested for SIBO if leaky gut is suspected. (See SIBO above.)

The diagnosis of leaky gut is easy to make, requiring nothing more than a urine test performed after the patient has ingested a special sugar solution. The amount of sugar that passes into the urine is an indication of the permeability of the intestinal mucosa. The test is available from Genova Diagnostics.

## TREATMENTS

Secretory immunoglobulin A (IgA), the most abundant immunoglobulin in external secretions, is essential for maintaining the normal function of the intestinal lining as an immune barrier. The synthesis of secretory IgA requires the amino acid L-glutamine. People with leaky gut can take L-glutamine as a supplement to support the production of secretory IgA. Secretory IgA can be taken orally as Probioplex, or as whey products. If L-glutamine is not well tolerated, it is usually an indication there that there is small intestine bacterial overgrowth (SIBO). In that case, L-glutamine should be halted.

N-acetyl-D-glucosamine (NAG) is another means of strengthening the mucosal layer of the intestines. NAG is a derivative of glucose, and is a precursor in the synthesis of the proteins that form the outer layer of the mucous lining of the

small intestine. Synthesis of NAG starts with L-glutamine, however, in some people the conversion of L-glutamine to NAG is abnormal, resulting in a deficiency. In addition to serving as an important element in formation of the mucosa, NAG promotes the development of beneficial bacteria and inhibits binding of *Candida* to the intestinal wall. PureFormulas.com markets several high quality NAG supplements (e.g., Allergy Research Group, Jarrow).

Gamma-linoleic acid (GLA), found in borage seed oil and evening primrose oil, is an essential fatty acid that serves as a precursor to prostaglandin E1 (PGE1), an anti-inflammatory agent. In both animal and human studies, GLA has been shown to protect the intestinal lining from damage caused by aspirin and other toxins. Most health food stores carry evening primrose oil and borage seed oil. A prostaglandin E1 analogue can also be taken in the form of the prescription drug, Cytotec (misoprostol), which protects the mucous lining of the stomach and small intestine. At lower doses misoprostol increases secretion of the mucus that lines the GI tract. It also increases mucosal blood flow, which, in turn, increases mucosal integrity

Gamma-oryzanol (rice bran oil) is another well-tested product that is effective in treating many gastrointestinal disorders, including duodenal ulcers, chronic gastritis, irritable bowel syndrome, nausea, heartburn, abdominal pain, eructation, and diarrhea. Researchers have proposed that the broad action of gamma-oryzanol is a result of its function as a potent antioxidant as well as its ability to normalize vagus nerve stimulation of gastric secretion. Gamma-oryzanol can be purchased in tablet form by Source Naturals, or as pure rice bran oil from health food stores.

Tocotrienols, which are components of vitamin E, are both powerful antioxidants and potent anti-inflammatories. Tocotrienols can penetrate tissues with saturated fatty layers more efficiently than tocopherols, making tocotrienols, particularly delta tocotrienols, effective against a wide range of inflammatory conditions. Delta tocotrienols are available in health food stores and online through PureFormulas.com.

Low amounts of hypoallergenic insoluble fiber, such as pure cellulose, can help heal leaky gut. Diets low in fiber perpetuate leaky gut, allowing bacteria to pass through the intestinal wall into the bloodstream in a process known as translocation. According to research conducted in 1986 and 1990, insoluble fiber maintains the intestinal barrier by stimulating the synthesis of mucosal growth factors. High amounts of fiber, however, can actually increase leaky gut, so make sure to keep the dosage at a minimum.

In a study published in 2008, Maes and Leunis found that after treating a group of 24 CFS/ME patients with natural anti-inflammatories and antioxidants such as glutamine, N-acetyl cysteine and zinc, in conjunction with a leaky gut diet over a period of 10-14 months, immune system (IgA and IgM) responses to translocated bacteria were normalized. The authors stated that their results support the view that leaky gut with subsequent gut-derived inflammation "is a novel pathway in CFS and that it is a new target for drug development in CFS.

Meanwhile, CFS patients with leaky gut can be treated with specific NAIOSs [natural anti-inflammatory and anti-oxidative substances] and a leaky gut diet.”

Zinc carnosine, a combination of zinc and the amino acid carnosine, has gained clinical attention since the publication of several Japanese studies in the 1990s. Recently, a team of researchers in London has demonstrated that zinc carnosine can both repair injured gut mucosa and protect its integrity. Zinc carnosine also shows promise in protecting the stomach lining from damage due to NSAIDs (non-steroidal anti-inflammatories).

SEE: ButyrEn, Essential Fatty Acids, NAC, Minerals (Zinc), Vitamins (E), Whey Products.

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## LARGE INTESTINE

Beyond the ileocecal valve lies the large intestine, which is where the liquid nutrients left by the small intestine will spend the next 30 to 40 hours. The large intestine begins in a pouch-like structure called the cecum, located in the lower right quadrant of the abdomen. While the vast majority of gut flora consist of anaerobic bacteria, the cecum contains almost entirely aerobic bacteria.

The colon is the part of the large intestine that extends from the cecum to the rectum. It is divided into three main segments: the ascending colon, located along the right side of the body; the transverse colon, which travels along the top of the abdomen; and the descending colon, which follows down the left side and then curves inward to form the rectum. The hepatic and splenic flexures, named after the organs they are closest to (liver and spleen), form the "angles" of the large intestine; the rest is relatively straight, unlike the highly convoluted small intestine.

The large intestine is responsible for the final stages of digestion, removal of excess water from digested food, and the formation of feces. All of these functions are aided by the presence of friendly bacteria, without which food could not be assimilated and processed. By the time the waste products (the remains of ingested food) are ready to be expelled, all that remains is water, bacteria, and undigested cellulose.

Problems in the large intestine are typified by the symptoms of irritable bowel syndrome (IBS): cramping, gas, bloating, constipation, or diarrhea. It is generally thought that these problems stem from faulty gut motility, that is, the rate at which the intestines propel food along is somehow out of sync. Recent research, however, suggests that "upstream" problems such as SIBO, hypochloridia, and gastroparesis (slow stomach motility) may lead to IBS. Bowel problems caused by sympathetic nervous system arousal (which alters motility), *Candida* overgrowth, underactive thyroid, viral infections, SIBO, and food sensitivities, are commonly found in the CFS/ME population.

## IRRITABLE BOWEL SYNDROME (IBS)

Much like ulcers, irritable bowel syndrome (IBS), was originally thought to be the product of neurosis, or, to use the more contemporary term, “anxiety.” Classic symptoms typical of IBS are: bloating, diarrhea, constipation, and abdominal pain.

As with other hard-to-diagnose syndromes, there is a set of criteria that is often referred to when making a diagnosis. The official “Rome III” diagnostic criteria for IBS are:

At least 3 months, with onset at least 6 months previously, of abdominal pain or discomfort associated with 2 or more of the following features:

- The pain is relieved by defecation, and/or
- The onset is associated with a change in frequency of bowel movements
- Onset is associated with a change in the appearance of bowel movements.

Other symptoms which may be included, but are not necessary for diagnosis are:

- Abnormal stool frequency (greater than 3 movements a day, or less than 3 movements a week)
- Abnormal stool form (lumpy/hard/loose/watery)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension.

These admittedly vague criteria allow gastroenterologists to arrive at a speedy diagnosis after performing a handful of tests to rule out problems that can be easily treated by drugs or surgery – which is probably why IBS is the most frequently diagnosed GI ailment in the country. Invariably, the patient is left with continuing symptoms, and with the uncomfortable feeling that he or she is somehow at fault.

In the majority of cases, functional problems of the gut are preceded by intestinal infections. Parasitic infections are commonly associated with IBS, as are enteric bacterial infections. However, it is not entirely clear whether the infection itself leads to functional problems, or the cure (antibiotics). Ensuing alterations in gut flora from antibiotic treatment will produce all the symptoms of IBS.

The large intestine is inhabited by somewhere between 100 and 1000 *trillion* microorganisms. This is roughly 10 times the total number of cells in our bodies. There are more than 1,000 species of microorganisms and 7,000 strains, consisting mostly of anaerobic bacteria. As well as performing necessary metabolic and digestive functions, these bacteria are responsible for maintaining the health and integrity of the gut. Once these bacteria are eradicated by antibiotics, functional problems (e.g., diarrhea, constipation, gas, bloating, changes in stool frequency, or appearance) are not only inevitable, they are completely predictable.

Logically speaking, in order for a bowel to be irritated, something must be irritating it. In some cases, IBS may be misdiagnosed during the course of a parasitic infection. *Giardia lamblia*, a protozoan parasite, can be difficult to diagnose with a stool test, as it colonizes the upper part of the small intestine. Because the symptoms are identical, cases of giardiasis may be incorrectly

diagnosed as IBS. (In a 2006 study, Grazioli et al found that 6.5% of patients diagnosed with IBS had ongoing giardiasis.)

Irritation can also be due to “upstream” problems with the stomach (especially hypochloridia), small intestine problems (including leaky gut, SIBO, and ongoing infections), mistiming of peristaltic contractions by the enteric nervous system, oxidative stress, and alterations in gut flora. The only way to fix IBS is to address the underlying cause, which will result in a gut that is less irritable – and less irritating.

Interestingly, a recent study conducted at the University of Gothenburg in Sweden found that patients with IBS exhibited alterations in gut hormones called granins. The granins are a family of prohormones secreted by the endocrine system which have various effects on the nervous, immune and endocrine systems. In the gut, they are often associated with inflammation and immune activation, particularly apoptosis of carcinoid cells. Patients with IBS showed high amounts of secretogranin II and low amounts of chromogranin B. The researchers believe that the alteration of granins may lead to a test which would serve as a biomarker for IBS.

However, of even greater significance is the fact that immune system activation, one to the principle underlying mechanisms of CFS/ME, may play a primary role in the development of IBS.

## TREATMENTS

In an interesting study of the use of melatonin for treating IBS conducted by Lu et al in 2005, 88% of the patients reported significant improvement of their GI symptoms after 8 weeks of treatment with melatonin as opposed to placebo.

Supplements that contain butyric acid (ButyrEn, Butyrex) are enormously helpful for all large intestine problems. Butyrates are vital nutrients for cells that line the colon. Without butyrates, these cells will die.

Probiotics are crucial for maintaining a healthy bowel, especially after a course of antibiotic therapy. Bifidobacteria are essential for colonic health. Prebiotics, such as inulin and FOS, which stimulate the growth of bifidobacteria should be taken in conjunction with probiotics – unless SIBO tests are positive. (With SIBO, prebiotics will simply be feeding the bacterial infection in the small intestine.)

SEE: Butyric Acid, Melatonin, Probiotics

## GAS

Flatulence is common in IBS. In the large intestine, gas tends to accumulate at the hepatic and splenic flexures, sometimes causing severe pain that radiates to the shoulders. Gas trapped at the hepatic flexure may cause such sharp pain that it precisely mimics a gallbladder attack or even a heart attack.

Gas, or flatus, is principally composed of five gases: nitrogen, oxygen, methane, hydrogen, and carbon dioxide. The first two, nitrogen and oxygen, are

found in air. The last three result from the metabolic processes of bacterial flora in the colon. While methane is popularly associated with flatulence, it appears that two-thirds of all humans do not have sufficient anaerobic bacteria in their colons to produce methane. (In an interesting aside, it is the incorporation of gas into feces that produces floating stools. In patients with GI infections and/or malabsorption, floating stools result mostly from gas and water content rather than fat content.) The foul odor of intestinal gas is due to sulfur-containing gases (methanethiol, dimethyl disulfide, and dimethyl trisulfide) that result from the breakdown of proteins.

Carbohydrates are the main source of flatulence. Hydrogen and carbon dioxide gas are produced in the colon during the process of digesting carbohydrates that can't be broken down by the small intestine, particularly starches. Gluten impairs the complete absorption of starch in most flours, even in people who do not have celiac disease, resulting in gas. (The only flour that is completely absorbed is rice flour, which does not contain gluten.) Lactose intolerance, caused by a deficiency of the enzyme lactase, which is responsible for breaking down the sugar in milk, also leads to the production of gas. Baked beans, soybeans, and other legumes result in increased production of hydrogen and carbon dioxide gas by colonic bacteria.

## TREATMENT TIPS

Treatment of gas is, for the most part, preventive. Foods that cause gas, such as onions, cabbage, broccoli, cauliflower, Brussels sprouts, milk (for those with lactose intolerance), and foods that are difficult to digest (beans) or to which there are sensitivities should be avoided. Gluten-free products will help reduce gas produced by starches.

Supplementing with enzymes is particularly helpful for those with compromised digestion. Because small intestine problems are rife in people with CFS/ME, an all-round enzymatic supplement which includes proteolytic enzymes for breaking down protein, lipase for fats, and amylase for carbohydrates is preferable over single enzyme supplements. The addition of Betaine HCl is also beneficial for enhancing digestion “upstream.” It goes without saying that treating SIBO will vastly reduce the amount of gas produced by bacterial overgrowth.

Some spices, notably cumin, caraway and turmeric can reduce gas. Charcoal tablets, if taken with known gas-producing foods, can also help reduce flatulence.

Food should be chewed thoroughly to maximize the breakdown of carbohydrates, which begins in the mouth with the salivary enzyme, amylase. If bloating and acidity occur immediately after eating, a little baking soda can help dispel gas before it descends to the intestines.

Peppermint tea or peppermint products are also effective as treatments for gas. For those with severe digestive problems, peppermint essential oil can be used in the form of aromatherapy for rapidly dispelling gas.

## DIARRHEA

Many people with CFS/ME experience diarrhea, particularly during the acute stage when the sympathetic nervous system is upregulated. In some cases, diarrhea can be severe, requiring medical interventions such as cortisol injections.

Diarrhea is basically caused by intestinal dysmotility. Intestinal motility consists of two kinds of contractions: segmental contraction, which mixes food, and propulsive contraction, which helps move the contents of the intestines forward. When propulsive contractions are too frequent or strong, food is passed along rapidly, resulting in diarrhea.

Anything that causes the small intestines to become inflamed will produce diarrhea, as will a number of toxins (cholera, typhoid), viruses, parasites (*Giardia*, amoebas), as well as nervous system or endocrine disorders. Food sensitivities, particularly lactose (milk sugar) intolerance, can produce mild or intermittent diarrhea.

## TREATMENTS

If diarrhea is severe, a doctor may prescribe an antispasmodic medication to slow intestinal motility. Questran, a bile sequestrant, will stop cases of severe diarrhea very quickly. Less severe cases may respond to over-the-counter antidiarrheal medications. Pepto Bismol (bismuth salicylate) will absorb toxins, but will not affect intestinal flora.

If food sensitivities are suspected, an elimination diet may be helpful. Avoiding the most common symptom-causing foods, such as milk, wheat, fructose and sorbitol (these are two sweeteners that often cause effects similar to lactose intolerance), citrus, and eggs can be helpful. Stevia, another non-sucrose sweetener, may also cause diarrhea. Certain drugs and medications can also cause diarrhea, so the medicine cabinet should be checked if diarrhea has started suddenly or worsened recently.

Good hydration is vital during episodes of diarrhea. If you become dehydrated, electrolyte solutions, such as Pedialyte, are essential. These can be purchased or made at home by mixing  $\frac{1}{4}$  tsp of table salt and  $\frac{1}{4}$  tsp of salt substitute (potassium chloride) into two cups of water.

## CONSTIPATION

Many, if not most people with CFS/ME experience constipation. Constipation is basically an alteration of peristalsis in which segmental contractions predominate over propulsive contractions. This leads to slowed movement through the bowel and increased reabsorption of water. Typically the symptoms of constipation are infrequency (fewer than three bowel movements a week), straining, small pellet-like or round stools, and hard stools. Low fiber diets, dehydration, dysautonomia, and hypothyroidism can all lead to constipation.

Diet restrictions that limit the intake of fresh fruits and vegetables can result in a decrease of dietary fiber. The absence of sufficient fiber creates a situation in which the bowel is not stimulated enough to produce regular contractions, resulting in slowed bowel motility, or constipation.



Another source of constipation in CFS/ME is dehydration. Hypovolemia (low blood volume), which is a common finding in CFS/ME patients, can force the bowel to conserve water, compacting feces and slowing their movement through the colon.

Metabolic changes can also lead to constipation. The alteration in cell metabolism common in people with CFS/ME (*CFIDS Chronicle*, Spring 1995) results in an increased tendency for anaerobic cell metabolism. Anaerobic cell metabolism requires more water than aerobic cell metabolism. If the extra water is not available, whether due to inadequate intake or mineral imbalances, dehydration results. As a person becomes dehydrated, more water is removed from the feces and stools become smaller, more compact, and more difficult to expel.

Parasitic infections can cause constipation as well as diarrhea (often alternating). Similar symptoms are produced when gut flora have been reduced by antibiotic treatment.

Constipation due to diet restrictions should improve with a small increase in fiber. For people with many food sensitivities, fiber should be taken as a hypoallergenic powder. Psyllium husk and flax seed powder are good sources of dietary fiber when food sensitivities are not a problem.

Water intake should also be increased (eight glasses is enough). In order to enhance water retention and reduce the effects of low blood volume, electrolytes should be added; ¼ tsp of salt and ¼ tsp of potassium (“No Salt”) can be added to 2 cups of water.

For those who can tolerate dried fruit, the old home remedy of a few prunes, or prune juice, is effective. Probiotics will help those who are constipated after a course of antibiotics. Laxatives are generally not recommended by physicians for long-term use because they ultimately lead to dependence.

SEE: Cardiac and Cardiovascular Problems (Dysautonomia)

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## RECTUM

At the nether end of the digestive tract is the rectum. Like the esophagus at the head of the GI system, the tail end is also directly controlled by the central nervous system. This allows for a certain amount of conscious control over the function of the rectum, which is important for obvious reasons. (Otherwise, we would all still be in diapers.) Predictably, for CFS/ME patients, the main problem that arises in this region is neurogenic pain and cramping, notably proctalgia fugax (acute pain) and tenesmus (a continual cramping sensation).

## PROCTALGIA FUGAX

Proctalgia fugax literally means a “transient pain in the butt.” (Medical conditions sound so much better in Latin.) It is characterized by an intense pain that feels just like a charlie horse, occurring most often at night. Although it can be triggered by severe diarrhea, the cause of proctalgia fugax appears to be neurological. In 2005 a Japanese researcher treated 68 proctalgia fugax patients with a pudendal nerve block. Symptoms disappeared in 65% of the patients, and diminished in 25%. Given the prevalence of neuropathic pain in CFS/ME patients, it is most likely that the cause of proctalgia fugax is an irritation of the pudendal nerve.

## TREATMENT

If the cramp does not disappear on its own after a few minutes, sitting on the toilet can help relax the muscles. The application of a warm washcloth also will help the sphincter muscles relax. When cramps occur on a regular basis, many doctors

recommend taking a small amount of a benzodiazepine before bed. In this instance, the tranquilizer basically has the effect of a muscle relaxant.

## TENESMUS

Tenesmus is a feeling of constantly needing to defecate, even when the rectum is empty. It is commonly associated with IBS and inflammatory bowel conditions which affect motility. The primary cause of tenesmus in CFS/ME patients is dysautonomia. Because the rectum is controlled by the autonomic nervous system, any alteration in the balance between sympathetic and parasympathetic function will affect defecation. This phenomenon is manifested in situations of extreme fright, in which a sudden increase in sympathetic activity releases excessive stress hormones. This release of stress hormones is countered by an equally strong response in parasympathetic function, which causes the anal sphincter to spontaneously loosen.

Acetylcholine (ACh), the neurotransmitter associated with parasympathetic function, is closely associated with defecation. Stimulation by acetylcholine serves to relax the anal sphincter, allowing the contents to be discharged. Several studies have shown that patients with CFS/ME are hyper-responsive to acetylcholine (a finding which is consistent with the acetylcholine-deficit theory posited by Snorrason and Stefansson in 1996). The excessive response to stimulation by acetylcholine can result in tenesmus, or the continuing sensation of needing to evacuate.

## TREATMENTS

Because tenesmus is associated with autonomic nervous system dysregulation, it is difficult to treat as an isolated symptom. Any treatment that helps regulate dysautonomia – including small doses of benzodiazepines, increasing blood volume via fluid and salt intake, and biofeedback – will help relieve tenesmus. Increasing insoluble fiber in small amounts also seems to help relieve tenesmus by improving gastric motility.

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## DIZZINESS AND VERTIGO

Vertigo can add a very unsettling element to CFS/ME. When the world suddenly turns sideways, starts spinning, or will not hold still, all activity comes to a halt. Simply lying in bed can be a Herculean task for people with severe vertigo, which, along with spatial disorientation, can produce nausea, headache, sweating, faintness, and feelings of panic. Many people with CFS/ME experience vertigo as an inability to watch television or read. Others merely feel mild, transient dizziness.

Vertigo is often caused by an inner ear problem. The function of the labyrinth, the part of the inner ear that controls balance, can be altered as a result of viral or bacterial infection (labyrinthitis), reduced blood supply to the ear, or conditions that affect the brain, such as migraine. Balance disorders can also be caused by eye problems. Optometrist Dr. Roderic W. Gillilan says motion sickness can be caused by sensitivity to rapid eye movements, particularly when seeing motion. In order to cure them of this problem, his patients undergo a process of desensitization called "dynamic adaptive vision therapy," in which they relearn how to use their eyes.

According to Dr. Samuel Whitaker, an otologist at the University of California at Irvine, patients with CFS/ME may have a viral infection of the inner ear that causes a balance defect. Dr. Whitaker examined 11 CFS/ME patients with vertigo and found that all had a viral condition called "endolymphatic hydrops" (*CFIDS Chronicle*, Summer 1993). Patients with this condition are unable to adjust to the difference between what they are seeing and what their inner ear is telling them about their environment. They may feel their bed is on its side and clutch it so as not to fall off, even though they can see it is still horizontal. This condition is may be caused by the reactivation of viruses found in most patients with CFS/ME. Other causes of vertigo related to ear problems may be due to alterations in inner ear fluid pressure caused by allergies, Candida, infection, and sinus problems.

Bouts of dizziness and light-headedness are closely linked to dysautonomia as well. In dysautonomia, the sympathetic nervous system, which controls "fight or flight" responses (e.g., heart rate, blood pressure, pupil dilation, glucose release) is dysregulated, causing a cascade of vascular symptoms. These include sudden drops in blood pressure, especially when standing (orthostatic hypotension), increase in heart rate upon standing (POTS), as well as a constellation of nervous system symptoms such as anxiety, panic, and flushing. Hypoglycemia, which can be caused by dysautonomia, reduces glucose supplies to the brain, which results in light-headedness and dizziness.

In a 2006 study, a group of Israeli researchers found that hypocapnia (hyperventilation due to low CO<sub>2</sub> levels in the blood) occurred in 9% to 27% of CFS/ME patients. Of the CFS/ME patients, 20% had reported spells of dizziness. The authors attributed the hyperventilation in CFS/ME patients to hypotension, though they observed that it also occurs in the absence of low blood pressure.

It is interesting to note that Dr. Cheney observed spontaneous hyperventilation in his severely ill patients. This does not mean that these patients were somehow breathing wrong, but that their blood level of CO<sub>2</sub> was low. The low

level of CO<sub>2</sub> cause sympathetic nervous system arousal, which in turn narrows blood vessels, restricting oxygen. This produces chest pain and irregular heartbeat, numbness, dizziness, fainting, seizures, tingling sensations in the face and hands, paralysis, chills, blurred vision, and panic attacks (which is why people with panic attacks are told to breathe into a paper bag – it increases CO<sub>2</sub> in the blood).

Notably, these are all symptoms of POTS.

Several medications commonly prescribed to treat CFS/ME (tricyclic antidepressants, for example) can cause vertigo as well. Patients who experience dizziness after starting a new medication should check with their doctor.

## TREATMENTS

Diamox, a diuretic normally used to treat cognitive disorders in CFS/ME, may help alleviate inner ear problems because it reduces fluid pressure. Other blood pressure medications sometimes used in CFS/ME, such as nitroglycerin and calcium channel blockers, may also help when ear problems are caused by excessive pressure.

Antivert, an antihistamine, is commonly prescribed to treat vertigo. Dramamine or scopolamine may be prescribed if Antivert is not effective. It should be noted, however, that because medications containing scopolamine affect neurotransmission in the brain, they may produce unwanted psychological and neurological side effects in people with CFS/ME.

Pharmaceutical treatments for dysautonomia, primarily beta-blockers and Florinef, will help reduce dizziness and vertigo caused by orthostatic intolerance. However, many people with CFS/ME respond poorly to these medications.

Clonazepam in low doses appears to be the most effective pharmacological means for treating dysautonomia in CFS/ME patients, and this may help control dizziness. Complementary treatments such as fish oil (which down regulates the sympathetic nervous system), licorice (which increases blood pressure), ginkgo (which improves blood circulation) and high-salt diets (to increase blood volume) as well as saline drips all help regulate the sympathetic nervous system.

SEE: Candida, Dysautonomia, Hypoglycemia; Antihistamines, Benzodiazepines, Calcium Channel Blockers, Diamox, Nitroglycerin; Herbs, Vitamins (B).

## MORE INFORMATION

Vestibular Disorders Association: <http://www.vestibular.org/>

*Excellent article on hypocapnia:* <http://www.livestrong.com/article/273319-the-indications-of-low-carbon-dioxide-in-the-blood/>

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## ENDOCRINE DISTURBANCES

### Thyroid Disorders, Adrenal Glands

The endocrine system is composed of a set of glands that secrete hormones directly into the bloodstream (as opposed to the exocrine system, which utilizes ducts). The endocrine hormones regulate basic physiological functions such as metabolism, growth, reproduction, and sleep. Unlike the nervous system, which generates rapid responses, the effects of the endocrine system are slow and prolonged, lasting from a few hours to several weeks. The endocrine system is comprised of the hypothalamus, the pituitary, the thyroid, the parathyroid, the pineal glands, the adrenals, the pancreas, and sexual glands (ovaries and testicles).

In an article published in the *CFIDS Chronicle* in Spring 2003, Dr. Theodore C. Friedman, a professor of endocrinology at the Charles R. Drew University of Medicine & Sciences, assembled a list of fatigue-related symptoms typical of endocrine disorders. The list bears a striking resemblance to many symptoms commonly found in CFS/ME.

<i>Symptoms suggestive of an Endocrine Cause of Fatigue</i>	<i>CFS/ME Symptom</i>
Irregular periods in women	Yes
Depression	Yes
Sleep disturbances	Yes
Loss of memory	Yes
Trouble concentrating	Yes
Carbohydrate cravings	Yes
Decreased interest in sex	Yes
Trouble with erections in men	Yes
Osteoporosis	Yes
Breast discharge	Yes, but infrequent
Body hair growth in women	Yes, but infrequent
Weight loss	Yes

Weight gain in spite of dieting	Yes
Dizziness on standing	Yes

While Dr. Friedman does not make the claim that CFS/ME originates in the endocrine system, based on symptoms alone it would be nearly impossible to distinguish CFS/ME from many endocrine disorders. However, the majority of CFS/ME patients when tested for established endocrine illnesses such as thyroid disease, diabetes, Cushing's Syndrome, and primary adrenal insufficiency fall within normal parameters. Falling within the norm, however, does not mean that the endocrine systems of CFS/ME patients are functioning as they should.

In 1991 Demitrack et al published what was to be a landmark study demonstrating abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) in patients with CFS/ME. (The HPA axis is the primary driver of the endocrine system.) The results of this study showed decreased levels of cortisol, blunted response of the pituitary gland to CRH, and enhanced sensitivity to ACTH. While the test results ruled out primary adrenal insufficiency (Addison's disease), they did indicate a dysregulation in the HPA axis, one which would lead to excessive fatigue, as well as many other symptoms typical of low adrenal function. The authors concluded that their test results indicated “a mild central adrenal insufficiency” in CFS/ME, most likely originating in the hypothalamus.

On the heels of Demitrack's research, further studies were conducted, some of which confirmed the original study, and some of which refuted it. Nevertheless, as research becomes more refined, studies increasingly support the theory that HPA dysfunction, if not the central cause of CFS/ME, is certainly the result. Whether instigated by neuroinflammatory responses, upregulation of the immune system, or chronic stress, there is now a substantial body of research indicating widespread abnormalities in endocrine function in CFS/ME patients. These typically include mild hypocortisolism, blunted ACTH responses in challenge tests, and enhanced negative glucocorticoid feedback.

Given the preponderance of hormone-related problems experienced by women with CFS/ME, it makes sense to investigate and treat endocrine disturbances, even if these are secondary.

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## THYROID DISORDERS

The thyroid is a butterfly-shaped gland located at the base of the neck just under the Adam's apple. It is regulated by the pituitary gland, which in turn receives instructions from the hypothalamus. Like the other hormone-secreting glands of the endocrine system, the thyroid's effects are far-reaching. The basic function of the thyroid gland is to regulate body metabolism (the rate at which the body uses calories to produce energy), which it accomplishes by secreting regulatory hormones. If the thyroid secretes excessive amounts of these hormones (hyperthyroidism), the body's metabolic rate increases, resulting in weight loss, nervousness, rapid heartbeat, heat intolerance, rapid growth of hair and nails, muscle weakness, and frequent bowel movements with soft stool.

If too few of these hormones are secreted (hypothyroidism), the metabolic rate slows, resulting in weight gain, lethargy, cold intolerance, rough, dry skin and brittle nails and hair, constipation, hair loss, edema (facial edema creates the puffy eyes characteristic of hypothyroidism), muscle soreness (due to water retention), memory loss, reproductive problems (infrequent ovulation, miscarriage, short menstrual cycles), and, in some patients, balance problems and difficulty walking. The symptoms of hypothyroidism so closely match those of CFS/ME that in most cases patients undergo thyroid testing—in some cases, a number of times—long before the diagnosis of CFS/ME is considered.

Hypothyroidism can result from either excessive or low iodine intake, certain medications (lithium), radiation, and from viral infections. (Two of the herpesviruses commonly found in CFS/ME patients, cytomegalovirus (CMV) and human herpes 6 (HHV-6), use the thyroid as a reservoir.) The most common cause of hypothyroidism, however, is chronic lymphocytic thyroiditis, or Hashimoto's disease. In Hashimoto's disease the thyroid becomes underactive as the result of an autoimmune response in which the immune system attacks thyroid gland tissue.



The resulting inflammation (thyroiditis) impairs thyroid function. If thyroid dysfunction is the suspected cause of symptoms, blood tests can be performed to determine concentrations of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). Thyroid antibody testing is performed if Hashimoto's disease is suspected.

Dr. Thomas Steinbach, a CFS/ME specialist (now retired) who practiced in Houston, Texas, found that 30% of his patients demonstrated thyroid dysfunction (as indicated by blood tests). The chief problem encountered in this group was decreased thyroid function, or hypothyroidism. In most people with CFS/ME, however, thyroid test results are normal, which is not surprising, because the thyroid problems are not due to primary thyroid failure but to dysregulation of hypothalamic hormones, which control activity of the thyroid gland.

In *The Doctor's Guide to Chronic Fatigue Syndrome*, Dr. David Bell speculates that the excess cytokine production brought about by CFS/ME could create functional impairment of the thyroid, not by altering the amounts of thyroid hormones, but by blocking their effect. This type of hormone problem (known as thyroid hormone resistance) would not be detected by standard thyroid tests, nor would impairment of hypothalamic hormones that regulate thyroid function.

When thyroid dysfunction is not the underlying cause of symptoms, the disorder is referred to as secondary, rather than primary, hypothyroidism. It appears that this is true of many people with CFS/ME, especially those with either inconsistent hypothyroid symptoms or symptoms that fluctuate between those of hypothyroidism and hyperthyroidism.

## TREATMENTS

Diagnosed hypothyroid conditions are usually treated with a thyroid hormone substitute (Synthroid or levothyroxine, and Cytomel). A naturopath may recommend kelp, thyroid gland extracts, or Armour thyroid. Nature-Throid, a hypoallergenic combination of thyroxine (T4) and triiodothyronine (T3) derived from natural sources, is increasingly being prescribed by integrative physicians as an alternative to synthetic formulations.

Certain foods should be avoided, such as kale, rutabaga, cabbage, and turnips, because they contain goitrogens (chemicals that can interfere with thyroid hormone production).

Treatment with thyroid hormones is not risk-free. Taking thyroid replacement hormones will essentially shut down the thyroid. Unlike taking hormones for birth control, which do not affect hormone production in the ovaries once discontinued, the thyroid stops functioning once thyroid hormones are replaced. Along the same lines, taking high doses of T3 can cause heart attack, even in an individual for whom thyroid replacement therapy is warranted. This means that there are pronounced risks associated with embarking on a course of thyroid hormone treatment without a firm rationale.

Dr. James Burton believes that while some doctors believe that a subtle form of hypothyroidism is common in CFS/ME patients, this form of subclinical

hypothyroidism is not recognized in the mainstream medical community. He observes that subclinical hypothyroidism can be treated with thyroid hormones and many patients improve on it; however, “the safety and long-term efficacy of this treatment is in question.”

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#### ADRENAL GLANDS

The adrenal glands are small, almond-shaped glands located at the top of the kidneys. Their main function is to produce hormones that regulate and respond to the body's reaction to stress. Adrenaline (epinephrine) and noradrenaline (norepinephrine)—the adrenal hormones produced in the inner part of the adrenal glands (the medulla)—speed up the nervous system to produce the well-known “fight-or-flight” response. The corticoid hormones—those hormones produced by the outer part of the adrenal glands (the cortex)—control water retention, inflammation, and immune system function.

The symptoms produced by adrenal dysfunction are among the more troublesome in CFS/ME because they carry a sense of urgency or panic. Typical adrenal, or catecholamine, symptoms are rapid heartbeat, chest pain, hyperventilation, and panic attacks. This set of symptoms indicates that too much adrenaline is being released into the body, overstimulating the sympathetic nervous system. Most acutely or severely ill people experience these symptoms frequently, particularly when under any kind of stress.

Curiously, the opposing set of symptoms, or those related to under-active adrenal function, are also common in people with CFS/ME. These include intolerance to cold and heat; lowered resistance to infections, toxic drugs, trauma, fatigue, and stress; hypoglycemia; low blood pressure; and, eventually, disturbance of electrolyte metabolism (excess excretion of sodium and retention of potassium).

Although these two problems seem very different, they are actually part of the same type of impairment that besets the thyroid. Like the thyroid, the adrenal glands are controlled by the pituitary gland and hypothalamus. By extension, the adrenal symptoms found in CFS/ME do not really represent primary failure of the

adrenal glands (as in Cushing's disease or Addison's disease), but are a consequence of brain signal abnormalities.

Studies performed by Dr. Mark Demitrack and associates confirm that the main problem with adrenal hormone production in CFS/ME arises from the hypothalamus (*Journal of Clinical Endocrinology and Metabolism*, 1991). It seems that the adrenal glands either under-react or over-react to stimuli, producing too much hormone when the stimulus is slight and none when the stimulus is great.

## TREATMENTS

The hypothalamus responds to all kinds of input (psychological, emotional, sensory) and thus adrenal output can be controlled using a number of techniques.

Meditation, stress reduction exercises, and self-hypnosis can all be effective treatments. Supplements for adrenal support include vitamin B12, vitamin C, vitamin B5 (pantothenic acid), zinc, and adrenocortical extract.

The herbs astragalus and licorice have been used with some success to support adrenal function as well. Low dose hydrocortisone is sometimes administered to severely ill patients, although its use in CFS/ME is controversial.

In less severely ill patients, low doses of beta blockers may be recommended, accompanied by careful monitoring of blood pressure. Stimulants, which act on the adrenal glands, are usually reserved for mild cases of CFS/ME, because they cause worsening of symptoms in the severely and moderately ill.

Those who experience faintness upon standing, bouts of nausea, tachycardia, chest pain, and other cardiac-related symptoms are probably suffering from dysautonomia. Treatments for dysautonomia will be effective in controlling many adrenal hormone-related sympathetic nervous system symptoms. (Please see section on Dysautonomia for more details.)

SEE: Dysautonomia; Beta Blockers. Florinef; Herbs, Minerals, Vitamins; Aroma Therapy, Biofeedback, Hypnosis, Meditation; Stress Reduction and Elimination.

## FATIGUE

Postexertional Fatigue; Lethargy; Agitated Exhaustion

Every person with CFS/ME suffers from fatigue. The term "fatigue," however, does not do justice to what people with CFS/ME experience. People with CFS/ME often find themselves at a loss for words when it comes to describing how exhausted they feel. Patients come to their doctors saying they feel "crushed," "totally wiped out," "comatose," or "paralyzed." Because the fatigue of CFS/ME falls so far outside the realm of normal tiredness, doctors are often skeptical when patients can't get out of bed, or lift a hairbrush.

The truth is that CFS/ME fatigue is unique. In its severe form it is an all-encompassing nightmare. It can rob a person of livelihood, family, career, hope, will, and feeling. Even in its milder forms, CFS/ME fatigue can put a stop to most

activities. Whether mild or severe, “fatigue” is a profound understatement, as it cannot capture the utter loss of vitality experienced by people with CFS/ME.

More than an understatement, the word "fatigue" is misleading, because its widespread use has led to a dismissive attitude on the part of the medical establishment, which views fatigue as a normal part of modern life. Considering the lack of adequate terminology to describe CFS/ME fatigue, it is incumbent on the CFS/ME community—clinicians, researchers, and patients alike—to find new terms to convey what is meant by "fatigue."

There is nothing normal or natural about the fatigue experienced by people with CFS/ME. Unlike the state of tiredness a person might feel after a busy day, the fatigue produced by CFS/ME is not relieved by a good night's sleep, in fact, it may even be worse upon waking. Neither is it relieved by a workout, a protein snack, a change in lifestyle, a vacation, or any of the other measures that normally help the healthy person "recharge." The reason none of these measures work is self-evident. CFS/ME fatigue is not the natural product of exertion. It is a reflection of the deep metabolic, neurological, and immunological dysfunction wrought by illness.

The ultimate cause of fatigue in CFS/ME has not yet been established, because the cause of the disease itself remains undetermined. However, there is ample evidence that the mechanisms of CFS/ME, which cause immune system dysregulation, oxidative stress leading to mitochondrial failure, and injury to the central nervous system all contribute to the exhaustion that is the most salient symptom of CFS/ME.

Central fatigue, that is fatigue generated by the central nervous system (CNS), has been implicated as the source of the unrelenting exhaustion characteristic of CFS/ME. Numerous studies have confirmed abnormalities in the brains of CFS/ME patients.

One of the earlier studies, conducted in 1994 by Schwartz et al, found significantly more defects throughout the cerebral cortex of CFS/ME patients on SPECT scans. These defects correlated with clinical status. A further study by Costa et al found evidence of hypoperfusion in the brain stems of CFS/ME patients. More recently, a study by Barnden et al found that in the midbrain, white matter volume decreased with increasing duration of the illness, which would seem to indicate a process that is cumulative. The researchers concluded that their results were consistent with an insult to the midbrain at onset, resulting in an inability to maintain homeostasis.

In confirmation of the ongoing nature of that process, Chaudhuri and Behan found that in CFS/ME patients, choline levels in the occipital cortex and basal ganglia were raised. The researchers concluded that the increase in choline was probably due to increased phospholipase activity (the enzyme that breaks down the phospholipids that make up cell walls). They theorized that viral activity could possibly contribute to the increased choline, as many viruses increase the activity of phospholipase.

All of these studies point to central nervous system involvement in the ongoing pathology of CFS/ME, but they do not explain why these CNS abnormalities persist long past the initial stage of the illness.

Martin Pall has proposed that oxidative stress caused by nitric oxide and peroxynitrite by-products, which he calls the NO/ONOO<sup>-</sup> cycle (“No! Oh no!”), produces the central abnormalities found in CFS/ME patients. In Dr. Pall's NO/ONOO<sup>-</sup> cycle theory, nitric oxide (NO) and peroxynitrite (ONOO<sup>-</sup>), two oxidants, form a positive feedback loop in the cell, leading to activation of neuroexcitatory NMDA receptors. The net result of prolonged NMDA activation is neurotoxicity due to oxidative stress.

The 2003 Chaudhuri and Behan study lends support to Pall's hypothesis. An increase in choline can signal an inflammatory process (even in the absence of NAA). The mechanism which induces release of choline (which Gasull et al identified as an inhibition of phosphatidylcholine synthesis), is closely related to NMDA receptor activity. One of the results of increased NMDA receptor activity is an increase in the production of inflammatory cytokines.

The normal immune system response to disease or infection causes a release of cytokines, especially interleukin-1. Many of these cytokines not only generate fever and flu-like symptoms but also promote slow (delta) wave activity in the brain. (Delta waves are normally found during deep sleep.) This type of immune activation leads to exhaustion in CFS/ME, not only by causing damage to the cells, but by slowing brain waves.

In addition, the release of cytokines – whether as part of the NO/ONOO<sup>-</sup> cycle, or as a response to latent viral infection – alters the metabolic function of the cell, in particular, the energy-producing mitochondria. What this means is that people with CFS/ME experience fatigue at the cellular level. With a disturbance of the body's energy-producing processes, specifically, disruption of adenosine triphosphate (ATP) production in the mitochondria, the body cannot recuperate its energy stores. The result is overwhelming exhaustion—at every level.

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## POSTEXERTIONAL FATIGUE

Although exercise is normally recommended to help alleviate tiredness, in CFS/ME exercise not only exacerbates fatigue, it can bring on a general worsening of all symptoms. In fact, fatigue and malaise that are directly generated by exertion defines CFS/ME. In severe cases, any form of exertion – a shower, a trip to the store, or balancing the checkbook – can trigger postexertional fatigue. In milder cases, more exertion is required to trigger postexertional fatigue, but the outcome is the same. Typically, the next day brings on a deepening of exhaustion and an exacerbation of all other CFS/ME symptoms. This exacerbation of symptoms can last for several days, until energy stores are replenished. It is this distinctive feature that should alert the attentive physician to the presence of CFS/ME.

The excessive fatigue that comes after exercise, or exertion, is directly related to metabolic responses that in CFS/ME have gone awry. Normally, metabolic processes increase after exercise. Blood circulates faster; heart rate increases, providing more oxygen to muscle tissue; and cortisol is released. In CFS/ME, exercise produces the reverse. heartbeat does not increase sufficiently to provide extra oxygen, leaving a person out of breath, tired, and, more crucial, without sufficient blood supply to the brain.

Numerous laboratory tests conducted on people with CFS/ME have not only confirmed this deficit, but have quantified it. Studies by Peckerman et al have revealed that the hearts of most CFS/ME patients actually pump out *less* blood both during and after exercise. Single-photon emission computed tomography (SPECT) scans obtained a day after exercise in people with CFS/ME show widespread hypoperfusion of brain tissue. Endocrine tests reveal that cortisol concentrations also decrease, inhibiting release of glycogen stores from the liver. The resulting lowered oxygen levels prompt a switch from aerobic to anaerobic metabolism, creating lactic acid buildup and tissue acidosis. This will be felt a day later as stiff, aching muscles and general malaise.

It is likely that the subjective impression of having "hit the wall" that most people with CFS/ME feel after even a short bout of exercise is entirely accurate. The

body's energy needs are met through metabolic processes at the cellular level (in mitochondria for the most part). Citric acid is broken down by a long series of enzyme-mediated reactions (the Krebs cycle) to produce ATP, the cellular source of energy. If the Krebs cycle is interrupted, ATP is not formed and energy simply is not available.

## TREATMENTS

A number of therapies can alleviate fatigue. Some patients find that vitamin B12 and magnesium help alleviate postexertional fatigue. Both of these supplements can also down regulate NMDA receptors, inhibiting neurotoxicity. D-Ribose, CoQ10 and branched-chain amino acids also help increase energy and stamina. Primary therapies such as Ampligen, and gamma globulin have also improved postexertional fatigue in CFS/ME patients, particularly those with flu-like symptoms. \

Above all, it is crucial to establish limits. In severely ill patients, any activity – visiting with friends, taking a shower, walking around the house – can produce the same symptoms as vigorous exercise. These patients should not attempt any form of exercise and should carefully monitor all activity. In milder cases of CFS/ME, exertion should be curtailed (done for less time and interspersed with rest periods), modified (walking or swimming instead of running), and rigorously monitored for negative effects.

In short, patients need to adjust their lifestyles according to the level of illness. It is of no benefit to people with CFS/ME to push themselves beyond their limits. Quite the contrary, "push" inevitably leads to "crash," in many cases producing unnecessary relapses. During recovery, activity levels can be increased judiciously with rate of improvement, while making allowances for the ups and downs of CFS/ME.

SEE: Cardiac and Cardiovascular Symptoms; Exercise; Ampligen; Antioxidants, CoQ10, D-Ribose, Minerals (Magnesium), Vitamins (B12).

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## LETHARGY

People with CFS/ME often describe a kind of tiredness characterized by a feeling of heaviness, lassitude, sleepiness, slowness, and inability to do anything. People who experience lethargy generally feel worst in the late afternoon or have trouble waking up in the morning. The feeling of lassitude or lethargy may be due to endocrine disturbances that create drops in blood sugar (as indicated by lethargy before or shortly after meals, or after not having eaten for several hours).

Treatments for this type of fatigue include low doses of chromium, Krebs cycle supports (such as alpha ketoglutarate, vitamin C, essential fatty acids, carnitine, CoQ10), a hypoglycemic diet (especially if fatigue or sleepiness is felt after meals), adrenal support, and rest.

Lucy Duchene, Ph.D., also points out that these symptoms can be caused by the edema and hypotension brought on by increased amounts of histamine released during allergic reactions (*CFIDS Chronicle*, Summer 1993). If you notice that fatigue increases during allergy seasons (fall, spring), treatments geared toward relieving allergies (antihistamines, vitamin C) may help relieve allergy-related fatigue.

A feeling of weariness can also result from changes in blood pressure, cardiac arrhythmias, water retention, electrolyte imbalance, and, at the neurological level, increased delta wave activity, all of which can be generated by excess amounts of histamine or by neurological and endocrine system disturbances.

If lethargy is accompanied by depression, suspect thyroid dysfunction. Low thyroid function is well known to cause a deadening lethargy, as well as weepy depression. If you experience this sort of fatigue consistently, make sure to have your thyroid hormones tested.

SEE: Allergies, Cardiac and Cardiovascular Symptoms, Endocrine Disturbances.

#### AGITATED EXHAUSTION

The term "agitated exhaustion" is used by Dr. David Bell in his book, *The Doctor's Guide to Chronic Fatigue Syndrome*, to characterize the type of fatigue typical of the acute stage of CFS/ME, and it describes very well the inability to "turn off" that the severely ill suffer. It is often described as a "tired and wired" feeling. A person with this type of fatigue does not feel sleepy, although the desire for rest is overwhelming. This type of exhaustion is usually accompanied by insomnia and catecholamine-related symptoms such as rapid pulse, hyperventilation, panic, and loss of appetite. The cause of this type of fatigue is upregulation of the sympathetic nervous system, which leads to the release of excess adrenaline.

Dr. Paul Cheney has put forth a possible explanation for this as well as many other neurological upsets experienced in CFS/ME (*CFIDS Chronicle*, Spring 1995). He proposes that toxins that accumulate in the brain as a result of cell dysfunction, liver toxicity, or excess cytokine production can lead to alterations in the normal firing pattern of neurons in the brain, resulting in a state of sustained neuronal arousal. In the state that Dr. Cheney describes, even small stimuli spark strong responses from the nervous system (this is known as "kindling"). The continued state of arousal characteristic of acute and severe CFS/ME results in agitated exhaustion.

Dr. Cheney has observed that nearly every treatment that slows nervous system responsiveness aids in controlling neurological symptoms, including benzodiazepines (Klonopin), magnesium, taurine, nimodipine (Nimotop), melatonin,



calcium channel blockers, butyric acid (ButyrEn), and gamma-aminobutyric acid (GABA). Meditation, hypnosis, acupuncture, and biofeedback can also provide relief. For those who are mildly ill, adrenaline is best cleared from the system by walking.

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## GENERAL TREATMENTS

In essence, treating fatigue is treating CFS/ME. Dr. Paul Cheney has noted that, in his experience, fatigue is the most difficult symptom to treat because it is so central to the disorder. He also makes the astute observation that fatigue may represent a defense response in sicker patients. "In this instance, excessive attention to the treatment of fatigue may actually worsen the patient's condition" (*CFIDS Chronicle*, Spring 1995). It might be well to keep this statement in mind before embarking on an aggressive program to combat CFS/ME fatigue.

Treatment for all kinds of fatigue should include lifestyle changes and adequate rest. Nutritional supplements that support the Krebs cycle give the body more energy at the cellular level. These include alpha ketoglutarate, essential fatty acids, acetyl-carnitine, NAC, vitamin C, vitamin B complex, vitamin B12, magnesium, CoQ10, branched-chain amino acids, D-Ribose, and all food-based general supplements. Other useful supplements include NADH, royal jelly, zinc, DMG, and herbs such as astragalus.

For mild CFS/ME, the occasional use of stimulants can be of benefit. Central nervous system stimulants (Lonamin and Ritalin) are sometimes recommended, as are antidepressants (Prozac, Zoloft, and Wellbutrin). Stimulants should be used with great care, however, as frequent dosing will only exacerbate the fatigue. SEE: Allergies, Candida, Cardiac and Cardiovascular Symptoms, Endocrine Disturbances, Hypoglycemia, Pain, Sleep Disorders: Ampligen, Antihistamines, Benzodiazepines, Calcium Channel Blockers, Central Nervous System Stimulants, Gamma Globulin: Alpha Lipoic Acid, Amino Acids, Antioxidants, CoQ10, D-Ribose, DHEA, Essential Fatty Acids, Herbs, Melatonin, Minerals (Magnesium, Zinc), NADH, Royal Jelly, Vitamins (Vitamin B12); Bed Rest, Biofeedback, Exercise, Meditation.

## FLU-LIKE SYMPTOMS

Sore Throat, Tender Lymph Nodes, Fever and Chills, Sweats

CFS/ME has often been described as the flu that never ends. Flu symptoms such as achiness, sore throat, tender lymph nodes, fever, chills, and malaise have appeared in nearly all case definitions of CFS/ME (with the notable exception of the

Oxford criteria) and figure prominently in most doctors' descriptions of typical CFS/ME.

In some people, flu-like symptoms appear early in the illness and decrease markedly over time; others may manifest few or mild flu symptoms. However, in people who have a strong viral onset and an increased susceptibility to colds and flus, flu-like symptoms predominate throughout the illness. This seems to be especially true in young people. Flu-like symptoms can be confusing for people who catch "every bug that's going around." It is hard for them to determine whether they have a new ailment, such as strep throat, a cold, or flu, or are merely experiencing a relapse of CFS/ME.

The presence of flu-like symptoms has been one of the primary motivations for attributing a viral cause to CFS/ME. Even though researchers have so far been unable to isolate a unique viral source for CFS/ME, antiviral treatments have been used with success in many cases in which viral symptoms persist. This may be due to persistent immune system dysregulation, rather than to an ongoing infection of the original triggering virus, which in young people seems to be primarily Epstein-Barr virus.

Reactivation of latent viruses is one of the more common clinical findings in people with CFS/ME. Latent viruses are those which have infected us, often in childhood, and which remain dormant in our systems, controlled by our immune systems. When the immune system fails to control these viruses, they can become active. In these cases, antiviral treatments will also be effective.

On the other side of the coin, the immune system can become upregulated, even in the absence of stimulation by latent viruses. Martin Pall has proposed that in people with CFS/ME a positive feedback loop develops, in which nitric oxide increases the production of inflammatory cytokines. These inflammatory cytokines are responsible for flu-like symptoms that occur in common viral infections, and, by extension, in CFS/ME.

## SORE THROAT

Throat pain, scratchiness, and tenderness are common in CFS/ME. In children, sore throats tend to be most pronounced in the morning; in adults, they can appear at any time, but tend to worsen after exercise, exertion, or before relapses. Sometimes, even though the throat is not sore, it may feel "clogged" and require constant clearing. Many people take this as a sign of an impending flare and scale down their activities accordingly.

Even when sore throat is severe, bacterial or viral cultures rarely reveal any infection. The throat itself may appear red or have characteristic "crimson crescents" around the tonsillar membranes of the upper throat upon examination, but there is rarely pus or mucus. Dr. Burke Cunha suggests that the presence of these singular deep red crescents may be diagnostic of CFS/ME because they have been noted in up to 90% of his patients (*CFIDS Chronicle*, Summer 1993). Like other flu-like symptoms, crimson crescents are indicative of immune system activation.

Sometimes, the more severely ill show signs of thrush, an oral *Candida* (yeast) infection. Thrush appears as a white lace-like coating of the tongue and cheeks that is hard to scrape off. Thrush is treated with prescription antifungals and adjunctive home remedies such as lemon gargles and yogurt oral "swishes." (*Candida*, like any fungus, will not grow in an acid medium.) The acidophilus in yogurt replaces *Candida* in its growing environment.

Irritated, scratchy throat that results from dry mouth (dry eyes may also accompany this symptom) can be relieved by herb teas, such as slippery elm, mullein, or sage, taken with honey. A simple home remedy if herbs are not available is hot lemon and honey tea to help coat the throat. Zinc can help nip a sore throat in the bud. Zinc should be consumed in very small quantities with food to avoid stomach upset – or take zinc carnosine which is more gentle.

Sambucol, an herbal extract made from black elderberry, is also effective against sore throat if it is accompanied by fever. Vitamin C and hot salt water gargles have been reported effective in relieving sore throat. Some people have reported cessation of sore throats after gamma globulin or antiviral therapy.

## TENDER LYMPH NODES

Although lymph node tenderness was included in the original CFS case definition from the Centers for Disease Control and Prevention, Dr. David Bell, in his book, *The Doctor's Guide to Chronic Fatigue Syndrome*, reports that only about 50% of his patients have tender lymph nodes. The lymph nodes in the front and back of the neck, armpits, elbows, and groin seem to be most frequently affected. Although the lymph nodes are rarely enlarged, they feel tender to the touch or sore upon movement. For example, rolling the head back may produce a tight, tender feeling under the jaw. Pain in the ears, teeth, jaw and side of the neck may also be lymph-node related.

Dr. Paul Cheney has found that the left side is usually affected more than the right (*CFIDS Chronicle*, Spring 1995). The fact that most people with CFS/ME can accurately identify most of the nodes in these areas, even if they are completely unaware of what they are identifying, should be enlightening to doctors who consider this symptom imaginary. The presence of lymph node pain, especially at onset, when it is most prominent, seems to indicate active involvement of the lymphatic system in CFS/ME; that is to say, an infection is present.

Lymph system involvement is typical in bacterial and viral infections, notably mononucleosis. The lymph system carries protein messages, or cytokines, which are released by T cells in an immune-activated state to aid in the mobilization of T and B cells. (These are the cells that combat invading pathogens.) When lymph production is accelerated, the fluid backs up, causing tissue swelling (edema). Most of the lymph-related edema in CFS/ME occurs on the left side. This is because 90% of lymph flows into the bloodstream at a point just below the left collar bone (supraclavicular area). Dr. Cheney suspects that backup from the congested lymph system is responsible for ear, neck, and jaw pain.

## FEVER AND CHILLS

Low-grade fever (temperature, 100° F or less), often occurring in the afternoon or after exercise, is not unusual in people with CFS/ME, although subnormal body temperature is more common. A resting temperature of below 98° F, although rare in the general population, is quite common in people with CFS/ME. Even more typical, although not commented on as often as fever, is abnormal daily temperature fluctuation, with a low of 97° F in the morning and a high around 99° F by afternoon.

What is most unusual about these temperature variations is that the accompanying sensations are so exaggerated. A slight fever of less than a degree produces a feeling of intense heat. Temperature drops can produce a bone-chilling sensation of cold that no warm bath, hot tea, or pile of blankets can remedy. Most researchers agree that the variations in temperature experienced by people with CFS/ME are typical of hypothalamic dysregulation. (Normally, the hypothalamus maintains body temperature between very narrow parameters – between 98° and 98.6° F.) Temperature variation tends to normalize during recuperation and can be one of the signs that recovery is under way.

## SWEATS

Night sweats and spontaneous daytime sweats unaccompanied by fever are typical of acute CFS/ME, although they also can accompany relapses, hormonal changes, and even fluctuations in barometric pressure. Some people also break into sweats when exposed for any length of time to electric lights, televisions, computer screens, or telephones. Sweating, like body temperature, is controlled by the hypothalamus and in all likelihood represents an aspect of the same neural dysregulation that produces temperature fluctuations.

Night sweats are a particular problem because they exacerbate insomnia. Many people have to get up in the night simply to change their nightclothes. Unlike the sweating associated with flu, both day and night sweats tend to be localized; that is, they affect only a limited part of the body, typically the upper torso and neck, although the legs, arms, and rib cage may also be affected.

Night sweats are generally difficult to treat. It helps to equip the bed with many light layers that can be easily thrown off and to wear absorbent cotton nightclothes. Some people find that a fan or opening a window at night is helpful. It also helps to maintain a careful diet; elimination of hard-to-digest foods can considerably reduce night sweats. If you are a woman in her forties, be sure to check your hormones levels with your gynecologist. Night sweats and hot flashes are signs of perimenopause.

## TREATMENTS

Primary antiviral and immunomodulatory therapies seem to have the greatest effect on flu-like symptoms. These consist primarily of antivirals: acyclovir, Famvir, Valtrex, and Valcyte. Experimental immune system modulators include GcMAF and rituximab.

In his book, *Treatment of Chronic Fatigue Syndrome in the Antiviral Revolution Era*, Roberto Patarca-Montero discusses several supplements which help modulate the immune system, and thus can help mitigate flu-like symptoms. DHEA helps promote cellular immunity, the aspect of the immune system which helps destroy pathogens that enter cells (e.g., viruses). Ginseng, an herb, stimulates immune system activity, although patients who are sensitive to stimulants will experience side effects. Mushroom extracts also have immunomodulatory effects.

Antioxidants, because of their anti-inflammatory properties, can also help reduce flu-like symptoms. These include bioflavonoids, alpha ketoglutarate, alpha lipoic acid, CoQ10, vitamin B12, vitamin C, vitamin E, magnesium, and essential fatty acids.

SEE: Ampligen, Antivirals, Gamma Globulin, GcMAF, Nexavir, Rituximab; Alpha Ketoglutarate, Antioxidants, Amino Acids, Butyric Acid, CoQ10, DHEA, Essential Fatty Acids, Herbs, Mushroom Extracts, Vitamins; Hydrotherapy.

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#### GYNECOLOGICAL PROBLEMS

Irregular Periods/Perimenopause/Early Menopause, Osteoporosis, PMS, Endometriosis

Due to the endocrine system disturbances produced by CFS/ME, women may experience a number of hormonal changes. In many women some of these changes may have either predated CFS/ME or served as “early warning” symptoms.

In a study led by Anthony Komaroff in 1998, 150 women with CFS/ME were administered questionnaires concerning their reproductive and gynecological history. Women with CFS/ME reported gynecological complications, including irregular cycles, periods of amenorrhea (absence of periods), and sporadic bleeding between menstrual periods prior to contracting the illness. Polycystic ovarian syndrome (PCOS) was also reported more often in CFS/ME cases compared with controls. While the researchers did not conclude that these gynecological symptoms caused CFS/ME, they raised the possibility that conditions which decrease progesterone (such as PCOS), may lower immune function, thus paving the way for future problems.

Not surprisingly, clinicians have noted an increase in the number of gynecological conditions among women with CFS/ME after contracting the illness. A study performed by the CDC in 2009 showed that women with CFS/ME not only

experience more frequent pelvic pain and amenorrhea, they are also prone to endometriosis and go through menopause earlier than controls. All of these conditions are associated with abnormal regulation of reproductive hormones.

Dr. Rosemary Underhill, a British gynecologist, wisely pointed out that gynecological symptoms in women with CFS/ME should not be assumed to be merely part of overall CFS/ME symptomatology. Their investigation and treatment in patients with CFS/ME should follow established gynecological practice, which in most patients will result in a relief of symptoms. Some of the treatable gynecological problems found in CFS/ME patients are early menopause, PMS, osteoporosis, and endometriosis.

It is interesting that a number of CFS/ME patients have reported a complete cessation of their symptoms during pregnancy. Some physicians have proposed that a sudden increase in pregnancy-related hormones is most likely the cause of recovery in these instances. Human chorionic gonadotropin (hCG), also known as the “pregnancy hormone,” is the hormone that is produced by the cells that form the placenta. (Pregnancy tests measure hCG). HCG coats fetal cells, in effect “hiding” them from the immune system. This protects the cells of the fetus from being attacked by the immune system which, otherwise, would identify these cells as foreign intruders.

In a fascinating study published in 2000 by Manna et al, the researchers found that hCG effectively down regulates NF-kappaB, the inflammatory pathway which has been implicated as an important part of the pathogenesis of CFS/ME. HCG also inhibits viral replication.

In addition to hCG, pregnant women also have a thousand times more progesterone in their systems than non-pregnant women. Progesterone is not only an important sex hormone, it reduces inflammation, modulates the immune system, and serves as a neuroprotective agent. Given that viral reactivation, inflammation, immune system dysfunction, and neurotoxicity lie at the heart of CFS/ME symptomatology, it makes sense that a thousand-fold increase of progesterone as well as hCG would alleviate CFS/ME symptoms. This is an area that certainly merits further investigation.

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## IRREGULAR PERIODS/PERIMENOPAUSE/EARLY MENOPAUSE

Many women with CFS/ME report an alteration of their cycles after contracting the illness. Cycles can become shorter, longer, irregular, or disappear altogether (amenorrhea). Bleeding can become lighter or heavier, and be accompanied by increased discomfort.

A number of women have reported that their CFS/ME symptoms vary according to the phase of their cycle. Some women experience an exacerbation of symptoms just prior to their periods, while others experience increased symptoms during ovulation (and some during both phases). Because these symptoms, along with many others, are typical of hormonal changes during menopause, the gynecologist may order blood tests for follicle stimulating hormone (FSH), the hormone which increases during menopause, and estradiol, which decreases. If these tests fall into the "normal" range, your doctor may diagnose your symptoms as "perimenopausal," that is to say, not yet menopause, but getting close.

Women with CFS/ME can experience perimenopausal, or even menopausal symptoms for years. In 1996 two gynecologists, John Studd and Nick Panay reported that 25% of their CFS/ME patients had normal FSH, but low levels of estrogen. When treated (with estrogen) their fatigue decreased. Patients also reported an improvement in mood. From this, Studd and Panay concluded that

there is a subset of CFS/ME patients who suffer from a state of chronically low estrogen.

While further research has not borne out this hypothesis, there is no doubt that the dysregulation of the HPA axis which is typical of most CFS/ME patients has a distinct effect on hormone levels. Recently, a team of Swedish researchers observed a decline in estrogen beta receptors in women with CFS/ME. Estrogen beta receptors are primarily found in the brain, bone, heart, intestines, and in blood vessels—all of which are profoundly affected by CFS/ME.

Women with CFS/ME can expect to experience early menopause – which is defined as menopause occurring before age 45. According to the CDC's study on gynecological history, the average age for menopause among CFS/ME patients was 41, four years earlier than healthy controls. In addition to the symptoms of menopause – which include hot flashes, insomnia, forgetfulness, vaginal dryness, and loss of libido – many women report a general worsening of symptoms, all of which, combined, can make menopause a very difficult passage.

## TREATMENTS

If estrogen levels are low, the standard treatment is hormone replacement therapy (HRT). Central nervous system symptoms, such as insomnia, can be greatly improved by supplementation with estrogen and progesterone. Drs. Studd and Panay found that symptoms improved in 80 percent of patients with low estrogen levels following HRT. In menopausal women, HRT also provides relief from night sweats, insomnia, mood swings, and forgetfulness.

For those who are hesitant to embark on HRT, there are a number of alternative treatments which have been shown to be effective in alleviating some of the milder menopause and perimenopause symptoms. Remifemin, an extract of black cohosh widely used in Europe, has a good track record for reducing hot flashes, night sweats, and mood swings. Red clover also has been shown to reduce hot flashes. A combination of red clover, vitamin E (essential for maintaining good blood flow, as well as for protective antioxidant activity) and calcium, called Promensil, is widely available in the U.S. and the U.K. for the treatment of menopausal symptoms. Mexican wild yam extracts should be avoided, as the hormone in wild yams cannot be utilized by the human body.

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## OSTEOPOROSIS



Osteoporosis is a condition in which bone is broken down faster than it can be produced. The resulting bone loss leads to porous, weak bones that break easily.

The National Osteoporosis Foundation estimates that 44 million Americans suffer from low bone density, representing 55% of the nation's population aged 50 or older. This is a staggering figure, and while knowledge about the prevention of osteoporosis is on the rise, so is the elderly population, making osteoporosis a major health problem.

The most frequently cited cause for osteoporosis is low estrogen, which among women with CFS/ME is common. Drs. Panay and Studd found low bone density among the majority of their CFS/ME patients with low estrogen levels, which would lead one to conclude that estrogen supplementation should provide an easy solution to this problem. However, for CFS/ME patients, the picture is more complicated.

While low estrogen states certainly contribute to the development of osteoporosis, there are a number of other factors which can enter into the pathogenesis of bone loss, one of which is chronic inflammation. Inflammatory chemical pathways, particularly NF-kappaB, can lead to the absorption of existing bone, while preventing the growth of new bone. As chronic inflammation is typical of both CFS/ME and fibromyalgia, this is a factor that must be taken into consideration.

By a similar route, viral and bacterial infections can also lead to bone resorption. Dr. Kenny De Meirleir has theorized that *Mycoplasma fermentans*, a bacterial infection which has been frequently associated with CFS/ME, may enhance bone resorption through stimulating the formation of inflammatory prostaglandins. He has also hypothesized that the activation of the antiviral RNase L pathway may lead to osteopenia through increased demands for calcium. As reactivation of latent viruses is nearly universal in CFS/ME patients (along with the subsequent activation of the RNase L pathway) viral causes should not be overlooked in CFS/ME patients with osteoporosis.

Oxidative stress, which is closely linked to inflammatory processes, is also implicated in the development of osteoporosis. When fatty acids are oxidized, free radicals are formed. Like inflammatory chemicals, these free radicals can directly affect new bone formation and lead to greater resorption of existing bones. Oxidative stress has been well documented in CFS/ME, and may very well constitute the primary underlying mechanism of the illness.

In addition to these important contributory mechanisms, functional nutritional deficiencies, particularly magnesium and calcium, can contribute to bone loss.

Tissue magnesium levels in people with CFS/ME have been found to be low, as has acetyl-L-carnitine, an amino acid linked to bone health. Several pharmaceuticals prescribed to people with CFS/ME – notably SSRIs, corticosteroids, and antacids – have also been linked to bone loss. When all these factors are taken into consideration, it should be clear that people with CFS/ME run a much higher risk of developing osteoporosis than the general population.

## TREATMENTS

There are a number of methods to treat existing osteoporosis, as well as to prevent it. Among the most commonly recommended pharmaceutical treatments are Actonel and Fosamax, synthetic drugs that mimic the mineral components of bone structure. These drugs help prevent bone loss by inhibiting bone resorption. However, because they do nothing to promote the development of new bone, they constitute a stop-gap measure at best. In addition, prolonged treatment with these drugs can lead to oxidative stress and the production of inflammatory chemicals, two processes that are known to contribute to bone loss.

Hormone replacement therapy (HRT) is generally recognized as a first-line treatment for preventing osteoporosis. Because loss of estrogen is recognized as a major contributory factor in developing osteoporosis, it makes sense that increasing estrogen levels would put a brake on the process of bone loss, and, in broad terms, this has proven to be the case. Many women on HRT have found, not just an overall improvement, but a slowing of all aging processes, including bone loss. The main impediment to beginning HRT is the risk of cancer, which most women are well aware of. Fortunately, there are a number of options, including bio-identical hormones and transdermal hormones, in which the risk of cancer is greatly reduced. Nonetheless, even during the course of HRT, women with CFS/ME may continue to experience bone loss.

Calcitonin, a thyroid hormone, can decrease the rate of bone resorption. Among its many functions, calcitonin inhibits the action of osteoclasts (cells that break down bones). It also regulates vitamin D and protects against bone loss during pregnancy. A form of calcitonin produced by salmon, called salmon calcitonin, has been found to be 40 to 50 times more potent than human calcitonin. This has led to a number of studies investigating the efficacy of this hormone in treating osteoporosis. Overall, these studies have found that salmon calcitonin is safe and efficacious, with a short half-life and rapid excretion through the kidneys. Calcitonin is marketed in the U.S. as Miacalcin or Fortica. Both injectable and oral forms are available. Nasal sprays are available to women who have been in menopause for at least five years.

There are a number of supplements which can help limit or prevent osteoporosis. Vitamin D, the “sunshine vitamin,” regulates calcium in the bloodstream and promotes the growth of new bone. Dr. Myhill recommends between 5000 and 10,000 IU a day to help maintain healthy bone. The minerals magnesium, calcium and boron are quite important. Calcium is what bones are primarily made of, so an adequate calcium intake is important in maintaining bone health. Magnesium, which regulates calcium transport, is essential for the formation of new bone, as is silicon, which reverses loss of calcium in the urine. Boron, a trace mineral, interacts with calcium, magnesium and vitamin D to assist in bone metabolism. Strontium, another trace mineral, has also been found to prevent fractures among menopausal women.

Some very interesting recent studies have indicated that carnitine can stimulate bone formation as well as improving bone density and bone size. In 2008

Patano et al fed carnitine fumarate to calcium-deprived mice. They found that supplementation with carnitine fumarate accelerated bone formation after calcium depletion. In another study, Colucci et al found that carnitine fumarate stimulated osteoblast activity (osteoblasts are the cells responsible for bone formation). The team concluded that carnitine supplementation in the elderly “may stimulate osteoblast activity and decrease age-related bone loss.” Given the documented deficiency in carnitine among CFS/ME patients, this is a compelling reason for including carnitine supplementation in CFS/ME protocols.

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## PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) is a common hormonal disturbance that affects 70% to 90% of women in the United States at one time or another during their reproductive lives, according to Harvard professor and gynecologist Dr. Joseph Mortola.

PMS can produce a plethora of symptoms, including weight gain, backache, acne, breast tenderness, sore throat, joint pain, swollen ankles, insomnia, cravings for sweets and starches, headache, irritability, anxiety, fatigue, lethargy, depression, and cystitis, among others. In many women, a few of these symptoms may predominate. For example, in some women, PMS is manifested as profound depression or outbursts of temper. Others primarily experience weight gain, breast pain, and edema.

Although PMS may constitute nothing more than minor aggravation for some, in about 10% of the women who experience PMS, symptoms can be overwhelming, necessitating treatment of some kind. In the CFS/ME population this percentage may be higher. Many women with CFS/ME report either new onset of PMS or a sudden worsening of symptoms. In addition, a number of women with CFS/ME bear a double burden, because they not only experience PMS symptoms but an exacerbation of habitual CFS/ME symptoms during this time as well.

There are three main patterns typical of PMS: (1) symptoms appear at ovulation (about 14 days before menstruation) and do not diminish until the end of menstruation; (2) symptoms appear at ovulation, then ease, only to reappear a few days before menstruation; and (3) symptoms appear a few days before menstruation and ease at onset. In all cases, the time after menstruation and before ovulation brings relief. For women with the first pattern, this relief may occur for a scant week. PMS is not limited to one or another of these patterns, and women may experience several, depending on the severity of the illness.

PMS is generally attributed to an imbalance in the hormones responsible for the onset of the luteal (post-ovulation) phase of the menstrual cycle. The delicate orchestration of the hormones produced by the hypothalamus, pituitary gland, and ovaries enables the complex processes of fertility that occur at ovulation. At ovulation, a woman experiences a surge of luteinizing hormone (LH) from the pituitary gland, which signals an egg to make its journey from the fallopian tube to the uterus. At that point, the two primary female hormones, estrogen and progesterone, are released, signaling the pituitary to stop producing luteinizing hormone. Levels of these hormones remain high until just before the onset of menstruation, when their sudden drop allows the lining of the uterus to slough off and menstruation begins.

In some women the levels of hormones responsible for the processes involved in ovulation and menstruation do not operate in concert. As noted in an early paper

by Dr. Leon Israel (*Journal of the American Medical Association*, 1938) and more recently by Dr. Katherine Dalton, many women who experience the myriad symptoms associated with PMS have an inadequate amount of progesterone during the luteal phase. They believe the overabundance of estrogen in relation to progesterone causes PMS. However, hormonal deficiencies may not be the only precipitating factor. Sensitivity to some hormones, even in normal amounts, can cause symptoms in some women. And, it is important to remember that the endocrine hormones have effects on the immune system as well, which may lead to an exacerbation of CFS/ME symptoms.

Estrogen receptors have been found in both animal and human thymus tissue, indicating a direct relationship between the immune system and the female sex hormone. Indeed, in a number of studies, estrogen has been shown to depress cell-mediated immunity (T cell function), even while elevating antibody responses to some antigens. This means allergic responses increase in the luteal phase, as cell-mediated immunity decreases. Estrogen also reduces natural killer cell activity, aids in the secretion of interleukin-1 and interleukin-6, and can influence the action of CD8 antigen, or T suppressor cells. These, in turn, have direct effects on hypothalamic and nervous system function.

In PMS, like CFS/ME, the complex interaction between the immune, endocrine, and nervous systems has gone awry. It is noteworthy that estrogen seems to be related to many of the prominent immune system abnormalities found in CFS/ME. In the light of these findings, it should not be surprising that all autoimmune diseases, including CFS/ME, predominate in women.

## TREATMENT TIPS

PMS treatment varies according to the type and severity of symptoms.

- Vitamin supplementation is widely used for PMS in which depression and irritability predominate. Because vitamin B deficiency can cause overproduction of estrogen, supplementation with vitamin B complex accompanied by an additional dose of vitamin B6 (pyridoxine) may be useful. Pyridoxine is usually administered in doses smaller than 100 mg to avert peripheral nerve injury (characterized by tingling in the extremities). The P5P form of B6 is the most easily absorbed. Vitamin A is reputed to be helpful for PMS-related agitation and insomnia, but as of yet no studies support these claims. Optivite, a supplement developed especially for women with PMS, is available in health food stores.
- Tiny doses of Prozac taken a few days before menstruation have been reported to ease PMS-related depression.
- Magnesium may be useful for alleviating mood swings, muscle aches, nervous tension, bloating, and breast tenderness. Dr. Guy Abraham and associates have directed studies in Los Angeles that show that women with PMS have lower levels of magnesium than those who do not. Whole grains, green leafy vegetables, legumes, seeds, shellfish, and mangoes all have high amounts of magnesium. Incidentally, so does chocolate, which may explain why so many

women with PMS crave chocolate. Magnesium supplements of up to 400 mg can be taken

- For sweet and carbohydrate cravings, edema, and hypoglycemia-type symptoms, a modified hypoglycemic diet seems helpful. Dr. Ronald Norris, senior consultant to the PMS Program, Inc., in Chapel Hill, North Carolina, recommends eating six small meals a day and limiting total protein intake to 20% of total daily calories. He also recommends increasing complex carbohydrates, eliminating sugar and refined carbohydrates, and reducing salt.
- For severe PMS, Dr. Norris recommends a direct hormonal approach. He administers progesterone to women in whom deficiency of this hormone is implicated. He cautions that progesterone must be administered in its bioidentical form (identical to the progesterone produced naturally in the body) to avoid side effects.
- Increasing intake of linoleic acid (found in safflower oil, evening primrose oil, borage oil, and linseed oil) can help reduce edema, cravings for sweets, and blood sugar-related problems. Results are fairly rapid (1 to 3 months).
- Cutting back on salt and drinking diuretic herbal teas (cornsilk, for example) can help relieve edema.
- The Chinese herb Dong Quai is reputed to have a positive effect in female hormone balance.
- Antihistamines seem to alleviate some PMS symptoms in women who are prone to allergies. It could be that because allergies exacerbate PMS, antihistamines act to reduce the compounding effects of histamine on related PMS symptoms.
- Supplementing with inositol may relieve pre-menstrual depression. In a study conducted in 2011, researchers found that 0.6 grams of myo-inositol in a gelcap (or 2 grams in powder) effectively treated premenstrual dysphoric disorder (PDD). Inositol acts as a second messenger of serotonin, mimicking the effects of SSRIs.
- Last, but not least, women with PMS should keep a calendar of their cycle. From ovulation to menstruation they are more susceptible to allergic reactions, less tolerant of stress, and much less capable of handling emotional upset. The second half of the cycle is not the optimal time to schedule stressful meetings, try new treatments, or make major changes in a relationship. An awareness of when PMS occurs makes it possible to at least avoid known pitfalls.

SEE: Antidepressant Drugs, Antihistamines; Essential Fatty Acids, Herbs, Inositol, Minerals, Vitamins; Acupuncture.

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## ENDOMETRIOSIS

Endometriosis is a condition in which cells from the lining of the uterus (the endometrium) migrate to other parts of the body (most commonly the ovaries, although endometrial tissue can spread as far as the intestines). The main symptom of endometriosis is pelvic pain, which can include pain during periods, cramping pain during the two weeks prior to periods, pain during intercourse, and pain during bowel movements. Women who have frequent or long periods, or who started having periods at a young age are more at risk for endometriosis.

While the cause of endometriosis is as yet undiscovered, there are studies which suggest that it is an autoimmune process. Research findings include increased polyclonal B cell activity, abnormalities in T and B cell function, familial inheritance, high T and B lymphocyte counts, reduced natural killer cell activity, and high serum levels of IgG, IgA and IgM autoantibodies.

This evidence is supported by a survey conducted in 1998 by the Endometriosis Association which revealed a high incidence of comorbid autoimmune disorders among women with endometriosis. Compared with the general female population in the U.S., women with endometriosis had higher rates of hypothyroidism, fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and multiple sclerosis. Allergies and asthma were more common among women with endometriosis alone (61% and 12% respectively) and highest in those with fibromyalgia or chronic fatigue syndrome (88%). Given the similarity in immune system abnormalities of CFS/ME and endometriosis, it is not entirely surprising that women with endometriosis should also share many of the same comorbidities.

## TREATMENTS

Treatment for endometriosis generally revolves around hormone modulation. Some women are prescribed the pill on a continuous basis. This effectively stops periods altogether. High-dose progesterone, in the form of progestin, also halts periods. Gonadotropin-releasing hormone (GnRH) analogs (GnRH) have also been effectively used to relieve pain and reduce the size of endometriosis implants. These drugs suppress estrogen production by the ovaries. As a result, menstrual periods stop. Predictably, the side effects of the drug mimic menopause: hot flashes, vaginal dryness, bone loss, and fatigue, all of which, combined, may make this drug an unfavorable choice for people with CFS/ME.

Newer hormonal treatments include aromatase inhibitors (Arimidex and Femara). These act by interrupting local estrogen formation within the endometriosis implants themselves. They also inhibit estrogen production in the ovary, brain, and other sources, such as adipose tissue. Unfortunately, aromatase inhibitors cause significant bone loss with prolonged use. In addition, they cannot be used alone in premenopausal women because they stimulate development of multiple follicles at ovulation.

NSAIDs are usually prescribed for pain. Although these do nothing to alter the progress of the condition, they help relieve some of the suffering.

When endometriosis implants have spread into neighboring organs, surgery is the only viable option. Endometriosis surgery is usually carried out by laparoscopy, or “keyhole” surgery, a procedure that requires only a small incision. Endometrial implants may be removed or destroyed by laser. If the disease is extensive and has spread to other organs, opening of the abdominal wall via a larger incision may be required.

Dietary adjuncts include celery and parsley, which contain flavones (chemicals that inhibit the conversion of androgens to estrogen). Cruciferous vegetables such as broccoli, cauliflower, kale, Brussels sprouts and bok choy contain indoles, which improve the metabolism of estrogen. Omega-3 fatty acids, which are found in flaxseed oil, fish oil and krill oil, will help reduce inflammation and, subsequently, pain. If possible, avoid the intake of conventionally produced dairy products and meats, as these contain growth hormones and other estrogenic hormones. Organic meats and dairy products can be purchased at health food stores, as well as regular grocery stores and supermarkets located in urban areas.

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#### HEADACHES

Migraine Headaches, Sinus Headaches, Tension Headaches

Headaches are among the most common CFS/ME symptoms. Dr. Jay Goldstein estimated that some 75% of his patients with CFS/ME experienced headaches. Most of these patients reported either worsening of previously experienced headaches or onset of a new type of headache, frequently described as “like nothing I've ever had before.”

As the brain has no pain receptors, the pain of a headache is actually generated in the structures around the brain. These include the meninges (the membranes that encase the brain), the large arteries and venous sinuses of the brain, the cranial and cervical nerves that enervate the brain, and the scalp, face, and neck muscles. Headaches are the direct result of pressure, inflammation,



traction, or displacement of any of these structures. Headaches can arise from a variety of systemic sources, such as endocrine disturbances, neurological disorders, low blood sugar and low blood pressure. (Headaches associated with low blood pressure are strongly associated with orthostatic intolerance.)

Headache pain comes in all varieties: dull, aching pain; throbbing pain; sharp, stabbing pain (“like an ice pick”); pressure pain (which feels like your head is going to either explode or implode); gripping pain (like a vice); localized pain; tingling pain; and throbbing migraine pain, which is in a class by itself. Though people with CFS/ME experience all of these, the most common types of headache are migraines, tension headaches and sinus headaches.

### GENERAL TREATMENT TIPS

Although most people simply take aspirin or acetaminophen (Tylenol) to relieve the immediate pain of a headache, the usual over-the-counter oral medications do not seem to provide as prolonged or immediate relief in patients with CFS/ME as they do in the general population. Some headache sufferers have mentioned that ibuprofen works best.

Ice packs placed at the back of the neck seem to relieve eye pain associated with headaches. Gentle massage may be helpful, although deep or vigorous massage can make migraine worse. Pain management techniques such as meditation, hypnosis, relaxation methods, and breathing exercises, which have some effect in controlling vascular headache, have limited effect on muscle tension or trigger-point headache. The herb, feverfew, taken as a tea, is well known as a remedy for headaches. Acupuncture is quite effective for headaches of all types.

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### MIGRAINES

The intense, throbbing pain of a migraine is most likely the result of a poorly-timed interaction between the nervous system and the vascular system. The prevailing theory is that the migraine headache is produced when a spasm in the carotid artery causes blood that is normally metabolized by the brain to be released directly into the veins. The initial constriction of the artery produces the

characteristic "aura," the zone of flashing, shining, or shimmering lights that can precede a migraine by fifteen to thirty minutes. The subsequent vasodilation – caused by parasympathetic backlash, and release of blood – causes severe pain. The sympathetic nervous system arousal that leads to the initial vasoconstriction can lead to nausea and vomiting, as well as pallor. Severe migraines are often followed by a period of exhaustion, or “spaciness.”

Migraines can be distinguished from tension headaches because they are one-sided (left or right) and can last for hours, sometimes days. Migraines can be triggered by bright lights, strong odors, eye strain from reading or watching television, emotional stress, changes in weather, and certain foods.

In a study conducted in 2003, Ciancarelli et al found that blood vessel nitric oxide (NO) levels were higher in patients with migraine than in controls. The researchers concluded that oxidative stress, caused by excess nitric oxide (which has vasodilatory effects) was responsible for the alterations in blood flow that precipitate migraines. It should be mentioned that this finding fits in very nicely with Martin Pall's theory that CFS/ME, like other “unexplained” illnesses, is caused by excess NO, which in turn leads to the production of free radicals and oxidative stress.

However tempting it may be to lay migraines at the door of oxidative stress, the underlying cause of migraine is widely considered to be neurological. The muscles that control the arteries responsible for releasing blood into the veins are regulated by the neurotransmitter serotonin. Changes in serotonin concentrations or function can lead to mistiming of the muscle contractions around the arteries. Simply put, initial high levels of serotonin cause vasoconstriction, then low levels cause excess dilation.

A recent theory proposed by Dr. Goadsby, a neurologist at the University of San Francisco, implicates the brainstem as the source of migraines. Normally, the brainstem filters sensory signals before they reach the thalamus. In people with migraines, the signals are amplified by an excess of glutamine, a neuroexcitatory neurotransmitter. Once the nerves are stimulated, a wave of electrical impulses makes its way across the brain, irritating nerves and causing pain. This theory accounts for the one-sidedness of migraines (which would indicate a neurological dysfunction), but, unfortunately, does not account for nausea, vomiting, or the “aura” which precedes the migraine.

Some doctors believe that norepinephrine, rather than serotonin, plays a key role in migraines. This is due to the observation that certain foods can provoke migraines. Foods high in tyramine, a derivative of the amino acid tyrosine, can trigger migraines. These foods include anything fermented, aged, smoked, or marinated. (Patients with headaches should take note if they also have interstitial cystitis as the list of foods implicated in both disorders is the same. See Interstitial Cystitis for a list of foods high in tyramine.)

Because tyrosine is an immediate precursor of norepinephrine, a vasoconstrictive neurotransmitter, it is theorized that the subsequent release of norepinephrine leads to reduced blood supply. Then as the amount of circulating norepinephrine wanes, the blood vessels compensate by excessive dilation,

producing a headache. Basically, this is the same mechanism as produced by serotonin, but controlled by the sympathetic nervous system.

A fourth theory proposes that people who have migraines have difficulty metabolizing all amines (serotonin, dopamine, norepinephrine, tyramine, etc.) due to deficiencies in the enzymes responsible for breaking down these substances. Because several amines influence blood vessel diameter, their incomplete or slow breakdown can lead to problems in blood vessel control.

All of these theories are relevant to people with CFS/ME because the dysregulation of these neurochemicals is related to many other CFS/ME symptoms—particularly dysautonomia.

People with dysautonomia (orthostatic intolerance, NMH, POTS) are especially prone to migraines. In fact, for many, migraines may be their most debilitating symptom. Dysautonomia is directly related to sympathetic nervous system dysregulation. When the sympathetic nervous system is stimulated, norepinephrine is released. With prolonged stimulation of the sympathetic nervous system, as occurs in dysautonomia, stores of norepinephrine become depleted, leading to an increase in dopamine (a precursor of norepinephrine), adenosine, and inflammatory prostaglandins.

The symptoms of dysautonomia are closely tied to the action of each of these neurochemicals. The nausea, dizziness and vomiting typical of a dysautonomic crisis are linked to the release of dopamine (as is yawning). The decrease in norepinephrine levels leads to low blood pressure. Pain is induced by inflammatory prostaglandins. The sedated feeling is caused by elevated adenosine levels. Migraine sufferers will recognize each of these symptoms as being typical of a migraine.

It is not surprising, given the neurological mechanisms of migraine that so many people with CFS/ME experience them. A 2011 study conducted at Georgetown University by Ravindran et al found a much higher prevalence of migraine in CFS/ME patients than in controls. Roughly 40% of the CFS/ME group had experienced migraines (as opposed to 5% of controls). Of those with headaches, 84% had migraines, indicating a prevalence of migraines over tension-type headaches in CFS/ME. Dr. James Baraniuk, one of the Georgetown researchers, had previously commented that migraines among people with CFS/ME are an indication of either autonomic abnormalities or neurogenic inflammation – both of which are common conditions in CFS/ME.

## TREATMENTS

At the first sign of an aura, retire to a quiet, dark room and apply ice. This will help mitigate the severity of the migraine and may even nip it in the bud. Dr. Goldstein has noted that although Prozac can trigger headaches, it is sometimes also helpful for treating migraine, as are calcium channel blockers and tricyclic antidepressants, which increase levels of circulating serotonin and norepinephrine, but not dopamine.

Once a migraine has begun, triptans (Imitrex, Sumatriptan) are the standard course of treatment. (It should be noted, however, that many people with CFS/ME do not find relief in the medications usually prescribed for migraine, and may find that they exacerbate dysautonomia.) Triptans are a class of drugs that operate by increasing serotonin in the brain. The increase of serotonin causes vasoconstriction in dilated blood vessels. Lidocaine drops (an inhalant), reportedly provides relief for some.

It goes without saying that anything that calms the sympathetic nervous system will help reduce migraines. As the sympathetic nervous system is closely linked to stress responses, avoiding stress should be a first line of defense. Relaxation techniques, bio-feedback and meditation are all tried-and-true methods for managing stress on a daily basis, as are a number of relaxing herbs: valerian, skullcap, hops, chamomile and kava.

Magnesium supplements may lessen the severity of migraine. Magnesium acts to reduce NMDA receptor activity, which is tied to sympathetic nervous system activation and to pain. While magnesium will not stop a migraine once it has begun, consistently taking magnesium will help lessen the effects of excitatory neurotransmitters, which will help control sympathetic arousal.

High-dose riboflavin (vitamin B2) has been shown to be an effective preventative for migraines. A Belgian study conducted in 1998 showed that high-dose riboflavin (400 mg) resulted in a 50% improvement in migraines. In a more recent study conducted in Germany, migraine sufferers who were given a daily dose of 400 mg of riboflavin for three months were able to cut their migraine medication in half. For those who suffer from frequent migraines, a 50% reduction makes a substantial difference in quality of life.

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## SINUS HEADACHES

Sinus headaches are common experiences for people with allergies, but they can also be caused by a cold, flu, or other secondary infections. Typically, these are dull, throbbing headaches at the front of the head.

The sinus headache results from excessive mucus that is generated in the sinuses to combat a virus or allergen. When the sinuses are blocked, stuffed, or inflamed, the pressure creates a headache, with localized pain in the forehead accompanied by runny nose or post-nasal drip. If neither of these last two symptoms is present, the sinus pain may not be due to sinus congestion but to nerve irritation. Because neurological pain can run the entire length of a nerve, the source of referred pain from sinus irritation may be as far away as the back of the neck (see Sinusitis).

Sinus headaches are often difficult to distinguish from tension headaches. A simple test is to bend over. If your head throbs when you straighten back up, you have a sinus headache. If your cheek bones hurt when pressed, you may also have sinusitis, even if you don't have nasal congestion. Sinus headaches, like some tension headaches, are often accompanied by pain in the teeth.

## TREATMENTS

Sinus headaches due to allergies can be relieved by taking antihistamines. Inhaling steam can also help relieve sinus pain, as can manual massage (pulling the face muscles downward can release the sinuses). Acupressure is quite effective for sinus headaches. If the pain is severe, or accompanied by yellow nasal discharge, you may have a sinus infection. Sinus infections are treated with a course of antibiotics.

## FURTHER READING

*The University of Maryland's informative page on sinus headaches.*

<http://www.umm.edu/altmed/articles/sinus-headache-000073.htm>

## TENSION HEADACHES

Dull, continual headaches that encircle the head are referred to as tension headaches. In people with CFS/ME they tend to originate in the back of the neck or at the base of the skull and can travel around the skull to the temples in a band of continuous pain. Sometimes the pressure can be so intense that it feels as though the head is in a vise.

In his book, *Could Your Doctor Be Wrong?*, Dr. Jay Goldstein states his belief that this type of headache is not generated by muscle tension, as has been previously thought, but by trigger points. The aggravation of the headache, he contends, is the result of the spreading pain brought on by the irritation of the trigger point, not by muscle contraction. Dr. Goldstein recommends that with this type of headache the patient should try to locate the trigger point. There may be two or three points on the edge of the trapezius muscle (which rises along the top of the shoulders when you shrug) that are tender to touch. The point implicated in headaches is the one closest to the neck. It can generate pain that spreads up the neck, along the side of the head, and around to a point just behind the eye.

Other headache trigger points are located on the shoulder blades (levator scapulae) and jaw (masseter) muscles. Pain that seems to originate in the teeth and course up the side of the face may be mistakenly attributed to temporomandibular joint (TMJ) dysfunction when masseter trigger points are involved. The masseter muscle is located about an inch in front of the earlobe and runs up to the top of the head, producing multiple trigger points.

## TREATMENTS

Treatments for pressure headaches include: localized heat or ice on back muscles when trigger points are in the shoulder blades and trapezius muscle, use of a transcutaneous electrical nerve stimulator (TENS) unit, gentle local massage, acupuncture, and saline solution injections into trigger points, followed by stretching of the surrounding muscle.

Some physical therapists have also recommended putting two tennis balls in a sock and resting the back of the neck on it to treat headaches associated with neck

pain. Patients with severe headaches have reported good results from using this technique.

Drug treatments effective for tension headache include ibuprofen (Advil), Flexeril, and some of the benzodiazepines (Valium and Klonopin). Omega-3 and omega-6 essential fatty acids found in fish oils are good dietary supplements to help relieve muscle tension.

It should be noted that this type of headache can also be brought on by a decreased glucose supply to the brain (low blood sugar). Low blood sugar headache is characterized by a generalized ache over the top of the head, often accompanied by sleepiness. Hypoglycemic headaches can be relieved by eating and lying down (see Hypoglycemia). Dull tension headaches over the top of the head can also be caused by low blood pressure.

SEE: Hypoglycemia, Pain, Sinusitis; Antihistamines, Calcium Channel Blockers, Diamox, Nitroglycerin, Pain Relievers; Essential Fatty Acids, Minerals (Magnesium); Acupuncture, Biofeedback, Hypnosis, Massage, Meditation, TENS.

## HEARING AND EAR PROBLEMS

Hyperacuity, Tinnitus, Pain, Itching, Hearing Loss

Problems with the auditory system don't tend to be as frequent or severe as visual problems, but they can still be very distressing. As many auditory problems are neurological in origin, routine ear examinations nearly always yield normal findings. Typical auditory symptoms experienced by people with CFS/ME are hyperacuity (sensitivity to noise), tinnitus (ringing in the ears), pain, itching, and hearing loss.

### HYPERACUITY

One of the most frequent auditory problems reported in CFS/ME is an intolerance to normal sound volume and range, particularly in the upper frequencies. Loud noises can generate a startle response in the acutely ill as well, producing rapid heartbeat and flushing. People with CFS/ME also find that multiple sound inputs become intolerable. A radio, television, and conversation occurring at the same time can produce profound discomfort.

According to Dr. Cheney, hyperacuity is the result of excitatory neurotoxicity. Essentially, too many neurons are firing in the brain, resulting in a nervous system that over-reacts to normal stimuli. Dr. Cheney recommends Klonopin (clonazepam) to calm the central nervous system and reduce the effects of sensory overstimulation.

### TINNITUS

Ringling, buzzing, humming, clicking, hissing, popping, and squeaking noises generated in the ear rather than from any outside source are not unusual in

CFS/ME. Tinnitus can be caused by blocked Eustachian tubes, which, during periods of sinus congestion and colds, become filled with fluid. People with allergies often find that they experience tinnitus during allergy season. Fluid retention in premenstrual syndrome (PMS) also can exacerbate tinnitus, as can increased blood flow to the area from exercise or vasodilators. Tinnitus can be caused by salicylates, notably aspirin, as well as some antibiotics.

Allergy-related tinnitus is usually treated with antihistamines. For other types, acupuncture and massage to release excess fluid sometimes provide relief. For some people, hypnosis can be effective. Wearing foam earplugs to block out excess noise from other sources is helpful for some patients, as is avoiding caffeinated beverages.

Martin Pall has linked tinnitus, as well as other ear-related problems such as vertigo, dizziness and hearing loss, to an increase in nitric oxide. Excess nitric oxide produces oxidative stress, a condition in which free radicals impair or destroy healthy cells. Studies have indicated that people with tinnitus show signs of oxidative stress in the cochlea due to nitric oxide production.

Antioxidants such as bioflavonoids and fish oil have been found to lower oxidative stress, along with Vitamin B12 and magnesium, which are important adjuncts for limiting damage caused by free radicals. Interestingly, a study by Shulman and colleagues at the Martha Entenmann Tinnitus Research Center in New York found that treatment with benzodiazepines and other GABAergic medications significantly improved tinnitus. This would seem to confirm Dr. Cheney's claim that benzodiazepines exert a neuroprotective effect in CFS/ME.

## RESEARCH

Shulman A, Strashun AM, Goldstein BA. "GABAA-benzodiazepine-chloride receptor-targeted therapy for tinnitus control: preliminary report." *Int Tinnitus J.* 2002;8(1):30-6. <http://www.ncbi.nlm.nih.gov/pubmed/14763233> (Abstract)

Takumida M, Anniko M, Popa R, Zhang DM. "Pharmacological models for inner ear therapy with emphasis on nitric oxide." *Acta Otolaryngol.* 2001 Jan;121(1):16-20. <http://www.ncbi.nlm.nih.gov/pubmed/11270488> (Abstract)

## PAIN

Sharp transient pain in the ears is not uncommon in CFS/ME. Although the pain may be severe, it rarely lasts more than a few seconds. Like many other ear symptoms, pain can be generated by increased pressure due to blocked fluid. As Dr. Goldstein has mentioned, pain can be caused by irritated trigger points as well.

Ear pain can also be caused by TMJ (temporomandibular joint disorder), which is a condition in which the joint which connect the jaw to the skull is inflamed. As joint pain is commonly found in CFS/ME patients, especially those with secondary fibromyalgia or low thyroid, TMJ should be investigated when there is inner ear pain.

## ITCHING



The left ear, in particular, seems to be susceptible to itching, which, because of its location deep in the ear, cannot be relieved. The itch and occasional accompanying pain do not, in most cases, signal the presence of an ear infection. The likeliest source of the itch is lymphatic fluid congestion. The lymph system drains at a point just above the left collar bone. If the fluid backs up, it can produce swelling along the left side of the neck, left-sided jaw and molar pain, and itching in the left ear. In some cases *Candida* overgrowth is also implicated, especially when there are concurrent yeast or topical fungal infections.

## HEARING LOSS

Some people with CFS/ME experience hearing loss. Sounds become muffled and indistinct. Sometimes only the high register is affected, making music sound curiously flat, as though a stereo channel were missing. The loss of auditory function, in most cases, is not related to inner ear problems, whether neurological or mechanical, but to sinus congestion. However, in some cases the immune system may be implicated.

A study published in 2008 by a group of German researchers found that in some cases of hearing loss an immune process is involved. Three antibodies, phospholipid antibodies (indicating an immune process which affects blood flow), serotonin antibodies and ganglioside antibodies, which operate on neural cells, were found in the blood of people with sudden and progressive hearing loss. Twenty-eight of the patients studied also showed symptoms typical of CFS/ME, including fatigue, muscle pain, joint pain, dry eyes and mouth and diarrhea. Because these three antibodies are also frequently found in patients with fibromyalgia and CFS/ME, the researchers recommended that patients with hearing loss be questioned for CFS/ME symptoms "since these diseases [CFS and ME] are often closely related to inner ear disorders."

## TREATMENT TIPS

For pressure-type ear pain and associated headache, massaging a point about an inch in front of the earlobe seems to help. Placing a drop of a 50-50 mixture of hydrogen peroxide and alcohol in the ear canal (the home remedy for swimmer's ear) also helps relieve some of the pain associated with congested sinuses, as do antihistamines. Similasan, a homeopathic remedy found in health food stores, is also effective for pain in the ear canal.

Ginkgo, CoQ10, and some of the treatments used to alleviate dizziness can be helpful in relieving some ear problems. Some people have reported success with "ear candles," an alternative treatment sold in some health food stores.

SEE: Allergies, *Candida*, Dizziness and Vertigo; Antihistamines, Benzodiazepines (Klonopin); CoQ10, Herbs (gingko), Fish Oil, Magnesium.

## FURTHER READING

Pall ML, Bedient SA. "The NO/ONOO<sup>-</sup> cycle as the etiological mechanism of tinnitus." *Int Tinnitus J*. 2007; 13 (2): 99-104.

<http://www.ncbi.nlm.nih.gov/pubmed/18229788>

*Patient thread on hearing problems:*

<http://forums.phoenixrising.me/showthread.php?1844-Hearing-loss-low-frequency-cfs-related>

## RESEARCH

Heller U, Becker EW, Zenner HP, Berg PA. "Incidence and clinical relevance of antibodies to phospholipids, serotonin and ganglioside in patients with sudden deafness and progressive inner ear hearing loss." *HNO*. 1998 Jun;46(6):583-6.

<http://www.ncbi.nlm.nih.gov/pubmed/9677490> (Abstract)

## HYPOGLYCEMIA

Our bodies need sugar to produce heat and energy. We normally obtain sugar from eating carbohydrates, such as grains, vegetables, potatoes, fruits, and beans. The complex carbohydrates found in vegetables and whole grains are slowly broken down to form simple sugar molecules (glucose), which are gradually absorbed through the wall of the small intestine and carried to the liver, where they are stored as glycogen. When the body needs sugar to increase energy output, operate muscles and organ systems, or produce warmth, the liver converts glycogen into its usable form, glucose, which is transported through the blood to any part of the body where it is needed. Because the need for glucose is almost constant – the brain, for example, is entirely fueled by glucose – blood sugar must remain fairly stable for the body to function normally.

When glucose concentrations in the blood drop below the norm, the brain (via the pituitary and thyroid glands) signals the adrenal glands to release cortisol. Cortisol stimulates the liver to release more glycogen to raise the blood sugar level and keep it steady. If, however, a person experiences chronic or repeated dips in blood sugar levels, whether from excess intake of simple sugars or malfunction of any of the organs or chemicals involved in glucose production and release, the adrenal glands become overtaxed and symptoms of low blood sugar develop.

A sudden or prolonged decrease in blood sugar levels can cause sleepiness, faintness, muscle tremor, cold hands and feet, muscle pain, irritability, depression, anxiety, blurred vision, numbness, indigestion, vertigo, exhaustion, insomnia, hot flashes, carbohydrate craving, itching, forgetfulness, ravenous hunger, moodiness, weakness in the legs, and heart palpitations. These could serve as a catalog of CFS/ME symptoms were it not for the notable absence of flu-like symptoms and exercise intolerance.

In CFS/ME, hypoglycemia is not the cause of the illness, but the result of profound metabolic upset. Numerous studies have revealed significant neuroendocrine abnormalities in CFS/ME patients. Among these, low cortisol levels are a common finding, especially following exercise. (Healthy people experience a rise in cortisol after exercise, not a drop.)

The normal functioning of the body requires endocrine hormones to keep the blood sugar level constant, so it goes without saying that disruptions of these hormones will in themselves cause fluctuations in blood sugar levels. Because the adrenal glands rely on signals from the pituitary and thyroid, and ultimately the hypothalamus, a problem in any of these areas will affect adrenal production. The resulting fluctuations in blood sugar levels are the inevitable consequence of erratic adrenal function.

Another likely cause of hypoglycemia in CFS/ME patients is a low level of vitamin B6. Vitamin B6 is an essential cofactor in the release of glucose from the liver, and therefore a deficiency will result in low blood sugar. In a study published in 1999, Heap et al found that CFS/ME patients had reduced functional status of B vitamins, particularly B6. This means that although there may be adequate circulating B6, it is not fully performing its role.

### TREATMENT TIPS

For treating common hypoglycemia, doctors rely principally on dietary changes.

The flood of simple sugars into the system ultimately provokes a decrease in blood sugar levels, which means the elimination of sugar will help control bouts of hypoglycemia. In his book, *Hypoglycemia: A Better Approach*, Dr. Paavo Airola recommends frequent small meals high in complex carbohydrates and protein (to slow the metabolism of sugars) and avoidance of stimulants (coffee, tea, caffeinated drinks) and sweets (cookies, cakes, candies, alcohol, refined flour products, dried dates, juices, including carrot juice, and anything containing sugar).

For people with CFS/ME, following Dr. Airola's advice seems to help: During episodes of hypoglycemia, eat something as soon as possible and either sit or lie down until blood sugar level rises. Because homeostatic regulation is slow in CFS/ME, this can take fifteen to twenty minutes. Then get up and eat something substantial. In any event, do not go for more than three hours without eating something (carry food with you when you go out). Eat some whole grains and proteins at each meal. Avoid all sugars. Do not fast. Stress, emotional upset, and overexertion, because they stimulate adrenal output, exacerbate the symptoms of hypoglycemia. Thus, including stress reduction exercises as part of your daily routine will be helpful.

Supplements that can help include vitamin C (to normalize blood sugar and improve adrenal function), vitamin B complex (vitamins B6, B5, and B12, in particular, are important to the adrenal, pancreas, and liver supports), magnesium (to aid in carbohydrate metabolism), calcium (for proper utilization of other minerals and vitamins), and low-dose chromium (to regulate blood sugar).

Supplementation with the bioactive form of B6, pyridoxine phosphate (P5P), is especially important. An herb that is particularly beneficial is licorice, long regarded by the Chinese as a powerful adrenal support and the "emperor" of all herbs.

If none of the above measures help, you may be suffering from dysautonomia, a dysregulation of the nervous system which is extremely common in people with CFS/ME. Up to 96% of CFS/ME patients have some form of dysautonomia, a condition which can cause rapid drops in blood pressure, nausea, weakness, heart palpitations, anxiety, light-headedness, as well as a host of other symptoms that *precisely* mimic hypoglycemia. Dysautonomia can be determined by a tilt table test, or by the careful monitoring of blood pressure and pulse. If you experience light-headedness upon standing (or after standing for a while), an increase of symptoms during hot weather, and heartbeat irregularities, it will be worth your while to investigate dysautonomia as the underlying cause of your symptoms.

SEE: Dysautonomia; Herbs (Licorice), Minerals (Magnesium, Calcium), Vitamins (C, B complex, B6); Stress Reduction and Elimination.

## FURTHER READING

*Good overview of hypoglycemia:*

[http://www.lef.org/protocols/metabolic\\_health/hypoglycemia\\_01.htm](http://www.lef.org/protocols/metabolic_health/hypoglycemia_01.htm)

“Hypoglycemia (low blood sugar) - a problem for many Chronic Fatigue Syndrome and Fibromyalgia patients, but treatable.” Sarah Myhill, MD. *ProHealth.com*. July 24, 2007 <http://www.prohealth.com/library/showarticle.cfm?libid=12991>

*How hypoglycemia produces insomnia:* <http://www.hypoglycemia.asn.au/2011/the-biochemistry-of-insomnia/>

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Heap LC, Peters TJ, Wessely S. “Vitamin B status in patients with chronic fatigue syndrome.” *J R Soc Med*. 1999 Apr;92(4):183-5.

<http://www.ncbi.nlm.nih.gov/pubmed/10450194> (Abstract)

## JOINT PROBLEMS

Pain, Gelling

NOTE: The joint problems most commonly experienced by people with CFS/ME are gelling (stiffness) and pain. Hypermobility of the joints, though it appears in some case definitions, is not a normal part of CFS/ME symptomatology. However, hypermobility is one of the constellation of symptoms found in Ehlers-Danlos Syndrome, a genetic connective tissue condition that shares many symptoms with CFS/ME and fibromyalgia (particularly POTS). It is not uncommon for people with Ehlers-Danlos Syndrome to receive an incorrect diagnosis of CFS or FM.

## PAIN

In his book, *The Disease of a Thousand Names*, Dr. David Bell reports that 65% of his patients with CFS/ME experience joint pain (arthralgia). Joint pain, for many, is a prominent, recurring symptom. Arthralgia tends to affect the ankles,

knees, elbows, shoulders, and sometimes hips. Arthralgia in CFS/ME is migratory, transient, and can develop after many of the other CFS/ME symptoms.

In most cases, joint pain is asymmetric (occurs on one side of the body). The pain is most often felt in the soft tissue around the joint. Knee pain, for example, is felt in the muscle above the knee and ankle pain in the top of the foot. Very rarely is the pain accompanied by swelling. Joint problems tend to predominate in children; some adults with CFS/ME never experience them.

Because the pain is rarely accompanied by any swelling or redness, most doctors do not test for arthritic conditions or joint-related diseases. However, if pain and stiffness persist, the patient may be tested for any of a number of conditions that affect the joints, such as Lyme disease, rheumatoid arthritis, or lupus.

Lyme disease is a bacterial infection that, in its late stages, can produce inflammation in the large weight-bearing joints (knees and hips) as well as fatigue, problems with thinking, memory loss, and emotional changes. If results of the Lyme test are positive, the disease is treated with antibiotics.

Rheumatoid arthritis is an autoimmune disease that causes inflammation of the synovial membrane, the thin sheath that cushions and lubricates the joints. Rheumatoid arthritis tends to start in the small joints of the fingers (usually the second and third), feet, and wrists, and develops symmetrically, affecting both sides of the body similarly. Because rheumatoid arthritis is systemic, it can produce low-grade fever, fatigue, achy muscles, weight loss, and depression in addition to joint pain. In the early stages of rheumatoid arthritis there may be no visible swelling or redness. Therefore, patients with any of these symptoms should have a blood test for rheumatoid factor (RF), a test that is about 80% accurate in identifying rheumatoid arthritis. Rheumatoid arthritis is treated with anti-inflammatory drugs. It should be noted that a number of people with chronic infections (including CFS/ME) also test positive for rheumatoid factor. If any swelling or redness develops, this may be an indication of rheumatoid arthritis, in which case you should see a rheumatologist.

Systemic lupus erythematosus, an autoimmune disease that primarily affects women, causes joint pain in the hands, wrists, elbows, knees, and feet. Other characteristic symptoms include a red rash over the cheeks and nose, hair loss, photosensitivity, Raynaud's phenomenon, kidney problems, and depression. The initial test for lupus is the antinuclear antibody test (ANA), which, in 95% of all cases, will indicate whether an autoimmune process has developed. Lupus is treated with anti-inflammatory drugs. Some people with CFS/ME test positive for antinuclear antibodies.

A number of factors contribute to joint pain in CFS/ME. The first of these is oxidative stress, a process which has been well documented in CFS/ME patients. During oxidative stress, healthy tissues are injured by excess free radicals. Because the mechanisms of oxidative stress can produce localized damage, only a specific joint, or set of joints, may be affected. The release of excess inflammatory cytokines caused by immune system dysregulation, one of the most important mechanisms of CFS/ME, leads to joint pain as well.

Reactivated parvovirus B19— which leads to release of inflammatory cytokines — has been shown to produce joint pain. Sub-clinical hypothyroidism, caused by endocrine system disturbances, also leads to joint pain, notably in the hips and shoulders. Allergies, because they lead to soft tissue swelling, are often accompanied by joint pain. All of these factors—oxidative stress, immune system dysfunction, reactivation of latent viruses, allergies, and endocrine system disturbances—are primary features of CFS/ME, and as a consequence, will all contribute to joint pain.

## GELLING

Gelling is stiffness in the joints that develops after holding a position (kneeling, crouching) that puts strain on the joints. It is especially noticeable after sitting in positions that require bending of the joints, such as sitting cross-legged or holding a book up while lying in bed for more than fifteen or twenty minutes without changing position. Gelling affects children as well as adults. The stiffness can be relieved with a few minutes of gentle movement of the affected joint.

## TREATMENTS

Joint pain is usually treated with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics such as ibuprofen (Advil) or acetaminophen (Tylenol). More severe pain can be treated with narcotics. Rheumatologists at Duke University Medical Center recommend that all of these medications should be used sparingly for joint conditions because of side effects, and because the benefits of these drugs are usually so short-lived. Nutritionists recommend evening primrose oil (essential fatty acids), zinc, and vitamin B6 for treatment of arthritic conditions.

Omega-3 fatty acids, found in fish oil, are among the most effective of natural anti-inflammatories. A recent meta-analysis of seventeen randomized double-blind studies showed that omega-3 fatty acids significantly reduced morning stiffness, tender joints, and pain. Herbal remedies include ashwagandha (an herb used in Ayurvedic medicine), cayenne (rubbed on the joint, not taken internally), feverfew tea, ginger, and licorice.

Gentle exercise such as rotation or other movement of the affected joint is also generally recommended for keeping good mobility. Acupuncture can sometimes ease the pain, as can transcutaneous electrical nerve stimulation (TENS). For people who suspect food allergies, a rotation diet and strict avoidance of offending foods (those of the nightshade family, in particular) can sometimes help prevent joint symptoms.

## FURTHER READING

*Herbal remedies for joint pain:* <http://www.herbalremedypro.com/joints.htm>

## RESEARCH

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Kerr JR, Bracewell J, Laing I, Matthey DL, Bernstein RM, Bruce IN, Tyrrell DA. "Chronic fatigue syndrome and arthralgia following parvovirus B19 infection." *Journal of Rheumatology*. 2002 Mar;29(3):595-602. <http://www.ncbi.nlm.nih.gov/pubmed/11911112> (Abstract)

## LOSS OF LIBIDO

Although people with CFS/ME rarely experience primary sexual dysfunction (impotence, frigidity), loss of sexual desire is common, not just in severe cases, but in mild cases as well. According to Dr. Bell (*The Doctor's Guide to Chronic Fatigue Syndrome*, 1995), roughly 20% of CFS/ME patients experience loss of libido – although, because many people are reluctant to bring the subject of sex up with their doctors, that figure is probably low.

A recent study conducted by researchers at the Department of Chronic Fatigue Syndrome, Vall Hebron Hospital and Delfos Medical Center, Spain, found, predictably, that the more fatigued the patient, the more likely she/he will avoid sexual activity. Loss of libido is a serious problem, not only because of a curtailed sex life but because in some cases it leads to the loss of partners and spouses, which, for many, can be as devastating as the illness itself. Like most other symptoms, loss of sexual desire can be coped with, and even treated. Unlike every other symptom, however, coping with loss of libido requires the active involvement of two people.

During any severe illness, lovemaking is simply unimaginable. Acute and severe CFS/ME can produce such overwhelming physical symptoms (especially pain) that the normal state of relaxation required for lovemaking is effectively eliminated. As one well spouse of a woman with CFS/ME put it, "If my wife had advanced cancer, and I told the doctor that she had sexual problems because she didn't want to make love, he'd think I was nuts." The profound depression that often accompanies severe CFS/ME also has the effect of limiting sexual interest. Even in milder cases of CFS/ME, in which physical symptoms are not incapacitating, the loss of sexual desire may represent a persistent, nagging problem.

Sexual desire, like all reproductive processes, is controlled by sex hormones and neurotransmitters (dopamine, norepinephrine, acetylcholine, vasoactive intestinal peptide). Testosterone, the male hormone that contributes to sexual drive, is regulated by the endocrine system, which is adversely affected by the neuroendocrine dysfunctions typical of CFS/ME. Testosterone is abundant in men but is also produced by women, especially around the time of ovulation. It is not surprising that many women feel the "urge" around that time of the month.

The neurotransmitters involved in sexual responses are numerous. In the early stage of arousal, acetylcholine and vasoactive intestinal peptide are released, signaling the parasympathetic nervous system to dilate blood vessels, decrease

blood pressure, and, in men, start an erection. The vasodilating effects of early sexual arousal create a feeling of relaxation, which sometimes leads to sleepiness.

Eventually dopamine and norepinephrine are released. These two neurochemicals stimulate the sympathetic nervous system. Heart rate increases, palms sweat, and blood vessels constrict. Because of the excitatory effects of adrenal hormones, people with severe CFS/ME usually find this stage of arousal overly stimulating and may feel ill as a result. Histamine is also released, producing a flush. Release of oxytocin, a neuropeptide produced in the pituitary gland, is responsible for the muscle contractions that occur at climax. Oxytocin is also credited with generating feelings of protectiveness, nurturing, and romance in people.

Given the many neuroendocrine abnormalities found in CFS/ME, it is not surprising that CFS/ME causes dysregulation of the hormones and neurochemicals that govern sexual responsiveness. The endocrine abnormalities discovered by Dr. Mark Demitrack and colleagues reveal both adrenal under- and over-responsiveness, resulting in altered production of adrenal hormones – in this case, norepinephrine (*Journal of Clinical Endocrinology and Metabolism*, 1991).

Deficiencies in oxytocin and acetylcholine have also been found in people with CFS/ME. With the general endocrine system upset and neurological dysregulation typical of CFS/ME, problems with libido can be expected.

## TREATMENT TIPS

Problems with libido are complex but can be effectively managed. The key to treating loss of libido is a thorough understanding of the problem. A firm belief on the part of both partners that decreased sexual motivation is the result of an illness rather than to loss of love can truly save a relationship. Communication is key. In the Blazquez et al study, 85% of the participants with CFS/ME reported that would like to change some aspect of their sex lives. Participants commented that they found themselves “yielding” to their partners, viewing sex as an obligation, rather than as a mutually satisfying experience. One has to wonder after reading these comments how many of the participants felt they could openly discuss their state of mind with their partners.

Counselors experienced with long-term illnesses may be able to offer invaluable support in this regard. A good counselor can help work out alternatives to previously established habits of emotional expression, appropriate ways to express sexuality during illness, and a means to open dialogue between partners in whom the frustration and despair of stymied intimacy may be long-standing.

If sexual problems persist, it is well worth examining your regimen of medications. Many doctors prescribe antidepressants to CFS/ME patients as part of their overall treatment protocol. With one exception (bupropion, brand: Wellbutrin), antidepressants produce loss of libido, and in some cases, outright sexual dysfunction.

On the other hand, certain drugs can help increase libido. Most of these are stimulants and must be used with caution. Wellbutrin, an antidepressant, and the



central nervous system stimulants (e.g., Ritalin) increase the amount of norepinephrine in the brain and concurrently act to increase sexual arousal. For those who are sensitive to pharmaceuticals, nondrug treatments may be equally effective.

Vitamins, minerals (especially zinc, which increases the production of testosterone), essential fatty acids, and the amino acids phenylalanine and tryptophan are vital in the formation and maintenance of the neurochemicals and hormones that produce sexual responsiveness. Look for foods high in these nutrients.

Tyrosine, a precursor to norepinephrine may also help. (Not recommended for insomniacs, however.) Chocolate contains a natural stimulant, phenylethylamine, which may be helpful to some people with CFS/ME. Herbs such as ginseng, maca root (a Peruvian herb), Cordyceps (a fungus), rhodiola rosea, and ashwagandha (which increases testosterone) have been traditionally used to increase libido. (Note that most of these herbs are stimulants and can lead to insomnia.) One patient with chronic CFS/ME discovered that folic acid taken in combination with vitamin B12 alleviated libido problems. Men may benefit from taking testosterone directly – but have your hormone levels tested first.

The best remedy for loss of libido is recovery. Nevertheless, those still struggling with the illness need not despair. The best approach is to take advantage of libido when it's there and not push things when it isn't. Sometimes just removing the stress of having to produce a response can act as a sexual stimulant. In all cases, remember there is no substitute for tender feelings, and these can be expressed whenever there is love and trust between two people.

SEE: Herbs (Ginseng), Minerals (Zinc), Vitamins (B12)

#### FURTHER READING

“Loss of Libido.” Dr. Teitelbaum

[http://www.endfatigue.com/natural\\_cures/libidoloss.html](http://www.endfatigue.com/natural_cures/libidoloss.html)

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Hirschfeld RM. “Management of sexual side effects of antidepressant therapy.” *J Clin Psychiatry*. 1999;60 Suppl 14:27-30; discussion 31-5.

<http://www.ncbi.nlm.nih.gov/pubmed/10408423> (Abstract)

Underhill, Rosemary. “Gynecological Concerns in Women with Chronic Fatigue Syndrome.” *CFIDS Chronicle*, Summer 2002.

<http://www.cfids.org/archives/2002rr/2002-rr3-article03.asp>

#### MUSCLE PROBLEMS

Weakness (Paresis), Tremor, Loss of Coordination, Twitches

Muscle-related problems are among the most frequently encountered symptoms in CFS/ME, affecting approximately 80% of the CFS/ME population. Although muscle pain, weakness, and tremor are common, their cause remains the subject of much debate.

Inflammatory muscle ailments that produce weakness and pain, such as polymyositis and polymyalgia rheumatica, although symptomatically similar, do not have much in common with the muscle problems generated by CFS/ME. Some researchers have speculated that a virus affecting the nervous system, perhaps similar to poliovirus, may lie at the root of the overwhelming weakness characteristic of the acute stages of the illness. Although the similarity in muscle symptoms between post-polio syndrome and CFS/ME is striking, there does not appear to be a breakdown in muscle tissue in CFS/ME. Others have proposed that an alteration in protein metabolism in muscle cells may be at fault, yet there is little evidence to support this view. The same is true for studies that examine enzyme levels.

Dr. Paul Cheney proposed that in CFS/ME, anaerobic cell metabolism predominates over aerobic cell metabolism (*CFIDS Chronicle*, Fall 1994; *CFIDS Chronicle*, Spring 1995). Unlike aerobic cell metabolism, which is fueled by circulating glucose (from carbohydrates) and oxygen, the evolutionarily older process of anaerobic cell metabolism is fueled by stored glycogen and fructose. While the by-products of aerobic metabolism (carbon dioxide and water) are harmless, the by-products of the more inefficient anaerobic metabolism (lactic acid and ammonia) are not. Accumulation of these anaerobic toxins results in acidosis, which can produce a generalized deep ache and hard, stiff muscles. Although Dr. Cheney formulated this hypothesis in the early 90s, it is worth noting that two recent studies conducted by Jones et al have confirmed prolonged tissue acidosis in the muscles of CFS/ME patients after exercise, lending substantial support to Dr. Cheney's observations.

Dr. Hirohiko Kuratsune and Dr. Audrius Pliplys have found in their own independent research that people with CFS/ME demonstrate consistently depressed concentration of acyl-carnitine (*CFIDS Chronicle*, Winter 1995). A deficiency in carnitine leads to mitochondrial dysfunction, which eventually causes muscle weakness. Mitochondrial dysfunction is also a by-product of oxidative stress. Aside from the numerous extracellular processes affected by oxidative stress, mitochondrial dysfunction leads to loss of cellular energy, which manifests itself in fatigue and muscle- and cardiac-related problems.

Various studies have found markers of oxidative stress in the skeletal muscles of people with CFS/ME. In 1999 Bounos and Molson proposed that depletion of glutathione, which is both a powerful antioxidant and essential for aerobic muscle contraction, was responsible for the weakness and pain experienced by people with CFS/ME. Glutathione depletion has been proposed as a primary mechanism for many other CFS/ME symptoms, as well.

In 2003 a group of Italian researchers confirmed higher TBARS (an indication of oxidative stress) in skeletal muscle of CFS/ME patients. And in 2005, a

group of French researchers found not only indicators of oxidative stress (higher TBARS and lower glutathione), but increased production of lactic acid (in accord with Cheney's acidosis hypothesis). The researchers concluded that “the response of CFS patients to incremental exercise associates a lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability.”

In a comprehensive analysis of urinary and plasma amino and organic acid markers published in 2005, Jones et al found that CFS/ME patients, along with patients with rheumatoid arthritis, had high levels of histidine. The researchers also found a reduction in hydroxyproline, which is similar to findings in patients with fibromyalgia. Jones' group suggested that the “highly significant” reduction in urinary hydroxyproline in patients with CFS/ME indicated reduced intramuscular collagen that might lead to muscle pathology. They concluded that “a reduced threshold for muscle micro-injury in combination with active inflammatory disease may provide a basis for the fatigue and muscle pain that are the major symptoms in patients with ME/CFS.”

All of these studies confirm that there is an alteration of muscle function in CFS/ME patients that not only differs radically from the healthy population, but is part of the profound metabolic disturbance that produces all CFS/ME symptoms.

(Please see Pain for more specific information on pain mechanisms and treatments.)

SEE: Pain, Hypoglycemia; Ampligen, Antidepressants, Pain Relievers; Amino Acids (Carnitine), Essential Fatty Acids, Malic Acid, Minerals (Magnesium); Acupuncture, Hypnosis, Massage, Meditation, TENS.

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## WEAKNESS (PARESIS)

Loss of muscle strength is nearly universal in severe cases of CFS/ME and may persist well into recuperation. Sometimes the weakness may be so profound that a person is unable to get out of bed without assistance, or must use a wheelchair. Weakness can be localized (arms, hands, legs, and neck) and can occur quite suddenly. Bouts of sudden weakness are often triggered by lifting (producing weakness in the legs), driving, or any form of weight-bearing exercise. In the very ill, even the amount of effort needed to maintain the weight of bed sheets, lift a toothbrush, or hold a telephone may be tremendous.

Although some doctors have made the assumption that weakness in CFS/ME is due to deconditioning, muscle weakness comes on so suddenly in CFS/ME, and often in people who just days before becoming ill had been jogging, swimming, hiking, dancing, and pursuing an active, healthy life, that it is highly unlikely that weakness is due to inactivity. Unlike poliomyelitis and other systemic illness, however, muscle weakness in CFS/ME is not usually progressive. Doctors have noted that even people who have been bedridden or housebound for one or two years demonstrate a near-normal level of muscle strength, an observation that implies that CFS/ME itself does not cause substantial muscle atrophy.

Muscle weakness, like pain, can be due to oxidative stress. Various studies have confirmed oxidative stress in the skeletal muscles of people with CFS/ME. In 1999, Bounos and Molson proposed that depletion of glutathione, which is both a powerful antioxidant and essential for aerobic muscle contraction, was responsible for the weakness and pain experienced by people with CFS/ME. Oxidative stress can be induced by a number of processes, including hypoxia, a metabolic condition in which cells do not receive sufficient oxygen.

In 1999 McCully and Natelson conducted a study to determine if CFS/ME symptoms were associated with reduced oxygen delivery. They measured oxygen resaturation in the blood of CFS/ME patients and sedentary controls following exercise. The researchers found that oxygen delivery was reduced in CFS/ME patients compared with sedentary controls, indicating abnormal autonomic control of blood flow. They concluded that reduced oxygen delivery could result in the muscle fatigue experienced by people with CFS/ME. Lowered oxygen is often the result of reduced or impaired blood flow.

There are a number of hematological abnormalities in CFS/ME, any one of which could lead to reduced oxygen delivery to muscle tissue. In the mid-1990s, Dr. Leslie Simpson proposed that higher blood coagulability and the resultant decrease in tissue oxygenation was due to an increased proportion of cup-shaped and flattened red blood cells in people with CFS/ME. According to Dr. Simpson, “shape-changed red cells are stiffer than usual and poorly deformable and they will pass through small capillaries very slowly, or even block the capillary.” As the midbrain is almost entirely fed through capillary action, Dr. Simpson proposed that patients with CFS/ME have a “functional lesion” of impaired blood flow to the hypothalamus. This would provide an excellent explanation for nearly all neurological symptoms, including the profound muscle weakness characteristic of CFS/ME.

## TREATMENTS

Supplementation with carnitine has been reported to alleviate muscle weakness in many people with CFS/ME.

Other treatments for weakness include amantadine (Symmetrel), interferon, gamma globulin, magnesium, vitamin B12, CoQ10, nitroglycerin, Prozac, antifungal agents, and Ampligen. It should be mentioned that, although antidepressants are commonly prescribed to relieve CFS/ME symptoms, some of the tricyclic drugs, as well as all anticholinergics (e.g., antihistamines, anti-diarrhea medication) can make muscle weakness worse. Patients who are taking antidepressants and experience increased muscle weakness should inform their doctor.

SEE: Amantadine, Ampligen, Gamma Globulin; Antifungals, Antidepressants; Antioxidants (CoQ10), Nitroglycerin, Minerals (Magnesium), Vitamins (B12)

## FURTHER READING

“Dr. Les Simpson – Rethinking the Pathogenesis of CFS/ME.”

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## TREMOR

Shaking of the arms, legs, and torso is not unusual in CFS/ME, although it tends to pass within the first few months in most people. Tremor can be caused by hypoglycemia (low blood sugar), hypotension, or be neurological in origin (dysautonomia). Even in those who do not experience overt shaking, a slight hesitation in movement, or “cogwheel” effect, has been observed by a number of

physicians who attended CFS/ME outbreaks in England and South Africa. Such hesitation is easily seen when a smooth, continuous motion is attempted, such as lowering an arm or leg from a raised position. As with twitches, disruption of normal basal ganglia function, whether from direct injury or disruption of the hypothalamus, causes tremor. Tremor is exacerbated by stress, fatigue, fasting, and decreases in blood sugar levels.

A broad-spectrum nutritional supplement may help relieve this symptom considerably. All of the treatments and management strategies for hypoglycemia will help if the tremor (especially in the legs) is due to drops in blood sugar.

Magnesium is also recommended, as it not only helps strengthen muscles, but acts to modulate an over-responsive sympathetic nervous system. (Sympathetic nervous system excitability lies at the root of dysautonomia, the disorder that encompasses orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), as well as many other regulatory problems that can lead to muscle tremor and weakness.)

SEE: Cardiac and Cardiovascular Symptoms, Hypoglycemia; Minerals (Magnesium)

## LOSS OF COORDINATION (ATAXIA)

Most people with CFS/ME experience some impairment of coordination. People who drop things, break dishes, spill food on themselves, run into doorjams, trip, or have difficulty negotiating stairs not only risk injury, but have embarrassment to add to their long list of difficulties. A number of factors can contribute to clumsiness.

Loss of muscle coordination is related to loss of strength. Sometimes the ability to coordinate muscles which can lose strength suddenly and unpredictably, leads to dropping things. Impairment in depth-of-field vision and nervous system feedback (proprioception) can also lead to difficulties in judging distance, placement, and relative velocity. A person may under-judge the counter when placing a dish on it, or over-judge a stair when placing a foot on it. Balance problems, which may be due to inner ear problems, are also quite common in CFS/ME, leading to falling or tripping.

A problem closely related to ataxia is akinesia, a disorder which is characterized by difficulty stopping, starting, or sustaining movement. Akinesia is caused by damage to dorsal root ganglia, which are clusters of neuronal tissue close to the spinal cord that act as intermediaries between the central and peripheral nervous systems. Those with dorsal root ganglia damage experience heightened sensitivity to nervous system stimulation, including pain, light, and sound. They also experience akinesia resulting from the brain being slow to respond to external stimuli. As inflammation in dorsal root ganglia has been implicated in CFS/ME, possibly due to herpesvirus reactivation, it likely contributes to loss of coordination.

Generally, ataxia improves as the rest of the illness abates. As always, treating the underlying cause is essential. If you experience sudden drops in blood pressure due to dysautonomia, treatments designed to regulate blood pressure, such

as beta-blockers, Florinef, licorice, and increased salt and liquid intake will be useful. If low blood sugar lies at the root of the problem, following hypoglycemic protocols will help. Antivirals and anti-inflammatory agents may also prove helpful. SEE: Cardiac and Vascular Problems, (Dysautonomia) Hearing and Ear Problems, Hypoglycemia, Vision and Eye Problems; Antiviral Agents.

## TWITCHES

Twitches (benign fasciculations) are common throughout the course of CFS/ME, although they tend to increase during exacerbations and relapses. Twitches can occur in any body part (legs, arms, torso, face). They can occur continuously, sporadically, be widely distributed, or be confined to one area only (often eyelids and thumbs). Twitches increase with fatigue and decrease with rest.

Research seems to indicate that twitches, like the loss of complex sequencing movements (as in speech), are due to a dysfunction of the basal ganglia. However, inasmuch as the nerve fibers that connect the basal ganglia to the cortex pass through the hypothalamus, disruption of hypothalamic function could just as well cause fasciculations.

Twitches are primarily associated with the cholinergic system. Acetylcholine is the neurotransmitter involved in the motor system, which means it is responsible for the innervation of muscles. Excess acetylcholine in nerve synapses will cause twitches. Paradoxically, people with CFS/ME have been found to have low, rather than high levels of acetylcholine. This results in an exaggerated response to acetylcholine.

Twitches are harmless in and of themselves and, although annoying, require no special treatment. Magnesium seems to reduce their frequency and extent, as does zinc. Benzodiazepines and other nervous system down regulators will also decrease twitches.

Anticholinergics (antihistamines, tricyclic antidepressants) will cause twitches, as will exposure to pesticides. Eyelid twitches are often caused by dry eyes (sicca). Good quality eye drops can help lubricate the eyes and relieve twitches. General dehydration will lead to twitches in many parts of the body, particularly the legs, so proper hydration is important.

SEE: Anticonvulsants, Benzodiazepines; Minerals (Magnesium, Zinc).

## ORAL PROBLEMS

Gingivitis, Sensitive Teeth, Canker Sores, Temporomandibular Joint Syndrome, Taste

Oral problems are common throughout the course of CFS/ME. They can occur in the gums, teeth, mandibular joints, oral cavity, and jaw muscles. Although oral problems can cause a great deal of discomfort, they are usually transient. Tooth pain, in particular, is notorious for coming and going, seemingly without reason. Its quixotic occurrence, however, is no reason to take tooth pain lightly. Dentists who

count people with CFS/ME among their patients have observed that gum problems are common in this group. The many teeth complaints reported by people with CFS/ME often are related to gum inflammation. Fortunately, most common oral problems respond well to treatment.

### GINGIVITIS

Gingivitis can be caused by a number of factors, but the most likely culprit in CFS/ME is dry mouth (*sicca*), which is a common problem among CFS/ME patients. Many of the medications prescribed to CFS/ME patients, such as antihistamines and antidepressants, will also cause dry mouth. In some cases, gum inflammation can be caused by allergic reactions, medications, viral infections, or poor circulation to the gums. Due to the nature of the pain, gum inflammation is often mistaken for toothache.

Saliva contains enzymes and natural bactericides which help to curtail infections. When there isn't enough saliva, the small residues of food that get trapped under the gums can easily lead to irritation. If the food particles are not removed, the gum becomes inflamed (gingivitis). Chronic inflammation can cause small pockets to form around the gums, leading to buildup of hardened plaque (tartar) under the gums. The gums respond to the tartar as they would to splinters. If the tartar is not removed, the gums eventually become diseased (periodontitis), and loss of teeth may ensue. Bad breath can be a sign of gum disease. If you have chronic halitosis not related to a sore throat or an upset stomach, a trip to the dentist may be in order.

Anyone with pain or bleeding due to gum inflammation needs to keep his or her teeth and toothbrush very clean. Having a professional cleaning every three to four months is advisable (although in most cases insurance will only pay for a cleaning every six months). Home care is extremely important. (Please see below for home care tips.)

Several studies have indicated that CoQ10 can help remedy gum disease by reconditioning the gum tissue, reducing inflammation and bleeding, inhibiting bacterial growth, and improving immune response to protect gums from future bacterial attacks. As early as 1975, clinicians noted that oral CoQ10 was extraordinarily effective in healing the gums. In a study by Wilkinson et al, 50 mg of CoQ10 was administered to eight patients for three weeks. The authors stated that "healing was so excellent 5-7 days post-biopsy that the biopsy sites were difficult to locate."

In a study conducted in 1994, a group of Japanese researchers compared the effects of a six-week topical application of 85 mg of CoQ10 with non-surgical periodontal therapy on adult periodontitis. The results showed significant improvement of pocket depths and bleeding. Because healing was only observed in the pockets where the CoQ10 had been applied, the researchers concluded that CoQ10 could be used as a sole treatment for gum disease.

There are various toothpastes available in health food stores and online which contain CoQ10 (with and without fluoride). For direct application, CoQ10 gelcaps can be broken open and applied topically with a soft toothbrush.



## SENSITIVE TEETH

Sensitivity to cold or heat in the absence of dental caries (cavities) is common among people with CFS/ME. This may be caused by damage to the tooth (such as chipping), or to increased nerve sensitivity. CFS/ME patients will often experience heightened sensitivity to temperature changes which can last for many months after having any kind of dental work done.

While sensitivity to cold or heat in the absence of caries is rarely a sign of incipient root problems, the dry mouth experienced by many people with CFS/ME can increase the risk of tooth decay. Decay undermining a filling can also exacerbate sore throat, headache, and jaw pain, and should be attended to at once. Be aware, however, that people with CFS/ME tend to react poorly to the epinephrine doctors and dentists add to anesthetics. Dr. Paul Cheney recommends requesting anesthetic without epinephrine, particularly for patients taking antidepressant medication (*Mass CFS/ME Update*, Summer 1991).

## CANKER SORES (APHTHOUS STOMATITIS)

Canker sores can result from injury (a toothbrush or food scraping along the inside of the teeth), from a bacterial or viral infection (notably herpes simplex), and by systemic immune system dysfunction. The sores look like small bumps with white heads on the inside of the cheeks or near gums. These sores can grow and are quite painful.

To treat canker sores, sweets, starches, and milk products should be strictly avoided (these feed bacteria) and the mouth rinsed with hot salty water before and after each meal. With this regimen, canker sores usually disappear in a day or two.

A number of reports have shown that vitamin B12 is an effective treatment for chronic canker sores. In a randomized double-blind study published in 2009, 74% of a group given 1000 mcg sublingual B12 every evening over a six-month period experienced a complete eradication of canker sores. Lysine, an amino acid, and Zovirax, an antiviral agent, also are helpful in treating canker sores.

## TEMPEROMANDIBULAR JOINT DISORDER

Temporomandibular joint (TMJ) disorder is a condition in which the joint that connects the jaw to the skull becomes inflamed. TMJ disorder can result from arthritis, trauma (such as a car accident), teeth grinding, and bite asymmetry. Diagnosis of TMJ disorder is usually made by a dentist.

In CFS/ME, TMJ disorder is usually caused by muscle spasms or joint inflammation and only rarely by bite asymmetry. The muscles leading from the jaw to the top of the head are among the strongest in the body, a holdover from the days when our ancestors had to crack nuts between their teeth. When these muscles spasm, the result is severe aching pain that extends from the jaw up the side of the head. The accompanying headache can be unbearable. Pain in the ears (often confused with otitis media), and face is very common. People with TMJ disorder

often grind their teeth and may have nocturnal bruxism (teeth grinding during sleep), which only makes the problem worse.

Sometimes opening the mouth wide stretches the muscles and helps relieve the pain of muscle spasms around the jaw. Localized heat also helps relieve the pain. The lengthy and expensive bite readjustments recommended by dentists for TMJ are not usually helpful, because the problem in CFS/ME patients is seldom mechanical.

Muscle relaxants, Flexeril, Klonopin, tranquilizers, herbal relaxants (e.g., valerian, skullcap), hypnosis, magnesium, massage, transcutaneous electrical nerve stimulation (TENS), and chiropractic are some ways in which TMJ has been alleviated in people with CFS/ME. Biofeedback is very useful for those who tend to clench their teeth, or who have bruxism.

## TASTE

Frequently, the sense of taste is affected in CFS/ME, making food taste bitter, metallic, or spoiled. Often the effect is transitory; the same food eaten a few hours later tastes fine. Alterations in taste are more frequent in the acute stage of CFS/ME and during relapses, during which previously palatable foods may entirely lose their appeal. Some people may lose their sense of taste altogether. This is most likely due to nervous system dysregulation. Children with CFS/ME seem to be especially affected by alterations in taste and may become picky eaters as a result.

Persistent alterations of taste can be due to limbic system disturbances, in particular those involving the hippocampus, which is responsible for processing taste and smell. Brain scan studies of people with CFS/ME have revealed various neural anomalies, including both reduced hippocampal mass and reductions in hippocampal activity. Any alteration in the function of the hippocampus will not only affect taste and smell, but memory. (In his famous novel, *Remembrance of Things Past*, Marcel Proust records a flood of memories provoked by a morsel of cake.)

Those with chemical sensitivities and hyper-responsive nervous systems may also experience a general upregulation in neurochemical responses which will lead to changes in all sensory perception, including taste and smell. Dr. Shoemaker has observed that patients who have been exposed to mold, a biotoxin with neurological effects, often complain of a metallic taste in their mouths.

There is no specific treatment for alterations in taste. Keeping the mouth well irrigated by sipping water or chewing sugar-free gum will help improve taste perception for those with dry mouth. Maintaining good oral hygiene will help keep taste-altering bacterial infections at bay. General systemic treatments to help calm a hyper-responsive nervous system, such as antioxidants, magnesium, fish oil, opiates and some antidepressants – although the latter two will induce dry mouth – can also lead to improvement in taste perception. A persistent bitter taste in the mouth can result from liver or gallbladder problems, both of which warrant immediate medical attention.

## TREATMENT TIPS

Oral hygiene is essential for maintaining healthy teeth and gums. This is particularly relevant for people with gum problems. People with CFS/ME should try to give their teeth a careful cleaning at least once a day with a toothbrush and dental floss. This can be accomplished in stages while sitting or even lying down.

Using a soft, small-headed dry brush, gently rotate the bristles over and around the gum line of each tooth, about ten times for each tooth. Start with the back molars and work around to the front. The tongue collects bacteria, so be sure to brush your tongue as well. Then floss and rinse thoroughly. This process should take about two minutes. Even if you can only accomplish one cleaning a day, this will be sufficient to keep plaque from forming.

Rinsing with warm salty water after brushing is an excellent way to control bacteria and to soothe the gums. After professional cleanings, many dental hygienists recommend rinsing the mouth and gargling three times a day with warm slightly salty water to help prevent infection. If you have frequent oral infections, you should soak your toothbrush in hydrogen peroxide after brushing. This will kill any germs that may have collected in the bristles. Following colds or other infections, it is best to replace the toothbrush with a new one.

Natural cleaners that are good for the teeth and gums include baking soda (a mild abrasive; good for use by people sensitive to the ingredients in toothpaste), Neem (a botanical gathered from the Neem tree in India; good for the gums), myrrh (an ancient herbal antiseptic available in health food stores; also good for the gums). Several studies have indicated that CoQ10 can help remedy gum disease.

## PRECAUTIONS

- Do not take antibiotics for gum problems unless a bona fide infection, with identified bacteria, can be verified. Antibiotics kill the bacteria needed for good oral ecology and may worsen gum problems in the long run – as will repeated rinsing with hydrogen peroxide.
- Try to avoid oral hygiene products that contain artificial colors, flavors, sweeteners, alcohol, or talc; these are often sources of gum irritation in people with CFS/ME.
- Do not have all your fillings removed to eliminate potential leakage of mercury. While mercury poisoning resembles CFS/ME in many ways, the two should not be confused. Elimination of numerous fillings is expensive, laborious, and thoroughly stressful, requiring use of anesthetics and other chemical substances that may cause harmful effects to a compromised immune system. Patients with silver amalgam fillings who wish to remove them should first have a hair test to check for elevated mercury concentration; then have the fillings removed gradually, taking care not to release mercury-containing filling fragments into the mouth. (Dentists use a rubber dam for this purpose.) Be forewarned that, although mercury is certainly toxic, it is not likely that the small quantity of mercury that can leak from old fillings will cause the myriad, persevering symptoms of

CFS/ME. The small number of people with CFS/ME who have had fillings removed have not reported improvement. A few have felt worse for days to several weeks afterward because of the exhausting nature of extensive filling removal and replacement.

- Avoid sugar.

SEE: Antihistamines, Antidepressants, Benzodiazepines; Antioxidants, CoQ10, Essential Fatty Acids, Magnesium; Biofeedback, Hypnosis, Meditation, TENS.

#### FURTHER READING

“Dental Problems in CFS and Fibromyalgia.”

[http://www.endfatigue.com/health\\_articles\\_d-e/Dental-problems\\_in\\_cfs\\_fibromyalgia.html](http://www.endfatigue.com/health_articles_d-e/Dental-problems_in_cfs_fibromyalgia.html)

*CFS/ME patient board on gum health/treatments:* <http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=641001>

*Dr. Teitelbaum on treating dry mouth:*

[http://www.endfatigue.com/health\\_articles\\_c/Cfs\\_fm-treating\\_dry\\_eyes\\_and\\_dry\\_mouth.html](http://www.endfatigue.com/health_articles_c/Cfs_fm-treating_dry_eyes_and_dry_mouth.html)

*CFS/ME patient thread on alterations of taste and smell.*

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#### PAIN

## Carpal Tunnel Syndrome, Spasms, Fibromyalgia

The principal regions in which chronic or recurring pain is experienced in CFS/ME are muscles (particularly legs and lower back), joints, head, and digestive system organs. While pain is common in CFS/ME, the frequency and degree may vary enormously. Some CFS/ME patients experience very little, or no pain at all. However, when pain is a predominant symptom it may overshadow all the others. The deep, burning, relentless pain felt by many people with CFS/ME can be unbearable. Pain can also become a source of great frustration when its origin is not clear.

Pain cannot be measured objectively, nor can pain levels be predicted by standard judgments of injury or trauma, and so doctors who do not see any specific cause for pain may dismiss the symptom as “all in your head” and refer you to a psychiatrist, a situation deeply distressing for patients with chronic pain.

The irony of pain is that it really is “all in your head.” The mechanism through which people feel pain is neurological, and completely subjective. Pain receptors in the skin (substance P, prostaglandins, bradykinin) respond to stimuli such as heat, pressure, and tissue injury, and relay pain messages to the brain through the nerves. The pain signal is eventually relayed to the thalamus, where it is differentiated into heat, cold, or pressure pain.

Conversely, the central nervous system itself can send pain messages through the efferent nervous system. (Phantom pain in amputees is a prime example of CNS-generated pain.) The degree of pain a person feels after receiving the stimulus (the pain threshold) is highly individualized, and depends on the extent to which chemical messengers that relay the pain signals to the thalamus are counteracted by endorphins. Endorphins, which are chemically similar to morphine, are the body's own painkillers. When few endorphins are released, the experience of pain is much greater.

The origins of chronic pain in CFS/ME are neurological, generated by increased irritability of the central nervous system, leading to overproduction of pain message chemicals (substance P has been implicated in fibromyalgia), lack of counter-regulation by endorphins, and/or excitement of the thalamus (damage to the thalamus can produce chronic burning pain).

Dr. Martin Pall and Dr. Kenny De Meirleir have proposed that excess production of nitric oxide (NO), may serve as the underlying mechanism of pain in CFS/ME. While NO is essential for many bodily functions, an overproduction ultimately leads to activation of inflammatory cytokines. The increase in inflammatory cytokine production (notably alpha interferon) that accompanies CFS/ME further complicates matters because interferon binds to opioid receptors, making it more difficult for endorphins to block pain.

Although the question of how this terrible cycle of inflammation and pain comes about has occupied researchers for decades, it may, in fact, have already been answered. In 2005 a young British woman named Sophia Mirza died of CFS/ME, becoming the first person in Great Britain to officially die of this ailment. Sophia had contracted CFS/ME after a viral illness from which she never recovered. Her

case was quite severe. Among her symptoms, Sophia could not bear the slightest touch without experiencing excruciating pain. Nor could she bear light or sound. Psychiatrists believed it was “all in her head” and sent her to a mental ward. However, as it turned out, it was all in her spine.

Sophia's autopsy revealed that 80% of the dorsal root ganglia of her spinal column were damaged. Dorsal root ganglia are small nodules located near the vertebrae. These ganglia serve as receptor sites for afferent nerves, which means their function is to relay information about perceptual stimuli back to the brain, particularly pain. At Sophia's inquest, Dr. O'Donovan, the neuropathologist who examined her spinal cord along with Dr. Chaudhuri, reported that the spinal cord appeared normal but that he had found that four out of five dorsal root ganglia were abnormal and showed disease. He was not able to find the cause, but the result was inflammation of the dorsal root. Dr. Chaudhuri has since documented inflammation of dorsal root ganglia in other CFS/ME patients as well.

While Dr. O'Donovan did not speculate as to the cause of the inflammation along Sophia's spine, it is well known that herpesviruses cause damage to dorsal root ganglia. Varicella zoster, the herpesvirus that causes chicken pox, replicates in dorsal root ganglia, causing the pain of shingles. Herpes simplex also travels to dorsal root ganglia. Neither should enteroviruses be overlooked. Polio infects the dorsal root ganglia, causing paralysis. During the epidemics of neurasthenia (now thought to be CFS/ME) of the 1930s to 1950s, monkeys which were injected with sera from patients with neurasthenia developed widespread lesions scattered throughout the nervous system from the brain to peripheral nerves.

Reasonably speaking, there is no scientific basis to reject the notion that viruses commonly found in CFS/ME patients can lead to CNS inflammation and subsequent pain. Nor is there any reason to believe that the pain produced by CFS/ME is anything other than organic.

## GENERAL TREATMENTS FOR PAIN

Pain is such an essential and primeval part of our physiological and emotional makeup that it is literally impossible to ignore. Chronic pain is incapacitating and may lead to the feeling that life is no longer worth living. Therefore, treatment of pain should not be neglected.

Pharmaceutical pain treatments usually recommended for people with CFS/ME and FM include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (Tylenol), Ultram, and narcotic agents. A number of people have also reported pain relief with use of antidepressant drugs, benzodiazepines, calcium channel blockers, nitroglycerin, Diamox, and Vistaril. Low-dose Naltrexone (LDN) is used to alleviate fibromyalgia pain.

Supplements that have been reported as helpful include malic acid, magnesium, and omega-3 fatty acids (which reduce inflammation).

Manual techniques for relieving pain include gentle massage, chiropractic, transcutaneous electrical nerve stimulation (TENS), low level laser therapy, and acupuncture

Effective mind-body techniques that alleviate neurological pain include hypnosis, meditation and relaxation techniques, and biofeedback.

An interesting observation about an unusual treatment for protracted pain was made by a former marathon runner with CFS/ME who experienced relentless, severe pain. A single shot of Demerol, given in the context of a medical procedure, relieved her pain for eight months. She believes that the drug broke the neurological cycle of pain. When strong measures are indicated, this type of treatment may be worth consideration.

SEE: Digestive System Problems, Headaches, Joint Pain, Muscle Problems; Antidepressants, Benzodiazepines, Calcium Channel Blockers, Diamox, Naltrexone, Nitroglycerin, Pain Relievers; Essential Fatty Acids, Minerals (magnesium); Acupuncture, Biofeedback, Chiropractic, Hypnosis, Massage, TENS.

#### FURTHER READING

*Good summary of alternative treatments for neuropathic pain.*

<http://www.townsendletter.com/AugSept2006/painfree0806.htm>

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SEE: Pain Relievers; Essential Fatty Acids; Acupuncture, TENS.

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#### CARPAL TUNNEL SYNDROME

Dr. Jay Goldstein noted that associated carpal tunnel syndrome is fairly common in CFS/ME (*CFIDS Chronicle*, Fall 1992). In carpal tunnel syndrome the median nerve that supplies blood to half the hand is pinched by excess fluid accumulating in the area around it (the carpal tunnel). The pressure on the nerve causes tingling and numbness in the tips of the fingers and aching in the wrist that can spread up the forearm to the shoulder. The condition is exacerbated by putting any stress on the wrist.

Dr. Karl Folkers, Director of the Institute of Biomedical Research at the University of Texas at Austin, believes that carpal tunnel syndrome is caused by a deficiency of vitamin B6 and has observed that the symptoms nearly always disappear when vitamin B6 supplementation is administered.

### SPASMS

CFS/ME patients often experience painful, and often prolonged, muscle spasms. Spasms commonly occur in the gluteal muscles (piriform muscle spasm), producing what feels like sciatica; the diaphragm, esophagus, and intercostal muscles, leading to chest and rib cage pain; small muscles of the eyes and ears, resulting in eye and ear pain; and head, resulting in localized "spike" headaches, and in the large muscles of the legs. Causes of muscle spasms include lactic acid accumulation, which will make the muscles clench; nervous system metabolic and hormonal dysregulation; dehydration, which leads to an imbalance in electrolytes; and oxidative stress.

Excess lactic acid, due to an alteration in cell metabolism, is the primary cause of muscle spasm in CFS/ME. When lactic acid builds up in the muscles, the muscle becomes hard and painful, even if the muscles are at rest. With enough pain, the muscle goes into spasm, preventing blood from entering or leaving. This, in turn, allows toxins to build up even more quickly, which causes more muscle spasm. The reduction of cellular mitochondrial function in CFS/ME ties into this vicious cycle as well. When ATP is reduced, inflammatory processes increase, primarily as a result of oxidative stress. Oxidative stress leads to alterations in mineral balance (calcium, magnesium, potassium), which affect the contraction of muscle, and allow for a buildup of lactic acid.

### TREATMENTS

The first-line treatment for muscle spasms is magnesium. Magnesium counteracts excess cellular calcium, which can eventually, through the mechanisms of oxidative stress, lead to muscle spasm. Magnesium also down regulates NMDA receptor activity, which leads to inflammation that can cause spasms. Spasms also respond to Flexeril, arnica gel, fish oil and other omega-3 fatty acids, and some of the benzodiazepines. Antioxidants, such as CoQ10, R-ALA, and vitamins A, C and E, are crucial for reducing oxidative stress and will help relieve pain, cramping, and spasms.

Physical means of treating spasms include pressing the muscle between two hands, which will increase circulation (increased blood flow chelates lactic acid), and moist heat, which also chelates lactic acid. If you are prone to muscle spasms, make sure to drink plenty of water. As well as helping to maintain the proper balance of metabolites, increased fluids will help flush lactic acid from the system.

### FURTHER READING

*Informative patient thread on treating muscle spasms.*

<http://forums.phoenixrising.me/archive/index.php/t-2094.html>

### FIBROMYALGIA



Dr. Dedra Buchwald, a physician from Seattle who conducted a long-term study of CFS/ME patients, found that as many as 75% of these patients also had fibromyalgia (FM). Fibromyalgia primarily affects women between the ages of 20 and 40 years. To date, this disorder has been diagnosed in 10 million patients in the United States. Of these, it is safe to conclude that many would also qualify for a diagnosis of CFS/ME because of the similarity of symptoms. Despite the overlapping symptoms, however, it would be misleading to conclude that the two illnesses are the same, because patients with fibromyalgia alone clearly suffer from a distinct illness.

Fibromyalgia, much like CFS/ME, is a syndrome that has perplexed the medical community for decades. The cause of fibromyalgia has not yet been determined, but physicians have observed that it can be triggered by an injury or accident, infection, sudden endocrine changes, such as childbirth, or exposure to toxins. Dr. Shoemaker has reported that *all* of his fibromyalgia patients have biotoxin (mold) toxicity. The predominant symptom in fibromyalgia is pain, although accompanying symptoms can include sleep disturbances, headaches, fatigue, and cognitive impairment. Typically, the pain waxes and wanes, but periods of physical exertion, illness, stress, and even changes in the weather may cause exacerbations.

While FM can be triggered by many events, the root of FM pain is clearly neurological. There is an ample body of research which shows an overall dysregulation of pain processing pathways in the central nervous system (CNS) in FM patients. Dr. Roland Staud, a rheumatologist at the University of Florida, has observed that CNS sensitization in FM occurs after prolonged input from pain receptors (nociceptors). In FM, these are activated in the dorsal horn of the spinal cord. Dr. Staud notes that other CNS pain mechanisms, such as a lack of inhibitory controls, are also found in FM patients.

In a follow-up study conducted in 2004 by Dr. Staud and colleagues at the McKnight Brain Institute at the University of Florida, pain responses of 104 subjects with FM were compared to healthy controls using electrical stimulation. Unlike healthy controls, subjects with FM demonstrated increased wind-up pain. Wind-up pain reflects increased excitability of spinal cord neurons. People with FM showed enhanced pain at very low stimulus frequencies, indicating that in FM prolonged pain can be produced with very little sensory input.

Dr. Martin Pall believes that the underlying mechanism for the CNS sensitivity in FM is the nitric oxide/peroxynitrite cycle of oxidative stress, which leads to inflammation in the CNS. Oxidative stress leading to inflammation in the CNS is the same underlying mechanism that is found in CFS/ME, so it is no wonder that many CFS/ME patients experience secondary FM.

In fibromyalgia, pain is often localized in the muscles of the neck and upper back, although patients with FM also report pain in the hands, lower back, thighs, shoulders, feet, and principal joints. A feeling of generalized achiness can accompany fibromyalgia, as well as pain that is described as "burning," "stabbing," "throbbing," or "shooting." Pain typically spreads – an injury to a single finger can

spread to the entire hand – and may build over a period of time. Prolonged periods of fibromyalgia pain can result in stiffness and exhaustion.

The diagnosis of fibromyalgia is based on a symptoms history and by the presence of tender points located on the surface of the body. There are 18 tender or "trigger" points that are commonly palpated to make a diagnosis, although the patient may feel pain in many other locations. Observable tenderness in 11 of 18 points can help confirm a diagnosis.

## TREATMENTS

The treatment of fibromyalgia is largely geared toward providing symptomatic relief. Rheumatologists commonly recommend nonsteroidal anti-inflammatory drugs (NSAIDs) for pain, as well as small doses of antidepressants or benzodiazepines to help with sleep disorders. Often correcting an existing sleep disorder also diminishes pain. Acupuncture, massage, and transcutaneous electrical nerve stimulation (TENS) are also effective, as are stress management techniques (meditation, self-hypnosis), to alleviate chronic pain. Patients with FM appear to respond quite well to hypnosis. In severe cases, narcotics may be required to quell persistent pain. Many patients report success with supplements such as magnesium injections, malic acid, and essential fatty acids. Muscle relaxants can be used to help relax muscle knots and spasms associated with fibromyalgia.

Unlike CFS/ME, in which exercise increases pain, patients with FM benefit from non-strenuous exercise. This is, in fact, one of the primary differences between the two illnesses. However, CFS/ME patients with secondary FM should not exercise to reduce pain unless well into recovery, as Light et al have shown that even moderate exercise exacerbates the neuroimmune processes of CFS/ME.

## MORE INFORMATION

National Fibromyalgia Association: <http://fmaware.org/PageServer.html>

*This is the largest non-profit group working to support people with fibromyalgia. The site includes the latest research, chat rooms, information about support groups, fact sheets, clinical trials, and overall information about FM. An excellent patient resource.*

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## SECONDARY INFECTIONS

### Viral Infections, Fungal Infections

Increased susceptibility to secondary infections is a problem for a significant proportion of the CFS/ME population. (However, about a third of CFS/ME patients report that they "never catch anything.") Some people find that during flu season they inevitably contract whatever "bug" is going around. In addition to catching the seasonal varieties of colds and flu, they also are more susceptible to other kinds of infections, such as upper respiratory tract or urinary tract infections, topical fungal infections, and recurring shingles. Compounding the problem, all of these infections last longer, occur more frequently, and, worst of all, may spark CFS/ME relapses, usually concurrently or just after the initial infection. This is true even in cases in which prior immunity has been established.

Different people tend to have different sensitivities. One may be plagued with recurring upper respiratory tract infections (this is particularly common in children) and another may have frequent bladder infections. Many infections seem to affect historically weak areas, that is, areas that have in the past been prone to infection or injury. Former smokers often develop respiratory tract infections, those with a history of allergies have an inordinate number of sinus infections, and those who have had many bladder problems may develop interstitial cystitis. The primary cause of recurring infections seems to be linked to immune system dysregulation.

Researchers agree that people with CFS/ME suffer from a variety of immune system malfunctions. Studies conducted over the past decade have revealed a

number of immune system abnormalities, including low numbers of natural killer cells, excess cytokine production (alpha interferon, interleukins, and tumor necrosis factor), and lowered cell-mediated immunity in the CFS/ME population. Unlike many other immune-related ailments, however, CFS/ME does not seem to affect the immune system consistently.

Dr. James McCoy, former cancer and CFS/ME researcher in Baton Rouge, Louisiana, found that CFS/ME patients tend to have fluctuating B and T cell proliferation rates; that is, immune system cells tend to multiply either faster or slower than normal (this type of measurement would relate to the actual function of the immune system more than to mere cell count). For example, B cells may replicate at an abnormally high rate during one stage of the illness, while T cells do not. The converse may be true at a different stage. It is not only possible, but likely, that a person with CFS/ME will have several immune system changes over the course of the illness, at times with symptoms associated with lowered immunity (increased susceptibility to flu) and at other times with symptoms associated with a heightened immune system response (*CFIDS Chronicle*, Fall 1993).

Regardless of the specific immune system abnormalities a person may undergo at any given time, certain problems tend to occur repeatedly in the CFS/ME population as a whole.

## VIRAL INFECTIONS

Frequent occurrence of colds, flu, and upper respiratory tract infections is related to immune system dysregulation and, as a consequence, these illnesses do not respond well to over-the-counter remedies – which, in any case, are not designed to alter the course of an illness. People with recurring viral infections report that injections of gamma globulin have helped lessen the frequency and severity of these infections. People who have been exposed to measles or chickenpox for the first time, however, must work with their doctor to check the progress of the disease before it gets fully under way. Acyclovir taken within 72 hours of the first sign of chickenpox can check development of the disease. Large doses of vitamin A taken within 24 hours of onset also help lessen the severity of measles, flu, and other infectious viral diseases.

## FUNGAL INFECTIONS

Topical fungal infections are usually an indication of immune system dysregulation. Fungal infections most often occur in moist areas, such as the feet (athlete's foot), but they may occur nearly anywhere. On the face and scalp, a reaction to a yeast found on the skin can cause seborrheic dermatitis, commonly known as dandruff. Fortunately, it is fairly easy to treat topical fungal infections with over-the-counter products. (See Skin, Hair and Nails for more information.)

## TREATMENT TIPS

A first course of action is to avoid situations or circumstances that may lead to greater risk for infection. For those who are susceptible to flu and colds, it is wise

to avoid exposure to people who are ill and young children, as well as crowded, confined areas (airplanes, movie houses), and other environments that might lead to greater exposure to germs. Because most colds are spread by hand-to-mouth contact, keeping hands clean (soap and water is sufficient) also reduces the risk of contagion.

Sambucol, an herbal remedy, is reported to be quite effective against flu. It can be purchased in liquid form or as lozenges. Unlike many pharmaceutical products, Sambucol is safe for use in children. Other herbal remedies include echinacea, goldenseal, and the antiviral agent St. John's Wort. Some people find that high doses of vitamin C are helpful to limit the duration of a cold. The homeopathic remedy *oscillococcinum* has also been reported as helpful.

For topical fungal infections, the best course of action is to keep the affected area clean and dry, and apply an over-the-counter antifungal ointment (such as Tinactin) once a day for 14 days. Tea tree oil, available in most health food stores, is also an effective topical antifungal agent. Zinc, taken orally and anti-yeast pharmaceuticals (Diflucan, Nystatin, etc.) are very helpful adjuncts for mitigating topical fungal infections.

People with other kinds of infections should follow the treatment advice for their specific problem.

SEE: Candida, Oral Problems, Shingles, Sinusitis, Urinary Tract Problems; Antivirals, Gamma Globulin; Herbs, Minerals (zinc), Vitamins.

#### FURTHER READING

“Treating Hidden Viral Infections in CFS/FMS Can Sometimes be a Cure.”

[http://www.endfatigue.com/health\\_articles\\_f-n/Infections-treating\\_hidden\\_viral\\_infections\\_cfs.html](http://www.endfatigue.com/health_articles_f-n/Infections-treating_hidden_viral_infections_cfs.html)

“Chronic Sinusitis—Actually a Yeast Infection.”

[http://www.endfatigue.com/health\\_articles\\_r-s/Sinusitis-actually\\_a\\_yeast\\_infection.html](http://www.endfatigue.com/health_articles_r-s/Sinusitis-actually_a_yeast_infection.html)

#### SEIZURES AND SEIZURE ACTIVITY

Absence Seizures (Petit Mal), Simple Partial Seizures, "Sensory Storms", Grand Mal Seizures

Although full-blown grand mal seizures are rare in CFS/ME, seizure-like episodes, especially during the first few months after onset, are not uncommon. These seizures do not usually involve loss of consciousness, however, and so may go unrecognized. Often the seizure is described as starting with a "wave" of bad feeling accompanied by feelings of intense discomfort or fear. This last component may lead doctors to misdiagnose the patient's experience as a panic attack.

Seizures and seizure activity are characterized by a sudden burst of electrical activity in the brain. The discharge can occur in both hemispheres, producing a

generalized seizure (e.g., grand mal) with loss of consciousness, myoclonus (jerks), muscle stiffness, and/or loss of muscle tone; or localized in one area of the brain, producing a partial (focal) seizure. Seizures generally occur when the brain is either fully active (characterized by beta waves) or in a state of light sleep (characterized by theta waves).

The reasons for this sudden neuronal discharge are not entirely understood. However, many neurologists believe that seizures are caused by an imbalance in neurotransmitter activity. Neurotransmitters deliver only two types of message: fire or cease fire. Neuroexcitatory chemicals induce the neuron to release its electrical charge, and the inhibitory chemicals prevent the neuron from firing. Seizures can be attributed to an imbalance in the two types of neurotransmitters, leading to excess nervous system activity.

Dr. Paul Cheney believes people with CFS/ME have a condition known as excitatory neurotoxicity, or a state of increased neuronal firing brought about by irritation of the nerve cells in the brain. In CFS/ME this is, in all likelihood, due to increased amounts of the cytokine alpha interferon. (Alpha interferon is one of the principal immune system components involved in combating viral infection.) Dr. Cheney has proposed that alpha interferon leads to an overstimulation of neurons, causing, in turn, a predominance of the neuroexcitatory chemical N-methyl-D-aspartate (NMDA), a chemical which is normally in balance with the primary neuroinhibitor GABA (gamma-aminobutyric acid) (*CFIDS Chronicle*, Spring 1994; *CFIDS Chronicle*, Spring 1995).

The imbalance created by excess NMDA receptor activity can create many central nervous system disturbances, including constant pain, insomnia, intolerance to stimuli of all kinds, and exhaustion. Given this explanation of how CFS/ME affects the nervous system, it is easy to see how seizures might occur as part of the illness.

As alpha interferon seems to primarily affect the limbic system, Dr. Cheney's hypothesis would predict a predominance of localized, rather than generalized seizures in CFS/ME patients. True to expectation, the type of seizure experienced by most people with CFS/ME is partial, involving neuronal discharge in the limbic system or neighboring temporal lobes. However, up until recently, it has been difficult to objectively determine which parts of the brain might be involved.

Most EEGs fail to capture brain wave abnormalities other than those caused by structural brain damage (e.g., epilepsy). Because CFS/ME patients seldom exhibit this type of nervous system impairment, their EEGs are rarely abnormal. The presence of numerous neurological symptoms in CFS/ME, including seizures, indicates that a more refined test would be required to both verify and locate the origin of abnormal brain wave activity.

In 2011 Duffy et al at the Children's Hospital in Boston and Harvard Medical School, took EEGs of CFS/ME patients and compared with people with major depression, and healthy controls. Using a more complex analysis of EEG data which estimates connectivity between different regions of the brain, the researchers were

able to distinguish the three groups with remarkable accuracy based on EEG results alone.

While the primary intent of the researchers was to establish the EEG as a reliable test for diagnosing CFS/ME, their test results also revealed that the only localized abnormalities in CFS/ME patients were bilateral, involving both right and left temporal lobes. The authors observed that “the one neurotropic virus associated with CFS, human herpesvirus-6, appears to selectively affect the temporal lobes and has recently been associated with temporal lobe seizure disorders.” This observation supports Dr. Cheney's earlier proposal that limbic damage caused by the virus-fighting chemical, alpha interferon, lies at the root of many of the neurological symptoms that typify CFS/ME.

The most common seizures experienced by people with CFS/ME are absence seizures, simple partial seizures, and “sensory storms.”

### ABSENCE SEIZURES (PETIT MAL)

In an absence seizure a person may be conscious but not aware of his or her actions. Absence seizures generally do not last long, from a few seconds to a few minutes at most. In periods of absence, a person may continue with an activity (such as driving) as though partially asleep. Sometimes people report that they find themselves in the driveway at home without the slightest recollection of how they got there. In general, absence seizures involve a lack of coordination between the part of the brain that controls awareness and the cortex.

### SIMPLE PARTIAL SEIZURES

Simple partial seizures do not involve loss of consciousness, but produce altered sensations, perception, mood, or body function. Parietal lobe disturbances can be experienced as tingling in the face and extremities, jerking or stiffening in one area of the body, or feeling odd, crawling sensations. One can also see flashing lights or other visual disturbances or hear things (hallucinations). Changes in perception of time and memory result from temporal lobe imbalances.

### "SENSORY STORMS"

Dr. Luis Leon-Sotomayor, the cardiologist who documented the 1965 CFS/ME epidemic in Galveston, Texas, described a type of neurological dysfunction that he called a "sensory storm." These storms affect the autonomic nervous system, which is regulated by the hypothalamus. A person experiencing a storm may first see an aura, or sense that something very bad is about to happen. Sensory storms produce sweating, pallor or flushing, elevated blood pressure, slowed respiratory rate, tachycardia, dizziness, and the feeling that one is about to lose consciousness. These storms are terrifying, but the effects generally pass within an hour. After such an experience, a person may feel lingering tiredness or malaise.

Dr. Byron Hyde has observed that storms tend to present spontaneously during the first few weeks of CFS/ME, although they often occur at specific times of day, then slowly pass as the illness progresses. A milder version may be experienced during relapses and after periods of stress.

While the term “sensory storm,” has not been retained in the CFS/ME vocabulary, the phenomenon bears a striking resemblance to the autonomic crisis, or “autonomic storm” experienced by children with familial dysautonomia, an inherited condition characterized by overwhelming sympathetic nervous system arousal. What is striking is that the symptoms of the autonomic crises of this genetic condition are identical to Leon-Sotomayor's “sensory storm”: sweating, pallor or flushing, hypertension, tachycardia, retching, vomiting, anxiety, and a general overwhelming feeling of discomfort. Usually the autonomic storm occurs in the morning, or after periods of stress, which also bears a striking similarity to this, and other, CFS/ME symptoms.

It is perhaps not surprising that the medications most often prescribed for autonomic crises are also frequently prescribed for patients with CFS/ME, namely, CNS down regulators such as benzodiazepines and anticonvulsants. Dr. Cheney maintains that these medications serve a neuroprotective function, preventing damage to the brain. (Please see Dysautonomia for more details.)

## GRAND MAL SEIZURES

A small percentage of people with CFS/ME experience grand mal seizures. The generalized electrical discharge characteristic of the grand mal seizure generates both motor disturbances and loss of consciousness. A person who experiences a grand mal seizure may have a warning sign or feeling (aura)—a bad smell, a peculiar physical sensation, or a strong emotion such as fear. It is essential for anyone who has experienced a grand mal seizure to consult a neurologist.

## TREATMENTS

Two frequently prescribed pharmaceuticals, clonazepam and Diamox, are helpful for partial seizures involving myoclonus (jerks). Gabapentin, a nervous system down regulator, and Lyrica, an anticonvulsant, are also used to protect the nervous system from overstimulation. Low-dose SSRIs and other pharmaceuticals that increase serotonin levels have also been shown to help down regulate nervous system reactivity.

Nutritional supplements that aid in controlling seizures include low-dose manganese, which helps to correct the biochemical imbalance that results from seizures; taurine, an amino acid that helps slow nerve impulses; vitamin B6, important for nervous system regulation; magnesium, which lowers NMDA receptor activity; and zinc in small amounts. GABA can be purchased as a supplement, but crosses the blood-brain barrier poorly.

People who have warnings of impending seizures or seizure-like episodes, either in the form of a rapidly escalating sense of urgency, surges of strange sensations, intense fear or rage, "spaciness," or any kind of sudden perceptual disturbance, such as a strong disagreeable smell, can sometimes prevent their full manifestation by immediately withdrawing from all sources of stimulation and entering into a relaxed state through meditation, relaxation exercises, or self-hypnosis techniques. This has the effect of changing the brain wave frequency to



alpha waves. Once the electrical frequency of the brain waves has shifted, the seizure often is prevented (seizures occur during beta or theta wave frequencies). This technique is effective for seizures with obvious triggers (flickering lights, television, emotional upsets, and excess stimulation of any kind). Biofeedback, mediation, and self-hypnosis techniques are very useful for controlling autonomic storms.

Avoiding stressors is essential for people with any kind of seizure activity. People who have experienced seizures must also be meticulous about avoiding the neurotoxins found in pesticides and other chemical products because of their potential seizure-inducing capacity. Prescription drug package inserts should also be examined for side effects and cautions regarding seizures and sympathetic nervous system symptoms. Wellbutrin, a medication sometimes prescribed to treat symptoms of CFS/ME, is strongly contraindicated in people who experience seizure activity.

SEE: Antidepressants, Anticonvulsants, Benzodiazepines, Diamox; Amino Acids (Taurine), Butyric Acid, Minerals, Vitamins; Biofeedback, Hypnosis, Meditation.

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<http://www.ncbi.nlm.nih.gov/pubmed/17276367> (Abstract)

#### SHINGLES

One of the more painful conditions that people with CFS/ME experience is recurring shingles. In fact, for many people (Dr. Martin Pall among them), a bout with shingles is what triggers CFS/ME. Shingles is an infection caused by the herpesvirus, varicella zoster, the same virus responsible for chickenpox. After a person has chickenpox, the virus lies dormant, controlled by the immune system. However, it can be reactivated by another illness or immune system suppression (radiation, cancer therapies, steroid treatments, immune system illnesses). The

reactivated virus attacks a nerve root in the brain or spinal column and follows the course of that nerve outward to the skin, where chickenpox-like blisters erupt.

The first sign of shingles can be an itching or stinging sensation on the skin, followed by intensification of pain, and finally a blistering rash. The rash can appear on any part of the body and is characteristically one-sided (left or right). The effects of shingles can be minimized if treated within the first 72 hours with antivirals. A person who feels pain, itching, or tingling in a specific area that is followed by a one-sided blistering rash should see a doctor immediately.

## TREATMENTS

First-line treatments for shingles consist of antivirals: acyclovir, famciclovir and valacyclovir, which, if taken early enough, can alleviate the worst symptoms. If the pain persists longer than a month after the initial infection, the resulting condition is known as postherpetic neuralgia. Valacyclovir has been shown to be effective in some long-term cases (6 months).

Zostrix, which can be purchased over the counter in cream form, is effective for dulling the pain of postherpetic neuralgia. Zostrix is made from a natural substance, capsaicin, found in hot peppers. When capsaicin is applied to the skin, it depletes the nerve of substance P, an inflammatory chemical that causes pain. Topical lidocaine patches can also reduce pain, as can ketamine (requires a prescription).

Antihistamines may relieve itching. For numbness, Thomas Thomsen, author of *Shingles*, recommends a vibrator. This advice has a sound basis in fact because the sense of touch operates largely through vibration. To heal blisters, oatmeal, baking soda, corn starch, or cold compresses can be used. Tea tree oil can help prevent infection of healing blisters. Other treatments include lysine, an amino acid that halts herpesvirus replication, and gabapentin (Neurontin), a prescription medication. Lyrica, an anticonvulsant used to treat fibromyalgia, has also been used for treating postherpetic neuralgia.

Needless to say, supplements that support the immune and nervous systems (e.g., vitamin B complex) and antioxidants are important adjuncts to any treatment for shingles.

SEE: Antivirals; Amino Acids (Lysine), Antioxidants, Bioflavonoids.

## FURTHER READING

“CFS & Fibromyalgia Patients At Risk for Shingles.” Sandy Robinson. 2007.

<http://www.fightingfatigue.org/?p=866>

*Natural treatments for shingles:*

[http://www.nationalnutrition.ca/healthconcerns\\_shingles.aspx](http://www.nationalnutrition.ca/healthconcerns_shingles.aspx)

## RESEARCH

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in immunocompetent patients 18 years of age or older.” *J Cutan Med Surg.* 2007 May-Jun;11(3):89-98. <http://www.ncbi.nlm.nih.gov/pubmed/17511925> (Abstract)

## SINUSITIS

The sinuses are air-filled cavities located behind and around the nose and eyes. Each sinus is connected to the nasal passage by a thin duct. These ducts can be easily blocked, making drainage difficult and eventually leading to irritation, inflammation, and infection. Air pollution, cigarette smoke, dry or cold air, dental problems, bacteria, and viruses can all contribute to sinus problems. It is noteworthy that sinusitis, with almost 40 million sufferers, has been rated the most common chronic disease in the United States by the National Center of Health Statistics—a testimony, perhaps, to growing environmental pollution.

Inflamed or infected sinuses can cause a wide range of symptoms, including headache, congestion, stuffiness, dizziness, nausea, tender cervical lymph nodes, sore throat, a feeling of facial pressure, "heavy head," and fatigue. Sinus pain can also mimic dental pain. Of these symptoms, the most frequently addressed is the sinus headache. The sinus headache differs from the pressure or vascular headache in that it is felt mainly around the face and eyes. This kind of headache can last for hours or even days. Sinus headaches become sharply worse with sudden increases in pressure to the region; the simple motion of bending over, air travel, a long car trip, or a change in barometric pressure can all spark intense face and head pain. The extraordinary fatigue associated with sinus problems ("nasal fatigue") has been well documented over the course of the century, receiving mention from a number of physicians from the late 1800s to the present.

Patients with CFS/ME seem to be particularly vulnerable to sinus problems. The large proportion – some say as high as 75% – of allergy-related problems alone in this population seem to implicate the sinuses as a major source of trouble for CFS/ME patients. Even those who do not show overt signs of allergy can have multiple sinus-related problems (e.g., headaches, increased chemical sensitivities).

Some of these problems may be related to impaired immune system function, which many believe to be primary mechanism of CFS/ME. Indeed, as Dr. Alexander Chester of Georgetown Medical Center has pointed out, sinusitis may be a precipitating factor in some cases of CFS/ME. Dr. Chester has proposed that, as in a similar case in which an apparent outbreak of multiple sclerosis followed sinusitis, viral diseases (particularly EBV) may be activated by a nasal mechanism. He suggests that in cases for which there are obvious signs of nasal involvement (such as acute onset following an upper respiratory tract infection, allergies, fluctuation of symptoms with weather changes), treating a possible underlying nasal disorder may produce substantial relief of headache, sleep disorder, mood swings, and fatigue.

Cases of chronic sinusitis may very well be due to inhaled mold spores. In 1999 the Mayo Clinic released a report in which 210 patients with chronic sinusitis were examined for pathogens in mucus. They discovered fungi in 96 percent of the patients. A total of 40 different kinds of fungi were found, with an average of nearly

three different kinds of fungus per patient. Dr. Sherris, who led the investigation stated that, "in fact, fungus is likely the cause of nearly all of these problems. And it is not an allergic reaction, but an immune reaction."

### TREATMENT TIPS

Although many cases of sinusitis are not bacterial in origin, and can be resolved with home treatments, sinusitis caused by bacterial infections can have serious consequences. Yellow or dark nasal discharge, severe sinus pain, or fever require a visit to the doctor. Bacterial infections are treated with antibiotic drugs. When taking antibiotics remember to supplement with acidophilus or some other probiotic to minimize potential side effects (the most problematic of which is Candida overgrowth). For chronic or persistent nonbacterial sinusitis, the following tips and suggestions may be useful:

- Saline nasal sprays are helpful in keeping nasal passages moist. They wash out mucus, dust, viruses, bacteria, and other sinus irritants and help reduce swelling. Dry nasal passages are much more susceptible to infections, irritation, and subsequent inflammation. Small, inexpensive bottles of premixed saline solution are available in any pharmacy. Spraying may be repeated as often as needed throughout the day.
- Nasal irrigation is helpful for more prolonged cases and, unlike some other treatments, has the benefit of being both inexpensive and completely without side effects. To make the irrigating solution, add  $\frac{1}{4}$  to  $\frac{1}{2}$  teaspoon of salt and a tiny pinch of baking soda to 1 cup of lukewarm water. Completely fill a large all-rubber ear syringe (available in most pharmacies). Leaning forward over the sink, pinch one nostril closed, insert the syringe into the open nostril, and gently squeeze the bulb, swishing the solution around the inside of the nose. Repeat the procedure for each nostril until you have used the entire cup of solution. The solution may run out of both nostrils or the mouth. Although this may be a bit messy, the relief provided by irrigation is well worth it. In place of a syringe, many doctors recommend a Neti pot, which is a ceramic pot with a spout used for nasal irrigation. Neti pots can be purchased at most drug stores.
- Moist, warm air often alleviates sinusitis. Even standing in a shower for five minutes or breathing steam from a pot of boiling water can be helpful. Vaporizers with a contoured face mask that directs the flow of temperature-controlled steam can be purchased online and from drug stores for as little as \$8. Eucalyptus, peppermint, or clove essential oil (one drop is sufficient) can be added to the water to help clear sinuses. These oils, available at most health food stores, can also be rubbed around the nostrils.
- Proper hydration is important, so remember to drink lots of pure water.
- Avoid alcohol and milk, as these tend to aggravate sinus problems. Milk thickens mucous discharge, making it more difficult to keep the nasal passages clear.

- Supplements and herbs normally recommended for sinus problems include garlic to help fight Candida and bacterial infection, vitamin A to help repair mucous membranes, vitamin C and zinc (immune system stimulants), echinacea (an herb that acts as an immune system stimulant), and goldenseal root, as a topically applied powder. To use goldenseal, mix ¼ teaspoonful of goldenseal powder with a drop or two of water to form a paste, spread lightly over the sinus area before bed, and wash off in the morning. Place a cloth over your pillow to prevent staining. Apply for up to three nights. Goldenseal is a powerful antimicrobial agent and should not be taken internally, even though it is common practice, because of potential harmful effects on the central nervous system.
- Sinusan, a homeopathic remedy that has been helpful for many people, can be purchased at most health food stores. Nonsteroidal anti-inflammatory drugs (NSAIDs, such as aspirin), as opposed to simple analgesics (such as Tylenol), can be useful to reduce inflammation and pain.
- Patients with allergies usually benefit from prescription and OTC nasal sprays (Nasal crom, Nasal cort). Although these contain cortisone, the fact that they are applied topically lowers the risk of immune system suppression normally associated with extended use of cortisone treatments.
- People with and without allergies should be careful to avoid potential sinus irritants and allergy triggers (air contaminants, sprays, fumes, dust, molds, pollen, dander). An air filter for the bedroom can be a worthwhile investment if sinus problems are severe. Air travel is especially problematic for people with sinus problems. Most doctors, in fact, recommend against air travel if an acute infection is present. For short-term relief, a decongestant spray may be useful. These sprays help open nasal passages, but should not be used for more than a day or two because they can become addictive. Saline sprays can also mitigate some of the effects of poor air quality and airplane cabin pressure changes.
- Anti-fungal nasal sprays containing fluconazole (Diflucan) are available by prescription. If you have mold allergies, an anti-fungal spray may make all the difference.

SEE: Allergies, Candida, Secondary Infections; Antihistamines; Herbs, Probiotics, Vitamins; Aroma Therapy, Homeopathy.

#### BOOKS

- Chester, Alexander. "Chronic Fatigue of Nasal Origin: Possible Confusion With Chronic Fatigue Syndrome." In Hyde, Byron M, ed. *The Clinical and Scientific Basis of ME/CFS*. Ottawa, Ontario: Nightingale Research Foundation, 1992.
- Ivker, Robert S. *Sinus Survival: The Holistic Medical Treatment for Allergies, Asthma, Bronchitis, Colds, and Sinusitis*. New York: Putnam Publishing Group, 1995.

## ONLINE READING

Fokkens WJ, Ebbens F, van Drunen CM. “Fungus: a role in pathophysiology of chronic rhinosinusitis, disease modifier, a treatment target, or no role at all?” *Immunol Allergy Clin North Am*. 2009 Nov;29(4):677-88.

<http://www.ncbi.nlm.nih.gov/pubmed/19879443>

“Mayo Clinic Study Implicates Fungus As Cause Of Chronic Sinusitis.”

<http://www.sciencedaily.com/releases/1999/09/990910080344.htm>

“Curing Fungal Sinusitis and Chronic Rhinosinusitis.” Dr. Donald P. Dennis.

<http://www.fungalsinusitis.com/>

“Chronic Sinusitis—Actually a Yeast Infection.” Dr. Teitelbaum.

[http://www.endfatigue.com/health\\_articles\\_r-s/Sinusitis-actually\\_a\\_yeast\\_infection.html](http://www.endfatigue.com/health_articles_r-s/Sinusitis-actually_a_yeast_infection.html)

Jen, Albert, Ashutosh Kacker, Clark Huang, Vijay Anand. “Fluconazole Nasal Spray in the Treatment of Allergic Fungal Sinusitis: A Pilot Study.”

<http://www.entjournal.com/Media/PublicationsArticle/JEN.pdf>

*Detailed instructions on how to use a Neti pot.* <http://www.neti-pot.com/how-to-use-a-neti-pot.cfm>

## SKIN, HAIR, AND NAIL PROBLEMS

Skin: Pallor; Rashes; Dry, Peeling Skin; Acne, Hypersensitivity, Spontaneous Bruising, Paresthesias, Loss of Fingerprints, Rosacea; Hair; Nails

Skin, hair and nail problems are fairly common in CFS/ME. These symptoms are readily observable, though they garner little attention. As other symptoms can be overwhelming, many patients don't even mention these symptoms to their doctors. Nonetheless, it is important to monitor skin, hair and nail changes, because they serve as an indication of metabolic disruptions that can otherwise be difficult to identify.

## MORE INFORMATION

*A detailed list of skin problems:* <http://www.apexdermatology.com/Dictionary.htm>

## PALLOR

“Ghastly pallor” is mentioned by nearly all doctors who have treated CFS/ME patients. Although pallor is one of the few objective physical signs of CFS/ME, it is the symptom least observed by patients themselves. People with CFS/ME are ghostly pale during the initial phase and during relapses. The whiteness of the skin (among Caucasians) is striking and can be perceived by anyone. Pallor is due to slowed blood flow to the skin. Those with syncope (fainting) and orthostatic intolerance will exhibit pallor when their blood pressure drops. Light-headedness and pounding heart are two symptoms that accompany pallor due to orthostatic intolerance. Pallor can also be a sign of anemia, so if your skin is always unusually pale, it is time for a blood test.

SEE: Cardiac and Cardiovascular Symptoms

## RASHES

According to the Invisible Disabilities Association of Canada, 15 percent of people with CFS/ME report skin rash. The rash most typical of CFS/ME is lace-like and covers the face and chest. Some doctors have observed that it resembles the rash characteristic of lupus. Rashes are often experienced by those who are prone to allergies and can represent an allergic reaction to any substance they have consumed (resulting in urticaria or "hives"). These rashes tend to itch, and can occur up to twelve hours after consuming an offending food. Itchy, or burning allergic-type rashes can also occur when a substance is touched (resulting in contact dermatitis).

Some likely sources of contact dermatitis include acid foods (oranges, tomatoes), plant oils, permanent press bedding (which is treated with formaldehyde), and synthetic clothes (indicative of chemical sensitivity). Rashes can also appear after ingestion of certain medications.

In his book, *Chronic Fatigue Syndrome: A Victim's Guide to Understanding, Treating, and Coping With This Debilitating Illness*, Gregg Fisher describes breaking out into hives after taking penicillin, which he explains is a classic reaction in people with infectious mononucleosis. He also describes breaking out into abdominal welts after taking acyclovir. Most skin rashes can be resolved by avoiding irritants and allergens.

## FURTHER READING

*Invisible Disabilities Association of Canada list of symptoms*

<http://www.nsnet.org/idacan/pain.html>

## DRY, PEELING SKIN

Dry skin is caused by loss of moisture in the outer layers of the skin. Dryness can result from dry air, harsh soaps, sun, fuzzy or woolen clothing, irritants (such as detergents not rinsed completely from clothes and sheets), and systemic conditions. Dehydration is the most common cause of dryness in CFS/ME, as people with the illness are typically dehydrated due to metabolic disturbances. Dry skin may also result from low thyroid function, which is not unusual in CFS/ME.

Paradoxically, a number of people say they have simultaneously dry and oily skin. However, as dry skin is not due to oil loss but to lack of water in the skin, it is quite possible to have an overproduction of oil due to hormonal changes while experiencing dryness due to malfunction in dermal moisture regulation. When people with CFS/ME experience endocrine swings (irregular hormonal output), alternation between dry and oily skin is the result.

Some people also notice that their skin peels – especially on the face – as if they have sunburn, even though they are spending all of their time indoors. Peeling skin can be a sign of low thyroid function, as well as a zinc or vitamin B6 deficiency,

both of which are common in CFS/ME. If low thyroid production is determined through endocrine tests, dry skin will improve with thyroid support.

If nutritional deficiencies are suspected, skin will improve with appropriate dietary supplements, particularly vitamin B, zinc, essential fatty acids, and vitamin A. Commercial lotions and creams are best avoided in patients who are prone to acne or hives because they can clog pores and may cause allergic reactions.

Jojoba oil is known for its skin rejuvenating properties. It is best applied after a shower. While the face is still wet, squeeze one drop of jojoba oil onto your palm and rub your palms together once or twice. Then gently rub your palms over your face. Allow the skin to air dry. Pure jojoba oil is expensive, but used in this manner a small 4-ounce bottle will last for years.

The best course of action is to avoid harsh soaps, such as soaps with deodorants, and use a pure bath oil to aid the skin in retaining moisture. Pure soaps and bath oils that do not contain chemical additives can be found in health food stores and online. Dry brushing of the skin with a soft, natural bristle brush, reputed to invigorate the skin, has helped some people with CFS/ME.

## MORE INFORMATION

*Article on dehydration in CFS/ME patients, including symptoms, causes and remedies.* <http://www.fatigueanswers.com/dehydration.html>

## ACNE

Women with CFS/ME are particularly prone to acne before menstruation – especially around the hairline, back of the neck, and chin. These pimples usually disappear with the onset of menstruation. Endocrine fluctuations resulting from hypothalamus dysregulation are the most likely cause of these periodic breakouts. Acne can also be exacerbated by stress, because stress hormones stimulate the production of male-type sex hormones, which in turn leads to overproduction of skin oil.

Certain medications, including low-dose birth control pills, cortisone, anticonvulsant medications, and vitamin B12 can exacerbate acne as well. A good diet, vitamin supplementation, thorough cleaning with mild, easily rinsed cleansers, avoidance of creams, makeup, and skin irritants, and adequate intake of water all help reduce acne. Medication is seldom needed because acne tends to be transient.

Antioxidants, such as grape seed extract and selenium, are particularly useful for treating acne. Vitamin C and pantothenic acid are also useful supplements. Both act as adrenal supports, which can help mitigate stress- and hormone-related acne. Tea tree oil is wonderful for preventing topical infection. However, tea tree essential oil may burn sensitive skin if applied directly. To use tea tree oil, dilute it in pure jojoba oil in a ratio of five drops of jojoba to one drop of tea tree oil. This also works for seborrheic dermatitis.

## FURTHER INFORMATION



*Non-pharmaceutical approaches to acne.*

<http://www.chronicfatiguetrements.com/wordpress/treatments/10-supplements-that-will-cure-your-acne/>

## HYPERSENSITIVITY

As with the other senses, touch becomes hyperacute in CFS/ME. Many people report that they cannot stand to be touched, or that certain textures, types of clothing, or temperatures bother them or cause pain (tactile allodynia). Even slight pressure can become unbearable. Sensitivity to heat and cold also increases with CFS/ME. Some patients report that cold “burns,” and that the sensation continues even after the trigger is removed. People with allergic responses are often hypersensitive because of the effects of histamine (histamine sensitizes nerve endings). Antihistamines may help reduce skin sensitivity in these cases. In most cases, however, sensitivities to heat, cold, pain and pressure are mediated by the nervous system.

Normally, when excess pressure, heat, or cold is experienced, these signals are transmitted through nociceptors (pain receptors) through afferent neural fibers to the dorsal root ganglia, where the tactile message is processed and sent along to the thalamus, which interprets the signal. (Outgoing signals from the CNS to the extremities are sent through *efferent* neural fibers in a reversal of this process.)

Although it seems complex, afferent pathways are an elegant and efficient means of communicating necessary information about the environment to the brain. But what happens when there is a glitch in the system? If the dorsal root ganglia, the intermediary step in the interpretation of tactile sensation, are inflamed (for example, by reactivated viruses), then all tactile information may be interpreted as pain. What is more, once the dorsal root ganglia are inflamed, the thalamus may send pain messages back through efferent nerve fibers, with resulting pain (usually burning) that is prolonged and intractable.

It has been demonstrated that people with CFS/ME not only show inflammation in the dorsal root ganglia, but also have oxidative stress – which can lead to inflammation – in the limbic system, the region of the brain that includes the thalamus. A combination of these factors will lead to extreme sensitivity of the senses, including touch.

Various coping mechanisms can reduce tactile hypersensitivity (such as avoiding triggers), but ultimately the solution to this problem is reducing inflammation. All anti-inflammatory agents, as well as antioxidants, can be useful in this regard. Omega-3 fatty acids are particularly effective in reducing inflammation, and should be added to the treatment plan of any patient with hypersensitivity.

SEE: Pain; Antioxidants, EFAs.

## MORE INFORMATION

*Website of CFS/ME patients with hypersensitivity. Contains useful coping strategies.* <http://css.dewarlorx.com/joints.html>

## SPONTANEOUS BRUISING

Some people wake up in the morning to discover they have one or more dark bruises unrelated to previous injury. Sometimes bruising is related to potassium depletion, especially if the bruises appear after exposure to hot weather or periods of adrenal stress. In CFS/ME bruising could be related to a number of factors, including altered red blood cell morphology, potassium depletion (which is not uncommon in CFS/ME), and vitamin deficiencies. The possibility of dehydration should also be considered.

If you bruise easily and suspect dehydration, liquids should be increased. Water or juices can be blended with a little salt, sugar, and baking soda to increase retention. Patients who experience easy bruising have reported that adding vitamin K as a supplement reduces bruising. Those with hypothyroidism, a common condition in CFS/ME, also experience easy bruising due to a lowered platelet count. If you have other symptoms of low thyroid function (e.g., easy weight gain, hair loss, puffiness in the face), ask your doctor to have your thyroid checked.

SEE: Endocrine Problems; Minerals (Potassium)

## MORE INFORMATION

*Patient thread on spontaneous bruising:*

<http://forums.phoenixrising.me/archive/index.php/t-6541.html>

## PARESTHESIAS

Tingling, numbness, itching, prickling, crawling, and stinging sensations on the skin are common throughout the course of CFS/ME. Some paresthesias are related to nervous system activity, others are not. Spontaneous hyperventilation, which is related to autonomic nervous system dysfunction, produces tingling in the neck and around the face, and sometimes in the hands and feet. Itching can be the result of allergic reactions, which release histamine. Dr. Felix Sulman has observed that stinging sensations (as though from an insect) and prickling can be produced by serotonin, an irritant that can produce skin responses similar to those of histamine.

There is no single treatment for paresthesias. Itching, tingling and stinging associated with allergic reactions improve with antihistamines. Paresthesias which are a result of nervous system irritation can be helped by taking antioxidants and anti-inflammatory agents. (See Hypersensitivity above.) The tingling of spontaneous hyperventilation is an aspect of dysautonomia, which is treated with a variety of pharmaceuticals (clonazepam, Lyrica, SSRIs, Florinef, and beta-blockers, as well as licorice and other supplements.) (See Dysautonomia for more detailed information.)

## LOSS OF FINGERPRINTS

The flattening of fingertip ridges is part of the normal process of aging, usually occurring in the seventh decade. In people with CFS/ME, however, this process seems to be accelerated. Dr. Philip Nelson, of Sarasota, Florida, studied a group of 165 CFS/ME patients in whom he observed that a flattening of ridges occurred as early as the fifth decade. Fingerprint loss seems to predominate on the left hand and usually begins with the smallest finger. It is generally thought that fingerprint loss reflects depletion of collagen in the skin.

Dr. Cheney has observed fingerprint loss in 50% of his patients. He has theorized that the loss of fingerprints is due to a combination of oxidative stress and a disorder of fibroblast function, leading to a loss of collagen. Dr. Jonathan Collin has noted some degree of fingerprint loss in 40% of CFS/ME patients, with 10% having a complete loss of fingerprints. Dr. Collin attributes the flattening of the ridges to periarteritis, an inflammation of the arteries. Chronic states of inflammation produce elastase, an enzyme that breaks down elastin, the substance that makes the skin elastic. Immune system activation also produces an enzyme known as MMP-9, which breaks down collagen.

## FURTHER READING

*Patient thread on loss of fingerprints, including instructions on how to take your own!* <http://forums.phoenixrising.me/archive/index.php/t-228.html>

*A patient's experience with loss of fingerprints. Includes an interesting slide of a CFS/ME patient's eroded fingerprint compared to a normal fingerprint.*

<http://nopostergirl.com/2011/02/27/the-fact-of-fingerprints/>

"Chronic Fatigue, Mycotoxins, Abnormal Clotting." *Townsend Letter for Doctors and Patients.*: <http://www.tldp.com/issue/157-8/157pub.htm>

## ROSACEA

Rosacea is an inflammatory skin condition which causes facial flushing and the eruption of papules (small red bumps) on the face, and sometimes on the scalp and neck as well. Rosacea can also affect the eyes (ocular rosacea), causing redness and irritation resembling conjunctivitis, but without bacterial involvement. The National Rosacea Society estimates that some 16 million Americans suffer from rosacea, with fair-skinned individuals predominating (*Rosacea Review*, Winter 2010). Individuals with allergies are particularly susceptible to rosacea, which is not surprising given the vasodilatory effects of histamine and mast cell activation.

Like many other chronic conditions, the ultimate cause of rosacea is yet to be determined. The mechanism, however, is clear. Inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , nitric oxide, metalloproteinases (enzymes that break down collagen), and increased levels of free radicals have all been found in patients with rosacea. It has been suggested that these elevated markers of inflammation may serve as an important clue as to the underlying cause of rosacea.

In fact, the specific set of immune markers characteristic of rosacea closely correlates with an infection of the bloodstream caused by gram-negative bacteria.

These bacteria are widely known to produce a variety of responses, ranging from mild to severe inflammation. While a number of bacterial infections have been associated with rosacea, *chlamydia pneumoniae*, a gram-negative bacterium, has been claimed by some researchers to be a central causative agent. Two researchers from the Hudson Dermatology and Skin Cancer Center in New Jersey found a predominance of *C. pneumoniae* in 80% of the patients in their study. A course of oral azithromycin eradicated rosacea in these patients.

Treating rosacea with antibiotics is not new. In fact, antibiotics are the standard course of treatment, with minocycline heading the list. However, no one is quite certain whether the curative effect of the antibiotics is because they eliminate rosacea-causing bacteria, or because they reduce systemic inflammation. This question was the focus of a study conducted in Italy in 2008 with 118 rosacea patients. The research team discovered that well over half of the rosacea patients also had small intestine bacterial overgrowth (SIBO). When these patients were treated with Xifaxan, a non-systemic antibiotic that works strictly in the gut, their rosacea cleared up.

What this study brings to light is the strong correlation between gut problems, inflammation, and surface presentation of inflammation (rosacea, in this case). Kenny De Meirleir, one of the world's most prominent CFS/ME researchers, believes that gut dysbiosis causes many CFS/ME symptoms, and may be causative in a subset of patients. The relationship between rosacea, an inflammatory comorbid condition, and gut problems, which are endemic in the CFS/ME population, lends much support to Dr. De Meirleir's hypothesis.

## TREATMENTS

If you visit a dermatologist for rosacea, he or she will no doubt treat you with a course of antibiotics (usually minocycline), especially if there are papules. While courses of antibiotics for rosacea have traditionally been quite long (a year or more), shorter courses of antibiotics are currently being recommended. In addition, topical antibiotic treatments (usually metronidazole) are often prescribed. Once the rosacea has subsided, a topical anti-inflammatory cream, such as Finacea, may be recommended for maintenance.

There are a number of non-pharmaceutical approaches to rosacea as well. The first is simple avoidance of triggers. The foods that trigger rosacea are frequently implicated in other inflammatory conditions, such as migraine and interstitial cystitis. These include foods high in tyrosine and tyramine (anything smoked, fermented, or aged—see Interstitial Cystitis for a complete list.) Spicy foods and caffeine should also be avoided as these cause flushing. People with rosacea should also avoid exposure to heat (saunas, hot showers, sunlight) for the same reason.

Ocular rosacea usually clears up with the cessation of papules and flushing. But, to minimize the irritation of conjunctivitis-like symptoms, a daily eyelid scrub helps tremendously. Simply wet the closed eyelids and apply a drop of baby shampoo, then rub gently with the finger or soft cloth. Rinse thoroughly. The eyelid

scrub loosens debris left by tearing and helps minimize the occurrence of blepharitis, an inflammation of the eyelid common in ocular rosacea.

While not all researchers agree as to the reasons why blepharitis develops in some people, an allergic reaction to the skin mite that lives near hair follicles (*Demodex*) has been implicated. Two Chinese studies have reported that tea tree oil is quite effective at eliminating *Demodex*. In one study, a weekly lid scrub with 50% tea tree oil, and a daily lid scrub with tea tree shampoo completely eradicated ocular *Demodex* in four weeks. As pure tea tree oil, even at a 50% dilution, cannot be applied directly to the eyelid without a great deal of discomfort, tea tree oil shampoo can be used in place of baby shampoo for daily eyelid scrubs.

Rosacea causes tremendous skin sensitivity, which means the usual soaps and skin cleansers may be irritating. Look for a pure soap, without harsh additives. After washing, pat your face dry with a soft towel. Once papules have been eliminated, daily skin care should include a light application of jojoba oil. (See Dry Skin above.)

Herbal rosacea treatments include *chrysanthellum indicum* cream, which you can purchase at health food stores, or make at home by mixing a teaspoon of *chrysanthellum indicum* extract into a cup (8 oz) of mild moisturizing cream. Apply twice a day. Other herbal creams which help rosacea are green tea, and licorice (which is a vasoconstrictor). Vitamin B3 helps reduce inflammation, as do omega-3 fatty acids.

There are a number of products on the market which claim to eradicate rosacea in a few short weeks. These contain proprietary blends and are usually quite expensive. “Customer” reviews for these products are uniformly enthusiastic, but should be taken with a grain of salt. In most cases, the proprietary blends consist of the above herbs, as well as a few other “cooling” herbs, mixed into moisturizing lotion.

#### MORE INFORMATION

National Rosacea Society: <http://www.rosacea.org/patients/index.php>

*This is a highly informative website. A free quarterly newsletter, the Rosacea Review, is available with a membership donation of any amount.*

International Rosacea Foundation: <http://www.internationalrosaceafoundation.org/>

*Provides up-to-date information on treatments.*

#### FURTHER READING

“Chlamydia pneumoniae and Rosacea: A potential link?”

<http://www.cpnhelp.org/node/2070>

*Alternative treatments for rosacea:*

<http://altmedicine.about.com/cs/treatments/a/Rosacea.htm>

#### RESEARCH

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## HAIR

The most frequently mentioned hair problem in CFS/ME is hair loss. Normally, 50 to 120 hairs are lost each day. More than that amount – that is, more than a tablespoon of hair removed from your hairbrush – is considered hair loss. Hair loss can be patchy (alopecia areata) or, as is usually the case in CFS/ME, a general thinning. In some patients hair loss is slight and can go relatively unnoticed. Other patients, however, "shed" copiously, which can be quite disturbing as an overt sign that "something is very wrong."

Hair loss in CFS/ME is often due to endocrine changes (e.g., hypothyroidism) and is usually not permanent. However, sudden loss of hair may be related to medications (notably Tagamet). Consuming excessive amounts of vitamin A can lead to hair loss as well.

An increase in stress hormones can also cause hair loss, which has direct implications for people with CFS/ME, who, during the acute stage and relapses, produce high amounts of cortisol. After a sudden influx of stress hormones, hair follicles go into a resting phase. (Normally, 10% to 15% of follicles will be resting at any given time.) After a few weeks of resting, the hair will fall out. When many follicles are resting at once, due to a general shock to the system, the subsequent hair loss will be noticeable.

People who are losing hair should use only mild shampoos and discuss thyroid tests with their doctor. Vitamin B and supplements that help increase circulation to the scalp, such as CoQ10 or ginkgo, may also be helpful. Inositol is reported to stimulate hair growth.

## FURTHER READING

*Good explanation of how stress can produce hair loss*

<http://www.follicle.com/section2/5.html>

## NAILS

Nail problems in CFS/ME are usually not as dramatic as skin and hair problems. The most commonly noted problems are increased brittleness, bluish nail beds, and vertical ridges. While in and of themselves, nail changes don't cause a loss of the ability to function, they are often an indication of underlying metabolic disturbances which should be investigated.

Brittle nails, often accompanied by dry skin, are a common problem among CFS/ME patients. Nails are made up of a soft protein called keratin, a substance composed largely of sulfur, which keeps nails hard. Nails become brittle and break or chip easily as a result of keratin deficiency or when the water content of the nail is decreased. Many CFS/ME patients are chronically dehydrated, which can contribute to brittle nails. CFS/ME researcher, Rich Van Konynenburg, believes that weak nails and hair that breaks off are due to a deficiency in cysteine, which leads to a disruption of sulfur metabolism.

Ridges running up and down (longitudinal), rather than across the fingernails can be an indication of low thyroid function. When thyroid function is low, the metabolic rate slows. As a result, the skin gets dry, sweat glands don't operate efficiently, and the nail bed becomes dry. Longitudinal ridges have been noted in many people with CFS/ME, which may be due to low thyroid function. However, longitudinal ridges are also often related to anemia, vitamin A deficiency, and flu.

A bluish nail bed is a sign that too little blood is being delivered to the nail. The nail depends on blood supplied by capillaries in the nail bed that give the nail its pinkish color. When the blood supply is diminished, nails turn blue and fail to grow. Dr. Alexander Gilliam noted in the 1934 CFS/ME outbreak in Los Angeles that both bluish nails and slow nail growth, usually on one hand, were common.

According to the new International Consensus Criteria for ME/CFS the disappearance of the “moons” of the fingernails is an indication of longstanding orthostatic intolerance. Like horizontal lines in the nail, the loss of moons is an indication of blood flow problems. As some form of orthostatic intolerance is nearly universal among CFS/ME patients, loss of moons is an inevitable consequence. Disappearing moons can also be indicative of low levels of functional vitamin B12, which is common among CFS/ME patients, in whom a drop in functional B12 can occur even with normal blood levels. (The B12 is available, but cannot be utilized.) A number of patients have reported a reappearance of moons after taking high-dose B12 supplements.

Various nutritional deficiencies can cause nail abnormalities. Deficiencies of folic acid, protein and vitamin C can cause nails that split and fray. Lack of iron can cause pale, spoon-shaped nails. Mineral deficiencies can cause soft nails.

The best treatment for nails is to avoid contact with harsh cleaners and other chemicals (wear rubber gloves), keep nails trimmed (soak them first to avoid chipping), and make sure nutrition is adequate. Vitamin B12 supplements are important for maintaining healthy nails, as are trace minerals. Calcium

supplements will not help nails to become stronger because the nail plate contains very little calcium.

#### FURTHER READING

*Informative patient thread on fingernail problems:*

<http://forums.phoenixrising.me/archive/index.php/t-15156.html>

*Excellent patient thread on fingernail problems:*

<http://www.mecfsforums.com/index.php?topic=8522.0>

*Nail abnormalities and what they signify. (Includes photos*

*)*<http://www.aafp.org/afp/2004/0315/p1417.html>

*A long list of nail abnormalities and associated conditions and illnesses.*

[http://www.naildoctors.com/nail\\_health.html](http://www.naildoctors.com/nail_health.html)

“International Consensus Criteria for ME/CFS.” <http://www.research1st.com/wp-content/uploads/2011/07/Carruthers-JIM-Table-1.pdf>

#### SLEEP DISORDERS

Insomnia or Difficulty Initiating and Maintaining Sleep, Phase Shifting, Hypersomnia, Light Sleep, Hypnagogic Sleep, Dysania, Myoclonus, Dreams and Nightmares, Night Sweats

Sleep disturbances are so common in CFS/ME that most doctors will not even make the diagnosis if a patient reports having normal, restful sleep. Virtually every CFS/ME patient has some trouble sleeping. Usually, problems consist of either sleeping too little or sleeping too much. In either case the quality of sleep is poor. Some sleep patterns are fairly consistent. One person cannot fall asleep before 3:00 AM "no matter what." Another can't fall asleep for a few nights, then sleeps too much for a few nights, then wakes up repeatedly in a fitful sleep. Every once in a while a person may be surprised by what feels like a normal night's sleep, only to have insomnia return with a vengeance the following night.

Although sleep disturbances can take many forms, the outcome is always the same—waking up tired. Nonrestorative sleep is a hallmark symptom of CFS/ME and is a condition that acts as a catalyst. Because poor sleep exacerbates other symptoms (pain, emotional swings, flu-like symptoms, fatigue) it is a focal point for treatment.

Normal sleep occurs in four stages, each of which is characterized by a distinct brain wave pattern. The first stage of sleep is light sleep, which is characterized by a reduction in the alpha waves characteristic of the relaxed waking state and an increase in theta waves (4 to 7 Hz). In the second and third stages, wave forms gradually slow and deepen until, by the fourth stage, the sleeper is producing more than 50% delta waves (3 Hz or less). In a normal sleeping adult, all four stages of sleep occur within approximately 90 minutes, followed by REM (rapid eye movement) sleep, better known as dreaming. The entire cycle is repeated three or four times during the night. Each time, stage four sleep shortens and REM sleep lengthens, which is why the deepest sleep is at the start of the night and the most vivid dreams occur before awaking.



The architecture of sleep is fairly straightforward. However, the chemical interplay that prepares the body for its nightly trip to Slumberland is quite the reverse. Sleep is controlled by the hypothalamus, which regulates all aspects of the autonomic nervous system, including the body's "biological clock." When cyclic environmental cues (light, darkness) are perceived by the brain, they provoke a well-timed release of neurochemicals that control sleep-wake cycles.

Environmental cues are conveyed first to the pineal gland through the optic nerve (although sight is not necessary for this transmission), which then relays a message to the suprachiasmatic nuclei (SCN) of the hypothalamus. There, the ventrolateral preoptic nucleus (VLPO) signals the parts of the brain responsible for maintaining arousal to begin shutting down operations. Soon afterward, messages flow to other parts of the brain to start the cascade of hormones and other neurochemicals responsible for initiating and maintaining sleep.

The chemical recipe for sleep is complex, and the timing of hormones, such as melatonin, amines, and other substances that send messages throughout the body must be perfect. Body temperature must be lowered, metabolism slowed, appetite inhibited, hormones released, elimination down regulated, and immune system upregulated. Think of it as a symphonic orchestra, with the hypothalamus as the conductor.

Any chronic alteration in normal sleep patterns is referred to as a sleep disorder. Common sleep disorders include insomnia (inability to fall or stay asleep), malsomnia (excessive light sleep or broken sleep), hypersomnia (excessive sleep), hypnagogic sleep (a state of being half awake, half asleep), and nightmares. Pain, drops in blood pressure, irregular heartbeat, and sinus congestion may lead to sleep disturbance. Decreased blood sugar levels can cause insomnia as well. As blood sugar levels drop during the night, the adrenal glands release cortisol, a "fight-or-flight" hormone. The startle reaction produced by the sudden spurt of adrenal hormones awakens the sleeper and prevents a return to sleep until the blood sugar level is raised again. (A drop in blood pressure or slowed heartbeat will cause the same startle response.)

Although most healthy people experience sleep disturbances at one time or another, whether due to short-term illness, pregnancy, emotional upset, or injury, relatively few have long-term alterations of sleep patterns. When they do, underlying physiological causes should always be suspected.

Most researchers agree that the sleep disturbance in CFS/ME is caused by an alteration in the normal brain wave patterns required for deep, restful sleep. Dr. Russell Poland has proposed that in CFS/ME the normal pattern of sleep phases is interrupted by alpha wave spikes (around 10 Hz); that is, when you should be in deep, restoring stage four sleep, your brain waves are acting as though you are awake (*CFIDS Chronicle*, Summer 1993). (It should be mentioned that alpha spikes are common in many autoimmune disorders.) Another CFS/ME anomaly is the presence of excess theta waves, which cause the sleeper to remain in a light sleep state. Dr. Jay Goldstein has theorized that the brain wave disturbances are the result of alterations in hypothalamic function (*CFIDS Chronicle*, Fall 1991).

In 1993 Krupp et al conducted sleep studies (polysomnography) in a group of 72 CFS patients with sleep disturbances. In 10 of 16 (62.5%) patients, the researchers found clinically significant sleep abnormalities. The disorders included periodic movement disorder, excessive daytime sleepiness, apnea, and narcolepsy.

A subsequent study in 1997 by Fischler et al revealed a lower ratio of stage 4 sleep, which would explain why sleep is nonrestorative in CFS/ME patients. The researchers also found sleep initiation problems and sleep maintenance disturbances. In keeping with the lower percentage of deep sleep they found a higher percentage of stage 1 (light) sleep and a lower percentage of stage 2 sleep. All of these findings confirm a significant disturbance in the sleep architecture of CFS/ME patients.

The cause of the dysregulation may be attributable to excess cytokines acting to stimulate the sympathetic nervous system (which is regulated by the hypothalamus). Many studies have found increased inflammatory cytokines in the plasma of patients with CFS/ME, including IL-6 and IL-1. Research indicates that IL-1 plays a role in the regulation of non-REM sleep by increasing delta waves, which may lead to hypersomnia and daytime sleepiness.

Interestingly, the only study which has actually measured cytokine levels of CFS/ME patients during sleep found not pro-inflammatory activity, but anti-inflammatory activity. In 2010 Nakamura et al found that in both CFS/ME and FM patients, increases in IL-10 levels correlated with fragmented sleep. The researchers concluded that “alterations in the balance of Th1 and Th2 cytokines toward a Th2 or sleep-disrupting response suggests a possible role for cytokine-induced, disturbed sleep in the pathogenesis of both syndromes.”

But cytokines are only one player in sleep disturbances. In 1996 Dr. Ernir Snorrason, Dr. Arni Geirsson and Dr. Kari Stefansson tested Galantamine, a selective acetylcholinesterase inhibitor, as a treatment for CFS/ME. The researchers theorized that a deficit in acetylcholine was responsible for many CFS/ME symptoms. Interestingly, the increase in acetylcholine, a neurochemical generally associated with arousal, resulted in a 70% improvement of sleep disturbances. Later studies conducted by Khan et al confirming hyper-responsiveness to acetylcholine seem to bear out the hypothesis that low levels of acetylcholine may contribute to sleep disturbance.

## INSOMNIA, or DIFFICULTY INITIATING AND MAINTAINING SLEEP (DIMS)

In the initial or acute stages of CFS/ME and during severe relapse, most people have great difficulty falling asleep and staying asleep. Typically it takes several hours to fall asleep, although some people may not drift off until close to dawn. (This is known as “phase shifting.”) People may find themselves either awaking several times during the night or waking after a few short hours and not being able to get back to sleep. Common wake-up times are between 11:00 PM to midnight, 2AM, 3:00 to 4:00 AM, and early dawn (followed by sleep for phase-shifters).

Dr. Cheney believes that waking up at 1 or 2 AM is an indication of immune system upregulation. Immune system activity is closely correlated with sleep, especially the pro-inflammatory cytokines TNF- $\alpha$ , IL-2, IL-6 and IL-1, which peak at certain times of the night. These cytokines perform many functions which may interfere with sleep. (TNF and IL-1 lead to the production of prostaglandin E2, which enhances perception of pain and therefore can cause arousal). As a consequence, reduction in pro-inflammatory cytokines may lead to more restful sleep.

Chrousos et al found that decreased overall secretion of IL-6, which is elevated in CFS/ME patients, is associated with a good night's sleep and a sense of well-being the next day. The researchers concluded that sound sleep correlates with “decreased exposure of tissues to the proinflammatory and potentially detrimental actions of IL-6 on the cardiovascular system, insulin sensitivity, and bones.”

In general, treating the underlying mechanisms and major symptoms of CFS/ME—inflammation, oxidative stress, immune activation, dysautonomia, gut dysbiosis—will help resolve insomnia. Sometimes, sleep inducers (such as hypnotics) will be helpful. But often as not, attempting to treat insomnia without addressing the fundamental metabolic disruptions caused by CFS/ME is putting the cart before the horse.

## TREATMENTS

The most frequently prescribed treatments for insomnia are antidepressants, many of which are sleep-inducing. The tricyclics trimipramine and amitriptyline are perhaps the most commonly prescribed, however, their side effects make them untenable for most patients with CFS/ME. Trazadone, a commonly prescribed sedating antidepressant, causes hangover. Therefore, a combination of therapies is usually recommended.

A combination of tricyclic antidepressants and benzodiazepines is often prescribed for people who wake frequently in the night. Dr. Cheney's recommendation is .25 mg of Klonopin (clonazepam) with two drops of liquid Sinequan (doxepin). As he says, one (Klonopin) puts you to sleep, and the other (Sinequan) keeps you asleep.

Dr. Lapp also uses a combination of clonazepam and doxepin in his practice. For people who wake up repeatedly in the night, he recommends trazodone (brand name: Desyrel), at 50 mg nightly. Trazodone induces stage 3 and 4 deep sleep. He also uses the hypnotics Ambien, Remeron, and Restoril.

Dr. Teitelbaum recommends valerian root, and passion flower, two herbs known for their soothing qualities. Kava Kava: 30% extract (250 mg capsules - 1 to 3 capsules at night) is also a relaxing herb that can help initiate sleep. Dr. Teitelbaum also recommends taking magnesium and/or calcium at night as a sleep aid. Dr. Teitelbaum uses a very low dose of melatonin (0.3 mg) prior to bedtime.

See General Treatments below for more treatments and tips on how to manage insomnia.

## PHASE SHIFTING

Phase shifting is a sleep disorder in which a person simply cannot fall sleep before 2AM. Some may not fall asleep until dawn. In healthy people, this is not necessarily a form of insomnia, though it may be inconvenient, because once sleep is achieved the sleep is normal. However, phase shifting during illness is a sign that the body's circadian rhythms are profoundly disturbed.

In CFS/ME, phase shifting is thought to be part of the general disruption in HPA axis activity, caused by viral infection (or reactivation), and subsequent hormonal and immune system responses. It is a common observation that viral illnesses, such as mononucleosis and viral pneumonia can cause phase shifting.

Dr. John Richardson observed that phase shifting, which he called “owl syndrome,” was a sequel of enteroviral infections among his patients. When he administered a buspirone challenge test to his patients with M.E., he found that the results in patients with “owl syndrome” correlated with increased prolactin, which is an indication of enhanced central serotonergic responses. In short, people who phase shift are unusually sensitive to serotonin, which might lead to a reversal of day/night circadian rhythms. (Normally, serotonin levels diminish at night. Increased sensitivity would enhance the effects of serotonin and lead to wakefulness.)

People who regularly cannot fall asleep until dawn may benefit from melatonin, a pituitary hormone that regulates diurnal cycles, combined with minerals. A recent study conducted in Italy indicates that a combination of zinc, melatonin and magnesium helps reduce insomnia. Nightly administration of 5 mg of melatonin, 11.5 mg of zinc and 225 mg of magnesium improved sleep significantly in all of the patients with primary insomnia.

Standard treatments for phase shifters include exposure to bright light in the morning for a half hour and melatonin administered in very low doses between two and six hours before the desired sleep time.

Anecdotal evidence suggests that anti-inflammatories may be successful for treating phase shifting.

SEE: Melatonin.

## HYPERSOMNIA

Hypersomnia is typical of flu-like onsets, particularly during the acute stage. Hypersomnia is defined as excessive sleep (more than 10 hours), and daytime sleepiness. Although hypersomniacs may spend most of a 24-hour period asleep, they do not necessarily sleep straight through. Hypersomniacs may awaken briefly at intervals, but will fall asleep shortly thereafter. For those who are able to get up at a reasonable time in the morning, a feeling of grogginess may persist throughout the day. Many people with hypersomnia report that they never feel fully alert. Sometimes a person may awaken feeling disoriented or feel semiawake for a period of time after waking. It may take hours to come fully awake.

Hypersomniacs often take naps during the day, sometimes lasting two hours or more, but do not feel refreshed afterward. Among CFS/ME patients, hypersomnia is more common in children than in adults, though many adults cycle through phases of alternating insomnia and hypersomnia.

As with insomnia, the hypothalamus is involved in disorders that produce excessive sleep. One of the neurochemicals responsible for maintaining wakefulness is histamine. All of the brain's histamine is produced in the tuberomammillary nucleus of the hypothalamus. Damage to this region through lesions, tumors, or head trauma produces hypersomnia.

A number of viral infections, including viral pneumonia and mononucleosis, can also cause hypersomnia. However, the sleep disturbance caused by these infections may have more to do with immune system responses than with the original infection. Inflammatory cytokines (tumor necrosis factor-alpha, interferon-beta, and IL-1), which are commonly elevated during viral infections, are well-known sleep inducers. Even when viral titers do not show active infection these cytokines may be elevated in CFS/ME patients.

Recently, a study in Japan conducted by Nushikai et al found an autoantibody indicating a similar autoimmune process in hypersomniac patients with CFS/ME and those with FM. The researchers noted that CFS patients with the antibody presented more frequently with hypersomnia and cognitive disorders, such as impaired memory and difficulty in concentration. This finding is confirmed by CFS/ME patients who report an increase in "brain fog" after excessive sleep. Autoimmune illnesses are characterized by inflammation, which means that whether hypersomnia is caused by a viral infection, and subsequent immune activation, or an autoimmune process, the end result is the same.

Standard treatments for hypersomnia usually revolve around stimulants, such as Provigil, Ritalin or Wellbutrin. While these may indeed wake you up, it should be remembered that they do not treat the underlying cause of hypersomnia. Antioxidants, anti-inflammatory agents, and antivirals may have better results in the long term.

Vitamin B12 increases sensitivity to light, which can help hypersomniacs awaken in the morning (rather than afternoon). Recently, histamine H3 antagonists (which activate histamine in the brain) are being explored as a treatment for hypersomnia. Sedatives are contraindicated.

## LIGHT SLEEP

Sleep that is too light is typical of CFS/ME. EEGs of patients with CFS/ME show an excess of theta wave activity, which is produced during light sleep. In addition, interference of alpha waves during deep sleep causes the sleeper to be too alert during deep sleep by allowing too much sensory information to be processed by the brain. And once a person is disturbed by alpha wave intrusion, he or she may feel the need to go to the bathroom, which wakes him or her up completely.

There are many contributory factors to light, unrefreshing sleep, one of which is low acetylcholine levels. While it may seem contradictory (acetylcholine is

associated with arousal), low levels of acetylcholine may actually produce the same effect as high levels, because a chronic deficit enhances sensitivity. Thus, a small amount of acetylcholine will produce a much greater effect than it would normally. Both acetylcholine deficiencies and hyper-responsiveness to acetylcholine have been documented in CFS/ME patients.

In 1996 Dr. Ernir Snorrason, Dr. Arni Geirsson and Dr. Kari Stefansson tested galantamine, a selective acetylcholinesterase inhibitor, as a treatment for CFS/ME. In accord with their hypothesis, the increase in acetylcholine resulted in a 70% improvement of sleep disturbances.

### HYPNAGOGIC SLEEP (HYPNAGOGIA)

Hypnagogia is the state between wakefulness and sleep that precedes falling asleep (or, conversely, coming awake). Typical sensations associated with hypnagogia are a feeling of falling (which may be followed by a jerk), emotions (usually fear), and spontaneous sights, smells, and sounds (hallucinations). Often, people hear their own name being called. While many people seem to enjoy, and even try to promote this state, the feeling of being neither asleep nor awake can be extremely uncomfortable if extended.

Among those with highly fragmented sleep, the hypnagogic state can occur at any time during the night. Those who are severely sleep deprived may even experience hypnagogic hallucinations during the day. These are usually produced in association with microsleeps, which are periods of sleep lasting only a few seconds, resulting from the body's attempts to catch up on missing sleep. Meditation can also produce hypnagogia.

Many of the drugs prescribed for sleep, notably hypnotics and those interfering with cholinergic pathways, can produce hypnagogia. Those with profoundly disturbed nervous systems (dysautonomia) may experience this effect more than others.

Any voluntary movement will shake off hypnagogia. However, those who are sleep deprived may simply wish to breathe deeply, relax, and allow this state to lead them into true sleep.

### DYSANIA

Dysania refers to a period lasting one to two hours after awakening in which a person simply cannot get out of bed. These hours of "morning fog" are typical of CFS/ME and are common in all stages of the illness. Dr. Lapp reports that dysania is the norm among his CFS/ME patients. Some medications commonly taken for insomnia, such as sedating antidepressants, benzodiazepines, hypnotics, and antihistamines may contribute to excessive morning grogginess (this is sometimes called a "sleep hangover").

### MYOCLONUS

Some people are wakened by involuntary jerks (myoclonus) of the arms, legs, or entire body. (When the arms and legs are involved, this is referred to as Periodic Limb Movement Disorder.) These jerks, in turn, can trigger a startle reaction and

pounding heart, making a return to sleep difficult. Typically, spontaneous jerks occur just before sleep (hypnic jerks), although they can also occur during light sleep.

While there are a number of triggers for myoclonus (caffeine, hormonal changes), the cause is central. A hyper-responsiveness in the parts of the central nervous system that control movement is what causes these muscle jerks. When too many neurons fire at once in these areas, the result is an involuntary contraction of the muscles. The neurotransmitter most closely associated with muscle movement is acetylcholine, to which people with CFS/ME are sensitive.

Treatments for myoclonus include calcium, magnesium, 5-HTP (a serotonin precursor), and small doses of clonazepam. For women who are going through menopause, which tends to increase the incidence of hypnic jerks, hormone-related treatments, such as black cohosh (Remifemin) and bio-identical hormones, will relieve the problem.

## DREAMS AND NIGHTMARES

Nightmares are a common early symptom in people with CFS/ME, as are vivid, disturbing, thematic dreams. These dreams often involve a level of graphic violence and sheer horror that would impress Stephen King. Usually, these frightening dreams will awaken the sleeper, leaving a persistent feeling of discomfort that persists well into the day.

Conversely, many people also experience a complete lack of dreams, or a sense that their dreams are vague and disjointed. This state of dreamlessness may last for months.

Some people also experience a frightening inability to move any part of their body for a few minutes after waking, even after becoming fully conscious. This is known as sleep paralysis, and is an extension of the suppression of movement that occurs during the dream state.

The nightmares experienced by people with CFS/ME are the result central nervous system dysregulation caused by immune system activation, cellular hypoxia, oxidative stress – or all of the above. Paradoxically, many people report that many medications prescribed for sleep—SSRIs, hypnotics, minor tranquilizers, and even herbals remedies like valerian—produce nightmares. Doxepin, a standard sleep remedy prescribed for CFS/ME patients, has been known to cause nightmares that are indistinguishable from reality, when taken in higher doses.

## NIGHT SWEATS

Night sweats are typical of the initial or acute stages of CFS/ME (or relapse). Night sweats are also common in premenstrual syndrome (PMS) and perimenopause. Night sweats can be drenching or can involve only the upper torso and neck. Keeping a change of nightclothes nearby can help minimize the disruption caused by having to change clothes during the night. Using light layers of bedclothes, which can be easily thrown off, is also helpful. Female patients have reported that Remifemin (black cohosh) helps with hormone-related night sweats.

## GENERAL TREATMENTS FOR SLEEP

A lot can be done to improve sleep. The most commonly prescribed pharmaceutical treatment is low doses of the benzodiazepine Klonopin (0.25 mg), and liquid Sinequan (1 mg), an antidepressant, taken together. Klonopin is rapid-acting and helps induce sleep and Sinequan (generic: doxepin) helps maintain sleep. Many people with CFS/ME-related insomnia have found this combination helpful, although people who are sensitive to antidepressants might want to try other treatments first.

Ambien, a sedative-hypnotic, is a medication for insomnia that does not affect sleep cycles, as do benzodiazepines and antidepressants. Some patients report success with Ambien, although others say it makes them feel like they're on a "bad trip." Tylenol PM also can help induce drowsiness, especially if fibromyalgia-type symptoms are present. Antihistamines such as Benadryl may induce sleep – although antihistamines can also produce the opposite effect in some people, making them feel jittery. As always, start with a very small amount of the drug to check for sensitivity.

Gabapentin, an anticonvulsant, is often prescribed as a sleep aid. In one study conducted in 2002, the researchers found that it increased slow wave sleep, which is lacking in CFS/ME patients.

Anticholinergics are often prescribed to promote sleep, however in the more severely ill these tend to induce an uncomfortable state of paralysis while still conscious. For most patients the experience is very disturbing.

Recently, Xyrem (aka GHB) has become a popular treatment for CFS/ME insomnia. This is a "hammer to the head" approach to insomnia, and while it will certainly knock you out, you may want to try some milder treatments first.

Interestingly, some over-the-counter medications containing stimulants have helped people with fragmented sleep. One patient reported that Zyrtec D, an allergy medication containing pseudoephedrine, actually helped her stay asleep. Her respiration and heartbeat were so slow when she was asleep that her body kept jolting her awake with what she called, "panic microarousals" (bursts of adrenaline). The result was that she simply never got into sustained deep sleep. She reported that after taking Zyrtec D, she experienced her first refreshing sleep.

Supplements that may be helpful include magnesium, calcium, and vitamin B complex. Patients have reported that magnesium taken before bedtime acts as a muscle relaxant, which helps them sleep. Calcium appears to have a similar effect. Vitamin B complex also can help induce sleep, especially if there is a deficiency, although it should be noted that vitamins produced from brewer's yeast can have the opposite effect in people sensitive to yeast products.

People with phase sleep cycle problems (falling asleep at dawn or sleeping only during the day) have found that melatonin, a pineal gland hormone, works well. A 2011 study conducted in Italy indicates that a combination of zinc, melatonin and magnesium helps reduce insomnia. Nightly administration of 5 mg of melatonin, 11.5 mg of zinc and 225 mg of magnesium improved sleep significantly



in all 22 of the patients with primary insomnia. However, it should be noted that this dose of melatonin is roughly 10 times the amount normally recommended for people with CFS/ME. If you wish to try this combination, start with a lower dose of melatonin.

The serotonin precursor, 5-HTP can also help to induce sleep, as can the amino acids theanine and taurine. The supplement GABA, the brain's principle inhibitory neurotransmitter, can also promote sleep. Although it has limited ability to cross the blood-brain barrier, some parts of the limbic system (which controls sleep) are not protected by the blood-brain barrier and will thus be accessible to the supplement.

Inositol can help induce sleep, although in some people with severe insomnia it may produce a rather light, unrefreshing sleep.

Galantamine, a selective acetylcholinesterase inhibitor, has also been shown to improve sleep in CFS/ME patients. Research also suggests that galantamine may correct sleep disturbance by increasing the amount of acetylcholine in the brain. Galantamine is sold as a supplement in the U.S., and as a drug in Europe. An alternative to galantamine is royal jelly. Because royal jelly contains natural acetylcholine, this nutritional product may be helpful for some people who are sensitive to pharmaceuticals.

Herbs that effectively induce sleep include valerian (which can be upsetting to the stomach and should be taken with a little milk), hops, kava, passion flower, chamomile (not for those allergic to ragweed), and skullcap. All of these can be combined in a tea or tincture, or taken singly.

Aroma therapy works well for some people. A drop of clary sage or jasmine essential oil on a handkerchief next to the bed produces a sedative effect, as does rose and lavender.

Those who wake up because of a decrease in blood sugar levels should eat something (a cracker, milk or tea with a little honey, or cereal) when they wake up. Often they can get back to sleep when their blood sugar level returns to normal. Grandma's cure for insomnia—a glass of warm milk at bedtime—also may help some people fall asleep. Warm milk contains high amounts of serotonin, which is why nursing babies often doze off before they're done nursing. Carbohydrates, such as bread or crackers, also increase the amount of serotonin in the brain. Salt sometimes helps restore sleep in people who experience insomnia as a result of low blood pressure.

Although the insomnia of CFS/ME is not caused by stress, it is certainly aggravated by it. Stimulating projects should not be undertaken after dinner. A relaxing bath about an hour before bedtime can help with sleep onset problems. The warm bath signals the body to cool down, which helps the person fall asleep. An interesting new invention, the “cooling cap,” reduces the temperature of the head, which also helps initiate sleep by cooling the body.

Reading some light fiction is helpful for creating a restful state. The rhythmic back-and-forth eye movements produced by reading help signal the brain to produce slower brain waves.

Watching television should be avoided in those who are sensitive to the effects of stimulants. The rapid frame changes, which force the eyes to refocus every few seconds, are arousing and may inhibit sleep onset. If reading is not an option, listening to a tape or CD may help induce sleep (this also works for night waking). The act of listening changes neurotransmitter activity to induce a restful state – as anyone who has dozed through a boring lecture can attest to. Listening to soothing music or to someone telling a calming story might help someone who wakes up in the night to stay relaxed. The more aroused and upset a person gets, the harder it will be to fall back asleep.

Skipping a night of rest to force the body into sleep is not a good idea. You will simply become even more exhausted, making it harder to sleep the second night. Exercise, the universal cure for bad sleep, will make CFS/ME insomnia much worse.

Remember, the CFS/ME sleep disorder is not caused by bad habits. It is caused by the brain. Rest whenever your body allows it. The more rested you are, the easier it will be to sleep. Also, be aware that the long-term use of tranquilizers and antidepressants can be disruptive of normal sleep cycles. These drugs should be used judiciously and under the careful supervision of your doctor. CFS/ME patients need smaller doses than normally prescribed.

SEE: Antidepressants, Antihistamines, Benzodiazepines, Central Nervous System Stimulants, Hypnotics, Pain Relievers; Amino Acids, Herbs, Inositol, Melatonin, Minerals (Calcium, Magnesium), Royal Jelly, Vitamins; Acupuncture, Aroma Therapy, Biofeedback, Hypnosis, Meditation; Stress Reduction and Elimination.

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*Cooling caps for insomnia:* <http://healthland.time.com/2011/06/17/tip-for-insomniacs-cool-your-head-to-fall-asleep/>

“Under the Brain's Control.”

<http://healthysleep.med.harvard.edu/healthy/science/how/neurophysiology>

*Harvard Medical School's clear and concise explanation of how sleep works.*

“Normal sleep, Sleep Physiology and Sleep Deprivation.” Dr. Suzanne Stevens.

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*Technical information about sleep physiology.*

“A Review of Sleep in Selected Immune and Autoimmune Disorders.” Felissa R.

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*This is a fabulous article about how the HPA axis affects sleep.*

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## URINARY TRACT PROBLEMS

### Cystitis, Interstitial Cystitis, Prostatitis

Bladder problems are not uncommon in CFS/ME. Dr. Jay Goldstein observed that some 20% of his patients experience pain on urination. Problems may include the need to go to the bathroom frequently (polyuria), difficulty urinating (dysuria), and the painful, aching, or burning sensations that are the typical symptoms of inflammation of the urinary tract (cystitis). Although both men and women can experience urinary difficulties, the origins of the problems can be somewhat different. Because of anatomical differences in urinary tract structure, cystitis is more frequent in women than in men. However, men may experience urological problems due to inflammation and infection of the prostate gland (prostatitis).

#### CYSTITIS

Cystitis, commonly referred to as a bladder or urinary tract infection, is normally caused by an overgrowth of bacteria (usually *Escherichia coli*) in the urinary tract. However, cystitis is not limited to bacterial causes. It also can be brought on by an allergic response, chemical poisoning, congenital defects, or hormonal fluctuations. The distinction between the common urinary tract infection caused by bacteria and the noninfectious bladder disorder known as interstitial cystitis (see below) is especially important because treatment for each of these disorders differs radically.

The diagnosis of a urinary tract infection is based on a urine culture. Once the bacterium has been cultured, the standard treatment is a course of antibiotics (usually furantoin). Bubble baths, bathing in contaminated water, synthetic underwear, and tight pants should be avoided. Pyridium can be taken for acute pain.

People who have frequent symptoms of cystitis but have negative urine cultures may have interstitial cystitis and should follow the suggestions in the next section.

#### INTERSTITIAL CYSTITIS

Interstitial cystitis (IC) is a painful condition which mimics bacterial cystitis in many respects. Women with IC experience near-constant bladder pain that is unrelieved by urination. In addition, most women with this painful condition also have concomitant conditions: irritable bowel syndrome, GERD, migraines, allergies, skin rashes, gingivitis, mouth sores, and a host of other problems.

In *You Don't Have to Live With Cystitis!*, Dr. Larrian Gillespie attributes interstitial cystitis to loss of the protective lining (glycosaminoglycans, or GAG layer) that normally insulates the bladder tissue from its contents. When the GAG layer is eroded – which Dr. Gillespie claims may be caused by excessive or

inappropriate use of antibiotics, radiation, or chemical exposure – painful, burning urination results. Once the GAG layer has been compromised, the bladder may become repeatedly irritated by the release of certain neurotransmitters (notably serotonin) that keep the bladder in its raw, painful state. The symptoms of interstitial cystitis can be so severe that a person can qualify for disability on this basis alone.

There is also convincing evidence that mast cell activation is involved in the mechanism of interstitial cystitis. In a paper describing interstitial cystitis as a “neuroimmunoendocrine” disorder, Theoharides et al state that proinflammatory molecules in the bladder can lead to immune cell infiltration, which then can cause neurons to secrete neurotransmitters that activate mast cells. Mast cells can directly cause tissue damage. Significantly, mast cell activation is increased by estrogen, which explains why symptoms often correspond with ovulation.

Diagnosis of interstitial cystitis is made on the basis of symptoms, history, and through a cystoscopy, a procedure in which the bladder is filled with water (hydrodistention), via a catheter. Hydrodistention allows the urologist to see changes inside of your bladder that are typical of IC, including the presence of pin-point sized red marks on the bladder wall. This procedure also allows doctors to see Hunner's ulcers, which are present in a small number of people with IC. Because this is an invasive procedure requiring anesthesia, many doctors prefer to make a diagnosis based on symptoms alone.

## TREATMENTS

There is currently only one pharmaceutical approved by the FDA for the treatment of interstitial cystitis: Elmiron. While the drug has been reported as successful in treating IC, it produces myriad side effects which can be as uncomfortable as the original condition: nausea, malaise, joint pain, acid reflux, easy bruising, GI symptoms (diarrhea, bloating), hair loss, and, paradoxically, bladder pain. The frequency of these side effects may be due to the fact that Elmiron is not readily absorbed. More than 94% of the medication is excreted, intact, in feces, while only 6% actually makes it into the bladder. The drug must be taken for several months for most patients to achieve some benefit, which for many of those experiencing side effects is far too long. Recently, it has been proposed that side effects can be avoided by infusing Elmiron directly into the bladder. However, this is not yet standard practice.

Doctors have also successfully used tricyclic antidepressants (Elavil) to treat interstitial cystitis. Tricyclics in low doses act to decrease pain, which is why they are often prescribed for treating fibromyalgia.

Hydroxyzine, an antihistamine, addresses the root of the problem. Biopsies of some interstitial cystitis bladders, particularly those with Hunner's ulcers, show high numbers of mast cells (immune system cells which produce inflammation). Treatment with hydroxyzine is aimed at reducing the production of mast cells in the bladder. Some CFS/ME patients respond poorly to hydroxyzine, which is a strong prescription drug. To minimize side effects, start with a very low dose.

Interestingly, cimetidine (Tagamet) has been shown to be effective in treating IC. Cimetidine is an H2 antagonist (it blocks histamine receptors). For those who respond poorly to other pharmaceuticals, Tagamet may offer an alternative.

Infusions with dimethylsulfoxide (DMSO) are frequently used to treat IC. DMSO is an industrial solvent derived from wood, whose sole approved medical use is for treatment of interstitial cystitis. DMSO is instilled into the bladder through a catheter. Heparin, bicarbonate of soda, or a steroid (such as Kenalog) may be added to DMSO to enhance its anti-inflammatory properties. DMSO, alone or in combination, is believed to stabilize the bladder lining and provide a medium for the cells to begin self-repair. The initial treatments are done in a urologist's office every one to two weeks for a total of four to eight treatments. After that point, patients can self-administer on an intermittent basis. The drugs require a prescription. People who have allergies should approach DMSO with caution because it causes the release of histamine.

Chondroitin sulfate, a supplement used for arthritis, has been shown to be an effective means of reducing inflammation in the bladder lining. In an interesting study published in 2011, a group of researchers infused chondroitin sulfate into damaged rat bladders. They found that after infusion, inflammatory cells (neutrophils and mast cells) were significantly reduced. The study not only demonstrated that chondroitin is effective for treating IC, it also showed a clear role for inflammation as a cause of the condition.

### *Home management*

Interstitial cystitis is such a painful condition that most women will not want to wait until medical science comes up with a safe, effective treatment. Fortunately, IC can be effectively managed by dietary modifications, as well as by avoiding conditions which will produce symptoms.

While most doctors recommend drinking cranberry juice for urinary tract infections, in the case of interstitial cystitis acidity worsens the condition. (Dr. Gillespie likens drinking cranberry juice for IC to throwing gasoline on a fire.) For immediate relief, try baking soda. Baking soda acts to make the urine more alkaline, which relieves burning pain. Dr. Gillespie recommends drinking a teaspoon of baking soda in water when symptoms are first noticed. In a few hours, repeat using half a teaspoon of trisodium compound (Tri-Salts). Tri-Salts are released more slowly into the system than baking soda, which will provide longer relief.

Diluting the urine to make it less irritating to the bladder lining is also important. To dilute the urine, at least 10 glasses of water should be drunk during the day. If herbs can be tolerated, horsetail or corn silk tea helps flush the bladder.

Acid foods and foods high in the amino acids which eventually form serotonin and norepinephrine can irritate the bladder lining. The following foods should be avoided:

### *Foods High in Tyrosine, Tyramine, Tryptophan, and Aspartate*

Avocados	Cranberries	Prunes
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Aged cheeses	Fava beans	Raisins
Bananas	Lima beans	Rye bread
Beer	Mayonnaise	Saccharine
Brewer's yeast	NutraSweet	Sour cream
Canned figs	Nuts	Soy sauce
Champagne	Onions	Vitamins buffered with aspartate
Chicken livers	Pickled herring	Wine
Chocolate	Pineapple	Yogurt

Garlic, onions and vitamin C (non-buffered) irritate the bladder as well, and should be avoided.

Not everyone notices complete relief of all symptoms by avoiding these foods, however, a substantial number of Dr. Gillespie's patients have obtained partial or significant relief. It may not be necessary to avoid all of these foods; perhaps only the very acidic foods such as citrus will trigger symptoms. Trial and error, along with keeping a food and symptoms diary, can help determine which of these foods to avoid. In addition, some dyes, additives, and chemical agents commonly found in food products can trigger symptoms. These include tartrazine (yellow dye No. 5), monosodium glutamate (MSG), sodium benzoate, and benzyl alcohol. Carefully read labels on foods and medications.

Herbal demulcents, which serve to soothe and protect irritated tissues, can also be helpful. These include: comfrey, dead nettle (also good for allergies), licorice, marshmallow root (not the candy), oatstraw, cornsilk, and slippery elm. These are best taken as weak teas rather than in capsule form. (Capsules tend to be too strong for irritated bladders.)

Vitamin B6 helps heal the bladder by preventing tryptophan metabolites in urine from converting to free radicals. B6 can also convert other amino acids into free radical scavengers, thus lessening damage to the lining of the bladder. This may be the only B vitamin that sensitive patients with interstitial cystitis can tolerate (the fermenting process used to formulate other B vitamins can cause bladder irritation). Dosage should not exceed 50 to 100 mg/day to avoid creating dietary deficiency of other members of the vitamin B complex.

*Caution!* Patients with a diagnosis of cystitis should always request a urine culture. Bacterial infections must be treated with antibiotics, however routine antibiotic therapy without a confirmed bacterial infection may substantially worsen interstitial cystitis and, in any case, will not help treat it.



SEE: Antidepressants (Elavil), Antihistamines (Atarax and Vistaril), Tagamet; Herbs (licorice).

#### MORE INFORMATION

Interstitial Cystitis Association of America

Telephone: 800-435-7422 (800-Help ICA)

Email: [ICAmail@ichelp.org](mailto:ICAmail@ichelp.org).

Website: <http://www.ichelp.org/>

*The ICA can help you find a doctor in your area who will treat interstitial cystitis. With membership (\$45) you receive their quarterly magazine containing useful treatment information and resource materials.*

The Urological Pelvic Pain Collaborative Research Network

[http://porter.cceb.upenn.edu:7778/servlet/page?\\_pageid= 389,391,400&dad=portal30& schema= PORTAL30](http://porter.cceb.upenn.edu:7778/servlet/page?_pageid=389,391,400&dad=portal30&schema=PORTAL30)

*The UPPCRN is comprised of ten research centers that focus on chronic prostatitis and interstitial cystitis.*

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Theoharis C. Theoharides and David E. Cochrane. “Critical role of mast cells in inflammatory diseases and the effect of acute stress.” *Journal of Neuroimmunology* 146 (2004) 1 – 1.

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<http://www.ncbi.nlm.nih.gov/pubmed/9629289> (Abstract)

## PROSTATITIS

The prostate is a small gland roughly the size of a large chestnut that surrounds the neck of the bladder and the urethra. Although the principal function of the prostate gland is to produce the fluid that comprises most of the semen, its location ensures that problems that arise in this gland will cause bladder symptoms.

Pressure from inflammation of the prostate, whether from bacterial or viral infection, excessive heat, radiation, or chemicals, causes pain and difficulty initiating or stopping urine flow. Infections of the prostate and urinary tract also produce a slight watery discharge (usually observed in the morning), an itching feeling inside the penis and discomfort while urinating, and pain in the perineal area. Acute bacterial prostatitis can cause fever and lower back pain.

A number of male patients have noted that prostate infections seem to have triggered CFS/ME. Dr. Byron Hyde, in his observations of CFS/ME outbreaks, has noted that early in the illness pseudoprostatitis was observed, often in quite young men (*The Clinical and Scientific Basis of ME/CFS*, 1992). Pseudoprostatitis is not linked to a specific pathogen. This implies that many of the urinary problems that beset men with CFS/ME are not due to bacterial infection. However, because so many other medical conditions can cause prostatitis, any associated symptoms require consultation with a urologist.

Given the increased susceptibility to infections experienced by many people who contract CFS/ME and the fact that inflammation is a common problem throughout the course of the illness, problems in this area always should be thoroughly investigated by a competent urologist.

## TREATMENT TIPS

Because infection and inflammation of the prostate gland produce similar symptoms, doctors sometimes have difficulty making a differential diagnosis based on symptoms alone. Bacterial and viral infections of the prostate, however, can be detected by means of urinalysis or examination of prostatic fluid. Nonspecific bacterial prostatitis usually is treated with an antibiotic. Chronic bacterial prostatitis is treated with a combination of antibiotics. (Nonbacterial prostatitis is not treated with antibiotics.)

Sometimes muscle relaxants are used to relieve spasms in the muscles of the pelvic floor. Hot sitz baths and the occasional use of tranquilizers are also recommended. Rarely, in cases where the pain seems to be related to inflammation in the pubic bone, nonsteroidal anti-inflammatory drugs (NSAIDs) have been

prescribed. Nutritional recommendations for prostate support include zinc (deficiency has been linked to some forms of prostatitis), essential fatty acids (important in prostate function), magnesium and calcium, vitamin A and vitamin E, and prostate glandular extracts, all of which can be found in health food stores and from online suppliers.

SEE: NSAIDs; Essential Fatty Acids, Minerals (calcium and zinc), Vitamins (A and E)

#### MORE INFORMATION

The Prostatitis Foundation

Website: <http://www.prostatitis.org/>

*The Prostatitis Foundation is a non-profit organization that provides resources for patients and doctors. Their website provides a support forum, relevant books, a newsletter, and information on the latest research.*

#### BOOK

Rous, Stephen. *The Prostate Book: Sound Advice on Symptoms and Treatment*. New York: W.W. Norton & Co., 1988.

#### ONLINE READING

*Patient thread on prostatitis:* <http://forums.phoenixrising.me/archive/index.php/t-9192.html>

#### VISION AND EYE PROBLEMS

Visual Processing Problems, Photophobia, Floaters and Spots, Tearing and Dry Eye, Sluggish Focus and Double and Blurred Vision, Tunnel Vision, Night Blindness, Depth-of-Field Loss, Nystagmus, Early Cataracts, Sjögren's Syndrome

About 75% of people with CFS/ME experience some difficulty with vision, covering a broad range of symptoms. Because the optic nerve is so long – it traverses the entire length of the brain to process visual information – vision problems can originate in a number of areas of the brain. Most researchers agree that in CFS/ME the problems probably stem from the area at the top of the brainstem (the midbrain) or in the hypothalamus (which controls pupil dilation).

Eye problems in CFS/ME can be both neurological (e.g., processing problems) and mechanical (e.g., dryness, tearing), although most are probably related to nervous system dysregulation. The majority of eye problems in CFS/ME tend to be transient and, though irritating, benign.

In 1995 M.E. Harnett and Richard J. Lanham conducted ophthalmological examinations on 24 CFS/ME patients, all of whom reported visual problems. In order of frequency, patients experienced: light sensitivity, foreign body sensation (without blepharitis, an inflammation of the eyelids), blurry vision, peripheral vision disturbances, trouble reading, pain, headache, floaters, glare, dryness, itchiness, hazy vision, double vision, crusting, and tired or weak eyes. The authors

concluded that many of these problems could be due to weakness on the muscles surrounding the eye.

Apart from the above visual problems people with CFS/ME report visual processing problems, tunnel vision, night blindness, depth-of-field loss, nystagmus, and cataracts. Some people with CFS/ME may also have concurrent Sjögren's Syndrome, an autoimmune disorder.

## VISUAL PROCESSING PROBLEMS

People with CFS/ME experience numerous visual processing problems: dyslexia, inability to read maps, difficulty recognizing faces (agnosia), as well as discrepancies between intended actions and consequent movements. (You reach for a glass and grab a bowl instead.) All of these problems are neurological in origin.

A recent study published in the *British Journal of Radiology* found that people with CFS/ME show a decrease in both white and gray matter in the occipital lobes. The occipital lobe is located at the back of the head and is the visual processing center of the brain. The researchers concluded that the decrease in white and gray matter could lead to “subtle abnormalities” in visual processing, as well as discrepancies between intended actions and consequent movements in CFS/ME patients.

During the Seventh International Irlen Conference, a group of researchers led by G. L. Robinson presented an interesting study comparing Irlen Syndrome to the visual problems experienced by people with CFS/ME. Irlen Syndrome (IS), also known as Scotopic Sensitivity Syndrome (SSS), is a visual processing problem in which letters and words appear to move on the page, or grow in size. Those with Irlen Syndrome also experience photophobia, blurring and shadowing of vision, headaches, eye strain, decreased span of recognition of words while reading, and difficulty tracking lines of print. The syndrome is unquestionably neurological.

Recognizing the overlap in visual symptoms, the researchers tested patients with IS for biochemical abnormalities and compared them with a group of patients with CFS/ME. The researchers discovered a complex array of biochemical changes were associated with vision difficulties in both the CFS/ME and IS subjects, with considerable overlap between the two. While the researchers observed that these biochemical changes were consistent with a viral etiology and ongoing immune activation, they concluded that the net result of these changes was an alteration in fatty acid metabolism, which would directly affect vision as well as neurological processing. (DHA, an essential fatty acid, is the principal component of both gray matter in the brain and the optic nerve.) Supplementation with essential fatty acids was recommended.

## PHOTOPHOBIA

Many people experience extreme sensitivity to light, especially in the acute or initial stages of CFS/ME. The cause of this sensitivity is a contradictory dilation of the pupil, usually on only one side, rather than the usual narrowing, when

subjected to a light source. The excessive influx of light causes pain and a spontaneous impulse to shield the eyes from damage.

Dilation of the pupils is regulated by the sympathetic nervous system, the part of the autonomic nervous system associated with “fight or flight” responses. Hyper-responsiveness of the sympathetic nervous system, due to an excess of excitatory neurotransmitters, is one of the fundamental mechanisms of CFS/ME, and is responsible for many of the neurological symptoms experienced by people with the illness. Once the sympathetic nervous system “settles” many hyper-reactions cease, however, light sensitivity seems to be one of the most recalcitrant symptoms.

Wearing dark sunglasses and keeping curtains drawn over windows are the best, and easiest, ways to help ameliorate light sensitivity.

### FLOATERS AND SPOTS

Specks or dots that seem to float across the field of vision are common in acute phases of CFS/ME. They are most noticeable against a light background and tend to follow the movement of the eye. Floaters are caused by bits of protein and other tissue that float in the gel-like substance that fills the eye. When the gel within the eye becomes more fluid, these little bits of protein move about, creating “floaters.” In general, floaters are harmless, requiring no treatment. If they become annoying, simply move your eyes up and down, which will cause the floaters to migrate out of the field of vision. However, when floaters or fields of spots persist, or are accompanied by light flashes or loss of peripheral vision, a trip to an ophthalmologist is warranted. These symptoms may be indicative of inflammation or damage to the retina.

### TEARING AND DRY EYES

People with CFS/ME report both excessive tearing and dry, irritated eyes, frequently in alternation. The periodic dry, burning eyes (keratitis sicca) common in CFS/ME can lead to conjunctivitis (pink eye), in which the eye turns pink and releases a sticky discharge. It should be noted that the conjunctivitis experienced by many people with CFS/ME is rarely the result of bacterial infection. In most of these cases, conjunctivitis results from excessive dryness, airborne allergies, or manual rubbing due to itching.

Tears are complex secretions that are designed to protect the eye. There are several types of tears, including the tears which are produced due to irritation (e.g., onions), the tears that constantly lubricate the eye, and tears produced under emotional stress. The tears produced to protect the eye contain water, lipids, hormones, immunoglobulins, glucose, urea, sodium, and potassium, as well as other compounds. Because they are stimulated by acetylcholine, a parasympathetic neurotransmitter, emotional tears also contain hormones and endorphins (natural pain killers).

In 1994 Caffrey et al published a study in which they found significant ocular disturbances in all of the 25 CFS/ME patients they examined. The most common

finding was tear film dysfunction. Lesley Vedelago, and Australian ophthalmologist, also observed rapid break-up time of protective tears, related to inadequate production of the oil or mucus layer in tears, among her CFS/ME patients. When the components of tears break up too quickly, the eye becomes dry.

Persistent dry eye can also be an indication of Sjögren's Syndrome, an autoimmune disease that causes all mucous membranes to dry (see discussion of Sjögren's Syndrome). In about half of all diagnosed cases, Sjögren's Syndrome accompanies other connective tissue disorders; thus it may be worth requesting an antibody test if symptoms are unusually persistent.

Dry eyes can be temporarily relieved with artificial tears or by hot compresses followed by an eyelid massage. The massages are done by placing a hot washcloth over the eyes for 20 to 30 seconds. Once the washcloth is removed, place your index finger at the inner corner of the closed eye, and gently draw it back to the outer corner. Repeat five times. This gentle massage helps the tear ducts to release tears. Many patients find that the simple measure of cupping warmed hands over the eyes is wonderfully soothing.

Restasis is a prescription drug that can help relieve dryness by reducing low-grade inflammation in the eyes. When subclinical inflammation is reduced, the eye naturally produces more tears. Restasis also extends tear break-up time, providing more lubrication for the sensitive surface of the eyes. Temporary side effects of Restasis include burning and redness, both of which are resolved once the eye becomes less dry. Typically, two months of treatment are required before the eyes regain an optimal level of tear production. Restasis is usually covered by insurance.

## MORE INFORMATION

Restasis website: [http://www.allergan.com/products/eye\\_care/restasis.htm](http://www.allergan.com/products/eye_care/restasis.htm)

## SLUGGISH FOCUS, BLURRED VISION, DOUBLE VISION

Seeing double (diplopia) can be disconcerting. Fortunately, it is usually transitory, as is blurred vision. People with CFS/ME also notice that it takes longer to focus the eyes, particularly when changing focus from near to far objects. All of these difficulties are most likely caused by nervous system or muscle coordination problems, in which the normally fine-tuned response between the small muscles controlling the lens and the brain is not synchronized. The result is that when the lens of the eye overreacts to stimuli, the normal corrective mechanisms that act to straighten the eye fail to operate as quickly as they should. An alteration in brain signals also can lead to uncoordinated eye tracking (one pupil dilates or contracts at a different rate from the other). The outcome is short-term blurring, double vision, and slow focus. All of these problems are exacerbated by tiredness and improve with rest.

Blurry vision can also be caused by low blood pressure. Dr. Rowe found that 96% of CFS/ME patients showed low blood pressure after a tilt table test. Typically,

these are patients who have difficulty standing, or who become light-headed or faint coming upright (orthostatic intolerance, or OI). Visual blurring is quite common in those with OI, as is blurry vision in response to barometric pressure changes, particularly before storms. Generally, once the blood pressure is normalized, blurry vision clears up.

### TUNNEL VISION

Sometimes people with CFS/ME experience loss of peripheral vision so severe that it appears as though they are looking through a tunnel. Tunnel vision may occur concurrently with loss of peripheral vision, making tasks such as driving risky.

### NIGHT BLINDNESS

Night blindness is common in people who also have other visual disturbances, particularly in those with low thyroid function. Night vision can decrease to the extent that a person cannot manage a trip to the bathroom at night. Leaving a night light on can remedy this problem.

### DEPTH-OF-FIELD LOSS

People with vision problems commonly experience difficulties in tasks that require relocating objects because they have lost the ability to judge distance. As a consequence, they may intend to place a glass on a counter but miss it by an inch, walk into doorjambs, stumble on uneven sidewalks, have difficulty calculating the distance between stairs (which leads to a lot of anxiety about falling), and have problems judging the speed of oncoming traffic. Depth-of-field loss also causes visual confusion when looking at repeating objects such as stairs – particularly if they are moving, as on an escalator – oriental rug patterns, and other dense, repetitive designs. When depth-of-field loss is severe, objects can appear two-dimensional.

### NYSTAGMUS

Dr. Alfredo Sadun, a neuro-ophthalmologist at the University of Southern California, has observed nystagmus (small, rapid eye movements) in one fourth of patients with CFS/ME. Nystagmus is rare (5%) in the general population and usually indicates an underlying neurological problem. Dr. Sadun has inferred from this and other vision problems common to CFS/ME that people with nystagmus may have a brainstem inflammation in the midbrain, which would cause dysfunction of the brain cells associated with vision.

### EARLY CATARACTS

Cataracts are a milky clouding of the lens that form when protein clumps abnormally on the eye. The result is blurred vision, loss of night vision, glare (often perceived as halos around lights), and fading of colors. Most cataracts develop in old age (by 80, over half of Americans can expect to have cataracts), through long-term

exposure to sunlight, or to smoke, and other environmental stressors. Various illnesses, such as diabetes, can also produce cataracts, as can certain drugs, the most prominent of which are steroids (e.g., prednisone).

Although there is not much reference to cataracts in CFS/ME literature, patients report an early onset of cataracts. This may be due to increased cortisol levels, which can be high, especially at the onset of CFS/ME. Many CFS/ME patients also have concomitant allergies, for which steroids are sometimes prescribed. However, oxidative stress, because it is universal among CFS/ME patients, is the most likely cause.

In 1995 Dr. A. Spector proposed that cataract formation was caused by a photochemically generated superoxide radical, hydrogen peroxide. While the damage caused by oxidative stress was not reversible, the formation of cataract tissue could be prevented by a glutathione peroxidase mimic.

The only effective treatment for cataracts, once they have formed, is surgery. In cataract surgery, the lens is removed and a new synthetic lens is put in its place. Cataract surgery is performed so often that there are special cataract centers that do nothing else. Several types of lenses are available: those that restore far vision, those that restore close vision, and those that do both. The third type of lens, while the most advantageous, is also the most expensive, costing upwards of \$2,500. Unfortunately, while the first two options are normally covered by insurance, the third is usually not.

## SJÖGREN'S SYNDROME

Sjögren's Syndrome is an autoimmune disorder that affects between two to four million patients in the United States, 90% of whom are women. In Sjögren's Syndrome, the moisture-producing glands in the body, particularly those in the eyes and mouth, are attacked by the immune system. Typical symptoms include dry eyes and mouth (*sicca*), leading to blurred vision, eye discomfort, photophobia, hoarseness, and difficulty swallowing.

Primary Sjögren's Syndrome is diagnosed in the absence of other autoimmune or connective tissue disorders. Secondary Sjögren's, the type patients with CFS/ME are likely to contract, is accompanied by other illnesses that affect connective tissue – for example, rheumatoid arthritis. About 50% of patients with Sjögren's Syndrome have the secondary type. Diagnosis of Sjögren's Syndrome is made on the basis of blood tests that detect autoantibodies, reduced tear production in the eyes, and taking a detailed history of symptoms.

In an interesting study conducted by a group of Japanese rheumatologists in 1996, CFS/ME patients were examined for the presence of Sjögren's Syndrome symptoms. Based on their examination, which included three different sets of criteria for Sjögren's, they determined that fully one-third of the CFS/ME patients met the diagnostic criteria for Sjögren's. However, they were “seronegative,” meaning their blood tests did not show the autoantibodies associated with Sjögren's. The researchers suggested “subclinical seronegative Sjögren's” in CFS/ME (and in fibromyalgia) as a viable diagnosis distinct from primary Sjögren's.



Treatments for Sjögren's Syndrome and dry eye include moisture replacement therapies, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids (although these increase the risk of developing cataracts). There are many high quality artificial tears available at drug stores. If you have chemical sensitivities, look for a brand that does not contain preservatives.

## TREATMENTS

A combination of vision and eye problems can make highly visual tasks such as reading or driving virtually impossible. Watching television, with its rapid shifts of scene and pulsating light effects, becomes particularly excruciating for those with focus problems.

Dr. Alfredo Sadun recommends that people with focus problems (double vision, slow focus, poor depth perception, uneven tracking) avoid the use of bifocal eyeglasses because they make inordinate demands on the musculature of the eyes. He recommends separate glasses for near and far sight. People who have never worn glasses may find that purchasing glasses to alleviate focus problems does not help. Because most eye symptoms are transient, a person may have severe problems one month and rush to buy glasses, only to find that vision has become completely normal the next month. Symptoms that persist or worsen over time, however, should be investigated by an ophthalmologist.

Dr. David Browning, an ophthalmologist who practices in Charlotte, North Carolina, has pointed out that many vision problems can be exacerbated with use of psychoactive drugs (such as Sinequan and Xanax). Because these drugs are commonly prescribed for many individuals with CFS/ME, people should be aware of potential visual side effects and exercise caution when driving or performing other demanding or dangerous tasks. It should be noted, however, that some people with CFS/ME experience improvement in vision problems while taking Klonopin.

Vision problems in CFS/ME are rarely due to vitamin A deficiency, yet some people report improved eye function after taking beta carotene (either in supplement form or as carrot juice).

Because the eye depends on microcirculation, it is quite sensitive to oxidative stress, which is why antioxidants are recommended to maintain eye health. The most commonly recommended antioxidants are bioflavonoids, ginkgo, bilberry, inositol, and CoQ10. Like the brain, the eye is unusually high in DHA, so fish oil supplements and essential fatty acids are highly recommended for all preventive eye care. Supplements that improve microcirculation, such as piracetam and ginkgo, may also be beneficial.

SEE: Antioxidants, CoQ10, Essential Fatty Acids, Inositol

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## WEATHER SENSITIVITY

The expression "feeling under the weather" has a literal meaning for people with CFS/ME, especially for those who suffer from concomitant fibromyalgia (FM).

In fact, so strong is the association between weather changes and exacerbation of pain in FM that weather sensitivity was included as one of its defining characteristics in Dr. Yunus's pioneering work on FM in the 1980s.

There are a number of reasons why changes in weather can affect joints and skeletal muscles. Decreases in barometric pressure allow the small fluid-filled sacs surrounding joints to expand, irritating and inflaming the tissue around them. Fluid expansion leads to increased sinus problems, toothaches, and even migraines. In a 1990 study by D. Guedj and A. Weinberger, two Israeli scientists, 83% of arthritis sufferers and 77% of FM patients could successfully predict rain based on increased joint pain.

It is common knowledge among people with CFS/ME that weather changes produce not just pain, but a general worsening of symptoms. CFS sufferers in the same geographic area often exchange sympathetic phone calls just before storms, during impending pressure fronts, and on windy days (which signal a drop in barometric pressure). In situations where more than one member of a family is ill, the response to weather may be particularly dramatic because all ill members experience an exacerbation of symptoms simultaneously.

Fully one-third of the general population may be sensitive to weather changes, according to studies performed at Hebrew University in Jerusalem. Those who are weather sensitive commonly experience symptoms such as muscle pain, aching joints, insomnia, irritability, and the "blahs" as much as a day or two before the weather changes. The worst weather for the sensitive individual is characterized by a falling barometer and high humidity. The reasons for the mysterious clairvoyance of those who seem to know when the weather is going to change may have to do with neurochemical changes stimulated by radio waves sent out by advancing fronts.

Studies directed by Dr. Felix Sulman, head of the Bioclimatology Unit at Hebrew University, demonstrated that people who reported sensitivity to weather changes had unusually high amounts of serotonin and histamine in their urine a day or two before a weather change. Histamine is an inflammatory agent released during allergic reactions. Serotonin, a neurotransmitter and vasoconstrictor, is also an irritant and can be released in the body during emotional stress. According to Dr. Sulman, excessive amounts of serotonin, like histamine, can produce agitation, insomnia, irritability, runny or stuffy nose, inflammation of the eyeballs and lids, shortness of breath, sore throat, edema in hands and feet, migraine headache, nausea, dizziness, palpitations, flushes accompanied by sweating or shivering, diarrhea, and the constant urge to urinate.

Dr. Sulman maintains that the "sferics," or radio waves, released as a consequence of the increased electrical activity preceding a front, produce positive ions that in turn act to stimulate the release of serotonin and histamine. He also speculates that weather sensitivity may be genetically adaptive because increased moodiness might have served as a warning to get back to shelter as quickly as possible. Animals may be subject to the same mechanisms. It has often been

observed that their uncanny foreknowledge of coming storms leads them to seek shelter before the weather changes.

People who are weather sensitive may also react similarly to changes in temperature. Dr. Sulman's group found that, in addition to increased histamine levels, hot weather produced decreased excretion of adrenal hormones (e.g., cortisol) signaling adrenal exhaustion. With prolonged hot weather, the symptoms of adrenal exhaustion become evident: low blood pressure, fatigue, listlessness, depression, confusion, difficulty performing mental tasks, and hypoglycemia. In some individuals the period of exhaustion may be preceded by transient hyperarousal of the thyroid – particularly at the onset of hot, dry weather – causing overactivity, insomnia, irritability, restlessness, palpitations, sweating, and diarrhea. Cold weather can produce similar effects.

Dr. Sulman has noted that prolonged hot weather stimulates the hypothalamus, the brain structure which signals the pituitary to release hormones that activate the adrenal glands. The hypothalamus-pituitary-adrenal (HPA) axis abnormalities common in CFS/ME (as noted by Dr. Mark Demitrack and colleagues) may be responsible for unusually rapid depletion of adrenal hormones and ensuing malaise brought about by heat. Increased histamine levels also have profound implications for the substantial number of people with CFS/ME who may also experience oversensitivity to histamine itself (*CFIDS Chronicle*, Summer 1993). Dr. Sulman's findings also predict higher reactivity to weather changes in women, who produce far fewer adaptive stress hormones than men and more histamine and serotonin in response to weather stress.

Dr. Michael Persinger, a neuroscientist at Laurentian University in Ontario, Canada, concurs that weather sensitive people may experience numerous symptoms from approaching weather fronts. Dr. Persinger found that dropping temperature, increased barometric pressure, and increased humidity cause sympathetic nervous system arousal. This results in increased urination, migraines, peripheral circulatory problems, and joint stiffness. Influxes of warm air with falling barometric pressure and high humidity are associated with parasympathetic responses (water retention, glaucoma, menstrual swelling). According to Dr. Persinger, the effects of weather fronts both precede and follow their passage. Parasympathetic activity is noticeable five to six hours before the passage of a cold front, while sympathetic activity increases from three to five hours afterward. Dr. Persinger has observed that the autonomic effects of weather fronts may continue for as long as 16 to 30 hours after the fronts have passed.

Dr. Persinger's theory is that those with unstable hypothalamic function have exaggerated responses to weather fronts. For example, those with parasympathetic dominant autonomic function will be “pushed over the edge” by oncoming storms, resulting in lethargy, increased pain, orthostatic hypotension, and depression. Sympathetic dominant individuals would experience euphoria and insomnia. Like Dr. Sulman, Dr. Persinger notes that there is a predominance of women among the weather sensitive.

Many people with CFS/ME and FM note a definite worsening of symptoms, including anxiety, myalgia, headache, inflammation, and insomnia just before storms and the passing of weather fronts, particularly during conditions of low barometric pressure and high humidity. Many also note a worsening of symptoms during hot weather. We are not aware of anyone with CFS/ME who has been tested for serotonin, histamine, or adrenal hormone levels in the urine before a storm or during hot or cold weather, so it cannot be certain that altered hormone levels cause the weather sensitivity experienced by people with CFS/ME. However, many of Dr. Sulman's findings support what is known about hormonal irregularities caused by CFS/ME, as do those of Dr. Persinger.

Some people, paradoxically, may actually feel better before a storm. It is possibly that increased serotonin levels—or, more likely, the constriction of blood vessels (leading to a rise in blood pressure) due to changes in barometric pressure—may contribute to increased energy. Some CFS/ME patients report that they can tell a storm is coming if they feel an urge to clean off their desks, do taxes, or pay bills that have been accumulating. This may, in fact, be the only benefit of weather sensitivity, so these individuals should make hay while the sun shines – or doesn't, in this case.

#### TREATMENT TIPS

To minimize the effects of impending storms, Dr. Sulman recommends avoiding sources of positive ionization (forced-air heating and cooling, friction between synthetic fabrics, and air pollution) as much as possible. Exposure to negative ions is also helpful. Ionizing machines can be purchased to increase negative ion ratios in your bedroom. However, make sure to read product descriptions carefully. Dust-removing ionizers, because they produce ozone and nitrous oxide, may, in fact, worsen health problems. If you are interested in purchasing a negative-ion ionizer, look for an ozone-free product. (These generally run about \$125.)

Some essential oils reputed to increase the effectiveness of negative ions are cypress, lemon, orange, bergamot, pine, bois de rose, cedarwood, grapefruit, pettigraïne, patchouli, and sandalwood. For people with SAD (seasonal affective disorder), full-spectrum lightbulbs and light boxes can be purchased.

For people sensitive to humidity, it may be worthwhile to purchase a dehumidifier for the bedroom. Air-conditioning systems also reduce the amount of humidity inside the house. Although Dr. Sulman cautions against forced-air cooling, sometimes the relief brought by the decrease in humidity offsets any negative effects of the machinery. For all types of weather sensitivity, it is important to be aware of impending storms and fronts. Listen to weather forecasts and keep a log of symptoms before weather changes to see which ones produce the most severe effects. Plan to take it easy on those days.

#### FURTHER INFORMATION

*Intellicast.com is a detailed weather service that not only includes current weather for any location on earth, but provides hourly changes in barometric pressure, temperature, and humidity over the previous 48 hours. This can be enormously useful for people who wish to track weather-related symptoms.*

<http://www.intellicast.com/>

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*This site provides good general information about barometric pressure and pain.*

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## WEIGHT LOSS OR GAIN

Weight fluctuations are common in CFS/ME. In the acute phase of the illness, and during relapses, weight loss is the rule, while in long-term cases there is a tendency to gain weight easily.

There are many competing theories to explain weight fluctuation in people with CFS/ME. Increases and decreases in weight can occur as the result of faulty cell metabolism, immune system overactivation, hypothyroidism or hypoadrenalism, loss of appetite due to excess catecholamine production (adrenaline), gastrointestinal upset, and carnitine deficiency. Hypothalamic dysregulation is, in all likelihood, the prime reason for weight fluctuation. The hypothalamus regulates the autonomic nervous system, which is responsible for all the unconscious aspects of maintaining homeostasis.

Essentially, the non-enteric aspects of the autonomic nervous system are divided into two components, sympathetic and parasympathetic. Sympathetic activation increases “fight or flight” responses, through the action of norepinephrine, while parasympathetic activation allows for digestion, slows heart rate, and facilitates the necessary resting activities of the body. There is evidence that weight loss is characterized by increased sympathetic activity, while weight gain is characterized by increased parasympathetic activity. Another function of the hypothalamus is to release leptin, the hormone that signals the body when it has eaten enough. Damage to the hypothalamus, or resistance to leptin, could result in continuing hunger, even after a meal has been eaten.

Experiments performed on rats over 50 years ago demonstrated that damage to the ventro-medial hypothalamus resulted in obesity, whereas electrical stimulation to the same region produced anorexia. More recent research has proposed that alterations in neurotransmitter activity in the hypothalamus, (specifically norepinephrine), are ultimately responsible for appetite.

The hypothalamus also controls thyroid and adrenal function, which have been shown to be abnormal in CFS/ME patients, as well as regulating aspects of the immune system. Since hypothalamic dysfunction is central in producing many other CFS/ME anomalies, there is good reason to suspect its involvement in appetite disorder and weight problems associated with this illness.

## WEIGHT LOSS

The sudden weight loss common in the acute stages of CFS/ME can be dramatic. First, surface fat reserves, then muscles seem to simply disappear. The reasons for the rapid weight loss are multiple. Many symptoms common in the acute stage (loss of appetite, gastrointestinal upset, changes in taste perception, exhaustion, difficulty swallowing, nausea, vomiting) are related to stimulation of the sympathetic nervous system. This results in a profound reduction in caloric intake. Lowered intake reduces the supply of available vitamin B complex, which in turn diminishes appetite. As intake is further reduced, nutritional deficiencies become established, leading to continuation of the vicious cycle.

Lack of food intake is not the only reason people lose weight in this stage. Immune system overactivity, in particular the expression of tumor necrosis factor (TNF), a cytokine released by activated T cells, causes severe weight loss. Dr. Nancy Klimas has found increased expression of tumor necrosis factor in patients with CFS/ME (*Journal of Chronic Fatigue Syndrome*, 1995). In theory, the acute stage of the illness, when the immune system is overactive, may produce sudden weight loss due to the increased production of tumor necrosis factor. This is true even for patients who eat copious amounts of food.

CFS/ME patients have remarked that when their weight loss ends, and they begin to regain some of the weight they have lost, they see a general improvement in symptoms. Perhaps, this is due to the fact that regaining weight signals the end of the acute phase of the illness and the beginning of more stable metabolic processes.

## TREATMENTS

Treatments that have been helpful in acute-stage weight loss include alpha ketoglutarate (a citric acid metabolite that halts wasting syndrome), L-carnitine, vitamin B complex, and general nutritional supplementation. Ensure, protein powders, and shakes are also effective in increasing weight. Antidepressants, mild tranquilizers (benzodiazepines), stress-reduction techniques (hypnosis, meditation) can all help increase appetite. Acupuncture is particularly effective in increasing appetite, and may be an attractive alternative to supplements for those with digestive system problems.

## WEIGHT GAIN

Several theories have been proposed for the weight gain typical of the chronic stage of CFS/ME. One is that thyroid function is reduced, leading to generally slower metabolism, constipation, drowsiness, and a tendency to gain weight. Given the well-known disturbances in endocrine function in people with CFS/ME, subclinical and borderline cases of hypothyroidism may well be the cause of many cases of weight gain.

A widely held theory is that along with altered cell metabolism (due to blocks in the Krebs cycle) comes an inability to utilize fat and carbohydrates. The L-carnitine deficiencies observed in CFS/ME seem to bear this theory out. The inability to utilize carbohydrates leads to their storage as fat in the body. Reduced levels of glucose resulting from insufficient carbohydrate metabolism can also produce carbohydrate craving. The late-afternoon sugar and starch cravings experienced by so many people with CFS/ME can lead to overeating and the consequent storage of underutilized carbohydrates as fat.

Leptin resistance has also been proposed as a possible cause of weight gain in people with CFS/ME. When fats are consumed, the hypothalamus releases leptin, which reduces appetite. Dr. Shoemaker has proposed that the weight gain in people with biotoxin illness (including FM and CFS/ME) is caused by leptin resistance, that is, an inability to respond to circulating leptin. Those with leptin resistance experience ravenous hunger, a frequently heard complaint in the CFS/ME community.

Another theory proposes that the weight gain in CFS/ME is largely due to edema, that is, water weight. According to this theory, water weight buildup is due to adrenal insufficiency, with adrenal hormones the agents responsible for regulating water retention. Because secondary adrenal insufficiency has been noted in CFS/ME, this theory is also relevant.

A number of the drugs prescribed for people with CFS/ME can lead to weight gain. These include antidepressants (with the exception of bupropion), beta blockers, Benadryl, Benicar, anticonvulsants (gabapentin, Topamax, Lamictal), and corticosteroids. In many cases there are alternative treatments that do not lead to weight gain. These should be explored with your doctor if weight gain due to pharmaceuticals is a problem.



One of the biggest concerns associated with weight gain is loss of self-esteem. Given the emphasis our society places on being thin, weight gain can be a major source of depression – all the more so because physicians routinely recommend exercise as the best way to lose weight. As exercise can exacerbate CFS/ME symptoms, this can lead to a feeling of being “boxed in” by the illness. Patients who, in addition to their illness, have to cope with a profound change in appearance often feel as if insult has been added to injury. Sometimes it helps to remember that the increase in weight is not due to personal shortcomings, but is a symptom of an illness. As the illness recedes and other symptoms wane, your weight will return to normal.

## TREATMENTS

*CAUTION: Many people with CFS/ME are sensitive to stimulants, the class of drug most commonly prescribed for weight loss. Side effects of weight loss drugs include dry mouth, diarrhea, nausea, weakness, anxiety, insomnia, dizziness, and gastrointestinal pain. The herbal equivalents of ephedrine, ephedra and ma huang, can produce similar side effects.*

Even though most weight problems in CFS/ME patients are not due to overeating, maintaining good dietary habits is essential. Pay careful attention to eating a wholesome, nutritious diet, even within the confines of food restrictions (see Food and Diet).

Some clinicians recommend taking the supplement L-carnitine for weight loss. L-Carnitine helps convert fat into muscle, which is beneficial for people who gain a lot of weight while ill. However, it should also be noted that CFS/ME patients with low-weight problems have gained weight while taking L-carnitine supplements. It is possible that L-carnitine acts to normalize weight.

The mineral chromium, taken at low doses, may help curb sugar cravings, as can the amino acid L-glutamine. (L-glutamine is an excitatory amino acid, and therefore should not be taken by people with sensitivities to stimulants.)

SEE: Endocrine Problems; Antidepressants; Amino Acids (Carnitine, Glutamine); Acupuncture, Hypnosis; Food and Diet.

## FURTHER READING

Wurtman, Judith J. *The Serotonin Solution*. New York: Fawcett Columbine, 1996. *An interesting and informative discussion of the role of serotonin in carbohydrate cravings; several chapters outline diet recommendations for specific problems.*

## RESEARCH

Arone LJ , Mackintosh R, Rosenbaum M, Leibe RL, Hirsch J. "Autonomic nervous system activity in weight gain and weight loss." *Am J Physiol*. 1995 Jul;269 (1 Pt 2):R222-5. <http://www.ncbi.nlm.nih.gov/pubmed/7631897> (Abstract)

## PART III: TREATMENT OPTIONS

The following chapters summarize the treatments currently used for CFS/ME and its major symptoms. For the sake of convenience, treatments are divided into three categories.

1. *Pharmaceutical agents.* These include all prescription and over-the-counter drugs currently recommended by CFS/ME clinicians. All of these treatments must be supervised by a physician, regardless of whether or not a prescription is required. The information in this chapter can be used to make preliminary investigations of medications referred to in the CFS/ME literature, to increase knowledge of medications suggested by physicians, or to inform physicians about currently used CFS/ME medications.
2. *Nutritional supplements and botanical agents.* These can be purchased without a prescription from health food stores, online vitamin suppliers, and some drugstores and supermarkets. The information in this chapter can be used to plan any treatment protocol designed with a nutritionist, chiropractor, osteopath, naturopath, herbalist, or physician.
3. *Alternative and complementary medical and supportive therapies.* Adjunct therapies are often useful in treating CFS/ME. Many, such as acupuncture, require the services of a trained practitioner. This chapter also presents information about many of the supportive therapies that have been used successfully to alleviate symptoms of CFS/ME.

The fact that these treatments are presented in separate chapters does not mean they must be kept separate in practice. Most CFS/ME clinicians use an eclectic approach, freely combining nutritional supplements, complementary and alternative medical practices, and conventional pharmaceutical-oriented medicine. Most patients with CFS/ME use the same strategy. With the plethora of symptoms and the ever-changing nature of CFS/ME, flexibility is the best policy.

## TREATMENT TIPS

- *Start small.* People with CFS/ME tend to be sensitive to many medications. By starting with small doses, the risk of negative reactions is minimized. A patient can always build up to a larger dose. CFS/ME clinicians nearly always start patients on a much lower than normal dosage for prescription medications.
- *Go slow.* Try one treatment at a time. Otherwise it will be impossible to identify which treatment was effective and which was not. Remember, many treatments, especially non-pharmaceutical treatments, may require several weeks to take effect.
- *Recycle.* During the different stages of the illness, treatment strategies will need to change appropriately. What was not effective at an earlier stage in the illness may be helpful at a later one. Don't throw away supplements or pharmaceutical agents. Store them in the refrigerator, but remember to check the expiration dates before using them.

We hope that somewhere among these pages will be a remedy that alleviates your worst symptom, or that helps you progress so that you can see the light at the end of the tunnel. Remember, keep trying. In the world of CFS/ME treatments, persistence pays.

## USEFUL RESOURCES

Partnership for Prescription Assistance

Phone: (888) 477-2669

Website: <http://www.pparx.org/>

“The Partnership for Prescription Assistance has assisted nearly seven million people in the medicines they need for free or nearly free.”

Rx Assist's List of Patient Assistance Programs.

Website: <http://www.rxassist.org/pap-info/default.cfm>

“RxAssist is a nationally recognized, web based medication assistance resource center. Established in 1999 with funding from The Robert Wood Johnson Foundation, RxAssist gives providers, advocates, consumer and caregivers comprehensive, up-to-date information in an easy to use format.”

Free Medicine Program

Website: <http://freemedicineprogram.org/>

“Our mission at the Free Medicine Program is helping patients in obtaining prescription drugs and medications absolutely Free of charge.”

BenefitsCheckUp

Website: <http://www.benefitscheckup.org/>

*BenefitsCheckUp is a free service of the National Council on Aging to help adults over 55 find help with prescriptions and other basic necessities. From the website:* “There are over 2,000 federal, state and private benefits programs available to help adults over 55. But many people don’t know these programs exist or how they can apply.”

The Medicine Program

Website: <http://www.themedicineprogram.com/>

*The Medicine Program is a patient advocate organization and is a free service. Our goal is to assist you and your family find, apply and qualify for the right Patient Assistance Program(s). By working closely with you, your doctor and the drug manufacturers we help cut through the red tape and assist you in receiving your medicine free-of-charge.”*

Needy Meds

Website: <http://www.needy meds.org/>

*The mission of NeedyMeds is to make information about assistance programs available to low-income patients and their advocates at no cost. Databases such as Patient Assistance Programs, Disease-Based Assistance, Free and Low-Clinics, government programs and other types of assistance programs are the crux of the free information offered online.*

## Rx Hope

Website: <https://www.rxhope.com/>

*Rx Hope specializes in helping small, emerging pharmaceutical companies manage their Patient Assistance Programs. From the website: “As an integral part of the Triplefin group of companies, we are a highly professional team of caring and concerned people dedicated to making the patient assistance process as easy and comfortable as possible for the patient, the healthcare provider and the pharmaceutical company.”*

## Ask a Patient

Website: <http://www.askapatient.com/>

*This is the best website for patient reviews of medications. “When you really want to know if a medication really works, why not ask a patient?”*

## AMPLIGEN

**DESCRIPTION.** Ampligen (poly I:poly C12U) is a mismatched double-stranded RNA (ribonucleic acid) with immunomodulatory and antiviral properties. Because Ampligen has not yet been approved by the Food and Drug Administration (FDA), its use to date has been experimental.

**BACKGROUND.** In the early 1980s, a molecule called Poly(I)-Poly(C) was discovered to inhibit tumor growth and stimulate interferon production. As a result, it was used in a number of cancer trials. However, it was found that the substance made patients quite ill with serious side effects. While Poly(I)-Poly(C) was extremely toxic, the toxicity decreased significantly when the structure of the RNA was altered. Fortunately, the effectiveness of the new substance (Ampligen) was not diminished, despite the change in structure.

In 1987 Ampligen was used experimentally in a small group of patients with AIDS (acquired immunodeficiency syndrome). The positive results of this trial seemed to confirm the claim that Ampligen works by enhancing natural killer cell function and influencing the 2-5A synthetase pathway. This pathway is vital in the defense against viral infections. According to Dr. Robert Suhadolnick of Temple University in Philadelphia, there are defects in key components in the antiviral system in some CFS/ME patients, the most notable of which are low latent 2-5A synthetase and upregulated RNase (ribonuclease) L activity (*Journal of Interferon and Cytokine Research*, 1997). Ampligen is thought to correct both of these defects.

**USES IN CFS/ME.** In August 1988, Dr. Daniel Peterson, a pioneer in CFS/ME treatment, was the first physician to use Ampligen on an extremely ill patient with CFS/ME. Because of the severity of the patient's illness, Dr. Peterson was able to obtain permission from the FDA to use Ampligen under compassionate care status. The results were impressive and encouraging. One year into therapy the patient had recovered near-normal function in some areas and demonstrated a 46-point increase in IQ. This justified the next pilot study by Dr. Peterson, as well as several other formal studies conducted independently.

At the 1990 CFIDS Conference in Charlotte, North Carolina, and at the Cambridge Symposium, Dr. Peterson reported positive results after treating 15 patients with Ampligen. At the end of 24 weeks, most of the patients demonstrated increased performance status (using Karnofsky scores) and exercise tolerance (as measured by treadmill testing). Cognitive improvement was demonstrated by improved memory and increased IQ scores. No significant toxicity was reported. Ampligen's antiviral properties were confirmed by evidence that human herpesvirus 6 (HHV-6) reactivation was absent after treatment and abnormal components of the 2-5A pathway returned to normal range. It is of interest that of the two or three patients who did not respond to Ampligen therapy, the only significant pretreatment difference was measurable differences in 2-5A synthetase pathways.

The encouraging results of Dr. Peterson's study paved the way for a larger FDA-approved double-blind study in 1991 involving 92 patients in four U.S. cities. Again the results were encouraging. Many of the participants had been severely disabled before treatment and required assistance for simple daily activities. More than half of those in the study who received Ampligen demonstrated improvement and many were able to carry out daily activities with minimal assistance.

A study in Brussels, Belgium, presented at the 1996 American Association for Chronic Fatigue Syndrome (AACFS) Conference, to evaluate the safety and efficacy of intravenously administered Ampligen also showed encouraging results. Eleven patients with myalgic encephalomyelitis (ME) were given intravenous Ampligen twice a week for 24 weeks. The Belgian physicians reported that at the end of 24 weeks, all 11 experienced some improvement. In addition, no adverse effects to treatment were noted. These positive results paved the way for expanded trials. It was hoped that with an expansion of clinical trials to Canada and Belgium, and Ampligen's subsequent approval for Canada's Emergency Drug Release Program, that the drug would soon be approved for use in the U.S.

Unfortunately, since 1996 little progress has been made in obtaining FDA approval of the drug. A seemingly endless series of lawsuits, missed deadlines and administrative setbacks effectively quashed the widespread support the drug had enjoyed in the 90s. To cap the matter, in 2009, after the completion of Phase III of Ampligen's drug trials, the FDA refused to grant Ampligen "new drug," status which, in effect, relegated Ampligen once more to clinical trials.

**PROTOCOL.** Because this drug is still, after more than twenty years, in the trial phase, treatment protocols are still evolving. Ampligen is quite fragile, which makes administration difficult (it must be given intravenously). Two intravenous injections a week of 400 mg are given over a 6- to 12-month period, though some doctors recommend a course of treatment up to 18 months for more severely ill patients. Longer courses of treatment seem to produce longer lasting results.

**PROS.** No other drug has received more attention from the CFS/ME community than Ampligen. But even in the wake of delays, reversals and lawsuits, many doctors still defend Ampligen as the most effective drug for those patients who have acute viral onset, persistent herpesvirus infections, depressed natural killer cell function, and 2-5A synthetase/RNase L up-regulation. For those who have

been bedridden for years, who are confined to wheelchairs, and whose lives have lost all semblance of normality, Ampligen may be a godsend, and the frustration of those who have experienced a return to a functional life during Ampligen trials, only to have it taken away again at the end of the trial, is more than justified.

Dr. Kenny DeMeirleir claims that close to 80% of his patients reported “complete clinical recovery” after taking an extended course of treatment. Patients report improvement in overall function, energy levels, cognitive performance, and some have been able to return to work. Dr. Lapp, who has been using Ampligen since 1998, reports significant improvement in 50% of his severely ill patients. It is important to note that while few doctors claim that Ampligen works for the majority of their patients, it seems to have a very positive effect on a subset of those who are the most seriously ill, and that, in and of itself, provides a good reason for Hemispherx to pursue Ampligen's final approval.

CONS. Although test results are encouraging, it is important to note that Ampligen is not a surefire cure. The percentage of patients who demonstrate substantial improvement with the drug has yet to be determined. Side effects are common. Although Hemispherx maintains that Ampligen is generally well tolerated, patients have reported diarrhea, constipation, flushing, temporary vision loss, muscle aches, depression, loss of libido, dizziness, chills, fever, malaise, anxiety, and loss of energy.

Dr. Peterson reported at the 1990 CFIDS Conference that some patients experienced an interferon-like reaction, with headaches, myalgias, and, rarely, hair loss. A puzzling effect noted by Dr. Paul Cheney was that although patients report overall lessening of symptoms, particularly cognitive symptoms, they do not necessarily equate this lessening of severity to “feeling good” (*CFIDS Chronicle*, Physicians Forum, 1991). Side effects usually subside after several months, but that may be too long for many patients to endure.

AVAILABILITY AND COST. As of 2011, Ampligen is available only at Dr. Lapp's Hunter-Hopkins clinic in Charlotte, NC, and Dr. Peterson's Lake Tahoe clinic under an open-label trial. (An open-label trial is one in which all patients receive, and pay for, the drug.) Dr. Bateman's Fatigue Consultation Clinic in Salt Lake City and Dr. Enlander's clinic in New York have also begun to seek recruits for an open-label trial. Hemispherx is planning to add several other sites around the U.S., as well as sites in Mexico and Argentina. In July 2012, Hemispherx announced that it had submitted a new drug application to ANMAT (Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica), the agency responsible for the national regulation of drugs, foods and medical technology in Argentina, under the ANMAT's Orphan Drug regulations.

Ampligen is quite expensive. A single infusion costs \$150. At two infusions a week, that amounts to \$1200 per month. Additional costs, such as medical visits, lab work and the administration of the infusions, can amount to \$1000 a month. Altogether, one year of treatment will cost over \$24,000. Patients must pay for the cost of the treatment because Ampligen is available on a cost recovery basis only. Some insurers will reimburse for administration costs and lab work, which can save

roughly \$12,000 a year. Medicare does not cover any expenses for investigational therapies.

## MORE INFORMATION

*The Hunter-Hopkins Center's report from the 9<sup>th</sup> Hemispherx Biopharma investigators meeting. Quite technical but very thorough:*

<http://www.drlapp.net/meLetterMar2011.htm>

*NIH webpage on clinical trials. Shows current status of Ampligen trials.*

<http://www.clinicaltrials.gov/ct2/show/NCT00215813?term=00215813&rank=1>

*Informative thread on patients' experiences with Ampligen.*

<http://forums.phoenixrising.me/showthread.php?12999-Ampligen-Experiences>

*Dr. Lapp's Ampligen protocol:* <http://www.drlapp.net/ampligen.htm>

*Hemispherx Biopharma's page on Ampligen.*

[http://www.hemispherx.net/content/rnd/drug\\_candidates.htm](http://www.hemispherx.net/content/rnd/drug_candidates.htm)

*A fascinating blog written by a New Zealand journalist who moved to the U.S. to participate in an open-label Ampligen trial:* <http://ampligen-treatment.blogspot.com/>

*San Francisco Ampligen trial (with prices):*

[http://phoenixrising.me/forums/showthread.php?12305-Ampligen-Treatment-Study-\(AMP-511\)-starting-in-San-Francisco-Bay-Area](http://phoenixrising.me/forums/showthread.php?12305-Ampligen-Treatment-Study-(AMP-511)-starting-in-San-Francisco-Bay-Area)

*ProHealth's history of Ampligen:*

<http://aboutmecfs.org.violet.arvixe.com/Trt/AmpHist.aspx>

*Cort Johnson's up-to-date news on the status of Ampligen:*

[http://phoenixrising.me/archives/8819?utm\\_source=newsletter+subscribers&utm\\_campaign=9dd3ad21ce-April Newsletter4 28 2012&utm\\_medium=email](http://phoenixrising.me/archives/8819?utm_source=newsletter+subscribers&utm_campaign=9dd3ad21ce-April+Newsletter4+28+2012&utm_medium=email)

## ANTIBIOTICS

**DESCRIPTION.** Antibiotics (derived from the Greek *anti* meaning 'against', and *bios* meaning 'life') are substances that either kill microbes or inhibit their growth.

**BACKGROUND.** As with so many monumental discoveries, antibiotics are the result of a mistake. In 1928, Alexander Fleming, a brilliant (but messy) Scottish biologist, was investigating the properties of the bacterium *staphylococcus*. He had left his samples piled up on a bench before going away on holiday. When he returned, he discovered that one of the petri dishes had been invaded by mold, and that the bacteria that had come into contact with the mold had died. After overcoming his initial annoyance, Fleming realized that he had stumbled across a remarkable substance. He named it penicillin.

Since Fleming's remarkable discovery, antibiotics have become an integral feature of modern medicine. Their ability to kill bacteria and protozoa has saved millions of lives worldwide, making them one of the medical miracles of our time. However, Fleming noted that when antibiotics were used at too low a dose, or for too little time, the bacteria would become resistant. With the passage of time, it turned out that bacteria become resistant even with the proper administration of



antibiotics. (Any microbe will adapt to a changing environment, producing, in the end, a stronger version.) This has led to the development of ever-stronger antibiotics, which, inevitably, have produced “super bugs” – bacteria which are resistant to all antibiotic therapy.

Basically, antibiotics kill bacteria by inducing oxidative stress. This is the same mechanism through which many parts of the immune system kill bacteria. Given the fact that bacteria are living organisms, it should not come as a surprise that bacteria utilize many of the same mechanisms to protect themselves from oxidative stress as do other cells. A recent study led by Evgeny Nudler, a professor of biochemistry at New York University, showed that nitric oxide (NO) produced by bacteria neutralizes many antibacterial compounds. By using NO's ability to destroy attackers, bacteria cleverly employ the body's own defense mechanisms to ward off the effects of antibiotics.

**USES IN CFS/ME.** The idea that CFS/ME is caused by a “bug” is not a new one. As early as the 1930s it was thought that CFS/ME (then called “atypical polio”) was caused by an enterovirus. The close association with Epstein-Barr virus (EBV) and other endemic viruses, as well as well-documented high levels of viral markers in CFS/ME patients, has led researchers to conclude that the illness is caused by a virus. However, a small, but significant, number of researchers has proposed the active involvement of bacteria in the development of CFS/ME.

One of the first researchers to propose a causal role for bacteria was Garth Nicolson. Nicolson found that both CFS/ME and Gulf War Syndrome (GWS) patients were infected with mycoplasma. (Mycoplasma are bacteria that lack a cell wall, and are thus impervious to many antibiotics). Nicolson proposed that ongoing mycoplasma infections were responsible for many immunological anomalies associated with both CFS/ME and GWS. He successfully treated GWS and CFS/ME patients with long courses of different antibiotics to eradicate mycoplasma infections. In a subsequent study, Nicolson found that many patients diagnosed with CFS/ME were subsequently diagnosed with Lyme Disease, which is caused by a rickettsial bacterium.

Several fascinating studies have indicated a causative role for rickettsial and chlamydial bacterial infections in CFS/ME. Phillippe Bottero, a French doctor practicing in Paris, found that all of his CFS patients tested positive for bacterial infections. An impressive 78.5% of Bottero's 98 CFS patients improved significantly after treatment with antibiotics. (His article is in *Chronic Fatigue Syndrome: Critical Reviews and Clinical Advances*). A smaller second group, composed of patients diagnosed with ADHD, schizophrenia and autism also showed a similar rate of improvement. Bottero proposed that due to the long survival of rickettsial infections in vascular linings, the resulting vasculitis could produce many of the symptoms common in CFS/ME.

Cecile Jadin, a Belgian surgeon, also found strong correlations between rickettsial infections and patients diagnosed with CFS/ME. Jadin reversed symptoms in five hundred patients previously diagnosed with CFS, FM, MS, depression, heart disease, and psychosis with a simple course of tetracycline.

In 2009 Frykholm found that ninety days of treatment with antibiotics, combined with vitamin B injections, cured one of his CFS/ME patients. When two patients with long-standing and incapacitating CFS/ME came to his clinic in 2007 he treated them both with antibiotics. After sixty days the first showed excellent improvement which continued on follow-up one year later, whereas the second, who also took antibiotics for sixty days, showed a significant improvement. While studies of this kind may ultimately raise more questions about the process of diagnosis than to etiology, it is nonetheless interesting to consider the role that bacterial infections play in perpetuating, if not causing, CFS/ME.

In the 1990s, Luther Lindner, a pathologist at Texas A&M, believed he had found the elusive agent that was the cause of CFS/ME, as well as other autoimmune diseases. While examining the blood of an MS patient, he found a novel bacterium. Lindner then identified the bacterium in the blood of patients with CFS/ME. Though the prospect of having discovered a potential cure for the illnesses was exciting, Lindner was cautious in his treatment recommendations. For while he noted good short-term response in CFS/ME patients, he also noted that the new strain was highly resistant to antibiotic treatment. Lindner cautioned against the use of antibiotic regimens without monitoring the number of organisms present. Paradoxically, he also found that “antibiotics can actually stimulate bacterial growth and make the patient worse.” He added that this can usually be predicted by sensitivity testing. Indeed, Lindner's theories may be borne out by the significant number of CFS/ME patients who report having taken long courses of antibiotics before falling ill.

An entirely different role for antibiotics as a CFS/ME treatment was explored by Vermeulen and Scholte. In their retrospective study of 99 CFS/ME patients, 58 patients reported a decrease in symptoms after taking azithromycin. All of the responding patients had low levels of acetylcarnitine. The authors concluded that “the efficacy of azithromycin in the responsive patients could be explained by the modulating effect on a chronic primed state of the immune cells of the brain, or the activated peripheral immune system. Their lower acetylcarnitine levels may reflect a decreased antioxidant defense and/or an increased consumption of acetylcarnitine caused by oxidative stress.” In short, the azithromycin was functioning as an immune system modulator in these cases, rather than as a bactericide.

**PROTOCOL.** Most CFS/ME physicians prescribe antibiotics when there is a clear indication of a bacterial infection. However, there are some protocols that involve low-dose antibiotics as part of an overall treatment strategy. The Marshall Protocol uses pulsed low-dose antibiotics to treat CFS/ME even in the absence of an active bacterial infection.

Dr. Teitelbaum also uses antibiotics to treat hidden infections. These are indicated if the patient has chronic lung congestion, low fever, recurrent scalp sores, a history of a bad reaction to other antibiotics, transient improvement with antibiotics, vertigo, and severe night sweats. In these instances, Dr. Teitelbaum assumes the presence of a bacterial infection that may be difficult to detect (e.g.,

Lyme, mycoplasma, chlamydia) and recommends a long course of antibiotics. Dr. Nicolson's course of antibiotic treatment can last as long as two years.

PROS AND CONS. CFS/ME patients report that antibiotics of various kinds can both exacerbate and improve symptoms. Common side effects include nausea, “brain fog”, and GI disturbances. Most CFS/ME patients find that they do better “pulsing” with low-dose antibiotics, and that longer courses of treatment are either ineffective or cause relapse. Some report that after initial “miraculous” improvement, they became much worse. A small number of patients have reported dramatic improvement.

#### FURTHER READING

“Study explains bacteria's resistance to antibiotics.” *AFP* Sept 13, 2009.

<http://www.google.com/hostednews/afp/article/ALeqM5jbBIAufNyKV0owj4rc08LmSA5GKg>

*Technical article explaining the mechanisms of antibiotics*

[http://www.bu.edu/abl/files/nrm\\_kohanski.pdf](http://www.bu.edu/abl/files/nrm_kohanski.pdf)

*Garth Nicolson's article on the role of bacterial infections in CFS/ME and Gulf War Syndrome.* [http://www.immed.org/illness/fatigue\\_illness\\_research.html](http://www.immed.org/illness/fatigue_illness_research.html)

*Garth Nicolson's antibiotic protocols*

<http://www.newtreatments.org/doc/Mycoplasma/12>

*Good summary of Nicolson's theories and protocols*

<http://www.rense.com/general7/microplasm.htm>

*Doris Jones proposes that antibiotics may be the cause of CFS/ME.*

[http://www.prohealth.com/fibromyalgia/blog/boardDetail.cfm?id=1015520&b1=C\\_HWEBO](http://www.prohealth.com/fibromyalgia/blog/boardDetail.cfm?id=1015520&b1=C_HWEBO)

*ringing in ears caused by minocycline*

<http://forums.phoenixrising.me/showthread.php?9291-Minocyclin>

*Article on Luther Linder's research:* <http://ottem.org/ccca/news/newsletters/vol16-1.htm>

*Luther Lindner's explanation of why antibiotics might potentially make CFS/ME worse.* <http://www.thisisms.com/forum/antibiotics-f28/topic572.html>

*Marshall Protocol and pulsed, low-dose antibiotics*

[http://mpkb.org/home/protocol/mp\\_antibiotics](http://mpkb.org/home/protocol/mp_antibiotics)

*Dr. Teitelbaum on the use of antibiotics in CFS/ME*

[http://www.endfatigue.com/health\\_articles\\_f-n\\_2/Infections-treating\\_hidden\\_antibiotic\\_cfs\\_fm.html](http://www.endfatigue.com/health_articles_f-n_2/Infections-treating_hidden_antibiotic_cfs_fm.html)

#### RESEARCH

Frykholm BO. “On the question of infectious aetiologies for multiple sclerosis, schizophrenia and the chronic fatigue syndrome and their treatment with antibiotics.” *Med Hypotheses*. 2009 Jun;72(6):736-9.

<http://www.ncbi.nlm.nih.gov/pubmed/19269110> (Abstract)

Nicolson, Garth L, Nancy L. Nicolson, and Joerg Haier. “Chronic Fatigue Syndrome Patients Subsequently Diagnosed with Lyme Disease *Borrelia burgdorferi*:

Evidence for Mycoplasma species Co-Infection.” *Journal of Chronic Fatigue Syndrome*. 2008; 14(4): 5-17.

<http://www.lymepa.org/Chronic%20Fatigue%20Syndrome%20patients%20subsequently%20diagnosed%20with%20Lyme%20disease%20and%20coinfections.pdf>

Vermeulen RC, Scholte HR. “Azithromycin in chronic fatigue syndrome (CFS), an analysis of clinical data.” *J Transl Med*. 2006 Aug 15;4:34.

<http://www.ncbi.nlm.nih.gov/pubmed/16911783>(Abstract)

## PATIENT REVIEWS

*CFS/ME patient reviews of doxycycline:* <http://www.revolutionhealth.com/drugs-treatments/rating/doryx-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Zithromax:* <http://www.revolutionhealth.com/drugs-treatments/rating/zithromax-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Biaxin:* <http://www.revolutionhealth.com/drugs-treatments/rating/biaxin-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of minocycline:* <http://www.revolutionhealth.com/drugs-treatments/rating/minocin-for-chronic-fatigue-syndrome-cfs-cfids-me>

## BOOK

Patarca Montero, Roberto and Kenny De Meirleir. *Chronic Fatigue Syndrome: Critical Reviews and Clinical Advances*. Informa Healthcare; 1st edition (October 30, 2000).

## ANTICONVULSANTS

Gabapentin (Trade name: Neurontin), Gabitril, Lyrica (pregabalin)

Anticonvulsants are used to treat seizure disorders (epilepsy). More recently, they have been used to treat neuropathic pain, anxiety and insomnia. The most commonly prescribed anticonvulsants for CFS/ME are Neurontin (generic: gabapentin), Gabitril, and Lyrica (pregabalin).

## FURTHER READING

*Maija Haavisto's website:* <http://maija-haavisto.suite101.com/anticonvulsants-cfsme-and-fm-a65954>

*Good overview of the use of anticonvulsants for CFS/ME and FM.*

## GABAPENTIN (NEURONTIN)

**DESCRIPTION:** Gabapentin (trade name: Neurontin) is a GABA (gamma aminobutyric acid) analogue used to treat epilepsy.

**BACKGROUND.** GABA is the chief inhibitory neurotransmitter in the nervous system. Basically, nerves have only two responses to stimuli—either they fire, or they don't. The role of GABA in the nervous system is to prevent neurons from firing, essentially turning them off. As the nervous system depends on a

balance of chemicals that promote firing (excitatory neurotransmitters) and those that don't (inhibitory neurotransmitters), GABA serves an essential regulatory function. Without GABA too many neurons would fire at once, resulting in seizures.

Neurontin was originally approved by the FDA for the treatment of epilepsy. However, since its approval, it has been marketed for many off-label uses, including pain, headaches, alcohol and cocaine withdrawal, hiccups, restless leg syndrome, hot flashes and fibromyalgia. In 2004, in one of the biggest lawsuits in pharmaceutical history, Pfizer, the manufacturer of Neurontin, was sued for fraud based on its marketing of the drug for many of these off-label purposes. A second lawsuit claimed that Pfizer engaged in "outright deception of the biomedical community, and suppression of scientific truth." However costly for Pfizer, lawsuits for off-label uses have not prevented doctors from continuing to prescribe Neurontin for insomnia, pain, anxiety disorders, and diabetes.

**USES IN CFS/ME.** Dr. Jay Goldstein (now retired) was one of the early proponents of Neurontin as a CFS/ME treatment. His theory was that the brain needed to be "reset" in CFS/ME patients, and to accomplish that goal, he used Neurontin. Dr. Seastrunk, a psychiatrist in Texas, believed that Neurontin helped minimize focal brain injury in CFS/ME and FMS patients. Dr. Cheney has also included Neurontin in his treatment protocol, believing that it exerts a protective effect on the brain.

In 2007, research supported by the National Institutes of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases showed that gabapentin can be an effective treatment for fibromyalgia. In a randomized, double-blind trial of 150 patients with FM, researchers found that patients taking daily doses of 1,200 to 2,400 mg of gabapentin experienced significantly less pain than those taking placebo.

**PROTOCOL.** Dr. Goldstein recommended a total daily dose of 5,000 mg (if lower doses were not beneficial). However, he first tested his patients with only 100-800 mg for possible reactions. Dr. Seastrunk recommended starting with small doses and increasing to 3,200 mg a day, taken throughout the day. Dr. Cheney's protocol started at 300 mg, taken three times a day. Dr. Teitelbaum recommends beginning with 100-300 mg at night, and slowly increasing up to 300-900 mg taken three times a day.

**PROS AND CONS.** CFS/ME patients report that gabapentin helps with pain and insomnia. However, because gabapentin reduces neuronal firing, it can also produce dizziness, tingling, "brain fog," and a "drunk" feeling. One of the reported side effects is an increase in bladder pain among people with interstitial cystitis. When going off gabapentin, slowly decreasing the dose rather than stopping all at once is advised.

**AVAILABILITY AND COST.** Gabapentin (generic) is available at any pharmacy. It requires a prescription. A 100-tablet bottle (100 mg) costs from \$24 to \$32. Insurance usually covers.

## FURTHER READING

*Good description of the different function that GABA plays in the nervous system.*

<http://www.denvernaturopathic.com/news/GABA.html>

*National CFS/ME foundation's report on Neurontin:* <http://www.ncf-net.org/forum/neurontin98.htm>

“Neurontin and Brain Injury Treatment.” *Dr. Seastrunk's views on Neurontin:* <http://www.ncf-net.org/forum/neurontin98.htm>

“Researchers explore many uses for Neurontin; no CFS/ME trials planned.” *CFIDS Chronicle*, March-April 1999 <http://www.cfids.org/archives/1999/1999-2-article04.asp>

“Gabapentin Shown Effective for Fibromyalgia Pain.” <http://members.boardhost.com/WellnessTrain/msg/1188292455.html>

## RESEARCH

Foldvary-Schaefer N, De Leon Sanchez I, Karafa M, Mascha E, Dinner D, Morris HH. “Gabapentin increases slow-wave sleep in normal adults.” *Epilepsia*. 2002 Dec;43(12):1493-7. <http://www.ncbi.nlm.nih.gov/pubmed/12460250> (Abstract)

Kesselheim AS, Darby D, Studdert DM, Glynn R, Levin R and Avorn J. “False claims act prosecution did not deter off-label drug use in the case of neurontin.” *Health Aff (Millwood)*. 2011 Dec;30(12):2318-27. <http://www.ncbi.nlm.nih.gov/pubmed/22147859> (Abstract)

## PATIENT REVIEWS

*A woman with interstitial cystitis recounts her experience with Neurontin:* <http://www.ic-network.com/iclifestyles/may03.html>

*CFS/ME patient reviews of Neurontin:* <http://www.revolutionhealth.com/drugs-treatments/rating/neurontin-for-chronic-fatigue-syndrome-cfs-cfids-me>

## GABITRIL

**DESCRIPTION.** Gabitril (generic: tiagabine) is a selective GABA reuptake inhibitor used to treat seizure disorders.

**BACKGROUND.** Gabitril was first developed in 1988 by the Danish pharmaceutical company, Novo Nordisk. Currently, it is approved by the FDA for the treatment of partial seizures, although doctors prescribe it for treating panic disorder and neuropathic pain (including fibromyalgia). Gabitril is also used in combination with antidepressants and benzodiazepines for treating anxiety.

**PROTOCOL.** Dr. Goldstein considers Gabitril to be safe and effective at low doses. He cautions that if the dose is increased too rapidly, patients may become delirious or manic.

**PROS AND CONS.** Some patients report that Gabitril is a “wonder drug” for treating insomnia. Patients also report a reduction in pain and fatigue. Other patients report either no effect at all, or excessive sedation. The most frequently reported side effects of Gabitril are sedation, increase in “brain fog,” and gastric upset, and, in doses over 8 mg, tingling (paresthesia) in the hands. Gabitril can

induce seizures in those without previous seizure disorder, particularly in people taking other GABA enhancers.

**AVAILABILITY AND COST.** Gabitril is available with a prescription at pharmacies. It is quite expensive. A 30-tablet bottle (2 mg) costs roughly \$170. Insurance usually covers the cost.

## PATIENT REVIEWS

*CFS/ME patient reviews of Gabitril:* <http://www.revolutionhealth.com/drugs-treatments/rating/gabitril-for-chronic-fatigue-syndrome-cfs-cfids-me>

## LYRICA

**DESCRIPTION.** Lyrica (pregabalin, pronounced “pruh-GA-buh-lin”) is an anticonvulsant used to treat neuropathic pain and partial seizures.

**BACKGROUND.** Lyrica was designed by Richard Silverman, a medicinal chemist at Northwestern University, as a stronger version of gabapentin. Aside from its anti-seizure effects, it is used for post-herpetic neuralgia (shingles), and diabetic peripheral neuropathy. Pfizer has also claimed that Lyrica is useful for treating anxiety. Although Pfizer was later sued for making that claim, Lyrica has been approved in Europe for treating generalized anxiety disorder. In 2010, sales reached \$3,063 million. Lyrica was the first medication approved by the FDA for the treatment of fibromyalgia.

**USES IN CFS/ME.** Lyrica is used mainly as a sleep aid and for pain. While most doctors feel that it is no more effective than gabapentin, the decreased risk of habituation makes it an attractive alternative.

In a study published in the journal *Pediatrics* in 2009, Drs. Felicia B. Axelrod and Dena Berlin successfully treated a small group of children suffering from daily dysautonomic crises with Lyrica. Dysautonomic crises are severe upsets to the sympathetic nervous system, which are characterized primarily by profound nausea and retching, as well as flushing, tachycardia, and excessive production of gastric and pulmonary mucus. After measuring the effects of Lyrica, Axelrod and Berlin found that 53% of the patients experienced a greater than 50% reduction in crises.

While this was a small study, it is highly significant for the CFS/ME community. Dysautonomia is found in 96% of the CFS/ME population, and while not all experience dysautonomic crises, those who do may find relief with Lyrica.

**PROTOCOL.** Physicians start patients with a low dose of Lyrica and increase it gradually. Therapeutic effects appear after one week. Dr. Teitelbaum recommends 50-250 mg a night as a sleep aid.

**PROS AND CONS.** In many respects, Lyrica is similar to benzodiazepines (minor tranquilizers). But, unlike benzodiazepines, effects do not decrease over time. Lyrica does not disrupt sleep cycles, and produces less cognitive impairment than benzodiazepines. It also has a low potential for dependence. Patient reviews of Lyrica are mixed. Some patients have found that it helps enormously with fatigue, while other report it increases fatigue. Most patients report that it helps them more

with pain than any other symptom. Side effects include jitters, dizziness, and nausea.

**AVAILABILITY AND COST.** Lyrica is available at any pharmacy with a prescription. It costs roughly \$3 a pill. Insurance usually covers the cost.

#### FURTHER READING

Axelrod, Felicia B., and Dena Berlin. "Pregabalin: A New Approach to Treatment of the Dysautonomic Crisis." *Pediatrics* 2009;124;74.

<http://pediatrics.aappublications.org/content/124/2/743.full.pdf>

#### PATIENT REVIEWS

*CFS/ME patient reviews of Lyrica:* <http://www.revolutionhealth.com/drugs-treatments/rating/lyrica-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### ANTIDEPRESSANT DRUGS

*CAUTION: The FDA has instituted a "black box" label warning for antidepressants, indicating that antidepressants may increase the risk of suicidal thinking and behavior in some children and adolescents. A black-box warning is the most serious type of warning in prescription drug labeling.*

**DESCRIPTION.** Antidepressant drugs are a class of pharmaceutical products that influence neurochemicals in the brain.

**BACKGROUND.** The National Institute of Mental Health estimates that one in five adults can expect to experience at least one episode of mood disorder in the course of a lifetime. Although antidepressants were developed to treat mood disorders such as anxiety and depression, clinicians have found that the symptoms of many chronic illnesses seem to respond to antidepressant therapy. Antidepressants have been used to treat chronic pain syndromes, migraine headaches, irritable bowel syndrome, bladder and urinary problems, and bulimia. Antidepressants are currently the third most prescribed drug in the U.S. According to the CDC, one in ten Americans over the age of twelve is currently taking an antidepressant.

The first antidepressants, monoamine oxidase inhibitors (MAOIs), were discovered by accident in the 1950s, when doctors in a Swiss tuberculosis clinic noticed euphoria in patients treated with an MAOI called iproniazid. By the late 1950s, MAOIs were developed to treat depression and severe panic disorder. This class of drug operates by inhibiting the action of monoamine oxidase, the enzyme that breaks down epinephrine (adrenaline), norepinephrine (noradrenaline), serotonin, and other monoamines.

In the late 1960s, a more targeted drug, the tricyclic antidepressant, was introduced. The tricyclics (TCAs) were originally developed from antihistamines, and like MAOIs induced heightened mood in patients. Tricyclics operate by increasing the amounts of serotonin and/or norepinephrine in the brain. However, the tricyclics produced several side effects, so in the late 1980s, a new



neurochemical modulator, Prozac (fluoxetine), was approved by the Food and Drug Administration (FDA). Prozac is one of the family of drugs known as selective serotonin reuptake inhibitors (SSRIs). These act directly on a brain cell's ability to reabsorb serotonin, a neurotransmitter involved in many neurological functions, including sleep, digestion, blood flow, and, of major importance, mood elevation.

Unfortunately, the SSRIs produced sexual dysfunction, so in 1994 yet another class of antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), was developed by Wyeth. It was thought that by acting on two neurotransmitters the SNRIs would avoid the major side effects of the SSRIs, as well as helping with chronic pain.

**USES IN CFS/ME.** Antidepressants are perhaps the most widely prescribed pharmaceuticals for CFS/ME. Patients often are dismayed and concerned when their physicians suggest an antidepressant. It appears they are being diagnosed with depression, which, although sometimes a symptom of CFS/ME, is clearly not the underlying cause. Nonetheless, low-dose antidepressants have a place in the treatment of a number of CFS/ME symptoms.

Most CFS/ME patients have low amounts of serotonin and dopamine, two neurochemicals which have profound effects on sleep, cognitive function, and digestion. As a consequence, antidepressants have proven helpful in improving sleep, energy levels, and cognitive function. In addition, SSRIs, SNRIs and tricyclics have been shown to have anti-inflammatory and immunomodulatory effects. A secondary, though significant, effect of antidepressants is to increase blood volume by reducing urinary output. Pain and fatigue often increase urinary volume, which in turn can lead to reduced blood pressure and blood volume, along with a loss of metabolites. Antidepressants can improve kidney function, leading to improved metabolism and a reduction of overall fatigue.

Although there are various antidepressants to choose from, not all patients with CFS/ME respond well to these medications. Often CFS/ME patients with sensitivities to medications cannot tolerate any antidepressant, even in the smallest doses. In a survey of patients with chemical sensitivities conducted by a DePaul University research team, more than 50% of respondents reported negative effects of antidepressants.

Dr. Fred Friedberg, author of *Coping With Chronic Fatigue Syndrome: Nine Things You Can Do*, also found that a substantial proportion (about one-third) of 249 patients with CFS/ME reacted negatively to antidepressants. This finding is borne out by a treatment survey conducted in 2010 by the ME Association in which 30%-38% of respondents reported that antidepressants, of all classes, made them feel worse.

It is crucial for physicians and patients to remember that CFS/ME patients usually require much lower doses of these medications than other patients, and therefore the dose prescribed should be one tenth or less (depending on the sensitivity of the patient) of the standard dose. In his book, *The Doctor's Guide to Chronic Fatigue Syndrome*, Dr. David Bell, pediatric CFS/ME specialist, states that

giving patients with CFS/ME a standard dose of antidepressants can virtually serve as a diagnostic test for the illness – most patients are immobilized by it.

That being said, antidepressants do provide some degree of symptomatic relief for many patients. It is important, however, to be attentive to side effects, which frequently mimic the symptoms of the illness itself. Excessive fatigue and drowsiness, headaches, nausea, diminished libido, insomnia, and agitation can either be due to the effects of the drug or to the CFS, so it is important to be observant and monitor the dosage carefully.

#### FURTHER READING

“Using Antidepressants to Treat Chronic Fatigue Syndrome.” Dr. Charles Lapp.

*CFIDS Chronicle*, Summer 2001. <http://www.cfids.org/archives/2001rr/2001-rr3-article01.asp>

*Dr. Lapp's treatment protocols for antidepressants. Contains a useful chart.*

<http://www.cfids.org/archives/2001rr/2001-rr3-article01.asp?view=print><http://www.prohealth.com/library/showarticle.cfm?libid=8801>

*Interesting thread on antidepressants used for gut problems.*

<http://phoenixrising.me/forums/showthread.php?6321-Thoughts-on-the-methylation-treatment-for-CFS/page5>

*Lists antidepressants, side effects, brand names by country, “things your doctor won't tell you.”* <http://www.crazymeds.us/pmwiki/pmwiki.php/Main/HomePage>

#### BOOK

Dr. Cheney recommends patients and physicians read the book *Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil and Other Antidepressants* by Joseph Glenmullen, M.D., a psychiatrist at the Harvard Medical School

#### TRICYCLIC ANTIDEPRESSANTS

*CAUTION: Tricyclic antidepressants increase the amount of norepinephrine in the brain. They cannot be given in conjunction with MAOIs because of the risk of producing dangerously high blood pressure. The National Institutes of Health (NIH) does not recommend tricyclics for children or teens.*

#### DOXEPIN

Brand: Sinequan, Silenor, Adapin

USES IN CFS/ME. Doxepin, one of the most commonly used medications in the treatment of CFS/ME, is of major benefit in treating sleep disturbance. In a study conducted by Weber et al, 3 – 6 mg of doxepin administered before bed improved total sleep time without causing next-day sedation. Krystal et al found that as little as 1 – 3 mg of doxepin increased slow wave sleep (stage 3 and 4) in

elderly patients. It is believed that doxepin may help correct the slow-wave sleep deficit found in both CFS/ME and fibromyalgia. Improvement in sleep often brings an increase in energy levels and reduction in the pain associated with CFS/ME and fibromyalgia. Many patients with CFS/ME also report improvement in allergies as a result of doxepin's potent histamine-blocking properties. In this regard, Dr. Cheney believes that doxepin at low doses may function as an immune modulator. By softening immune system activation, doxepin can relieve sore throats, swollen glands and congestion.

**PROTOCOL.** Low doses (2 to 10 mg) of doxepin, taken 1 to 2 hours before bedtime, are usually prescribed to treat CFS/ME symptoms. Liquid formulations allow for even smaller doses. Because CFS/ME patients can be very sensitive to doxepin, Dr. Cheney recommends starting at two drops of liquid doxepin (10mg/cc) on the tongue, increasing up to 10 drops (5mg or ½ cc). Liquid doxepin can mixed into four ounces of water or juice.

**PROS.** Most patients report improved quality of sleep, better endurance, and energy. While some patients experience daytime sedation during the first few days, this problem usually resolves rapidly. Benefits are often noted fairly quickly, within a few days.

**CONS.** Side effects include weight gain, constipation, and dry mouth. Too high a dose can result in nightmares. Many patients with CFS/ME report excessive sedation or a drugged feeling and therefore cannot tolerate treatment. Paradoxically, some feel depressed after taking the drug (but not before).

**AVAILABILITY AND COST.** Liquid doxepin costs about \$17 for a 120 cc bottle. (If you are taking two drops on the tongue, 120 ccs will last a very long time). Both pill and liquid forms are available by prescription in generic and brand-name formulations. Insurance usually covers.

#### FURTHER READING

*Good review of sleep studies with low-dose doxepin*

<http://brainposts.blogspot.com/2011/01/low-dose-doxepin-for-insomnia-treatment.html>

#### AMITRIPTYLINE

Brand: Elavil, Vanatrip, Endep (Australia; Canada; New Zealand; South Africa); Domical (United Kingdom)

**USES IN CFS/ME.** Amitriptyline is beneficial for treating pain, sleep disturbance, headaches, and gastrointestinal problems and may be recommended if doxepin produces excessive sedation. In addition, amitriptyline is often helpful in treating interstitial cystitis, a disorder that affects many women with CFS/ME. Interstitial cystitis symptoms that may respond to amitriptyline are frequent urination, and bladder and pelvic pain. Dr. Alan Wein, a urologist who specializes

in treating interstitial cystitis, has noted that amitriptyline is effective for nearly 50% of his patients, probably because of its antihistamine properties.

**PROTOCOL.** Dosage varies, but generally 10 mg or less nightly is prescribed. Dr. Myhill starts at 5 mg to minimize side effects. Some patients report better results with amitriptyline by “pulsing” the medication (taking it every third or fourth night).

**PROS.** Benefits are noted quickly. The most frequent benefits reported by people with CFS/ME are improved sleep and reduced pain.

**CONS.** The side effects of amitriptyline are similar to those of doxepin, although exacerbation of muscle weakness in CFS/ME seems to be more common with amitriptyline than with other antidepressants. Some patients have had to discontinue the drug because of weight gain, dry mouth, and palpitations. Dr. Lapp notes that while amitriptyline may help patients improve sleep, it can reduce deep sleep, which impairs its effectiveness over the long term. There is some evidence that amitriptyline may cause CoQ10 deficiency, resulting in oxidative stress and altering the function of mitochondria. In a 2011 study, Bautista-Ferrufino et al recommend supplementation with CoQ10 during treatment with amitriptyline.

**AVAILABILITY AND COST.** Amitriptyline is available by prescription and is inexpensive. The generic drug costs about \$10 for a 30-day supply. Insurance usually covers.

#### FURTHER READING

*Good summary of the uses of Elavil for CFS/ME:*

[http://phoenixrising.me/?page\\_id=4710](http://phoenixrising.me/?page_id=4710)

#### PATIENT REVIEWS

*CFS/ME patients' reviews of Elavil:* <http://www.everydayhealth.com/drugs/elavil-for-chronic-fatigue-syndrome-cfs-cfids-me/review?page=2>

#### RESEARCH

Bautista-Ferrufino, María Rosa, Mario D. Cordero, José Antonio Sánchez-Alcázar, Matilde Illanes, Ana Fernández-Rodríguez, Plácido Navas, Manuel de Miguel. “Amitriptyline induces coenzyme Q deficiency and oxidative damage in mouse lung and liver.” *Toxicology Letters*. [Volume 204, Issue 1](http://www.sciencedirect.com/science/article/pii/S0378427411001342), 4 July 2011, Pages 32-37. <http://www.sciencedirect.com/science/article/pii/S0378427411001342> (Abstract)

#### NORTRIPTYLINE, DESIPRAMINE, IMIPRAMINE, CLOMIPRAMINE, TRIMIPRAMINE

Generic: Nortriptyline Brand: Pamelor, Sensoval, Aventyl , Allegron, Noritren, Nortrilen

Generic: Desipramine Brand: Norpramin, Pertofrane

Generic: Imipramine Brand: Tofranil

Generic: Trimipramine Brand: Sermontil

Generic: Clomipramine Brand: Anafranil

USES IN CFS/ME. Nortriptyline, desipramine and imipramine are second-generation tricyclic antidepressants which primarily block the reuptake of norepinephrine, and, to a lesser degree, serotonin. All three are used in patients with CFS/ME, though not as frequently as first-generation tricyclics. They are helpful in treating fatigue, pain, sleep disturbance, and anxiety. Their main side effects are similar to those of other tricyclic antidepressants: dry mouth, constipation, and weight gain (due to increased appetite). Although the second-generation tricyclics are often prescribed for sleep, they often interfere with sleep onset. Other side effects experienced by people with CFS/ME include shakiness, agitation and nausea.

Clomipramine and trimipramine, both of which were first developed in the 1960s, are in wider use in Europe than in the U.S. Like the other tricyclics, their mode of action is to block the uptake of serotonin and norepinephrine.

AVAILABILITY AND COST. Prices for second-generation tricyclics vary. Nortriptyline (generic) can be purchased for as low as \$10 for a 30-day supply. Desipramine is slightly more expensive, ranging from \$15 - \$30 for a 30-day supply, while imipramine can be purchased for less than \$10 for a 30-day supply. Insurance usually covers.

#### PATIENT REVIEWS

*CFS/ME patient reviews of Pamelor:* <http://www.revolutionhealth.com/drugs-treatments/rating/pamelor-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of trimipramine:* <http://www.revolutionhealth.com/drugs-treatments/rating/surmontil-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of clomipramine:* <http://www.revolutionhealth.com/drugs-treatments/rating/anafranil-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### FURTHER READING

*General information on trimipramine:* <http://en.wikipedia.org/wiki/Trimipramine>

#### SELECTIVE SEROTONIN REUPTAKE INHIBITORS

*CAUTION: SSRIs must not be taken within 14 days of discontinuing MAOIs. The NIH recommends against giving SSRIs to children or teens.*

#### FLUOXETINE

Brand: Prozac, Sarafem, Rapiflux, Selfemra, Lovan (Australia), Oxactin (United Kingdom), Fluctin (Germany).

BACKGROUND. Fluoxetine (Prozac), the first SSRI to be approved in the late 1980s, differs from earlier antidepressants in that its mode of action is more

specific. It works directly on altering the level and action of serotonin only (the tricyclic antidepressants inhibit uptake of norepinephrine as well). The SSRIs are often prescribed in place of tricyclic antidepressants because they have fewer side effects. Unlike other antidepressants, SSRIs do not cause sedation. In fact, fluoxetine can often act as a stimulant to increase energy. Nor does it cause the dry mouth, palpitations, and dry cough that are common with tricyclic drugs.

**USES IN CFS/ME.** Dr. Nancy Klimas, CFS/ME specialist and immunologist at the University of Miami, has studied the effect of SSRIs on the immune system. At the 1990 CFIDS conference in Charlotte, North Carolina, Dr. Klimas reported that more than half of 25 CFS patients given fluoxetine for three months showed moderate to marked improvement. Improvements in the number of natural killer cells seem to indicate that fluoxetine (and other serotonin-influencing drugs) may have a modulating effect on the immune system. However, in spite of these encouraging reports, no subsequent study has shown that fluoxetine has a greater effect than placebo on CFS/ME patients.

**PROTOCOL.** When used in CFS/ME, fluoxetine is generally given in considerably smaller dosage (2 to 10 mg, taken in the morning) than the standard dose used to treat depression.

**PROS.** Fluoxetine is effective in treating the fatigue of CFS/ME, the hallmark symptom of the syndrome. Other symptoms that may respond to treatment are pain, cognitive dysfunction, and sometimes excessive sleep. The drug is also helpful in treating the physiological depression that may accompany CFS/ME as a result of metabolic changes, as well as the secondary depression that stems from the devastating experience of having a chronic, debilitating illness. An additional benefit is that, unlike the tricyclic antidepressants, fluoxetine does not cause weight gain.

Fluoxetine has been shown to have a significant effect on patients with FM. In 2002, Arnold et al conducted a randomized, double-blind study, which showed improvement in pain, fatigue and depression in fibromyalgia patients. A similar study conducted in 1996 by Goldenberg et al found that the combination of fluoxetine and amitriptyline produced improvements in pain, sleep, and global well-being. (In *Handbook of Primary Care Psychology*, by Leonard J. Haas)

**CONS.** A number of people with CFS/ME are unable to tolerate the side effects of fluoxetine and have stressed emphatically that they will never try it again. Reports of anxiety, agitation, and even excessive sedation (a paradoxical reaction not unusual in CFS/ME patients) are common. In some cases the side effects of fluoxetine are profound, producing dissociation, flatness of affect and loss of a sense of self.

Because fluoxetine acts as a stimulant, people who have difficulty sleeping almost universally report worsening of insomnia. In addition, many clinicians advise their patients who have been taking MAOIs to allow a longer than usual interval (up to 5 weeks) before taking fluoxetine. This drug's long half-life may also require a longer interval after discontinuation before starting new antidepressant treatments. A double-blind study conducted by Dr. J.H. Vercoulen of the University

Hospital of Nijmegen in The Netherlands concluded that fluoxetine (20 mg/day) had no beneficial effect on fatigue or any other symptoms of CFS (*Lancet*, 1996). Dr. Cheney has strongly advised against long-term use of fluoxetine, citing possible permanent disruption of serotonergic pathways.

**AVAILABILITY AND COST.** Fluoxetine is available in liquid to allow smaller doses. The cost can be as low as \$4 a month for generic. Insurance usually covers the cost. Not recommended for patients with diabetes.

## PATIENT REVIEWS

*CFS/ME patient reviews of Prozac:* <http://www.revolutionhealth.com/drugs-treatments/rating/prozac-for-chronic-fatigue-syndrome-cfs-cfids-me>

## REFERENCES

Haas, Leonard J, ed. *Handbook of Primary Care Psychology*. Oxford University Press, USA, 2004.

Vercoulen J et al. "Randomized, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome." *Lancet*. 1996; 347: 858-61 and 1770-2.

## SERTRALINE, PAROXETINE

Generic: Sertraline Brand: Zoloft, Lustral (Britain, Ireland, Israel)

Generic: Paroxetine Brand: Paxil, Pexeva, Seroxat (Britain), Aropax (Australia, New Zealand)

**USES IN CFS/ME.** Sertraline (Zoloft) and paroxetine (Paxil) are two newer drugs that are similar to fluoxetine, but because they are associated with fewer side effects may be more easily tolerated. Both drugs have a shorter half-life than fluoxetine does. Both have been used to treat CFS/ME for treating symptoms such as fatigue, cognitive dysfunction, mood swings, pain, sleep disorders, and immune dysfunction.

**PROS AND CONS.** As with other SSRIs, patient experiences vary widely. Some patients report an increase in energy and relief from pain, while others report nausea, loss of appetite, a "floating feeling," and hormonal complications. Withdrawal symptoms of paroxetine may be intense, producing flu-like symptoms, nausea, irritability, anxiety, and crying jags. A few patients have mentioned that they felt as bad while taking these drugs as they did with other antidepressants, reminding us that many patients cannot tolerate any form of antidepressant. For these patients, alternative treatments have been suggested, including vitamins, amino acids, herbs, and other complementary therapies.

## PATIENT REVIEWS

*CFS/ME patient reviews of Zoloft:* <http://www.revolutionhealth.com/drugs-treatments/rating/zoloft-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Paxil:* <http://www.revolutionhealth.com/drugs-treatments/rating/paxil-for-chronic-fatigue-syndrome-cfs-cfids-me>

## CITALOPRAM

Brand: Celexa; Cipromil (Britain, Australia)

**USES IN CFS/ME.** Celexa is sometimes prescribed for POTS (postural orthostatic tachycardia syndrome), so those patients with syncope (fainting), NMH (neurally mediated hypotension), and related disorders may benefit from Celexa. It is not as frequently prescribed for CFS/ME as other antidepressants, due to numerous side effects.

**PROS AND CONS.** Some patients report a lessening of symptoms, particularly those associated with PMS. Others report severe migraines, nose bleeds, insomnia, nightmares, and confusion. Sexual dysfunction is a common side effect. Patients should start at a very low dose.

## PATIENT REVIEWS

*CFS/ME patient reviews of Celexa:* <http://www.revolutionhealth.com/drugs-treatments/rating/celexa-for-chronic-fatigue-syndrome-cfs-cfids-me>

## EXCITALOPRAM

Brand: Lexapro, Cipralex, Seroplex, Lexamil, Lexam, Entact

Excitalopram is an SSRI noted for its high selectivity of serotonin. It is reputed to be a more potent antidepressant than its “parent,” citalopram. Excitalopram has had a history of controversy since its introduction in the 1990s, and has generated a number of lawsuits. Nonetheless, excitalopram is one of the SSRIs that has been used for CFS/ME, though not as widely as other antidepressants.

## PATIENT REVIEWS

*CFS/ME patient reviews of Lexapro:*  
[http://www.google.com/search?rlz=1C1GGGE\\_enUS379US379&aq=f&gcx=w&sourceid=chrome&ie=UTF-8&q=lexapro](http://www.google.com/search?rlz=1C1GGGE_enUS379US379&aq=f&gcx=w&sourceid=chrome&ie=UTF-8&q=lexapro)

## MONOAMINE OXIDASE INHIBITORS (MAOIs)

*CAUTION: Foods and medications containing a high amount of tyrosine (fermented foods, wine, cheese, pickles, decongestants) can interact with MAOIs, producing sharply elevated blood pressure and increasing the risk of stroke.*

## PHENALZINE, TRANYLCPROMINE



Generic: Phenelzine Brand: Nardil, Nardelzine

Generic: Tranylcypromine Brand: Parnate, Jatrosom

**USES IN CFS/ME.** MAOIs are used much less frequently than other antidepressants to treat CFS/ME. The side effects associated with phenelzine (Nardil) and tranylcypromine (Parnate) can be severe. An additional drawback is the dietary restrictions that accompany MAOI use. Foods that contain the amino acid tyramine (aged cheese, yogurt, wine, avocado, among many others) must be avoided to prevent severe hypertensive crisis. Because these foods are so common, patients may find compliance difficult. While some patients with CFS/ME have found MAOIs effective, others have reported agitation and insomnia. One patient believed an MAOI may have contributed to a prolonged relapse, producing even greater neurological and cognitive problems than she had experienced previously.

**AVAILABILITY.** MAOIs are available from any pharmacy with a doctor's prescription. Most major insurance carriers do not cover MAOIs for the treatment of CFS/ME.

### *OTHER ANTIDEPRESSANTS*

#### **BUPROPION**

Brand: Wellbutrin, Aplenzin, Budeprion, Buproban, Zyban

*CAUTION: Bupropion should not be taken by patients with a history of seizures.*

**USES IN CFS/ME.** Bupropion is an atypical antidepressant frequently used to treat the fatigue associated with CFS/ME. Bupropion is the first antidepressant to increase dopamine, a neurotransmitter often found to be low in CFS/ME patients. Bupropion is believed to be both a norepinephrine and dopamine reuptake inhibitor.

**PROS.** Physicians who specialize in the treatment of CFS/ME have prescribed bupropion when SSRIs have failed, and find it of benefit in improving energy and controlling mood. In some patients, bupropion does not produce the unpleasant side effects noted with other antidepressants. The drug may be taken alone or with other tricyclic antidepressants to improve sleep. Patients have reported increased energy, alleviation of depression, increase in concentration, and better sleep.

**CONS.** Bupropion is short acting, much like stimulants (e.g., Ritalin). Because bupropion raises dopamine, it is more habit-forming than other antidepressants. Side effects can be similar to those of SSRIs (jitters, anxiety, insomnia). Many patients find that bupropion, like CNS stimulants, provides only a short burst of energy, followed by a crash. Even patients who feel that bupropion has provided significant relief for cognitive symptoms have reported "cyclic thoughts" (like having a song stuck in your head). Patients have also reported headaches, nightmares, shakiness, rapid heartbeat, weight gain, and stomach

irritation. The biggest drawback to the use of bupropion is the risk of seizures. Bupropion is not recommended for patients who are sensitive to stimulants, or who have a history of seizures or heart problems.

**PROTOCOL.** The standard initial prescribed dose is 75 mg daily. CFS/ME patients may wish to start with a third of the standard dose to check for tolerance.

**AVAILABILITY AND COST.** Bupropion is available at any pharmacy with a prescription. A one-month supply costs from \$10-\$24. It can be ordered online with a prescription. Insurance usually covers.

## PATIENT REVIEWS

*CFS/ME patient reviews of Wellbutrin:* <http://www.revolutionhealth.com/drugs-treatments/rating/wellbutrin-for-chronic-fatigue-syndrome-cfs-cfids-me>

## TRAZODONE

Brand: Desyrel, Oleptro, Trialodine (Deprax in Spain, Molipaxin in Britain, Thombran in Europe, Trazorel in Canada )

**USES IN CFS/ME.** Among the most sedating antidepressants, Desyrel is often used to treat insomnia. Desyrel stimulates deep sleep (stage 3 and stage 4) and is particularly helpful for those who wake up too early. It is not, however, as helpful as many of the other antidepressants in treating anxiety and depression in CFS/ME. Some patients report improved sleep with a low dose of Desyrel, but experience severe orthostatic hypotension with higher doses. Desyrel has fewer anticholinergic side effects than tricyclics, but patients still report dry eyes and mouth, and constipation. The most commonly reported side effects include nausea, excessive sedation, nightmares, dizziness, and unrefreshing sleep. Morning grogginess (“hangover”) is common.

**PROTOCOL.** The prescribed dose in CFS/ME is generally 25 to 50 mg at bedtime. Dr. Bell recommends 25 mg taken ½ hour to two hours before bed.

**AVAILABILITY AND COST.** A 30-day supply of the generic drug (25mg) costs about \$7.

## VENLAFAXINE

Brand: Effexor

**USES IN CFS/ME.** When it was approved for commercial use, Effexor (venlafaxine) received a remarkable amount of publicity and was touted as a newer and better Prozac. Effexor is chemically unrelated to the other antidepressants and has a unique mode of action, blocking serotonin, norepinephrine, and dopamine reuptake. However, effects of the drug in CFS/ME have been less than dramatic. Many patients report that Effexor worsens anxiety, and, paradoxically, depression. Withdrawal symptoms can be severe, including dizziness, nausea and headaches. Dr. Jay Goldstein commented that, while Effexor may have been marketed as “the

best thing since sliced bread," his experience taught him to view it simply as another alternative treatment, rather than the most effective antidepressant (*CFIDS Chronicle*, Physicians Forum, Fall 1993). Dr. Goldstein reported nausea and hypertension as possible side effects.

**AVAILABILITY AND COST.** The generic is available at pharmacies and online regardless of dosage at roughly \$10 for a 30-day supply (prices vary).

#### PATIENT REVIEWS

*CFS/ME patient reviews of Effexor:* <http://www.revolutionhealth.com/drugs-treatments/rating/effexor-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### DULOXETINE

Brand: Cymbalta; Yentreve and Ariclaim (Europe)

**USES IN CFS/ME.** Cymbalta, one of three medications currently approved for the treatment of fibromyalgia, is a serotonin-norepinephrine reuptake inhibitor (SNRI) primarily prescribed for pain. Although Cymbalta is often prescribed by rheumatologists for their patients with fibromyalgia, most CFS/ME doctors prefer tricyclics or SSRIs over Cymbalta.

**PROS and CONS.** Many CFS/ME patients report that Cymbalta makes them restless and anxious. But patients who have had success with other stimulants may find that Cymbalta improves energy and mood. Because of its short half-life, discontinuation symptoms can be quite severe, including depression, irritability, agitation, sensory disturbances, dizziness, headache, insomnia, and seizures.

**PROTOCOL.** Doctors recommend beginning at a low dose (20 mg) and then gradually increasing as needed. Cymbalta can be pulsed (taken every second or third day).

**AVAILABILITY AND COST.** Cymbalta is available at any pharmacy with a prescription. A month's supply of the generic at 20 mg costs roughly \$28.

#### PATIENT REVIEWS

*CFS/ME patient reviews of Cymbalta:* <http://www.revolutionhealth.com/drugs-treatments/rating/cymbalta-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### MIRTAZAPINE

Brand: Remeron; Avanza, Axit (Australia); Zispin SolTab (Britain and Ireland); Norset (France); Remergil (Germany)

**BACKGROUND.** Remeron is a tetracyclic antidepressant, one of the few drugs that falls into the class of noradrenergic and specific serotonergic antagonists (NaSSAs). The NaSSAs act by inhibiting adrenergic and serotonin receptors. Remeron is dispensed orally in a tablet that dissolves on the tongue.

**PROS AND CONS.** The most common side effect of Remeron is weight gain, but as with tricyclics, CFS/ME patients may also experience blurred vision, dry mouth, constipation, dizziness and sedation. Many patients report sugar cravings. On the positive side, some patients report that Remeron has helped improve sleep. Dr. Lapp prescribes Remeron when there has been significant weight loss coupled with insomnia.

**AVAILABILITY AND COST.** Remeron is available at most pharmacies. A month's supply of 15 mg of the brand version costs roughly \$25.

#### PATIENT REVIEWS

*CFS/ME patient reviews of Remeron:* <http://www.revolutionhealth.com/drugs-treatments/rating/remeron-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### ANTIFUNGAL AGENTS

Nystatin, Diflucan, Nizoral, Sporanox

**DESCRIPTION.** Antifungal drugs are used to treat *Candida albicans* and other fungal infections.

#### NYSTATIN

**BACKGROUND.** In the 1940s, two scientists found a bacterium in soil that inhibited the growth of molds. They discovered that the bacterium binds to ergosterol, a major component of the cell membrane of the fungus. When the bacterium was sufficient concentrations, it formed pores in the membrane that produced leakage and eventually led to the death of the fungus. They named the substance “nystatin,” after New York State, where it was discovered. The drug was patented in the 1950s, and for the next twenty years nystatin was primarily used in suppositories to treat vaginitis. It was popularized in the early 1980s, when studies by several clinicians chronicled the successful treatment of chronic candidiasis (yeast infection) with nystatin.

**USES IN CFS/ME.** Because candidiasis is a condition that produces extreme fatigue, depression, muscle pain, concentration problems, along with other symptoms which are common in CFS/ME, many CFS/ME patients turned to antifungal regimens in the 1980s. Although some physicians consider candidiasis controversial and without scientific basis, many CFS/ME clinicians use nystatin and other antifungal agents to treat *Candida* overgrowth. Dr. Murray Susser and Dr. Michael Rosenbaum, among other physicians, used antifungal medications when symptoms of *Candida* infection were present, especially when accompanied by a medical history of antibiotic or steroid use that may have contributed to *Candida* overgrowth. As an additional aid to determining whether an antifungal regimen might be helpful, a number of physicians use stool tests to measure *Candida*.

**PROTOCOL.** Many CFS/ME physicians suggest using the powdered form of nystatin, citing that it works better than the pill form and is more pure (free of dyes

or additives). The target dose is  $\frac{1}{4}$  teaspoon, four times a day. A much lower dose (1/16 tsp once a day) should be used initially to prevent die-off reactions.\

Dr. Teitelbaum recommends a target dose of two tablets three times a day (500,000 units), starting with one tablet a day and increasing by one tablet a day until you are up to the target dose for five to eight months. He recommends that if nausea occurs the dose be reduced to two tablets a day, or replaced by nystatin powder mixed in water. In *Chronic Fatigue Syndrome and the Yeast Connection*, Dr. William Crook notes that flushing, fever, and agitation may indicate that the dose is too high. Indications that the dose is too small include excessive fatigue, cold, and achiness.

**PROS.** Nystatin is considered safe when taken in oral or topical form. As nystatin is not absorbed through the gut, side effects from the drug are minimal. A surprisingly large number of patients report that nystatin (in combination with dietary changes and nutritional supplements as part of Candida control) has helped improve symptoms of CFS/ME. Patients often report increased energy, improved immune function, and better overall health after taking nystatin. Some symptoms (e.g., thrush, gastrointestinal complaints) respond quickly to treatment, but it can take weeks or months before overall improvement is observed.

**CONS.** While a number of patients note steady improvement over time, others experience no benefit after long trials of nystatin, and still others are not able to tolerate the drug at all. It is important to note that with all antifungal medications the phenomenon of "die-off" may be the actual cause of side effects; that is, as the antifungal medication kills the yeast cells, the dead cells secrete toxins into the body and symptoms may worsen initially. Symptoms of die-off include increased fatigue, muscle aches, and headaches, as well as diarrhea, nausea, upset stomach and vomiting. It can be difficult to differentiate between symptoms that could be due to die-off, intolerance for the drug, or perhaps simply a "bad day."

**AVAILABILITY AND COST.** Nystatin is available over the counter in suppository form to treat vaginitis and is widely available in creams for topical use. It is available in pill, tablet, liquid, lozenge, and powder form by prescription at most pharmacies. The powder comes in 15-, 30-, and 60-gram bottles. Hi-Tech Pharmacal Co, Inc. Amityville, NY 11701 and Paddock Laboratories, Inc. Minneapolis, MN 55427 are the two companies that currently produce nystatin powder. The powder is quite expensive at over \$100 for a 30-gram bottle. Nystatin, in all forms, is usually covered by insurance.

## DIFLUCAN

**BACKGROUND.** Diflucan (fluconazole), an antifungal introduced in the United States in 1990, is extremely valuable in treating the life-threatening Candida infections that sometimes occur in immunocompromised patients, such as those with AIDS or advanced cancer.

Diflucan differs from nystatin in that it is absorbed through the intestinal wall and traverses the bloodstream, thereby penetrating anywhere excessive yeast

colonization is found. Therefore, in theory at least, Diflucan may be more beneficial than nystatin to treat pervasive yeast infections.

**USES IN CFS/ME.** Many clinicians have found Diflucan beneficial for treating CFS/ME symptoms. A respected CFS/ME specialist, Dr. Carol Jessop, has used antifungal therapies when patients have symptoms suggestive of *Candida* overgrowth. She has stated that although other agents may be of benefit, Diflucan was her treatment of choice. Dr. Jessop found that because Diflucan penetrates the central nervous system, her patients experienced improvement in cognitive problems. This was not the case with nystatin or Nizoral. On the other hand, Dr. Jay Goldstein, who used Diflucan chiefly to treat gastric disturbances, reported only limited success (*CFIDS Chronicle*, Physician's Forum, Spring 1991).

**PROTOCOL.** Dr. Teitelbaum prescribes 200 mg for 6-12 weeks. If die-off symptoms appear, he recommends dropping the dose to 25 mg a day for 3 to 14 days.

**PROS AND CONS.** Diflucan is usually well tolerated. The principal side effects are nausea and other gastrointestinal complaints. Diflucan works very quickly, which means patients will see results almost immediately. For some patients this means an immediate improvement—for others, immediate side effects.

**AVAILABILITY AND COST.** Diflucan is available by prescription. The generic (fluconazole) costs roughly \$1 a tablet. Insurance plans usually cover the cost (if your insurance does not include Diflucan, you may qualify for a compassionate low-cost supply; contact Pfizer, Inc., 866-706-2400 or, for an application form and more information go to:

<http://www.pfizerhelpfulanswers.com/pages/misc/Default.aspx>

## PATIENT REVIEWS

*CFS/ME patient reviews of Diflucan:* <http://www.revolutionhealth.com/drugs-treatments/rating/diflucan-for-chronic-fatigue-syndrome-cfs-cfids-me>

## NIZORAL

Nizoral (ketoconazole) is somewhat similar to Diflucan but is used less frequently because of its serious side effects, including liver toxicity and endocrine system disturbances. Nizoral can also lower adrenal hormone levels. Although the drug is effective and inexpensive, many physicians are cautious about prescribing it. Patients taking Nizoral generally undergo blood tests, including a liver profile, every thirty days. Nizoral is available by prescription. A 30-day supply generally costs about \$85. It is usually covered by insurance.

## SPORANOX

**USES IN CFS/ME.** Like Diflucan and Nizoral, Sporanox is used to treat *Candida* overgrowth. Because it is less toxic to the liver, it is safer than Nizoral. Dr. Teitelbaum has observed that yeast that is resistant to Diflucan is usually resistant to Sporanox. The drug is generally well tolerated. The most common side effects are transient nausea and headache. As with Diflucan, Sporanox can cause liver

inflammation. Dr. Teitelbaum recommends taking lipoic acid as a liver protector when taking either drug.

**PROTOCOL:** Doses range from 100 to 200 mg/day.

**AVAILABILITY AND COST:** Sporanox is available at most pharmacies. The cost of a month's supply of 100 mg tablets is roughly \$450 brand, \$250 for generic (itraconazole). Because the drug is expensive, it is advisable to check with your insurance carrier to see if it is covered.

## PATIENT REVIEWS

*CFS/ME patient reviews of Sporanox:* <http://www.revolutionhealth.com/drugs-treatments/rating/itraconazole-for-chronic-fatigue-syndrome-cfs-cfids-me>

SEE: Candida

## ANTIHISTAMINES

Benadryl, Claritin, Allegra, Zyrtec, Chlor-Trimeton, Atarax and Vistaril, Dramamine

**DESCRIPTION.** Antihistamines are a class of drugs that compete with histamine for cell receptor sites on effector cells, thereby blocking the effects of histamine.

**BACKGROUND.** Antihistamines have been used for many years to treat allergies and allergic reactions. Some antihistamines are also used to treat motion sickness and mild Parkinson's disease.

**USES IN CFS/ME.** Because many patients with CFS/ME have allergies (usually preceding but often developing after the onset of CFS/ME), antihistamines are often prescribed for relief of seasonal allergies. But in addition to allergies, patients with CFS/ME often develop an intolerance to histamine itself. (For this reason, anesthesiologist Patrick Glass recommends that CFS/ME patients avoid anesthetics containing histamine releasers, such as sodium pentothal, during surgery. For more tips on anesthesia see: <http://www.squidoo.com/anesthesia-with-cfs>)

Histamine is found in a number of foods, particularly fermented foods, and additives. Because histamine is a vasodilator, reactions to these foods and additives can mimic true allergies, producing flushing, lowered blood pressure, headache and palpitations. Aside from treating allergies, antihistamines are also of benefit in treating many other symptoms of CFS/ME, including insomnia, bladder problems (interstitial cystitis), anxiety, and muscle pain. Benefits are noted rapidly, usually within 24 hours.

**BENADRYL (diphenhydramine)**

**USES IN CFS/ME.** Benadryl is useful for treating hives, seasonal allergies, upper airway congestion, and severe allergic reactions (anaphylactic shock). The drug is very sedating and can be used as a sleep aid for CFS/ME-related insomnia if

taken at bedtime. Like other antihistamines, Benadryl is not addictive, and thus may offer a good alternative to habit-forming sleeping pills. However, as Dr. David Bell points out in *The Doctor's Guide to Chronic Fatigue Syndrome*, Benadryl can lose effectiveness with continuous use for longer than a few weeks and therefore may be better used only occasionally.

Some patients note that, although Benadryl ensures a good night's sleep, rotating it with a benzodiazepine prevents developing a tolerance to either drug (see Benzodiazepines). Although Benadryl is generally well tolerated, adverse reactions – notably agitation and tachycardia – have been reported. If you are taking other medications, it is important to check with your physician before trying Benadryl, especially if you are prone to heartbeat irregularities.

**AVAILABILITY AND COST.** Benadryl is inexpensive, costing less than \$7 per bottle or package. It is also available as a dye-free pill and in liquid form, which may be of benefit to CFS/ME patients with chemical sensitivities. Benadryl can be purchased without a prescription.

#### CLARITIN (loratadine)

**USES IN CFS/ME.** Claritin is a second-generation antihistamine useful in the treatment of seasonal allergy symptoms, such as runny nose, sneezing, itching, and watery eyes. Because it is very similar in structure to the tricyclic antidepressants, it may cause similar side effects (urinary retention, blurred vision, dry mouth, GI disturbances). In spite of being described as a “non-sedating” antihistamine, Claritin does produce drowsiness. Some patients have reported that they feel “zombie-like” after taking Claritin. Others report that Claritin has brought great relief from hay fever symptoms without adverse effects.

**AVAILABILITY AND COST.** Prescription strength Claritin is available over the counter at pharmacies supermarkets. A package of 24 gels costs roughly \$20.

#### PATIENT REVIEWS

*CFS/ME patient reviews of Claritin:* <http://www.revolutionhealth.com/drugs-treatments/rating/claritin-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### ALLEGRA (fexofenadine)

Fexofenadine is a second-generation antihistamine that does not readily cross the blood-brain barrier, and so causes less drowsiness than first-generation antihistamines (such as Benadryl). Like other antihistamines, it works by antagonizing the H1 receptor. As Allegra is non-sedating, it is recommended for patients who suffer from allergies, and who also have hypersomnia. Allegra comes in a tablet and as a liquid. Allegra works better if it is not taken with fruit juices such as orange, grapefruit, or apple juice. It is available over-the-counter at pharmacies and supermarkets. A package of 15 tablets costs roughly \$7.

#### ZYRTEC (cetirizine)

Zyrtec is a second-generation antihistamine that crosses the blood-brain barrier only slightly, thereby reducing its sedating effects. In 2008 it was the highest grossing non-food product in the U.S., generating sales in excess of \$300



million. Unlike other antihistamines, Zyrtec is only taken once a day, preferably at the same time. Paradoxically, Zyrtec D's (decongestant) stimulating effect may help insomnia. One CFS/ME patient reported that after suffering from frequent panic micro-arousals on a nightly basis, taking Zyrtec D actually helped her stay asleep. The Zyrtec elevated her metabolic rate, preventing the sudden release of adrenaline that was preventing her from getting into a deep sleep.

**AVAILABILITY AND COST.** Zyrtec is available at pharmacies and supermarkets. A package of 30 tablets costs roughly \$20.

#### CHLOR-TRIMETON (chlorpheniramine maleate)

Chlorpheniramine is a first-generation antihistamine with relatively weak sedative effects. Chlorpheniramine is normally used to treat allergies, however, it also functions as a serotonin and norepinephrine reuptake inhibitor (SNRI). One patient with long-term CFS/ME reported that a dose of 2 mg of Chlor-Trimeton improved her sleep and she felt less miserable in the day. "There was less aching, less fatigue, a little more mental clarity." After the drug effect reached a plateau, she increased the dose and noticed that all her symptoms improved, not just sleep disturbances (*CFIDS Chronicle*, Winter 1994).

**AVAILABILITY AND COST.** Chlor-Trimeton is available over the counter. It is relatively inexpensive at less than \$8 for 24 tablets.

#### ATARAX, VISTARIL (hydroxyzine)

**BACKGROUND.** Hydroxyzine is an older first-generation antihistamine used for allergies, motion sickness, nausea and mild anxiety. Although it has sedative effects, it is not addictive, nor does it produce the side effects common to tranquilizers and anxiolytics. Hydroxyzine is frequently used in conjunction with opioid pain killers to increase the effectiveness of the drugs without increasing toxicity.

**USES IN CFS/ME.** Hydroxyzine has a wide range of uses in treating CFS/ME symptoms, including anxiety, pain and interstitial cystitis. Dr. Paul Cheney prescribes Vistaril to treat muscle pain (*CFIDS Chronicle*, Spring 1995).

Two physicians who specialize in treating interstitial cystitis, Dr. Grannum Sant and Dr. Theoharis Theoharides of Tufts University, have published several papers detailing the effectiveness of hydroxyzine. Dr. Theoharides noted that several patients given hydroxyzine experienced improvement in urinary frequency and bladder pain. He theorizes that this drug may inhibit secretion of mast cells, a type of cell involved in allergic reactions that may be responsible for many symptoms in interstitial cystitis. Dr. Theoharides states that hydroxyzine is unique in that other antihistamines do not seem to be effective in treating interstitial cystitis (*Seminars in Urology*, 1991). Symptoms often recur after discontinuation of the drug. However, the success rate is high and the risks low, compared with more invasive therapies for interstitial cystitis.

**PROS AND CONS.** Although Vistaril is often prescribed for anxiety, it can paradoxically cause panic and anxiety attacks. Some patients report that Vistaril "knocks them out," which may be beneficial for people with insomnia.

**PROTOCOL.** The initial dosage is 25 mg a day, which can be slowly increased to 100 mg. Daytime sedation, the most common side effect, generally disappears in a few days. Hydroxyzine is fast-acting, with results seen within 30 minutes. When used for anxiety, its effectiveness is generally limited to a few months. Hydroxyzine is not recommended for the elderly.

**AVAILABILITY AND COST.** Atarax and Vistaril are available by prescription, in brand-name or generic formulations. The generic form of these drugs is inexpensive. Thirty tablets of 25 mg generic drug cost about \$12.

#### DRAMAMINE (meclizine)

Meclizine is a first generation antihistamine very similar to hydroxyzine. It is used primarily to treat vertigo, dizziness, and motion sickness. In CFS/ME, it is frequently prescribed to treat vertigo as well as balance problems, nausea, motion sickness, and Meniere's disease. Dramamine is safe to use. The most common side effect is excessive sedation. DiVertigo, a natural herbal alternative to Dramamine can also be purchased at pharmacies, as well as health food stores. DiVertigo is a liquid blend of lavender peppermint, frankincense, chamomile, myrrh and *ylang-ylang*, which is rubbed behind the ear rather than swallowed.

**AVAILABILITY AND COST.** Over-the-counter Dramamine costs roughly \$15 for 36 tablets. In-house pharmacy brands are considerably less expensive. DiVertigo costs roughly \$20.

SEE: Allergies, Sleep Disturbances, Urinary Problems

#### REFERENCE

Theoharides TC, Sant GR. "Bladder mast cell activation in interstitial cystitis." *Semin Urol*. 1991 May;9(2):74-87. <http://www.ncbi.nlm.nih.gov/pubmed/1853017> (Abstract)

#### ANTIVIRAL AGENTS

Acyclovir, Famvir, Amantadine, Valacyclovir, Valganciclovir

**DESCRIPTION.** Antiviral agents are a group of drugs used to inhibit the replication of viruses.

**USES IN CFS/ME.** Most CFS/ME physicians in the United States adhere to the theory that CFS/ME is caused by a virus. Although the causal virus has not yet been identified, reactivated latent viral infections are not only quite common in CFS/ME patients, but highly problematic, as the reactivated viruses produce many of the symptoms characteristic of the illness. As a consequence, antivirals have a long track record in treating CFS/ME. Most CFS/ME doctors have incorporated antivirals of one kind or another into their protocols, particularly for patients with either high viral titers, or who have had a viral onset of the illness.

Dr. Guyer, Director of The Advanced Medical Center in Indianapolis, Indiana, uses antivirals for patients with viral onset of CFS/ME, that is, those patients who initially had mononucleosis, or “flu,” from which they never recovered. Dr. Guyer reports that these patients typically have lab findings of depressed natural killer cells, hormone deficiencies, elevated RNase L levels, and elevated antibodies to Human Herpesvirus 6 (HHV-6), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and other viruses.

Several doctors have reported success with antiviral treatments for a subset of their patients. Dr. Lerner, an infectious disease specialist who has been investigating and treating CFS/ME for more than 20 years, found that long-term antiviral therapy was very effective for his patients with high viral titers, sometimes providing these patients with nearly full recovery.

## ACYCLOVIR

**BACKGROUND.** In the early 1980s, acyclovir (Zovirax) was hailed as one of the first drugs to be proven effective against genital herpes. Although later shown to be not as universally helpful as researchers first thought, acyclovir does relieve the severity, duration, and frequency of outbreaks for many patients with genital herpes. Acyclovir is not a cure for the infection because it does not kill the virus but merely inhibits its ability to replicate. In addition to treating herpes simplex, which causes genital herpes, acyclovir has been used with some success to treat other types of herpesvirus infections, such as chickenpox (varicella zoster virus), shingles (herpes zoster), cytomegalovirus (CMV), and infectious mononucleosis (Epstein-Barr virus), among others.

**USES IN CFS/ME.** In the mid-1980s, Epstein-Barr virus was thought to be the cause of the illness now known as CFS/ME. Because Epstein-Barr virus is one of the herpesviruses, it was logical for acyclovir to be used to treat cases of what was then called chronic Epstein-Barr virus or chronic mononucleosis. At that time, physicians using acyclovir noted symptomatic improvement in many of their patients. However, the first formal study was not completed until 1988, when Dr. Steven Straus of the National Institutes of Health (NIH) headed a double-blind, placebo-controlled study to determine the effectiveness of acyclovir against CFS/ME. Dr. Straus' results revealed no difference between the placebo group and patients given acyclovir (*New England Journal of Medicine*, 1988).

Notwithstanding these inconclusive results, many physicians familiar with CFS/ME continue to prescribe acyclovir, citing both their success rate and the flawed methods of the Straus study as justifications. Dr. Charles Lapp, for example, reported “remarkable results with this medication.” Dr. Guyer, Director of The Advanced Medical Center in Indianapolis, Indiana, recommends acyclovir for patients with viral onset of CFS/ME (after mononucleosis or other viral infection), especially in the presence of high titers of herpesvirus, recurrent shingles, or other clinical evidence of viral infection (*CFIDS Chronicle*, Spring 1991).

**PROTOCOL.** The oral form is most commonly recommended because intravenous injections carry some risk of toxicity. Daily doses range from 800 to

4000 mg divided throughout the day. Topical creams or ointment can be applied directly to the skin to treat surface blisters and other lesions. Despite the associated risks, patients with acute infections may require intravenous administration. Because resistance can develop, 30- to 60-day intervals between courses of therapy are recommended to ensure continued effectiveness.

**PROS AND CONS.** Acyclovir, while not a cure for CFS/ME, may lessen the viral load in patients with CFS/ME who demonstrate a lot of viral activity (high titers of herpesvirus, recurrent flu-like symptoms, shingles). A number of patients with CFS/ME have reported success with acyclovir in controlling shingles and eliminating chronic sore throat.

In their book, *CFIDS: An Owner's Manual*, Barbara Brooks and Nancy Smith reported success with acyclovir, claiming it to be the most important component of their respective treatments. Positive results are far from universal, however. An equal number of patients with CFS/ME report little or no benefit, even after months of trial. For those who do receive some benefit, the results are generally short-lived. Many patients must take the drug daily to see any result at all. Acyclovir, although usually well tolerated, produces frequent side effects, notably light-headedness, nausea, and headache. Patients with kidney disease should not take acyclovir.

**AVAILABILITY AND COST.** Oral acyclovir is available by prescription. Oral acyclovir can be purchased for as little as \$30 a month (200 mg tablets). Insurance plans usually cover the cost.

## PATIENT REVIEWS

*CFS/ME patient reviews of Zovirax:* <http://www.revolutionhealth.com/drugs-treatments/rating/zovirax-for-chronic-fatigue-syndrome-cfs-cfids-me>

## REFERENCES

Physician's Forum. *CFIDS Chronicle*, Vol 1, Issue 1, March 1991.  
Straus, Steven, Dale, JK, Tobi, M, et al. "Acyclovir Treatment of the Chronic Fatigue Syndrome." *New England Journal of Medicine*. 26:1692-1698,1988.

## FAMVIR

Famvir (famcyclovir) is an oral antiviral used for herpesviruses, particularly herpesviruses 6 and 7, two viruses that play an important role in CFS/ME. Technically, Famvir is a prodrug; that is, a substance that is converted into an active drug once in the body. Famvir functions the same as Zovirax, but with fewer side effects. There is some indication that it may be more effective, as well.

Currently, only a few CFS/ME clinicians prescribe Famvir, so not much information is available as to its effectiveness in treating CFS/ME. Dr. Guyer has observed the patients who experience milder symptoms of shorter duration, accompanied by elevated levels of IgG to EBV, seem to do well with Famvir.

**AVAILABILITY AND COST.** Famvir is available by prescription. This drug is quite expensive. A one -month supply can cost as much as \$700, depending on the dosage.

## REFERENCE

“Dale Guyer, M.D., on Treating Chronic Fatigue Syndrome & Fibromyalgia: 'Covering the Bases & Peeling Back the Layers of the Onion.'” *ProHealth.com*. June 13, 2006

<http://www.prohealth.com/library/showarticle.cfm?libid=9761>

## AMANTADINE

Amantadine (Symmetrel) is prescribed for viral infections (type A influenza virus) and Parkinson's disease. It acts by blocking the penetration of cell membranes by the infectious material from viruses. As an antiviral agent, it is of no benefit unless administered at the onset of infection. In patients with CFS/ME who cannot tolerate flu shots, amantadine might be a good alternative, especially for those patients susceptible to frequent episodes of influenza. In CFS/ME, its most common use is not as an antiviral agent but as a stimulant. It is used to treat fatigue and lethargy in mild cases. Common side effects include insomnia, confusion, headaches, and dizziness. Amantadine interacts with antidepressants and antihistamines. Some patients with CFS/ME cannot tolerate this drug so the initial dose should be small.

**AVAILABILITY AND COST.** Amantadine is available by prescription. A one-month supply of the generic amantadine costs approximately \$12.

## PATIENT REVIEWS

*CFS/ME patient reviews of amantadine:* <http://www.revolutionhealth.com/drugs-treatments/rating/symmetrel-for-chronic-fatigue-syndrome-cfs-cfids-me>

## VALACYCLOVIR (Valtrex)

**DESCRIPTION.** Valacyclovir is an oral pro-drug that converts to acyclovir once ingested. It is more bioavailable than acyclovir and is therefore more effective.

**BACKGROUND.** Valtrex is marketed for herpes simplex, but in 2009 Hoshino et al found that it also reduced the replication of EBV. They concluded that latent EBV (Epstein-Barr virus) might be completely eradicated by Valtrex if reinfection did not occur.

**USES IN CFS/ME.** A 2007 study by Dr. Lerner of CFS/ME patients with EBV reactivation found that Valtrex resulted in both increased physical functioning and improved heart functioning (reduced sinus tachycardia, decreased abnormal cardiac wall movements) as well as reducing EBV antibody levels. By the end of the 36-month trial many patients were able to resume normal activities. Patients with both EBV and CMV infections did not improve.

**PROTOCOL.** Valtrex is prescribed at 2000 mg/day, and then reduced. Patients can expect to take it for over a year.

**PROS AND CONS.** Valtrex may be very effective for patients with high herpesvirus and EBV titers alone. It is less effective against HHV-6 than Valcyte.

**AVAILABILITY AND COST.** Valtrex is available with a prescription from most pharmacies. It is expensive. A one-month supply can cost upwards of \$350.

#### PATIENT REVIEWS

*CFS/ME patient reviews of Valtrex:* <http://www.revolutionhealth.com/drugs-treatments/rating/valtrex-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### VALGANCYCLOVIR (Valcyte)

**DESCRIPTION:** Valcyte is an antiviral drug approved for treating cytomegalovirus (CMV) infections. Valcyte is a prodrug, converting quickly to ganciclovir after oral administration.

**USES IN CFS/ME.** In 2001 and 2002, Lerner et al conducted small trials of Valcyte which showed that the drug reduced EBV titers and significantly improved the symptoms of a subset of patients. In 2007 Dr. Jose Montoya of Stanford Hospital Infectious Disease Clinic, conducted a double blinded placebo controlled clinical trial to determine whether CFS/ME patients with elevated antibody titers for HHV-6 and EBV would benefit from valganciclovir treatment. The trial enrollment was small (30 patients), however the study indicated that patients on Valcyte experienced significant cognitive improvement.

Valcyte is one of the newer antivirals, so there is not yet a lot of feedback on its success rate in the CFS/ME population. The Holtorf Medical Group in Torrance, California, has used Valcyte since 2003 for treating CFS/ME, and has found it to be effective in patients with “flu-like symptoms or having symptoms that started with a flu-like illness; elevated IgG or EA against Epstein bar virus, cytomegalovirus and/or HHV-6; low natural killer cell activity; high RNase-L activity; high ACE (>35); coagulation activation; high tumor necrosis factor (TNF); low melanocyte stimulation hormone (MSH); high interleukin-6 (IL-6); low WBC; increased 1-25 vitamin D/25 vitamin D ratio and/or elevated or decreased total IgA, IgM or IgG levels.” In the absence of similar testing, it would be difficult to evaluate which patient sub-group would best benefit from Valcyte.

**PROS AND CONS.** Patients who have taken Valcyte for several months have reported significant side effects, including muscle weakness, flu-like symptoms and joint pain in spite of a dramatic decline in viral titers. Nearly all patients feel significantly worse for the first two to four weeks. Valcyte is prohibitively expensive. A one-month supply costs between \$1500 and \$2000.

SEE: In Search of a Cause

#### FURTHER READING

*Summary of Valtrex studies:*

<http://aboutmecfs.org.violet.arvixe.com/Trt/TrtValtrex.aspx>

*Summary of Dr. Lerner's antiviral research and treatment of CFS/ME patients.*

<http://aboutmecfs.org.violet.arvixe.com/Int/Lerner.aspx>

*Dr. Guyer discusses his antiviral protocol:*

<http://www.prohealth.com/library/showarticle.cfm?libid=13222>

## RESEARCH

Lerner, A Martin, Safedin Beqaj, James T Fitzgerald, Ken Gill, Carol Gill, James Edington. "Subset- directed antiviral treatment of 142 herpesvirus patients with chronic fatigue syndrome." *Dovepress Journal*: May 2010 Volume 2010:2 Pages 47 – 57

## ARTESUNATE (Hepasunate)

**DESCRIPTION.** Artesunate is a semi-synthetic anti-malarial drug derived from *artemisia annua* (wormwood).

**BACKGROUND.** While artemisia has been used for centuries as an herbal anti-parasitic, it wasn't until the 1960s that Chinese scientists developed an artemisinin drug to combat malaria. Since then, artesunate and other artemisia-based drugs have been used worldwide to combat malaria. However, it was not until 2007 that the FDA approved artesunate for the treatment of severe malaria in the United States. The action of artesunate is still unclear, but it is thought to kill the parasite by destroying its mitochondrial membrane.

**USES IN CFS/ME.** Recent cell studies indicate that artesunate significantly reduces viral protein production in HHV-6 infected cells. An *in vitro* study in 2005 confirmed that artesunate also significantly reduces cytomegalovirus (CMV) replication in cells. Because so many CFS/ME patients test positive for HHV-6 and CMV reactivation, artesunate may provide a means to control, if not eliminate, the symptoms associated with the proliferation of the viruses. Although this drug is experimental, some doctors are using it to treat CFS/ME, with positive results. Dr. Cheney has observed a reduction in viral titers, and a cessation of diastolic heart dysfunction.

**PROTOCOL.** Dr. Cheney puts his patients on 50 mg of Hepasunate (the form of artesunate available for online purchase) three days a week (empty ½ capsule under the tongue, hold for a minute, swish, and spit), and wormwood elixir 4 days a week (½ tsp in water, swish and spit).

**PROS AND CONS.** This supplement is highly experimental for CFS/ME, which means that few doctors use it, and, as a consequence, patients who take it independently may not be monitored for side effects, toxicity, or drug interactions.

As one might expect, reports from patients who have tried artesunate are mixed. Some report a significant reduction in fatigue and flu-like symptoms. Others report dizziness, diarrhea and malaise. There is no way of determining from these reports whether the side effects (or improvements) are due to the dosage, brand or, perhaps, completely independent factors. This is a "use at your own risk" medication, so you are advised to exercise caution and go slowly. The twice a week swish and spit method is the gentlest way to introduce artesunate.

**AVAILABILITY AND COST.** Hepasunate (the brand Dr. Cheney uses) can be purchased online for \$50 for a bottle of 50 capsules. Before trying artesunate, please

read the following Phoenix Rising forum discussing the experiences of patients who have followed Dr. Cheney's artesunate protocol. It contains details of the experiences of patients who have taken artesunate, as well as links to useful articles.

#### FURTHER READING

*CFS/ME patient forum on artesunate:*

<http://forums.phoenixrising.me/showthread.php?601-Artesunate-Cheney-dosage-and-benefits>

*This thread provides detailed information about side effects, dosage, and efficacy.*

*Supplier of Hepasunate in the U.S.:* <http://www.hepalin.com/hepasunate50.htm>

Efferth, Thomas, Marta R. Romero, Dana G. Wolf, Thomas Stamminger, Jose J. G. Marin, and Manfred Marschall. "The Antiviral Activities of Artemisinin and Artesunate." *Clin Infect Dis.* (2008) 47 (6):804-811.

<http://cid.oxfordjournals.org/content/47/6/804.long>

*This is an excellent article on the history, mechanisms and effects of artesunate.*

#### RESEARCH

Auerochs S, Korn K, Marschall M. "A reporter system for Epstein-Barr virus (EBV) lytic replication: anti-EBV activity of the broad anti-herpesviral drug artesunate." *J Virol Methods.* 2011 May;173(2):334-9. Epub 2011 Mar 17.

<http://www.ncbi.nlm.nih.gov/pubmed/21396962>

Chou S, Marousek G, Auerochs S, Stamminger T, Milbradt J, Marschall M. "The unique antiviral activity of artesunate is broadly effective against human cytomegaloviruses including therapy-resistant mutants." *Antiviral Res.* 2011 Nov;92(2):364-8. <http://www.ncbi.nlm.nih.gov/pubmed/21843554>

Efferth T, Kaina B. "Toxicity of the antimalarial artemisinin and its derivatives." *Crit Rev Toxicol.* 2010 May;40(5):405-21.

<http://www.ncbi.nlm.nih.gov/pubmed/20158370>

Gordi T, Lepist EI. "Artemisinin derivatives: toxic for laboratory animals, safe for humans?" *Toxicol Lett.* 2004 Mar 1;147(2):99-107.

Milbradt J, Auerochs S, Korn K, Marschall M. "Sensitivity of human herpesvirus 6 and other human herpesviruses to the broad-spectrum antiinfective drug artesunate." *J Clin Virol.* 2009 Sep;46(1):24-8.

<http://www.ncbi.nlm.nih.gov/pubmed/19501020>

#### BENZODIAZEPINES

Klonopin (clonazepam), Valium (diazepam), Xanax (alprazolam)

**DESCRIPTION.** Benzodiazepines are central nervous system depressants. They are classed as minor tranquilizers. Benzodiazepines comprise a very large group of drugs, with over 30 distinct formulations, and nearly 100 brand names.



**BACKGROUND.** The benzodiazepines are a group of drugs used to treat anxiety, skeletal muscle spasm, insomnia, and panic. Their calming effect is produced by a general slowing of the central nervous system. Within a decade of their introduction on the market, they had become one of the most frequently prescribed medications in the United States and, by the late 1980s, more than 10% of the U.S. population had taken some form of tranquilizer.

Although the benzodiazepines do not pose as many problems as the major tranquilizers, they also produce tolerance and dependence. Benzodiazepines can be classified into two main groups, depending on their half-life (how long it takes to clear half the drug from the body). In general, the shorter acting benzodiazepines (with a half-life of 4 to 20 hours) are more habit forming than those with a longer half-life (24 to 72 hours). In cases where dependence develops, doses should be tapered off slowly to avert withdrawal symptoms (anxiety, jitters, insomnia, confusion, sweating, heart palpitations, and depression).

**USES IN CFS/ME.** The benzodiazepines are frequently prescribed, often in combination with a small dose of antidepressant, to treat insomnia. The logic behind prescribing both drugs is that one gets you to sleep and the other keeps you asleep. The majority of CFS/ME physicians also recommend some form of benzodiazepine for patients with panic disorder or agitation due to upregulation of the sympathetic nervous system.

It is important to note that benzodiazepines are usually prescribed in small doses to treat CFS/ME. Normal doses of these drugs can produce paradoxical reactions, creating the very symptoms the drug is supposed to control. Even tiny doses can produce adverse reactions in patients hypersensitive to chemicals and drugs. It may be worthwhile to do a toothpick test (crush the pill and take only what clings to the end of a moistened toothpick) before embarking on a full program.

**KLONOPIN** (in Canada, Rivotril) (clonazepam)

**BACKGROUND.** Klonopin (clonazepam) acts directly on the limbic system, thalamus, and hypothalamus to produce anticonvulsant effects. It has been used since the late 1970s to control seizures. Klonopin is easily absorbed through the digestive tract and has a half-life of 24 to 72 hours. Effects are noticeable within 20 minutes and can last for 12 hours.

**USES IN CFS/ME.** Klonopin is the most widely recommended benzodiazepine for patients with CFS/ME. Dr. Cheney, a long-time proponent of the benefits of Klonopin, prescribes it to protect the brain against what he calls “excitatory neurotoxicity.” Most CFS/ME patients have excess amounts of neuroexcitatory neurotransmitters in their nervous systems, resulting in a brain which is overstimulated. The “tired and wired” feeling CFS/ME patients so often describe is the result of this excess stimulation. Because Klonopin is so long-acting, it serves to down regulate the nervous system. Klonopin is also beneficial for treating insomnia, especially if taken in conjunction with Sinequan. A number of patients have reported that Klonopin helps improve cognitive symptoms,

particularly poor concentration and “brain fog.” Some patients also report that Klonopin helps alleviate flu-like achiness.

**PROTOCOL.** The dose recommended to treat CFS/ME-related insomnia is low, generally 0.5 to 1 mg taken before bedtime for insomnia. Dr. Cheney also recommends daytime doses of a quarter of a tablet to increase energy and concentration.

**PROS AND CONS.** The side effects of Klonopin are mild, especially compared to those of some of the other benzodiazepines. Some patients with CFS/ME, however, experience sedation, excessive thirst, depression, and gastrointestinal upset even with small doses. Like all benzodiazepines, it loses its efficacy over time. If taken for longer than a month, Klonopin should not be discontinued suddenly. On the positive side, Klonopin appears to be well tolerated by many patients with CFS/ME. Patients report that the generic form is less effective than brand.

**AVAILABILITY AND COST.** Klonopin is available by prescription. A 30-day supply of the generic drug (clonazepam, 0.5 mg) costs about \$2. The cost is usually covered by insurance (but check for time limitations).

## PATIENT REVIEWS

*CFS/ME patient reviews of Klonopin:* <http://www.revolutionhealth.com/drugs-treatments/rating/klonopin-for-chronic-fatigue-syndrome-cfs-cfids-me>

## VALIUM

**BACKGROUND.** Valium (diazepam) was introduced in the United States in 1963. It acts by depressing the area of the central nervous system that controls the emotions (limbic system). It is also used as an anticonvulsant in patients with epileptic seizures and to relieve skeletal muscle spasms. Side effects from long-term use can include depression, drowsiness, lethargy, fainting, slurred speech, tremor, blurred or double vision, gastrointestinal disorders, nausea, and respiratory depression. It has a half-life of 20 to 50 hours. Onset occurs within 30 minutes to an hour, with peak action in 1 to 2 hours.

**USES IN CFS/ME.** Valium is less frequently recommended than Klonopin, nevertheless some people have found it to be very effective. In most cases, Valium is used for insomnia. It is taken just before bed. As with Klonopin, it should be taken at the lowest possible dose. If side effects or tolerance develop, Valium should be eliminated by slowly tapering off the dose.

**AVAILABILITY AND COST.** Valium is available by prescription. A one-month supply (30 tablets) of the generic drug at the lowest dose (2 mg) costs about \$15.

## XANAX

**BACKGROUND.** Xanax (alprazolam) was introduced in 1982 to treat anxiety, muscle spasms, and insomnia. It is also widely prescribed to treat panic attacks, agitated depression, and phobias. Xanax is more rapidly metabolized and eliminated than other benzodiazepines and causes less “hangover.” It has a half-life

of 12 to 15 hours, rapid onset (about 15 minutes), and its peak action occurs within 1 to 2 hours.

**USES IN CFS/ME.** Because Xanax acts so quickly, it is usually recommended to treat panic and anxiety attacks. It is not often prescribed for persistent insomnia, although it may be recommended on a short-term basis. As with other benzodiazepines, Xanax should be taken at the lowest possible dose. It is not recommended as a daily medication, but only as needed to alleviate the effects of panic or anxiety due to overactive nervous system responses. It is highly addictive.

**AVAILABILITY AND COST.** Xanax is available by prescription. It is inexpensive; a supply of 30 tablets of the generic drug (alprazolam) at the lowest dose (0.25 mg) costs about \$7.

SEE: Cognitive and Emotional Symptoms, Sleep Disorders

#### PATIENT REVIEWS

*CFS/ME patient reviews of Xanax:* <http://www.revolutionhealth.com/drugs-treatments/rating/xanax-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### BETA BLOCKERS

Propranolol (Inderol), Atenolol (Tenormin), Labetalol (Normodyne), Nebivolol (Bystolic)

**DESCRIPTION.** Beta blockers slow heart activity by interfering with adrenal hormones.

**BACKGROUND.** Beta blockers are used primarily to treat angina and high blood pressure, and to control irregular heartbeat in damaged hearts. They can also be used to prevent migraine headaches, control ocular fluid pressure, and reduce anxiety. Beta blockers work by occupying the specific receptors in the heart, airways, and blood vessels (beta1 and beta2 adrenergic receptors) designed to receive the stimulating neurohormone, norepinephrine. By preventing the action of norepinephrine, beta blockers reduce the force and rate of heartbeats and prevent dilation of blood vessels surrounding the brain and of the airways leading to the lungs. The action of most beta blockers makes them useful for treating neurally mediated hypotension (NMH), an abnormal reflex interaction between the heart and brain. Patients with NMH experience sudden drops in blood pressure, leaving them feeling faint and weak. Beta blockers are used to help maintain constant blood pressure in NMH.

**USES IN CFS/ME.** According to Dr. Lapp, various forms of dysautonomia (including NMH), postural orthostatic tachycardia syndrome (POTS), and other forms of orthostatic intolerance occur in 96% of CFS/ME patients. Researchers of the Northern CFS/ME Clinical Network and Newcastle University found that POTS is three times more likely to occur in CFS/ME patients than in the general population. And researchers at Johns Hopkins University have published findings that seem to demonstrate a link between CFS/ME and NMH. Beta blockers have

been prescribed to treat to treat low blood pressure common in CFS/ME, NMH and POTS as well as idiosyncratic heart problems (palpitations, mitral valve prolapse, and rapid or irregular heartbeat) and, in some circumstances, anxiety and headaches.

**PROTOCOL.** The beta blockers usually recommended for NMH are propranolol and atenolol (Tenormin). CFS/ME doctors recommend a very low dose. Beta blockers are normally prescribed as part of a program that includes increased intake of dietary salt and Florinef (fludrocortisone), a steroid drug (see Florinef). Beta blockers should not be taken with any food, drug, or other medication that contains caffeine or alcohol because the combination may increase heart rate or blood pressure. Dr. Light proposes that low-dose Nordyne, a combined alpha and beta adrenergic antagonist used to treat high blood pressure, might be of benefit for patients who don't respond to propranolol.

**PROS.** In 1995 a Johns Hopkins University study led by Issam Bou-Holaigah and Peter Rowe created quite a stir in the CFS/ME community (*Journal of the American Medical Association*, 1995). Of the 22 patients with CFS/ME and NMH treated in this study, nine reported full recovery and seven noted some improvement on beta blockers. (However, it should be noted that not all of these patients received beta blockers; some were given only Florinef.) These initial results were encouraging. Reports from CFS patients have since been mixed, but some claim substantial improvement from beta blockers.

**CONS.** Symptoms of CFS/ME do not always respond favorably to beta blockers. Some patients report little or no effect. A little over 50% report that symptoms actually get worse. Moreover, long-term and severe cases have not shown substantial improvement using this regimen. Beta blockers can cause the very symptoms they are supposed to alleviate: orthostatic hypotension (the feeling of fainting on standing), fatigue, dizziness, light-headedness, depression, and headaches.

Other common side effects include drowsiness, decreased sex drive, nervousness, depression, nightmares, upset stomach, constipation, and diarrhea. An additional consideration for those who have taken beta blockers for a long period of time is that the drug should not be discontinued suddenly but should be tapered off gradually over several weeks to avert irregularities in heart rate. People with poor circulation in the arms and legs, a frequent problem in CFS/ME, are also cautioned not to take beta blockers because these drugs make the problem worse. Beta blockers may also lower melatonin levels in the body, which may lead to insomnia. Those with mast cell disorders should not take beta blockers.

**AVAILABILITY AND COST.** Beta blockers are available by prescription. The cost ranges from \$4 a month for the older beta blockers to \$10 a month for the newer ones. Beta blockers are usually covered by insurance.

#### FURTHER READING

*Dr. Lapp on orthostatic intolerance:* <http://www.cfids.org/about-cfids/diagnostic-testing.asp>

*CFIDS Association of America's review of medications used to treat orthostatic intolerance.* <http://www.cfids.org/cfidslink/2009/070104.asp>  
*Survey of CFS/ME patients using beta blockers:*  
<http://www.cfidsresearch.com/2011/02/22/beta-blockers/>

## PATIENT REVIEWS

*A patient's experience with atenolol:* <http://www.revolutionhealth.com/drugs-treatments/rating/tenormin-for-chronic-fatigue-syndrome-cfs-cfids-me>

## RESEARCH

Bou-Holaigah, Issam, Rowe, Peter C, Ran, Jean, and Calkins, Hugh. "The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome." *Journal of the American Medical Association*. 274(12):961-967,1995. <http://www.ncbi.nlm.nih.gov/pubmed/7674527> (Abstract)

Raj, Satish MS, Bonnie Black, RN, Italo Biaggioni MD, Sachin Y. Paranjape, Maricelle Ramirez, William D. Dupont, PhD, David Robertson, MD. "Propranolol Decreases Tachycardia and Improves Symptoms in the Postural Tachycardia Syndrome: Less is More." *Circulation*. 2009; 120: 725-734. <http://circ.ahajournals.org/content/120/9/725.full>

## CALCIUM CHANNEL BLOCKERS

Nicardipine, Nimodipine, Nifedipine, Verapamil

**DESCRIPTION.** Calcium channel blockers inhibit the transmembrane influx of calcium ions into cardiac and smooth muscle.

**BACKGROUND.** Calcium channel blockers work by preventing calcium ions from entering smooth muscle cells. Calcium is especially important for the functioning of these cells and specialized cells in the heart. When calcium levels are lowered, the result is a relaxation of blood vessels, allowing an increased supply of blood and oxygen to the heart while decreasing its work load. As a consequence of their effect on blood vessels, calcium channel blockers are useful in treating cardiovascular disorders, such as angina (chest pain) and coronary artery disease, and to lower blood pressure. These drugs also may improve exercise capacity and subsequently reduce the need for surgery in patients with cardiac problems.

**USES IN CFS/ME.** At the 1990 CFIDS conference in Los Angeles, Dr. Ismael Mena presented evidence of cerebral dysfunction in patients with CFS/ME. Using neurological spectroscopic scanning techniques, Dr. Mena reported that 71% of CFS/ME patients have low blood flow (hypoperfusion) in the temporal lobe of the brain. He further reported that after treatment with calcium channel blockers, some of these patients exhibited clinically improved cerebral blood flow (*CFIDS Chronicle*, Spring/Summer 1990).

A number of CFS/ME clinicians have noted improvement in cognitive function in patients given calcium channel blockers. Cardene also is helpful in

treating migraine-type headaches. Dr. Jay Goldstein also observed improvements in cognitive function and energy level in patients given calcium channel blockers. He also noted increased exercise tolerance, decreased tender point sensitivity, and alleviation of panic disorder with nimodipine.

In October 1994, Dr. Robert Keller, Medical Director of the Center for Special Immunology in Miami, reported improvement of symptoms in 25 patients with CFS/ME after treatment with the calcium channel blocker verapamil. Within one month of finding the optimal dose of verapamil, patients reported improvement in fatigue, memory, and myalgia. Dr. Keller also reported a decrease in the number of activated T cells, demonstrating that calcium channel blockers may have some immunomodulatory properties.

In 2000, Chauduri et al correlated the symptoms of CFS/ME, particularly fluctuating fatigue, with abnormal ion channel function. This finding appears to have been borne out by an interesting double-blind study carried out by Dr. Weibe, in which a patient reported dramatic declines in fatigue, sleep disturbance, pain and mental “fog” after being given nimodipine as opposed to placebo.

**PROTOCOL.** The most commonly prescribed calcium channel blockers in patients with CFS/ME are nimodipine, nicardipine, and verapamil. Doses must be individualized for each patient, but generally are quite low.

- Nimodipine 30 mg, 2 or 3 times daily
- Nicardipine 20 mg, 2 or 3 times daily
- Verapamil 120 to 240 mg, taken nightly

**PROS.** Symptomatic relief can be obtained quickly with calcium channel blockers; therefore a trial is often worthwhile in many cases, even in the absence of a single-photon emission computed tomography (SPECT) scan. Improved cognitive function, fewer headaches, increased energy, and decreased muscle spasms have all been reported with use of these drugs.

**CONS.** Although calcium channel blockers can be effective for some of the more problematic CFS/ME symptoms (e.g., cognitive dysfunction), side effects can be a problem. The most common are lowered blood pressure (which can be serious if blood pressure is already low), severe pressure headaches, dizziness, gastrointestinal problems (diarrhea, constipation), and weakness. In addition, hypertensive effects can be exaggerated by concomitant use of other drugs that affect blood pressure, such as beta blockers. Tagamet (cimetidine) also increases the effects of calcium channel blockers. The use of calcium channel blockers requires close supervision by a physician due to their effects on blood pressure. Most CFS/ME doctors do not include calcium channel blockers in their protocols, except for patients who have high blood pressure. Not recommended for people with a history of kidney problems.

**AVAILABILITY AND COST.** Calcium channel blockers are available by prescription. Nimodipine is expensive, costing between \$1.75 and \$5.00 a pill. Nicardipine and verapamil are much less expensive, about \$10 - \$15 for 30 tablets. Insurance usually covers.

## FURTHER READING

*A detailed discussion by Cort Johnson of the role ion channels play in CFS.*

<http://aboutmecfs.org.violet.arvixe.com/Rsrch/NeurologicalChannelopathy.aspx>

Weibe, E. "Managing Chronic Fatigue Syndrome: Two Case Reports." *Can Fam Physician*. 1996 November;42: 2214–2217.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2146911/?page=1>

## RESEARCH

Chaudhuri, A., W.S. Watson, J. Pearn and P.O. Behan. "The Symptoms of Chronic Fatigue Syndrome are Related to Abnormal Ion Channel Function." *Med Hypotheses*. 2000 Jan;54(1):59-63.

<http://www.ncbi.nlm.nih.gov/pubmed/10790725> (Abstract)

## CENTRAL NERVOUS SYSTEM STIMULANTS

Ritalin, Dexedrine, Lonamin, Provigil, Strattera

**DESCRIPTION.** Central nervous system (CNS) stimulants are a class of drugs that, much like the amphetamines, speed CNS responses by releasing stored norepinephrine from nerve terminals in the brain.

**BACKGROUND.** CNS stimulants have played an important role in human history. The cultivation of chocolate, which contains small amounts of caffeine (a xanthine alkaloid) goes back to 1100 B.C. Chocolate's reputation as an aphrodisiac is, no doubt, partially due to its stimulating effects. Tea, which contains about 3% caffeine, has been under cultivation since the 10<sup>th</sup> century B.C. Coffee, which is approximately 1.2% caffeine, has been consumed as a stimulant since the 13<sup>th</sup> century. In fact, coffee was so stimulating that it was banned under Charles II, who blamed the drink for inciting the people to sedition. (Pope Clement VIII also banned coffee until it was revealed that he himself was a major importer of the "devil's drink," whereupon he immediately baptized the brew, making it safe to drink.)

In the 19<sup>th</sup> and early 20<sup>th</sup> century, cocaine, another CNS stimulant, was used to treat depression. Sigmund Freud, an early proponent of the curative powers of cocaine, recommended cocaine as a cure for depression, sexual impotence, and as an anesthetic. Amphetamines, first synthesized in 1887, were used for asthma, and in the 1940s became widely used for weight loss. By the 1960s CNS stimulants were prescribed as treatments for a variety of disorders, including hyperactivity, depression, and attention deficit disorder (ADD). In 2004 the FDA approved the stimulant modafinil (Provigil) for the treatment of narcolepsy.

**USES IN CFS/ME.** CNS stimulants are generally used to increase energy and cognitive function. The drug most commonly recommended for CFS/ME patients is Ritalin (methylphenidate), although Dexedrine (dextroamphetamine) is also sometimes prescribed. Lonamin (phentermine), a mild CNS stimulant that activates dopamine in the brain, is sometimes recommended in CFS/ME patients with hypersomnia or significant cognitive impairment. The mild stimulation induced by a low dose of any of these drugs can often dispel feelings of lethargy and

“brain fog” and, because effects are so immediate, they can act as a quick fix in an emergency.

While there is great appeal in seeing immediate improvement in energy levels and cognitive function, most CFS/ME clinicians prescribe these drugs with caution. Dr. Cheney believes that the disabling fatigue of CFS/ME may be a protective mechanism. Therefore, creating energy artificially may in the long run cause relapse and may even exacerbate the disease process.

**PROTOCOL.** Dosage varies according to the individual needs of the patient, as determined by a physician. Patients with CFS/ME, however, are advised to start with the smallest dosage to avert the negative effects of overstimulation. Dexedrine, for example, is prescribed at the lower than usual dose of 5 to 10 mg. Lonamin dosage varies between 15 and 30 mg (taken in the morning).

- For the subset of CFS/ME patients with fibromyalgia, Dr. Bateman recommends Adderall, starting with the lowest dosage and working up to 5-20 mg. two to three times a day. Dr. Bateman also uses Provigil (modafinil) 50-400 mg (long-acting) as well as Wellbutrin, a stimulant antidepressant.
- Dr. Lapp recommends using low doses of CNS stimulants such as Ritalin, Adderall or Provigil for fatigue. Dr. Lapp has found that “Provigil not only improves fatigue, but also somnolence, mental clarity, attention deficits, and depression.”
- Surprisingly, while Dr. Teitelbaum advises that CFS/ME patients steer clear of coffee, he recommends 10-30 mg of Ritalin taken three times a day up to a maximum of 60 mg/day. Dr. Teitelbaum observes that “the medications ritalin and dexedrine can be very helpful at lower doses in those with chronic fatigue syndrome, as they help stabilize the low blood pressure and the low dopamine levels found in chronic fatigue syndrome.”
- Dr. Rowe recommends that ME/CFS patients with orthostatic intolerance take low doses of vasoconstrictor medications, including Ritalin and Dexedrine to treat blood pooling. He recommends 5 mg in the morning repeated, if necessary, four hours later.

**PROS.** It appears that the less ill the patient the better the response. The boost received from these drugs may enable patients with mild symptoms to work full-time or part-time. Most people use CNS stimulants on an "as needed" basis to provide extra energy on particularly long or important days. Many patients report a lessening of “brain fog” as well as increased focus and stamina. Doses for these patients have been very small.

**CONS.** Whereas CNS stimulants have been effective in some patients, they are of modest to little benefit for most. Stimulants, while appearing to provide more energy, tax the system. As a consequence, they are beneficial only if the system is strong to begin with. A number of patients report feeling much worse while taking stimulants. The most common side effects are anxiety, excitation, insomnia, gastrointestinal problems, dizziness, headache, palpitations, dry throat, appetite loss, chest pain, and hypertension. Patients also report that Ritalin causes anxiety



and paranoia. With nearly all CNS stimulants, patients report rebound fatigue after the drug wears off.

As with other medications that affect the CNS, some patients experience a paradoxical reaction of extreme fatigue and weakness. Drug interactions are numerous, including antidepressants (especially MAOIs), anticonvulsants, and caffeine. As with MAOIs, foods high in tyramine should be avoided (see Urinary Tract Problems). CNS stimulants are contraindicated in patients with cardiovascular disease or hyperthyroidism.

**AVAILABILITY AND COST.** CNS stimulants are available by prescription, either as brand name or generic drug. Most of the older varieties are fairly inexpensive. Ritalin, for example, costs about \$25 a month. Provigil, a newer drug, costs upwards of \$250 a month. Insurance usually reimburses the cost.

### FURTHER READING

*Dr. Bateman's protocol, including stimulants:*

<http://www.offerutah.org/cfsmetreatment.htm>

*Drs. Bateman, Natelson, and Lapp discuss CNS stimulant protocols for fibromyalgia and CFS/ME.* <http://www.fmnetnews.com/articles-hot.php>

*Summary of CNS stimulants used for CFS/ME patients:*

[http://phoenixrising.me/?page\\_id=2299](http://phoenixrising.me/?page_id=2299)

*Summary of Provigil's use in CFS/ME:* [http://phoenixrising.me/?page\\_id=4803](http://phoenixrising.me/?page_id=4803)

*Summary of dexedrine's use in CFS/ME:* [http://phoenixrising.me/?page\\_id=4762](http://phoenixrising.me/?page_id=4762)

*Effects of caffeine and CNS stimulants on patients with CFS/ME. Observations on use of CNS stimulants by Drs. Teitelbaum and Papernik:*

<http://www.everydayhealth.com/chronic-fatigue-syndrome/relief-with-caffeine.aspx>

### PATIENT REVIEWS

*CFS/ME patient ratings of Adderall:* <http://www.revolutionhealth.com/drugs-treatments/rating/adderall-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of dexedrine:* <http://www.revolutionhealth.com/drugs-treatments/rating/dexedrine-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of methylphenidate (Ritalin and Concerta).*

<http://www.revolutionhealth.com/drugs-treatments/rating/methylphenidate-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of phentermine:* <http://www.revolutionhealth.com/drugs-treatments/rating/phentermine-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Provigil:* <http://www.revolutionhealth.com/drugs-treatments/rating/provigil-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Strattera:* <http://www.revolutionhealth.com/drugs-treatments/rating/pamelor-for-chronic-fatigue-syndrome-cfs-cfids-me>

CYTOTEC (misoprostol)

*CAUTION: Do not take Cytotec during pregnancy.*

**DESCRIPTION.** Cytotec (misoprostol) is a synthetic prostaglandin analogue that replaces depleted gastric prostaglandins.

**BACKGROUND.** Cytotec is routinely used to prevent gastric ulcers in elderly or debilitated patients who are receiving nonsteroidal anti-inflammatory drug (NSAID) therapy. In these patients, the actions of natural prostaglandins (hormone-like substances that regulate inflammation, blood vessel dilation, and a host of other physiological responses) are blocked.

**USES IN CFS/ME.** Cytotec is primarily recommended for patients who are taking non-steroidal anti-inflammatory drugs (NSAIDs). Cytotec not only protects the stomach lining from the damaging effects of pain killers, it also appears to protect the small intestines. Dr. Leo Galland believes the drug can prevent “leaky gut,” a condition in which the small intestine becomes overly permeable, thereby leading to food sensitivities and allergies. Cytotec is also used to treat Interstitial Cystitis (IC), a condition experienced by many people with CFS/ME. In 1998 Kelly et al found that 24 out of 25 patients with IC improved after receiving misoprostol, with minimal side effects.

**PROTOCOL.** Physicians recommend taking four 100 mcg tablets a day (one with each of three meals and one before bedtime). When reducing dosage, the bedtime dose should be the last tablet eliminated.

**PROS AND CONS.** Patients who have taken Cytotec to treat the symptoms of IC describe it as a “miracle.” Many patients who have tried Cytotec for food sensitivities report an increase in the number of foods they can tolerate and a decrease in related gastrointestinal symptoms. Patients with severe food intolerance have noted sustained improvement even after eventually discontinuing Cytotec. Cytotec has relatively few side effects. The most common side effects are diarrhea, flatulence, nausea, headache, and, rarely, vaginal bleeding. If side effects last longer than a week or are severe, the dosage should be lowered. Cytotec is contraindicated in pregnant women, because it may induce miscarriage.

**AVAILABILITY AND COST.** 100 pills of the generic cost between \$30 and \$55. Cytotec is available by prescription, and the cost is covered by most insurance plans. Uninsured patients may meet the manufacturer's criteria for its "Patients in Need" program and qualify for a free supply (contact Searle, 5200 Old Orchard Rd., Skokie, IL 60077; 800-542-2526).

#### FURTHER READING

*A general review of the therapeutic uses of misoprostol.*

<http://www.ncbi.nlm.nih.gov/pubmed/11191738>

#### RESEARCH

Kelly JD, Young MR, Johnston SR, Keane PF. “Clinical response to an oral prostaglandin analogue in patients with interstitial cystitis.” *Eur Urol.* 1998;34(1):53-6. <http://www.ncbi.nlm.nih.gov/pubmed/9676414> (Abstract)

## DIAMOX

**DESCRIPTION.** Diamox (acetazolamide) is a carbonic anhydrase inhibitor.

**BACKGROUND.** Diamox was introduced in 1953 as a diuretic. Because it reduces intraocular pressure, it is used to treat glaucoma. Diamox can also be used to treat edema, high-altitude sickness, and as an anticonvulsant. Diamox blocks the action of carbonic anhydrase, an enzyme that helps form hydrogen and bicarbonate ions from carbon dioxide and water. It promotes excretion of sodium, potassium, water, and bicarbonate. By blocking carbonic anhydrase in the central nervous system and increasing carbon dioxide tension, Diamox also helps decrease abnormal neuronal discharge that may lead to convulsions. Because Diamox lowers blood pH, and encourages respiration, it has been prescribed to help with sleep apnea as well. Other uses include absence seizures, periodic paralysis and congestive heart failure.

**USES IN CFS/ME.** Dr. Cheney has found Diamox very useful to treat pressure-type headaches in CFS/ME patients. He also found that it helped balance problems, and, over time, improved neurocognitive function, as it increases blood flow to the brain. Patients taking Diamox often report increased energy.

**PROTOCOL.** Diamox usually is prescribed at 250 mg to be taken two or three times a day. The Academy of Medicine of New Jersey recommends 500 mg of Diamox prior to bedtime to lower cerebral spinal blood pressure in patients with headaches. In *A Doctor's Guide to Chronic Fatigue Syndrome*, Dr. Bell advises starting Diamox at very low doses. He recommends using this drug with caution and discontinuing if side effects should appear. Because Diamox is a diuretic, potassium supplementation or potassium-rich foods (bananas and apricots) may be necessary. Diamox can be taken with food to lessen the chance of nausea or stomach irritation.

**PROS AND CONS.** For severe, hard-to-treat headaches, Diamox can be a real boon. It is also one of the few drugs that can actively help with cognitive impairment. Diamox acts within a couple of weeks; therefore, a long trial is not necessary. On the negative side, it can create metabolic acidosis, weakness, skin tingling, loss of appetite, and near-sightedness; may cause allergic reactions in people allergic to sulfa drugs; and may activate gout or cause syndromes similar to lupus if taken for extended periods. Diamox can increase the effects of tricyclic antidepressants. Not recommended for patients with kidney stones.

**AVAILABILITY AND COST.** Diamox is available by prescription only. It is inexpensive. A one-month supply costs roughly \$10. Insurance usually covers.

SEE: Headaches

## FURTHER READING

*The Academy of Medicine of New Jersey's 2002 manual on treating CFS/ME.*

<http://www.njcfsa.org/Manual.pdf>

*The 1995 Cheney lectures.*

<http://homepage.mac.com/doctormark/Medical/CFS/CFSpapers/cheneylecturescfs.html>

## EPOGEN (PROCRIT)

**DESCRIPTION.** Epogen is human erythropoietin, a glycoprotein that controls red blood cell production in bone marrow.

**BACKGROUND.** Epogen has been approved for treating anemia caused by kidney failure or chemotherapy, and after certain types of surgery in order to decrease the need for blood transfusions. Epogen has also been used to treat orthostatic hypotension, a condition in which blood pressure drops upon standing, causing light-headedness, dizziness or fainting.

**USES IN CFS/ME.** Dr. Hugh Calkins, a cardiologist at Johns Hopkins, has observed that CFS/ME is closely associated with neurally-mediated hypotension (NMH). He found that 90% of CFS/ME patients have some form of NMH. This observation was independently confirmed by Dr. David Streeten who discovered that among two groups of patients with orthostatic intolerance (OI), one had an abnormally low volume of red blood cells, and another had low plasma circulation. As it turned out, both of these were people with CFS/ME. Dr. Streeten treated these patients using protocols and medications for OI, including Florinef, beta-blockers and epogen to raise standing blood pressure. It wasn't until he was contacted by Dr. Bell, whose CFS/ME patients were exhibiting the same symptoms, that Dr. Streeten realized he had successfully treated a group of CFS/ME patients. Since that time, most doctors in the CFS/ME community have incorporated NMH treatments into their protocols.

In an important study conducted at the University of Miami, Hurwitz et al observed that 60-70% of CFS/ME patients show below normal red blood cell volume. The authors concluded that “the findings indicate that lower cardiac volume levels, displayed primarily by subjects with severe CFS, were not linked to diminished cardiac contractility levels, but were probably a consequence of a co-morbid hypovolaemic condition.” This study was significant because it proved that diminished blood volume was pervasive among CFS/ME patients. Unfortunately, while Procrit increased red blood cell volume, fatigue and exercise intolerance did not improve in the treated group.

**PROTOCOL.** Very few CFS/ME doctors use Procrit. Dr. Shoemaker treats his patients with 8,000 units of Procrit twice a week for five doses and then decreases the dosage to 4,000 to 6,000 every three to five days. This rather intensive protocol has not gone without criticism from doctors who point out that the “off label” use of Procrit for non-anemic patients is risky.

**PROS AND CONS.** Procrit is by no means a proven treatment for the correction of low blood volume in CFS/ME. In fact, even weeks after correcting low red blood cell volume in CFS/ME patients, Hurwitz et al noted that there was no corresponding reduction in symptoms. Procrit includes a boxed warning that “ESAs [Erythropoiesis-Stimulating Agents] increase the risk of death, myocardial

infarction, stroke and thrombosis.” Needless to say, CFS/ME patients should give careful thought to the possible risks before embarking on a protocol that includes Procrit.

#### FURTHER READING

*Safety update from the makers of Procrit:* <http://www.procrit.com/>  
*CFS/ME Forum review of treatments for NMH in CFS/ME:* <http://www.ncf-net.org/forum/orthostatic98.htm>  
*Fall 2002 CFIDS Chronicle Q&A with Dr. Hurwitz about Procrit.*  
<http://www.cfids.org/archives/2002/2002-4-article01.asp>

#### RESEARCH

Hurwitz, Barry E., Virginia T. Coryell, Meela Parker, Pedro Martin, Arthur LaPerriere, Nancy G. Klimas, George N. Sfakianakis and Martin S. Bilsker. “Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function.” *Clinical Science* (2010) 118, (125–135) (Printed in Great Britain) <http://www.clinsci.org/cs/118/cs1180125.htm>

#### FLEXERIL

**DESCRIPTION.** Flexeril (cyclobenzaprine) is a muscle relaxant used to treat pain and skeletal muscle spasms.

**BACKGROUND.** Flexeril is closely related to tricyclic antidepressants such as Elavil and Tofranil. The drug works by blocking nervous system impulses from the spinal cord to skeletal muscle. Researchers are not entirely sure how Flexeril specifically blocks pain impulses. Some claim that the drug's tricyclic properties (blocking the uptake of serotonin and norepinephrine) exert direct analgesic effects. Other studies seem to indicate that the inhibition of serotonergic pathways alone are responsible for a decreased firing of motor neurons.

**USES IN CFS/ME.** Flexeril is a commonly prescribed medication that can be extremely beneficial in treating the fibromyalgia component of CFS/ME. Because it is sedating, it is also used to treat insomnia.

**PROTOCOL.** For muscle pain, 10 mg one to three times a day is recommended. To treat insomnia, Dr. Teitelbaum recommends 10 mg at bedtime. Patients who are sensitive to medications may wish to start with 5 mg or lower.

**PROS AND CONS.** Flexeril is an older drug with a good safety record and minimal side effects. The most common side effects are excess sedation the next day (a “sleep hangover”) and dry mouth. Both CFS/ME and fibromyalgia patients report that Flexeril is most useful for episodes of muscle spasms or back pain. Most patients who are intolerant to other sleep medications report that it relieves insomnia. Flexeril is not addictive, but, as is the case with many sleeping pills, it tends to lose its effectiveness over time. Because of its anticholinergic effects, Flexeril is contraindicated in patients who have taken an MAOI within 14 days, have a history of heart arrhythmias, or are taking other anticholinergic drugs (such as antihistamines).

**AVAILABILITY AND COST.** Flexeril is available by prescription, in generic or brand-name formulations. The drug is inexpensive. A one-month supply of the generic costs as little as \$7 and is covered by most insurance policies.

SEE: Pain, Sleep Disorders

## PATIENT REVIEWS

*CFS/ME patient reviews of Flexeril:* <http://www.revolutionhealth.com/drugs-treatments/rating/flexeril-for-chronic-fatigue-syndrome-cfs-cfids-me>

## FLORINEF

**DESCRIPTION.** Florinef (fludrocortisone) is a synthetic corticosteroid.

**BACKGROUND.** Florinef is primarily used to treat patients with Addison's disease, a condition in which the adrenal glands do not produce sufficient adrenal steroids. Florinef is also a first-line treatment for orthostatic intolerance; it helps the body retain salt which otherwise would be passed in the urine. Because it has mineralocorticoid activity, its effects are limited to regulation of electrolyte and water balance. Like other corticosteroids, Florinef will raise blood sugar levels.

**USES IN CFS/ME.** Florinef received considerable attention as a CFS/ME medication as the direct result of a highly publicized Johns Hopkins study of neurally mediated hypotension (NMH). In NMH, sudden decreases in blood pressure leads to fainting (syncope), light-headedness, trouble concentrating, and dizziness. As nearly all of the CFS/ME patients in the Johns Hopkins study tested positive for NMH, researchers have been hopeful about treatments that would address this particular symptom. Florinef, because of its ability to increase sodium retention, helps to raise blood pressure. In so doing, many symptoms associated with decreased blood pressure can be relieved.

**PROTOCOL.** Most physicians currently working with CFS/ME patients recommend starting at a low dose to avert any possible drug reactions. Prior to taking Florinef, Dr. Rowe recommends increasing salt and fluid intake, then beginning with ¼ tablet. He increases the dose by ¼ tablet every 4 to 7 days until a final dose of one tablet (0.1 mg) is reached. If there are no significant side effects, he recommends increasing to a maximum of 1½-2 tablets a day. Dr. Bell has observed that Florinef seems to work best on younger patients. One patient noted that Florinef must be taken exactly every 24 hours or symptoms return; thus a rigid schedule is advised once the medication is started.

Because Florinef causes the body to excrete more than the usual amount of potassium, a potassium supplement is advised. In addition, plenty of fluids should be consumed while taking this medication. The side effects of headache or stomach ache can be lessened when Florinef is taken with a full glass of water. The small amount of lactose in Florinef may cause some discomfort to those who are lactose intolerant or allergic to milk protein.

**PROS AND CONS.** Although Florinef has been highly touted as an overall CFS/ME treatment, CFS/ME specialists have pointed out that the success rate is

not high with this drug. Two randomized control studies conducted in 1998 and 2000 failed to show any improvement in a group of adult CFS/ME patients. In 2001 Rowe et al found that mono-treatment with Florinef fared no better than placebo in a group of 100 CFS/ME patients. Dr. Myhill has listed Florinef as one of the treatments “not worth trying.” She noted that Florinef produced nothing but swollen ankles in her patients.

Florinef can produce serious side effects, the most common of which are high blood pressure and depression. Florinef can also deplete the body of electrolytes (potassium, calcium and magnesium). Common side effects include difficulty sleeping, light-headedness, headache, appetite changes, nausea, increased sweating, and nervousness. Because of these side effects, some doctors recommend starting with licorice, which can mimic the action of steroids, but is a more gentle treatment.

Before embarking on a course of treatment with Florinef or its substitutes, patients are advised to undergo thorough testing to confirm NMH. Because these drugs affect blood pressure, treatment must be closely supervised by a physician.

AVAILABILITY AND COST. Florinef is available by prescription. A 30-day supply of 0.1 mg tablets costs about \$14.

SEE: Cardiac and Cardiovascular Symptoms; Herbs (licorice).

#### FURTHER READING

*Cort Johnson's excellent review of Florinef.*

<http://aboutmecfs.org.violet.arvix.com/Trt/TrtFlorinef.aspx>

*The Outs and Ins of OI. Excellent article by Kimberly McCleary on OI in CFS/ME.*

*Includes treatments:* <http://www.research1st.com/2011/06/19/the-outs-and-ins-of-oi/>

#### PATIENT REVIEWS

*Review of Florinef by an Australian with CFS/ME who has tried (and reviewed) many treatments.*

<http://livingwithchronicfatiguesyndrome.wordpress.com/2010/07/27/fludrocortisone-for-cfs/>

*CFS/ME patient reviews of Florinef:* <http://www.revolutionhealth.com/drugs-treatments/rating/fludrocortisone-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### RESEARCH

Peterson PK, Pheley A, Schroepel J, Schenck C, Marshall P, Kind A, Haugland JM, Lambrecht LJ, Swan S and Goldsmith S. “A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome.” *Arch Intern Med.* 1998 Apr 27;158(8):908-14. <http://www.ncbi.nlm.nih.gov/pubmed/9570178> (Abstract)

Rowe PC, Calkins H, DeBusk K, McKenzie R, Anand R, Sharma G, Cuccherini BA, Soto N, Hohman P, Snader S, Lucas KE, Wolff M, Straus SE. “Fludrocortisone

acetate to treat neurally mediated hypotension in chronic fatigue syndrome: a randomized controlled trial.” *JAMA*. 2001 Jan 3;285(1):52-9.

<http://www.ncbi.nlm.nih.gov/pubmed/11150109> (Abstract)

## GAMMA GLOBULIN

**DESCRIPTION.** Gamma globulin is a class of blood plasma proteins that contain antibodies.

**BACKGROUND.** Gamma globulin, or immunoglobulin, is a blood product pooled from many donors and processed so that it contains a high concentration of immunoglobulin G (IgG) and other antibodies that mitigate against and prevent certain diseases. Gamma globulin has been in use for more than 40 years to prevent hepatitis, particularly in health care workers, as a prophylactic during epidemics of measles and rubella, as an immune modulator in Kawasaki syndrome and in myasthenia gravis (a disease that affects the muscles).

**USES IN CFS/ME.** Although it has fallen out of favor in recent years, gamma globulin was one of the earliest CFS/ME treatments. The rationale behind the use of gamma globulin is twofold. First, it was reasoned that if CFS/ME were caused by a virus, particularly a common virus that most of the general public had been exposed to (such as Epstein-Barr virus), gamma globulin would contain certain antibodies to fight the virus.

Second, certain patients with CFS/ME had demonstrated deficiency of IgG subclasses and it was proposed that gamma globulin could correct this deficiency. While gamma globulin has sometimes been helpful in treating CFS/ME, it is not easy to determine why. It seems that patients who demonstrate IgG deficiency do not always respond better to gamma globulin therapy than do those without IgG deficiency. Several studies, both controlled and open, have been completed in the United States and other countries with inconclusive results.

- In 1986 Dr. James Oleske and colleagues from the New Jersey School of Medicine in Newark conducted an open trial of 12 patients with chronic Epstein-Barr virus infection (CFS/ME) with IgG or IgG subclass deficiency. These patients underwent intravenous gamma globulin therapy for one year. Symptoms improved in eight and showed no improvement in four, but did not worsen in any patients.
- Also in 1986, Dr. Richard DuBois of Atlanta, Georgia, reported the results of a double-blind controlled study of patients with chronic mononucleosis syndrome (CFS/ME) treated with intramuscular gamma globulin. Symptoms in 52% of the patients who received gamma globulin improved after treatment.
- In 1988 Dr. Phillip Peterson of the University of Minnesota headed a double-blind controlled trial of intravenous gamma globulin in 30 patients with CFS/ME. Patients received an infusion of gamma globulin every month for 6 months. Of these 30 patients, 12 (40%) had low IgG concentrations and 29 (9%) had a viral onset. Given the immunological deficiencies, a presumed viral component, and a severely affected group of patients, the results fell



short of expectations. No significant difference was demonstrated between the placebo and drug responses.

- In 1991 Dr. Denis Wakefield of Sydney, Australia, concluded a study of 49 patients with CFS/ME enrolled in a double-blind placebo-controlled study of intravenous gamma globulin. Twenty-three patients received gamma globulin infusions over 90 days, with encouraging results. Symptoms in 10 patients improved. In addition, several immune parameters tested showed improvement after treatment. Some side effects were reported, but they may have been due to the high dose of gamma globulin. Dr. Wakefield and his colleagues reported interest in undertaking a larger trial with a lower dose of gamma globulin.
- In 1997 Australian pediatrician Dr. K.S. Rowe published the results of a study of 70 adolescents (ages 12 to 18 years) with chronic fatigue syndrome who received intravenous gamma globulin therapy. After three months of treatment, significant improvement was noted, but there were some side effects.
- In 2001 Dr. Rowe's long-term study of pediatric patients who were followed for seven years also showed that patients experienced significant improvement. Unfortunately, there has been little research after 2001 into the potential benefits gamma globulin.

**PROTOCOL.** Intravenous gamma globulin may be infused once a month for six months or longer. Intramuscular (IM) gamma globulin can be injected once or twice a week for six weeks, after which the patient is reassessed. Dr. Paul Cheney has noted that IM gamma globulin is not as effective as intravenous administration (*CFIDS Chronicle*, Spring 1995).

**PROS.** Many leading clinicians continue to use gamma globulin therapy, with varying degrees of success. Gamma globulin is not usually a first-line treatment and is often used after other therapies have been attempted. Dr. Cheney has found gamma globulin particularly useful in helping reduce the frequency of upper respiratory tract infections in some patients. Dr. Murray Susser and Dr. Michael Rosenbaum, authors of *Solving the Puzzle of Chronic Fatigue Syndrome*, state that, although CFS/ME requires an integrative approach, if they had to choose the single most effective treatment, it would be gamma globulin. A number of more severely ill patients note improvement of almost all symptoms – notably, cognition, energy, and mood.

**CONS.** A significant number of patients note little or no benefit. Side effects include headaches, dizziness, and nausea, particularly if the dose is high or the rate of infusion is too fast. A number of patients with CFS/ME have expressed concern about the safety of gamma globulin, inasmuch as it is a blood product. Most physicians believe it is safe because, to date, there is no record of anyone contracting human immunodeficiency virus (HIV) from gamma globulin therapy. However, in early 1994 there were reports in newspapers concerning batches of gamma globulin overseas that were contaminated with hepatitis C virus.

In May 1994 a new manufacturing process for intravenous gamma globulin was developed that inactivates any viral contaminants. Gamma globulin therapy is now considered safe. Nevertheless, it is important to carefully discuss the risks and benefits with a physician.

**AVAILABILITY AND COST.** Gamma globulin is obtained through a physician and is usually administered in the office. Intravenous infusions are costly and can run as much as \$3000 a month. Some insurance companies reimburse the cost if the claim carefully documents specific immune dysfunction such as IgG subclass deficiency or hypogammaglobulinemia. Intramuscular gamma globulin is much less costly, generally around \$50 a vial.

## RESEARCH

Rowe KS. "Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents." *J Psychiatr Res.* 1997 Jan-Feb;31(1):133-47.

<http://www.ncbi.nlm.nih.gov/pubmed/9201655> (Abstract)

Rowe, Katherine S. MBBS, MD, MPH, Dip Ed (Lond), FRACP. "Five-Year Follow-Up of Young People with Chronic Fatigue Syndrome Following the Double Blind Randomised Controlled Intravenous Gammaglobulin Trial." *Journal of Chronic Fatigue Syndrome* (The Haworth Medical Press, an imprint of The Haworth Press, Inc.) Vol. 5, No. 3/4, 1999. <http://www.co-cure.org/infores6.htm>

## GcMAF

**DESCRIPTION.** GcMAF is a naturally occurring substance in the human body which destroys pathogens by activating macrophages. The acronym stands for Gc (a vitamin D binding protein) Macrophage Activating Factor.

**BACKGROUND.** In the early 1990s, Dr. Nobuto Yamamoto, director of the Division of Molecular Immunology and Immunotherapy at the Socrates Institute for Therapeutic Immunology in Philadelphia, Pennsylvania, discovered a substance that inhibited tumor production in mice. Throughout the 1990s Dr. Yamamoto continued his research, expanding it to cases of cancer in humans. But it wasn't until 2008 that Dr. Yamamoto published his groundbreaking study on breast cancer. In this study, weekly injections of GcMAF were given to 16 breast cancer patients. Within three months the tumors were eradicated, with no recurrence over the next four years.

Subsequent studies with GcMAF used for colorectal and prostate cancer yielded similar results. In all cases the tumors disappeared with no recurrence. The rationale behind the success of GcMAF is that when the naturally occurring Gc protein is destroyed by cancer cells (more specifically by an enzyme called nagalase) it hamstring the immune system's ability to make sufficient tumor-destroying macrophages. The result is an immunosuppressed state which allows the cancer to spread. Injecting GcMAF into cancer patients restores the compromised immune system, which then successfully combats the cancer.

The implications for other immune compromised patients are enormous. In 2009 Dr. Yamamoto published a study demonstrating that after fewer than 18 weekly administrations of GcMAF, HIV infection was also completely eradicated. According to the study, "no recurrence occurred and their healthy CD + cell counts were maintained for 7 years."

**USES IN CFS/ME.** Given the spectacular results of the Yamamoto studies one would have expected to have seen front-page spreads in the New York Times. However, apart from Reuters, the news agencies barely took notice. As of today, no clinics in the U.S. are using GcMAF as a treatment for cancer. Several prominent CFS/ME physicians, however, have begun using GcMAF for patients who test high in nagalase.

Dr. Kenny De Meirleir treated 108 of his CFS/ME patients with weekly administration of GcMAF. This group of patients showed high amounts of nagalase, which Dr. De Meirleir notes can be produced by intestinal bacterial infections as well as herpes and retroviral infections. (Dr. Chia also points out that nagalase can be elevated as a result of enteroviral infections, which produce small intestinal bacterial overgrowth (SIBO) leading to subsequent immune system dysregulation.) After an average of 15 weeks of treatment, 68 of the 108 patients reported significant improvement in fatigue, sleep, pain, cognitive impairment, orthostatic intolerance, and digestive disturbances. (See below for a link to Dr. De Meirleir's presentation.)

Because GcMAF causes an increase in immune system activation, Dr. De Meirleir recommends starting with a very low dose of GcMAF. Some CFS/ME patients have undiagnosed infections which could lead to Immune Reconstitution Inflammatory Syndrome (IRIS). Once the immune system is stimulated, symptoms due to co-infections can worsen. Of Dr. De Meirleir's 108-patient cohort, 20-30% of them experienced IRIS.

Dr. Cheney has also begun to treat patients with GcMAF, as well as with a natural yogurt probiotic MAF (MAF 314) developed by Professors Ruggiero and Pacini in Italy. GcMAF demonstrated a response rate of 79% (15 out of 19 patients), which is similar to Dr. De Meirleir's results. The oral MAF 314 demonstrated a response rate of 76% over a period of only 28 days.

**PROTOCOL:** There are several protocols currently in use. Most CFS physicians begin with 0.20 - 0.25 ml via injection (IM) weekly. Dr. Cheney starts his severely ill patients at a much lower dose administered sublingually, then gradually increases the dose. Typically, the full course of treatment is 8-20 weeks. In order to be effective, GcMAF requires adequate levels of vitamin D. Patients should be tested for vitamin D levels prior to beginning treatment. (Optimal ranges fall between 42 and 60). Patients should also be tested for nagalase levels before treatment and on a monthly basis after beginning GcMAF.

Physicians may recommend concurrent antiviral treatment with Nexavir if the viral load is high. Artesunate may also be prescribed, as well as adjunctive supplementation with B vitamins.

Anti-inflammatory drugs, such as corticosteroids (prednisolone, prednisone, etc.) and NSAIDs (ibuprofen, aspirin, etc.) should be avoided while taking GcMAF as these will interfere with the treatment. Morphine analogs (oxycodone, tramadol, etc.), beta blockers, and cytotoxic medications (Sendoxan, Vepesid, Taxol, etc.) should be avoided. Aspartame and carrageenan, two food additives, can also block GcMAF.

GcMAF is contraindicated for patients with MS.

**PROS AND CONS.** GcMAF is an experimental drug, which means not much is known about its effects on the CFS/ME population other than the few studies performed by Drs. De Meirleir and Cheney. As with other medications, patients report a wide range of responses, from feeling significantly worse to an almost miraculous recovery of strength and energy. Frequently, a patient will notice improvement over the first six weeks, and then experience a decline. This may be due to exhaustion of vitamin D reserves. For this reason, continuing supplementation with vitamin D may be advised.

**AVAILABILITY AND COST.** Drs. Cheney, Enlander and De Meirleir are currently using GcMAF with their CFS/ME patients. The price for 2.2 ml of GcMAF (about 8 doses at .25 per dose) is roughly \$1000 (\$800 euros). Because of the risk of IRIS, it is not recommended that CFS/ME patients take GcMAF without the supervision of a knowledgeable physician. MAF 314 can be obtained from Dr. Cheney's clinic for \$3500. Dr. Enlander is currently developing a less expensive form of probiotic MAF (MAF 378) in New York. The test for nagalase levels can be ordered by physicians from Health Diagnostics. It costs \$65. GcMAF *must* be refrigerated

## TESTING

Health Diagnostics and Research Institute (formerly Vitamin Diagnostics, Inc.)  
South Amboy Medical Center  
540 Bordentown Ave., Suite 2300  
South Amboy, New Jersey 08879  
Telephone: (732) 721-1234  
Fax: (732) 525-3288

*Testing for nagalase.*

## SUPPLIERS

GcMAF

Clos de Balade 21

1140 Evere

Brussels

Belgium

Website: <http://www.gcmf.eu/info/>

BGLI Bio Group Laboratories

Tel: 31-3576-00-176 (GMT+2) (Netherlands)

Website: <http://www.bgli.nl/> (*There is a contact form on the site*)

## FURTHER READING

*Dr. Kenny De Meirleir's talk on GcMAF and its use in treating CFS/ME:*

<http://cfspatientadvocate.blogspot.com/2011/11/mt-sinai-mecfs-conference-de-meirleir.html>

*Dr. Cheney's GcMAF studies:* <http://www.cheneyclinic.com/gcmaf-studies-presented-at-iacfsme-meetings-in-ottawa/833>

*Excellent information on GcMAF, including where to find clinics in Europe that use GcMAF, patient forums, and purchasing information:* <http://www.gcmaf.eu/info/>

*European lab that offers testing for nagalase:* <http://www.europeanlaboratory.nl/>

*Phoenix Rising forum threads on GcMAF discussing Kenny De Meirleir's use of GcMAF, where to purchase, and how to obtain testing for nagalase:*

<http://forums.phoenixrising.me/showthread.php?6019-GcMAF-for-XMRV-Gc-protein-derived-macrophage-activating-factor-anyone-taking-it/page116>

*and*

<http://forums.phoenixrising.me/showthread.php?6019-GcMAF-for-XMRV-Gc-protein-derived-macrophage-activating-factor-anyone-taking-it/page117>

*Patient thread on MAF 314:* <http://phoenixrising.me/forums/showthread.php?14838-MAF-314>

*"Who Responds to GcMAF." Very technical discussion of gene types*

<http://www.cfscentral.com/2011/01/who-responds-to-drug-gcmaf.html>

*Good article about cancer and GcMAF by Bill Sardi*

<http://www.thenhf.com/article.php?id=633>

*Another good follow-up article by Bill Sardi:*

<http://www.thenhf.com/article.php?id=771>

*Cancer and GcMAF:* <http://www.center4cancer.com/glyco-protein.php>

*Professor Ruggiero's website on GcMAF and MAF 314*

<http://www.marcoruggiero.org/pdf/Oct%2022.pdf>

*"Compassionate Use Treatment of CFS with GHP (GcMAF)" Dr. Paul Cheney, Sept. 2011.*

[http://www.gcmaf.nl/documents/research/Compassionate%20use%20Treatment%20of%20CFS%20with%20GHP%20\(%20GcMAF%20\).pdf](http://www.gcmaf.nl/documents/research/Compassionate%20use%20Treatment%20of%20CFS%20with%20GHP%20(%20GcMAF%20).pdf)

*Dr. Cheney's pilot study of GcMAF.*

## PATIENT EXPERIENCES

*A Cheney patient blog about her experience with GcMAF. This blog is very detailed, with information about dosage, testing and patient responses.*

<http://nopostergirl.com/2011/04/16/the-post-appointment-post/>

*Cheney patient blog on GcMAF*

<http://blogwormwood.blogspot.com/2011/05/gcmaf.html>

## RESEARCH

Yamamoto N, Suyama H, Yamamoto N, Ushijima N. "Immunotherapy of metastatic breast cancer patients with vitamin D-binding protein-derived macrophage

activating factor (GcMAF).” *Int J Cancer*. 2008 Jan 15;122(2):461-7.

<http://www.ncbi.nlm.nih.gov/pubmed/17935130> (Abstract)

Yamamoto N, Suyama H, Koga Y. “Immunotherapy of metastatic colorectal cancer with vitamin D-binding protein-derived macrophage-activating factor, GcMAF.” *Cancer Immunol Immunother*. 2008 Jul;57(7):1007-16.

<http://www.ncbi.nlm.nih.gov/pubmed/18058096> (Abstract)

Yamamoto N, Suyama H, Yamamoto N, “Immunotherapy for Prostate Cancer with Gc Protein-Derived Macrophage-Activating Factor, GcMAF.” *Transl Oncol*. 2008 Jul;1(2):65-72. <http://www.ncbi.nlm.nih.gov/pubmed/18633461> (Abstract)

Yamamoto N, Ushijima N, Koga Y. “Immunotherapy of HIV-infected patients with Gc protein-derived macrophage activating factor (GcMAF).” *J Med Virol*. 2009 Jan;81(1):16-26. <http://www.ncbi.nlm.nih.gov/pubmed/19031451> (Abstract)

## GUAIFENESIN

**DESCRIPTION.** Guaifenesin is an expectorant that helps clear mucus from congested passageways by increasing production of respiratory tract fluids. It is the primary active ingredient in many cough syrups.

**USES IN CFS/ME.** Dr. Paul St. Armand, an endocrinologist at the University of California at Los Angeles, first began working with patients with fibromyalgia in the 1960s. From his observations, Dr. St. Armand speculated that patients with fibromyalgia and CFS/ME might have an inherited metabolic defect that causes faulty excretion of phosphates. According to Dr. St. Armand, if phosphate accumulates in the mitochondria of cells, then the production of adenosine triphosphate (ATP) is impaired, leading to a loss of cellular energy. The accumulation of phosphates also leads to increased calcium within the cells, possibly creating the tender points so commonly seen in fibromyalgia. It appeared to Dr. St. Armand that this defect in phosphate excretion could account for the symptoms of fibromyalgia and CFS/ME.

In support of his theory, Dr. St. Armand observed that gout medications, which increase excretion of both uric acid and phosphate, produced positive results in FM patients, although they did have serious side effects if used long term. To Dr. St. Armand's delight another medication, guaifenesin, produced the same results, without the side effects.

**PROTOCOL.** For people with CFS/ME, guaifenesin LA (long acting) is usually prescribed. It can be purchased in pill form, without added antihistamines or decongestants. Dr. St. Armand recommends an initial dosage of 300 mg of pure guaifenesin twice a day. If that proves ineffective, the dosage is increased to 600 mg twice a day. About 30% of his patients may require higher doses. Dr. St. Armand claims that two months of treatment reverses a year of illness, which should provide a baseline for calculating how long the medication may be needed – for example, a person who has been ill for four years will need eight months of treatment.

Dr. St. Armand cautions that for guaifenesin to be effective, salicylate must not be used (salicylate or salicylic acid ingredients are in Pepto-Bismol, Ben-Gay, Myoflex Creme, aspirin, Alka-Seltzer, cosmetics, plant-containing shampoos and

conditioners, plant-derived vitamins, and herbal remedies). Dr. St. Armand also recommends that patients take a calcium and magnesium supplement with meals to block absorption of phosphates in food.

**PROS.** No controlled studies have been performed to confirm or disprove the effectiveness of guaifenesin in treating symptoms of CFS/ME, so commentaries on this drug are anecdotal. One patient with long-term CFS/ME reported dramatic symptomatic improvement with guaifenesin (*Mass CFS/ME Update*, Summer 1996). She began taking guaifenesin in 1994 to treat a stubborn bout of bronchitis and was surprised to note a number of other symptoms began improving. After several months she noticed she was beginning to have clusters of "good days" and that her pain was "almost nonexistent." She also noted improvements in cognitive function, energy, and vision.

**CONS.** Although few side effects are directly attributable to guaifenesin, most CFS/ME patients report that their symptoms initially worsen while their systems are being "cleaned out." Often a patient may feel much worse for the first two to four months of treatment (some even longer), the most common side effect being severe pain. Dr. St. Armand warns that this treatment "takes confidence and strength" because results may not be seen for several months. He also warns that patients with both fibromyalgia and hypoglycemia will not notice any improvement with guaifenesin treatment unless the hypoglycemia is corrected (see Hypoglycemia for dietary and other recommendations). Although Dr. St. Armand believes the long-term benefits are worthwhile for patients with fibromyalgia, many patients with CFS/ME may be justifiably wary of risking relapse.

Patients interested in trying guaifenesin should also note that although Dr. St. Armand claims significant improvement among his patients, studies have not replicated his results. A double-blind controlled study conducted at the Oregon Health Sciences University by Dr. Robert M. Bennett and Dr. Sharon Clark found no difference between the guaifenesin and placebo groups after a year of treatment. Neither did they find an increase in urinary excretion of phosphates, which seems to undercut the basis for guaifenesin's theoretical mode of action. In addition, muscle studies by Muhammad Yunus, M.D., of University of Illinois College of Medicine, and Dr. Robert Simms have shown that calcium phosphate deposits have never been a problem in fibromyalgia. Currently, none of the major CFS/ME clinics or doctors include guaifenesin in their protocols.

**AVAILABILITY AND COST.** Guaifenesin is available through online distributors. ProHealth sells a 100-pill bottle of fast-acting guaifenesin (400 mg) for \$15.79. The long-acting variety costs about \$50.00 a bottle.

## BOOKS AND ARTICLES

St. Armand, Paul and Claudia Craig Marek. *What Your Doctor May Not Tell You About Fibromyalgia: The Revolutionary Treatment That Can Reverse the Disease*. Wellness Central. 2006.

St. Armand, R. Paul M.D. "Chronic Fatigue and Fibromyalgia: One Disease, Two Names." 1999.

[http://www.fibromyalgiatreatment.com/Research\\_TwoNames.htm](http://www.fibromyalgiatreatment.com/Research_TwoNames.htm)

#### FURTHER INFORMATION

*Guaifenesin protocol. Includes a list of doctors and practitioners*

<http://fibromyalgiatreatment.com/>

*The Fibromyalgia Network's consumer alert on guaifenesin*

<http://www.fmnetnews.com/resources-alert-product6.php>

*Guaifenesin support group. Last updated in 2007: <http://www.psha-inc.com/guai-support/sf/FAQ-GuaiProductTroubleshooter.htm>*

#### PATIENT REVIEWS

*CFS/ME patient reviews of guaifenesin: <http://www.revolutionhealth.com/drugs-treatments/rating/mucinex-for-chronic-fatigue-syndrome-cfs-cfids-me?page=2&view=treatment>*

#### H2 BLOCKERS - TAGAMET AND ZANTAC

**DESCRIPTION.** Tagamet (cimetidine) and Zantac (ranitidine) are histamine H<sub>2</sub> receptor antagonists that inhibit acid secretion in the stomach.

**BACKGROUND.** Before the Food and Drug Administration (FDA) approval of Tagamet in 1977, the pain resulting from duodenal ulcers was nearly impossible to treat with standard medications. While not a cure, Tagamet is thought to allow ulcers to heal by blocking acid secreted by the stomach in response to histamine. Millions of patients now take Tagamet and Zantac (approved in 1983) and a substantial number have obtained significant relief from pain. Tagamet, Zantac, and two other approved H<sub>2</sub> blockers, Axid (nizatidine) and Pepcid (famotidine), are also prescribed to treat heartburn and gastritis.

In the early 1980s, Dr. Jay Goldstein used Tagamet to treat infectious mononucleosis (confirmed by monospot test, enlarged spleen, and other clinical findings consistent with the diagnosis) in a college student. The symptoms resolved within 24 hours. Dr. Goldstein's rationale for treatment was based on the fact that Epstein-Barr virus, which causes mononucleosis, is a herpesvirus and, in most herpes infections, there is an increased number of T suppressor cells. It had been recently demonstrated that T suppressor cells had H<sub>2</sub> receptors on their surfaces, and it was thought that the cells were activated by histamine. Dr. Goldstein theorized that perhaps the T suppressor cells could be inactivated by Tagamet, an H<sub>2</sub> blocker. His theory appears to have validity, as Dr. Goldstein reported positive results in 90% of cases of mononucleosis treated with Tagamet. He has received positive feedback from physicians around the United States who have replicated his results (*CFIDS Chronicle*, 1988 Compendium).

In 1990 Ashir Kumar, a researcher at Michigan State University, supported Dr. Goldstein's findings with his own research. In several studies, he found that cimetidine (Tagamet) enhanced immune function. "Patients who received cimetidine



were shown to exhibit enhanced cell-mediated immunity as evaluated by increased response to skin-test antigens, restoration of sensitivity following development of acquired tolerance, and increased responses of lymphocytes to mitogen stimulation. Patients also demonstrated that patients with herpes zoster and herpes simplex who were given cimetidine may have benefited therapeutically from the drug.”

In an interesting corollary to its other uses, some urologists prescribe H2 blockers for interstitial cystitis when other medications are not tolerated.

**USES IN CFS/ME.** In 1985 Dr. Goldstein began to see his first cases of what was then called chronic Epstein-Barr virus infection (now CFS/ME). Using the same logic that he used to treat mononucleosis, Dr. Goldstein gave his patients Tagamet and Zantac. He found over the course of years that at least 20% of patients with CFS/ME responded favorably to treatment with H2 blockers. Although the cause of CFS/ME remains undetermined, it is known that in CFS/ME there is activation of T suppressor cells, probably due to viral activity. It is believed that H2 blockers have a modulatory effect on the immune system in that they probably inhibit overproduction of lymphokines responsible for some of the flu-like symptoms of CFS/ME.

Several leading CFS/ME clinicians, including Dr. Charles Lapp, use H2 blockers to treat gastrointestinal symptoms as well as for immune system modulation. Dr. Murray Susser and Dr. Michael Rosenbaum used H2 blockers to treat immune system dysfunction.

**PROTOCOL.** Most patients take only low doses of these H2 blockers (even a sliver of a pill can be effective, according to Dr. Goldstein). Others are able to tolerate the standard prescribed dose for ulcers: Tagamet 300 to 400 mg, one or more tablets per day; Zantac 75 to 300 mg/day.

**PROS.** H2 blockers work rapidly, and results can often be seen in less than two weeks, thereby making a trial worthwhile. Many patients have reported a variety of benefits. CFS/ME patients with allergies feel much better overall after taking Zantac. Some have found significant relief from digestive disturbances. Not surprisingly, given the effects that H2 blockers have on the immune system, people with CFS/ME also report that Tagamet gives them more energy and lessens the weak, achy feeling of CFS/ME.

**CONS.** Dr. Goldstein has noted that some patients feel nervous and agitated while taking Tagamet. Other clinicians believe H2 blockers cause depression (a less common side effect according to the *Physicians' Desk Reference*). Because Tagamet may interact with and increase blood concentrations of many drugs, some of which are commonly prescribed in CFS/ME (e.g., antidepressants and benzodiazepines), it is important to advise your physician of all medications you are taking. Zantac may be prescribed more frequently than Tagamet to treat symptoms of CFS/ME, because it interacts with fewer medications and may pose less risk for side effects. Both Tagamet and Zantac will either aggravate pre-existing hypochloridia, or cause it. High levels of Zantac are known to cause an unusual condition in men which produces breast enlargement (gynecomastia).

AVAILABILITY AND COST. Tagamet and Zantac are available by prescription and over the counter at any pharmacy. Over-the-counter Tagamet HB 200 and Zantac 75 mg are available for between \$10 and \$15.

#### FURTHER READING

Kumar A. "Cimetidine: an immunomodulator." Department of Pediatrics and Human Development, Michigan State University, East Lansing 48824. DICP 1990 Mar;24(3):289-95. <http://www.ncbi.nlm.nih.gov/pubmed/2138376> (Abstract)

*Overview of immunological effects of H2 blockers.*

[http://www.lef.org/magazine/mag2001/mar2001\\_report\\_tagamet\\_1.html](http://www.lef.org/magazine/mag2001/mar2001_report_tagamet_1.html)

*Thread discussing histamine blockers in CFS/ME patients, including Zantac and Tagamet.* [http://forums.phoenixrising.me/showthread.php?2077-Tagamet-\(cimetidine\)-for-CFS/ME-\(worked-for-me\)/page2](http://forums.phoenixrising.me/showthread.php?2077-Tagamet-(cimetidine)-for-CFS/ME-(worked-for-me)/page2)

*Article discussing gynecomastia after excess Tagamet.*

<http://gerd.emedtv.com/cimetidine/cimetidine-and-gynecomastia.html>

#### HORMONES

Growth Hormone, Testosterone, Thyroid Hormones

Hormones are chemical messengers that are released from glands in the endocrine system. Because hormones can be released directly into the bloodstream, they affect nearly every function in the body. Hormones are responsible for stimulating growth, regulating the immune system, initiating "fight or flight" responses, sexual maturation and reproduction, hunger, thirst, mood swings, metabolic regulation, and maintaining homeostasis. A deficiency or dysregulation of hormone production will produce profound effects on the body.

Endocrine system disturbances are common, if not universal, among CFS/ME patients. As a consequence, hormone production is also affected. Unfortunately, hormones are usually released in spurts, and their effects, while widespread, are not constant. This makes hormone regulation through medical intervention problematic. A steady dose of hormones may, in fact, worsen symptoms. That being said, patients who consistently test low in certain hormones may benefit greatly from supplementation with bio-identical or synthetic hormones. Because of their widespread effects on the body, hormone treatments should always be monitored by a physician.

#### FURTHER READING

"Endocrine Causes of Chronic Fatigue: A Review of Symptoms, Treatments." *CFIDS Chronicle*, Spring 2003. <http://www.cfids.org/archives/2003/2003-2-article02.asp>  
*This is a good summary of various endocrine disturbances that can cause fatigue.*

#### GROWTH HORMONE

**DESCRIPTION.** Growth Hormone (GH) is a peptide hormone produced in the pituitary gland.

**BACKGROUND.** Growth Hormone is primarily responsible for increasing height in children, although it has a number of other functions as well, including increasing protein synthesis, stimulating the growth of internal organs, maintaining pancreatic islets, and stimulating the immune system. Medically, it is prescribed for children with growth failure stemming from GH deficiency.

In rare cases, adults will develop GH deficiency. Usually, this is caused by structural problems in the pituitary gland (tumors), although unexplained disruptions in hormone production can also occur. When a physician suspects GH deficiency, he or she will test for the presence of IGF-1 in the body to determine if GH levels are low. (GH secretion leads to IGF-1 production.) As most GH is secreted during deep sleep, patients may be kept overnight to measure GH levels.

Because GH builds muscle mass, strengthens bones and increases energy, it has become a popular, if dubious, supplement for athletes, who use it to improve performance. Too much GH can result in acromegaly, or gigantism. Due to its reputed anti-aging effects, GH has also been promoted as a “fountain of youth,” which has no doubt spurred the increase of off-shore manufacturers.

**USES IN CFS/ME.** Disturbances in the HPA (hypothalamus-pituitary-adrenal) axis have been well-documented in CFS/ME patients. One of the earliest studies to show that GH is affected by HPA axis dysfunction was conducted by Allain et al in 1997. The research team found that people with CFS/ME showed abnormalities of the GH-IGF (insulin growth factor) axis. A subsequent study by Moorkens et al, using a larger cohort, found that CFS/ME patients showed significant impairment of GH response during insulin-induced hypoglycemia, as well as a low nocturnal GH secretion. A number of studies have also shown low GH secretion among fibromyalgia patients. (See Holtorf article below for an excellent summary of relevant research.)

The causes of GH deficiency in CFS/ME and FM patients are various. Disruptions in the HPA axis will certainly contribute to lower production of GH. It has also been speculated that because GH is secreted during stage 3 and 4 sleep, widespread insomnia in these two groups, and the subsequent reduction of deep sleep, may be a contributory factor.

**PROTOCOL.** The synthetic equivalent of GH, Somatropin, is administered through injection. The standard dose is 0.2 mg three times a week. Dr. Cheney uses a much lower dose with his patients, as little as 0.2 mg once a week. He notes that higher doses cause “crashes.”

**PROS AND CONS.** Like most hormone treatments, the effects of Somatropin are felt throughout the body, which means it should be used with caution. Because GH upregulates the immune system, this could potentially aggravate symptoms in people with CFS/ME. Those for whom Somatropin has been of benefit report a dramatic increase in energy, as well as the additional benefit of “beautiful skin.”

**AVAILABILITY AND COST.** Somatropin is available by prescription only (although there is a large black market of suppliers). Somatropin is highly

regulated, and difficult to obtain without a confirmation of deficiency. A single 5 mg vial costs \$1500. Unfortunately, there is no substitute for GH. Taking natural GH precursors (arginine, ornithine, lysine, glutamine, GABA) is ineffective.

#### FURTHER READING

*Good general information on Somatropin:* <http://www.somatropin.net/>

*Dr. Holtorf's excellent article on HPA axis dysfunction and GH in CFS/ME and FM. (Scroll down to find it.):*

[http://www.holtorfmed.com/index.php?section=downloads&file\\_id=57](http://www.holtorfmed.com/index.php?section=downloads&file_id=57)

*Excellent article about GH deficiency in FM*

[http://www.myalgia.com/growth\\_hormone\\_deficiency\\_in\\_fib.htm](http://www.myalgia.com/growth_hormone_deficiency_in_fib.htm)

*Dr. Cheney discusses the role of GH in CFS/ME. Includes treatment protocols*

<http://www.dfwcfids.org/medical/advances.html>

*Interesting patient discussion of GH:* <http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=999131>

#### PATIENT REVIEWS

*Patient review of somatropin:* <http://www.revolutionhealth.com/drugs-treatments/rating/somatropin-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### RESEARCH

Allain TJ, Bearn JA, Coskeran P, Jones J, Checkley A, Butler J, Wessely S, Miell JP. "Changes in growth hormone, insulin, insulinlike growth factors (IGFs), and IGF-binding protein-1 in chronic fatigue syndrome." *Biological Psychiatry*. 1997 Mar 1;41(5):567-73. <http://www.ncbi.nlm.nih.gov/pubmed/9046989> (Abstract)

Moorkens G, Berwaerts J, Wynants H, Abs R. "Characterization of pituitary function with emphasis on GH secretion in the chronic fatigue syndrome." *Clin Endocrinol (Oxf.)* 2000 Jul;53(1):99-106. <http://www.ncbi.nlm.nih.gov/pubmed/10931086> (Abstract)

#### TESTOSTERONE

**DESCRIPTION.** Testosterone is the principal male hormone. It is produced in the testes.

**BACKGROUND.** Testosterone is the hormone responsible for the development of primary male sexual characteristics (sex organs), as well as secondary characteristics such as growth of body hair, increase in bone and muscle mass, and deepening of the voice. Testosterone promotes energy and a sense of well-being, and helps regulate the HPA axis. Women also produce testosterone, although at only a tenth of male levels. Low-dose testosterone is sometimes recommended for women at risk of osteoporosis.

As men age, their production of testosterone decreases. While this is a natural process, some men experience an abrupt or dramatic decline, sometimes brought about by disease processes. This abrupt decline has been dubbed "male menopause" (although gradual declines are often referred to as "male menopause")

as well). The medical community has mixed views on male menopause. Some doctors offer hormone replacement therapy, just as they do their female patients, while others view male menopause as a myth.

**USES IN CFS/ME.** As with other hormone deficiencies, low levels of testosterone are fairly common in CFS/ME patients. In men, this will be felt as a loss of libido, as well as a decrease in muscle strength, depression, anxiety, and bladder problems – all of which are symptoms common among CFS/ME patients of both sexes. As testosterone has such wide-ranging effects on the body, doctors should prescribe testosterone only after blood tests confirm low levels.

**PROS AND CONS.** Men who have taken testosterone report an increase in energy. Some men experience "teenage problems" (acne).

**AVAILABILITY AND COST.** Testosterone is available as an injection, gel or patch. Of the three modes of delivery, the gel (AndroGel) is the least problematic. (Patches can fall off, and injections require a doctor.) AndroGel is applied to the arms. It dries quickly, and leaves no residue. A 30-day supply of AndroGel costs about \$100, so check to see if your insurance will cover the cost.

#### FURTHER READING

*Article about male menopause:* <http://men.webmd.com/guide/male-menopause>

*Good summary of male menopause and CFS/ME*

<http://www.prohealth.com/library/showarticle.cfm?libid=8114>

#### PATIENT REVIEWS

*CFS/ME patient reviews of testosterone:* <http://www.revolutionhealth.com/drugs-treatments/rating/testosterone-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### THYROID HORMONES

*CAUTION: Taking an initial high dose of T3 can lead to heart attack.*

**DESCRIPTION.** Thyroid hormones are tyrosine-based hormones produced in the thyroid, a butterfly-shaped gland in the neck.

**BACKGROUND.** Thyroid hormones regulate metabolism and, as a consequence, can act on nearly every cell in the body. They increase basal metabolic rate, regulate long bone growth (along with growth hormone), and increase the body's sensitivity to adrenaline and noradrenaline. Thyroid hormones also regulate protein, fat, and carbohydrate metabolism. They stimulate the metabolism of vitamins, which means thyroid hormones regulate how much energy is available to cells. There are two primary thyroid hormones, T4 (thyroxine) and T3 (triiodothyronine). T4 is first converted in the body to T3, which is two to three times more potent than T4, and then to T2 and T1. All four are essential for the basic functioning of the human body.

**USES IN CFS/ME.** Fatigue is one of the hallmark symptoms of low thyroid function, therefore it is not surprising that CFS/ME patients are often suspected of

having hypothyroidism. Other hypothyroid symptoms, such as low body temperature, cold intolerance, depression, hair loss, and weight gain are also quite common among CFS/ME patients, indicating that low thyroid function could be the root of many CFS/ME symptoms.

According to Dr. Teitelbaum, low thyroid function is one of the most underdiagnosed conditions in America. The reason many doctors miss the diagnosis, even in the presence of "text book" symptoms, is that testing is inadequate. Up until a few years ago the gold standard for testing the thyroid was to measure TSH levels (thyroid stimulating hormone). TSH, the hormone which stimulates the thyroid to release hormones, is produced in the pituitary gland, which means that as long as a patient has a normally functioning pituitary, the TSH results will be within normal range – regardless of how faulty his or her thyroid may be.

When clinicians realized the TSH test was inadequate, they began to use free T3 and T4 levels to determine low thyroid function, but those tests, like the previous one, missed many patients with low thyroid function, including Hashimoto's disease patients, whose thyroids are being attacked by their own immune systems, as well as nearly everyone with HPA axis dysfunction (e.g., fibromyalgia and CFS/ME patients).

This lack of sensitivity in testing has led some CFS/ME physicians to prescribe thyroid hormone supplementation to their patients even in the absence of abnormal test results.

**PROTOCOL.** Thyroid hormones come in two forms, synthetic and natural. T4 (Synthroid, levothyroxine) and T3 (Cytomel) are both synthetic. (T4 helps with lethargy and T3 helps with cognitive problems, "brain fog," and mental focus.) Armour Thyroid is a natural glandular which contains all four thyroid hormones (T1, T2, T3, and T4). Nature-Throid, another natural glandular, contains T3 and T4.

How patients respond to thyroid hormone therapy is highly individualized. Some do well on synthetic formulations, others do better with natural glandulars. (Although, it should be noted that Hashimoto's disease patients tend to respond better to synthetic formulations.) People with primary hypothyroidism need to take both T3 and T4, as their thyroids will not make the conversion.

Dr. Myhill advises that CFS/ME patients have their thyroid hormones checked often while on medication. Too high a dose can lead to thyrotoxicosis, a dangerous condition in which the patient experiences sweating, fever, heart palpitations, and, potentially, heart attack. Patients starting thyroid hormone therapy should *always* begin with the lowest possible dose.

**PROS AND CONS.** There is no doubt that patients with concomitant hypothyroidism experience an overall improvement with the administration of thyroid hormones. Patients report a cessation of fatigue, improvements in mood, stamina and strength, normalization of weight, and hair regrowth. Patients whose thyroid levels are normal also experience improvement in energy levels after taking thyroid hormones. However, in similar fashion to CNS stimulants, the improvement is often followed by a crash. The main drawback of taking thyroid hormone is that

once hormone replacement has begun, the thyroid ceases making its own hormones. For people taking long-term thyroid hormones, discontinuation may not be possible.

#### FURTHER READING

*Dr. Teitelbaum's recommendations for thyroid supplementation*

[http://www.endfatigue.com/health\\_articles\\_d-e/Diet-thyroid\\_hormone\\_deficiency.html](http://www.endfatigue.com/health_articles_d-e/Diet-thyroid_hormone_deficiency.html)

*Mary Shomon's discussion of low thyroid function in CFS/ME*

<http://thyroid.about.com/cs/fibromyalgiacfs/a/cfsfibrothyroid.htm>

*Good general information about thyroid testing and CFS/ME:* <http://blog.nutriliving.com/?p=405>

*Dr. Myhill's discussion of underactive thyroid in CFS/ME*

[http://www.drmyhill.co.uk/wiki/Hypothyroidism -  
A Common Hormonal Problem in CFS](http://www.drmyhill.co.uk/wiki/Hypothyroidism_-_A_Common_Hormonal_Problem_in_CFS)

*James Burton's article about thyroid hormone deficiencies in CFS/ME patients*

<http://www.prohealth.com/library/showarticle.cfm?libid=10827>

#### PATIENT REVIEWS

*CFS/ME patient ratings of Cytomel:* <http://www.revolutionhealth.com/drugs-treatments/rating/cytomel-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Synthroid:* <http://www.revolutionhealth.com/drugs-treatments/rating/synthroid-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Armour thyroid:*

<http://www.revolutionhealth.com/drugs-treatments/rating/armour-thyroid-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### HYDROCORTISONE/CORTEF

**DESCRIPTION.** Hydrocortisone is the pharmaceutical name for cortisol, a glucocorticoid hormone excreted by the adrenal cortex in response to stress, inflammation, and low blood sugar levels.

**BACKGROUND.** Cortisol is produced in the outer layer of the adrenal gland, known as the adrenal cortex. The release of cortisol is controlled by the hypothalamus, which secretes corticotropin-releasing hormone (CRH) to the pituitary gland, which in turn releases adrenocorticotrophic hormone (ACTH). ACTH is carried by the bloodstream to the adrenal glands, where cortisol is then released.

Cortisol has numerous effects on body functions, including reduction of inflammation, maintenance of sodium and potassium balance, and regulation of blood sugar. Cortisol also has profound effects on protein and carbohydrate metabolism. Because cortisol can suppress the immune system (specifically the proliferation on T cells), hydrocortisone is used medically to treat inflammatory conditions such as rheumatoid arthritis, lupus, and allergies.

**USES IN CFS/ME.** Whether hydrocortisone should be used to treat CFS/ME is a topic of much debate among CFS/ME clinicians. Studies performed by Dr. Mark Demitrack and colleagues showing endocrine system deficiency along the

hypothalamic-pituitary-adrenal axis (HPA axis) seem to indicate that there is a chronic adrenal insufficiency in patients with CFS/ME (*Journal of Clinical Endocrinology and Metabolism*, 1991). The low levels of cortisol found in some CFS/ME patients, combined with increased or new inflammatory responses, such as allergies, irritable bowel syndrome, and rheumatic conditions, also seem to point to the use of cortisol as a potentially effective treatment.

Several studies have confirmed that treatment with low-dose hydrocortisone increases energy levels and stamina in CFS/ME patients. In 1999 Cleare et al found that in a group of 32 CFS/ME patients treated with 5-10 mg of cortisol daily for a month, energy levels were significantly improved. In a subsequent study published in 2001, Cleare also found that low-dose cortisol restored normal adrenal responses to CRH in CFS/ME patients.

A number of prominent CFS/ME doctors include low-dose hydrocortisone as part of their CFS/ME protocols. In a 2008 study of 500 patients, Dr. Holtorf found that 5-15 mg a day of time-release hydrocortisone resulted in an overall improvement in 94% of his patients. Moreover, Dr. Holtorf states that “physiologic [low] doses of cortisol have been shown to improve cellular and hormonal immunity, including natural killer cell activity” both of which are problems with CFS/ME patients.

However, not all clinicians agree that treatment with hydrocortisone is beneficial. Cortisol can be an immune system suppressant and, in cases in which the immune system is already compromised, its effects could be disastrous. Clinicians who are critical of hydrocortisone's usefulness as a CFS/ME treatment point out that glucocorticoids are best used as a short-term treatment for severe allergic reactions. Long-term use may exacerbate the disease process.

**PROTOCOL.** Hydrocortisone (cortisone, cortisol) may be given as a single injection to treat severe allergic response or in acute cases of CFS/ME when immediate intervention is required. It may also be administered in pill form (Cortef) in low doses (5 to 15 mg) on a daily basis.

**PROS.** Many patients report a significant increase in energy and stamina from hydrocortisone. For some patients hydrocortisone makes the difference between having to lie in bed all day and being able to get up, which can make all the difference in the world for the severely ill. Single ("pulse") administrations of cortisol can be lifesaving for patients with severe allergic reactions or acute-onset CFS/ME.

**CONS.** Cortisol is a naturally occurring chemical. However, its use on a long-term basis, carries significant risks. When the body registers the presence of hydrocortisone, the adrenal glands decrease production. Although proponents of low-dose hydrocortisone claim that the risks are minimal, when taken over a long period of time the adrenal glands may fail to produce glucocorticoids altogether, making the patient entirely dependent on a drug source for this essential hormone.

In addition to the risk of dependency, the dosage must not be excessive or Cushing's syndrome may eventually develop, with tendencies for obesity, hypertension, osteoporosis, and mental disturbances. Side effects of even small



doses of cortisol include headache, gastrointestinal disturbances, insomnia, and weakness. Hydrocortisone is strongly contraindicated for people with fungal infections.

**AVAILABILITY AND COST.** Hydrocortisone is available by prescription, in generic and brand-name formulations. The cost of brand (Cortef) or generic is similar, ranging from \$15 to \$30 a month, depending on the dosage. It is usually covered by insurance.

## BOOKS

Jeffries, William. *Safe Uses of Cortisol*. Charles C Thomas Pub Ltd , 3rd edition. 2004. (Originally published in 1970, this is the “bible” for physicians who prescribe hydrocortisone for CFS/ME and FM.)

## FURTHER INFORMATION

*Excellent discussion of low-dose hydrocortisone by a CFS/ME patient detailing the dosage and effects:* <http://www.revolutionhealth.com/groups/me-chronic-fatigue-syndrome-support/discussions/topic/c433312d-35c5-41b1-a2b2-7be3aacc6987>

*Pro-health's patient thread on low-dose hydrocortisone*

<http://www.prohealth.com/fibromyalgia/blog/boardDetail.cfm?id=1058069&b1=C HWEBO#1058069/>

*A review of the literature concerning low-dose hydrocortisone treatment in CFS/ME and FM:* [http://www.endfatigue.com/health\\_articles\\_f-n/Hormones-adrenal\\_problems\\_in\\_cfs.html](http://www.endfatigue.com/health_articles_f-n/Hormones-adrenal_problems_in_cfs.html)

*Discussion of low-dose hydrocortisone in CFS/ME*

<http://enotes.tripod.com/fatigue2.htm>

*Dr. Teitelbaum's excellent review of HPA axis dysfunction and low-dose hydrocortisone treatment in CFS/ME patients:*

[http://www.endfatigue.com/health\\_articles\\_f-n/Hormones-adrenal\\_problems\\_in\\_cfs.html](http://www.endfatigue.com/health_articles_f-n/Hormones-adrenal_problems_in_cfs.html)

*Dr. Holtorf's review of HPA axis dysfunction and study of 500 patients receiving low-dose hydrocortisone:* <http://www.holtorfmed.com/dr-pdf/Diagnosis%20Treatment%20CFS%20FM.pdf>

*Dr. Baschetti discusses the benefits of low-dose cortisol and makes a comparison of 36 shared features between Addison's disease and CFS/ME*

<http://jcem.endojournals.org/content/84/6/2263-a.full>

## PATIENT REVIEWS

*CFS/ME patient reviews of Cortef (hydrocortisone)*

<http://www.revolutionhealth.com/drugs-treatments/rating/cortef-for-chronic-fatigue-syndrome-cfs-cfids-me>

## RESEARCH

Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. “Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial.”

*Lancet* 1999 Feb 6;353(9151):455-8.

<http://www.ncbi.nlm.nih.gov/pubmed/9989716> (Abstract)

Cleare AJ, Miell J, Heap E, Sookdeo S, Young L, Malhi GS, O'Keane V.

“Hypothalamo-pituitary-adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy.” *J Clin Endocrinol Metab.*

2001 Aug;86(8):3545-54. <http://jcem.endojournals.org/content/86/8/3545.full>

Demitrack, Mark A, Dale, Janet K, Straus, Stephen E, Laue, Louisa, Listwak, Sam J, Dreusi, Markus JP, Chrousos, George P, and Gold, Philip W. “Evidence for Impaired Activation of the Hypothalamic-Pituitary-Adrenal Axis in Patients With Chronic Fatigue Syndrome.” *Journal of Clinical Endocrinology and Metabolism.* 73:1224-1234,1991.

## HYPNOTICS

Ambien, Lunesta, Rozerem, Xyrem

Sleep disturbance is found in 100% of people with CFS/ME. This can manifest itself in either too much sleep (hypersomnia) or, more commonly, in poor, unrefreshing sleep. As sleep deprivation tends to worsen all other symptoms, nearly every CFS/ME physician includes an arsenal of insomnia treatments, both pharmaceutical and natural, in their protocols.

### AMBIEN (zolpidem)

Ambien (generic: zolpidem) is a hypnotic that potentiates gamma aminobutyric acid (GABA) in the brain. It works very quickly (15 minutes) and has a short half-life. It is most effective for sleep initiation problems, rather than sleep maintenance. Because tolerance is easily developed, a low dose (10 mg) used intermittently for not more than twelve weeks is recommended. Common side effects are sedation, rebound insomnia, GERD, and impaired psychomotor and cognitive function the following day. While some CFS/ME patients report that Ambien gives them a good night's sleep, others report rapid heartbeat, a “trippy” feeling (hallucinations), and a general worsening of CFS/ME symptoms. Because Ambien has been associated with several deaths, (including actor Heath Ledger), it is under review in the U.S. In Australia, Zolpidem (brand: Stilnox) contains a “black box” warning.

## PATIENT REVIEWS

*CFS/ME patient reviews of Ambien:* <http://www.revolutionhealth.com/drugs-treatments/rating/ambien-for-chronic-fatigue-syndrome-cfs-cfids-me>

### LUNESTA (eszopiclone)

Lunesta (eszopiclone) is a short-acting sedative hypnotic used for the treatment of primary insomnia. It acts as a GABA agonist, stimulating GABA

action in the brain. It is rapidly absorbed, with levels peaking at one to three hours after ingestion.

There has been considerable controversy surrounding Lunesta. In an article published in the *New England Journal of Medicine* in 2009, Drs. Lisa Schwartz and Steven Woloshin examined the manufacturer's clinical trials and found that Lunesta only improved sleep onset by 15 minutes as compared to placebo. Sleep duration was increased by 37 minutes. The authors concluded that “FDA approval does not mean that a drug works well; it means only that the agency deemed its benefits to outweigh its harms.”

**PROTOCOL.** The recommended dose is 2 mg–3 mg for adults (roughly equivalent to 10 mg of Valium). Lunesta is not available in Europe.

#### FURTHER READING

Schwartz, M Lisa M.D., and Steven Woloshin, M.D. “Lost in Transmission — FDA Drug Information That Never Reaches Clinicians.” *N Engl J Med* 2009; 361:1717-1720. [October 29, 2009.](http://www.nejm.org/doi/full/10.1056/NEJMp0907708)

<http://www.nejm.org/doi/full/10.1056/NEJMp0907708>

#### ROZEREM

Unlike most other sleep medications, Rozerem (Ramelteon) does not bind to GABA receptors. Instead it binds to melatonin receptors. Like melatonin, it is used to treat delayed sleep onset. There are no published studies indicating whether Rozerem is more effective than melatonin (which has the advantage of being much less expensive and widely available over-the-counter in the U.S. and Canada).

Like Lunesta, Rozerem came under the scrutiny of Drs. Lisa Schwartz and Steven Woloshin, who found that clinical trials revealed no subjective improvements in total sleep time, sleep quality, or the time it took to fall asleep. Outpatient trials confirmed that people didn't notice much benefit from Rozerem. Nor did it improve the ability to fall back asleep after waking, number of awakenings, total sleep time, or sleep quality.

#### FURTHER READING

*CFS/ME patient reviews of Rozerem:* <http://www.revolutionhealth.com/drugs-treatments/rating/rozerem-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### XYREM

**BACKGROUND.** Xyrem (sodium oxybate) – also known as the “date rape drug,” or GHB – is a central nervous system depressant. Chemically, Xyrem is the equivalent of gamma hydroxybutyric acid (GHB), a naturally occurring substance found in the central nervous system. While Xyrem is widely (and illegally) available as a street drug, its use for medical purposes is highly restricted. To date, the only approved use of Xyrem is for narcolepsy, a rare condition in which people suddenly fall asleep during the day. In 2010 the makers of Xyrem, Jazz Pharmaceuticals,

submitted a New Drug Approval to the FDA for fibromyalgia. Approval was denied. Xyrem is currently listed as an “orphan drug” (a drug used for rare conditions).

**USES IN CFS/ME.** Xyrem has gained some popularity among CFS/ME physicians for treating the intractable insomnia experienced by many CFS/ME patients. CFS/ME doctors who use Xyrem include Dr. Enlander and Dr. Klimas. Because of its potential for illegal use, physicians and patients who wish to use Xyrem must be registered with Jazz Pharmaceuticals. Registration includes a precise set of instructions for how to take Xyrem. These include not getting up after ingestion and using the bathroom before ingestion. Side effects include nausea, dizziness, headache, vomiting, sleepiness, and bed-wetting (for those who did not use the bathroom first).

**PROS AND CONS.** Given the popularity of Xyrem as a party drug, there is an unusual amount of data available about dosage and safety. In the general population, it is well-tolerated, safe, and quite definitely effective. Some CFS/ME patients have reported that Xyrem is a “godsend,” providing them with their first deep, refreshing sleep in years. The adverse reactions most commonly reported are nausea and headaches.

SEE: Sleep Disorders

#### PATIENT REVIEWS

*Detailed patient experiences with Xyrem:* <http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=809597>

*CFS/ME patient reviews of Xyrem:* <http://www.revolutionhealth.com/drugs-treatments/rating/xyrem-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### MIDODRINE (Amatine, Proamatine)

**DESCRIPTION.** Midodrine is an anti-hypotensive agent, that is, it causes an increase in blood pressure. It is classed as an alpha-agonist.

**BACKGROUND.** Midodrine was developed to treat orthostatic hypotension, a form of orthostatic intolerance (OI) in which a person's blood pressure drops upon standing. The most common cause of orthostatic hypotension is diabetes mellitus. The drug works by acting on alpha-adrenergic receptors in arteries and veins, producing an increase in vascular tone. Unlike beta-blockers, midodrine does not affect cardiac beta-adrenergic receptors. Nor does it cross the blood-brain barrier, which means it has little effect on the central nervous system.

Several studies have proven the efficacy of midodrine in patients with orthostatic hypotension. In 1997 Low et al found that in a group of 171 patients there was significant improvement in standing blood pressure, as compared to placebo. Side effects, including urinary retention, goose bumps, itching, and a feeling of "pins and needles," were minimal. In 2011 Chen et al found that midodrine was more effective than conventional therapies in 53 children with Postural Orthostatic Tachycardia Syndrome (POTS). Midodrine has also been

recommended as a treatment for vasovagal syndrome (fainting), spinal cord injuries, and dysautonomia caused by Parkinson's disease.

Currently, the status of midodrine in the U.S. is unclear. After being approved and marketed, the FDA withdrew its approval of midodrine because the manufacturer had failed to complete required studies confirming its safety. Later the FDA agreed to keep it on the market as an “orphan drug” provided that the manufacturer (Shire) completed standard testing.

**USES IN CFS/ME.** Dysautonomia, including OI and POTS, is so common in CFS/ME that many physicians find the conditions to be virtually synonymous. In fact, Naschitz JE et al found that specific responses to a tilt table test can be used to accurately diagnose CFS/ME. A recent study in 2009 by a group of researchers at Newcastle University in England confirmed that people with CFS/ME not only have lower blood pressure but abnormal diurnal blood pressure regulation. They found that the greater the dysregulation in diurnal blood pressure, the greater the fatigue. The researchers recommended midodrine as a possible treatment. A number of CFS/ME physicians have used midodrine to treat OI in their patients, including Dr. Klimas, Dr. Rowe, and Dr. Chia.

**PROTOCOL.** Dr. Hugh Calkins, a cardiologist at Johns Hopkins University, recommends starting midodrine at 2.5 mg taken three times a day. Dr. Klimas suggests taking midodrine before meals. Regular blood pressure monitoring is advised. Because it lowers blood pressure, midodrine should not be taken before bed.

**PROS.** People with CFS/ME report an increase in stamina, a decrease in dizziness and light-headedness, and an improvement in their ability to stand for periods of time. Some report an overall improvement in symptoms. Midodrine does not pass through the blood-brain barrier, which is advantageous for patients with drug sensitivities.

**CONS.** Midodrine is used for patients with consistently low blood pressure. However, patients in a double-blind study also experienced a significant number of adverse effects (*Journal of the American Medical Association*, 1997). Nausea and headache appear to be the two most common side effects of midodrine. Chills, goose bumps, tingling, and frequent urination have also been reported. Some patients experience a sudden rise in blood pressure that feels “stroke-like.” Paradoxically, some patients experience a “crash” a few hours after taking midodrine, in which their blood pressure falls dramatically. Midodrine cannot be taken by anyone with a heart condition, hypertension or kidney disease.

**AVAILABILITY AND COST.** Midodrine is available from pharmacies. A bottle of 90 pills at the lowest dosage costs roughly \$60.

SEE: Cardiac and Cardiovascular Symptoms

#### FURTHER READING

*Good summary of how midodrine is used in CFS/ME.*

<http://aboutmecfs.org.violet.arvix.com/Trt/TrtMidodrine.aspx>

“Tilt-Test Formula: A Diagnostic Marker for CFS?” *CFIDS Chronicle*. Spring 2003.  
<http://www.cfids.org/archives/2003rr/2003-rr1-article02.asp>  
*CFS/ME doctors discuss treatments for OI:* <http://www.co-cure.org/experts.htm>

## PATIENT REVIEWS

*Patient reviews of midodrine:* <http://www.revolutionhealth.com/drugs-treatments/rating/proamatine-for-chronic-fatigue-syndrome-cfs-cfids-me?rid=13060>

## RESEARCH

Chen L, Wang L, Sun J, Qin J, Tang C, Jin H, Du J. “Midodrine hydrochloride is effective in the treatment of children with postural orthostatic tachycardia syndrome.” *Circ J*. 2011 Apr;75(4):927-31.

<http://www.ncbi.nlm.nih.gov/pubmed/21301135> (Abstract)

Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. “Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group.” *JAMA*. 1997 Apr 2;277(13):1046-51. <http://www.ncbi.nlm.nih.gov/pubmed/9091692> (Abstract)

Newton JL, Sheth A, Shin J, Pairman J, Wilton K, Burt JA, Jones DE. “Lower ambulatory blood pressure in chronic fatigue syndrome.” *Psychosom Med*. 2009 Apr;71(3):361-5. <http://www.ncbi.nlm.nih.gov/pubmed/19297309> (Abstract)

## NALTREXONE

**DESCRIPTION.** Naltrexone (Depade or ReVia) is an opioid antagonist. Naltrexone binds to opioid receptors in the nervous system, blocking the effects of narcotics.

**BACKGROUND.** Naltrexone was first synthesized in 1963 by a small pharmaceutical company in Long Island. Because of its limited application, there was virtually no interest in the drug until 1971 when the Federal government stepped in and endorsed the use of naltrexone for the treatment of heroin addiction. After ten years of trials with narcotics, the drug was determined to be useful for alcoholism. In 1995 naltrexone (ReVia) was formally approved by the FDA for the treatment of alcoholism. Derivatives of naltrexone have been also been used to treat smoking addiction.

While the Federal government was pursuing the use of naltrexone for narcotics addictions, Dr. Ian S. Zagon, Professor of Neuroscience and Anatomy at Pennsylvania State University, discovered that, in contrast to normal doses of naltrexone (50 mg), low dose naltrexone (LDN) blocked the growth of certain cancer tumors. Dr. Zagon's studies drew considerable attention from the scientific community, and researchers began to investigate other possible medical applications of LDN. In 1985 Dr. Bihari, director of the Division of Alcoholism and Drug Dependence, SUNY/Health Science Center at Brooklyn, New York, began to prescribe LDN to AIDS patients, and in the 1990s he successfully used LDN to treat multiple sclerosis. In the decade following Dr. Bihari's success with LDN,

researchers found that LDN was also successful in treating Crohn's disease, rheumatoid arthritis, celiac disease, lupus and other autoimmune disorders.

Theories explaining the mechanism of LDN are still evolving. It is believed that low doses of naltrexone act to stimulate endorphins by temporarily blocking opioid receptor sites. (Endorphins are naturally occurring substances present in high concentrations during various illnesses, including viral and autoimmune disease.) Simply stated, when low dose naltrexone blocks opioid receptors for a few hours, the body produces more endorphins to compensate for the temporary lull. One particular endorphin, Opioid Growth Factor (OGF), is an important immune system regulator. When LDN blocks the receptor site for OGF, the body responds by producing more OGF, which, in turn, acts to regulate the immune system.

LDN also appears to block pain receptors along the spine. In 2009 Drs. Sean Mackey and Jarred Younger of Stanford University completed a successful trial of LDN in ten patients with fibromyalgia. The researchers found that low-dose naltrexone reduced fibromyalgia symptoms in the entire cohort, with a greater than 30% reduction of symptoms over placebo. In addition, laboratory visits showed that mechanical and heat pain thresholds were improved by the drug. Side effects were minor. They concluded that "low-dose naltrexone may be an effective, highly tolerable, and inexpensive treatment for fibromyalgia."

**USES IN CFS/ME.** CFS/ME clinicians have expressed interest in naltrexone, especially in light of findings regarding naltrexone's effect on the immune system. Dr. Susan Levine, a well-known CFS/ME expert affiliated with Mt. Sinai Hospital, New York, explains the rationale for the use and success of naltrexone. "Naltrexone can act to counteract some of the negative effects of excess stimulation by endorphins, such as diminished immune function, and may help to improve cognition and listlessness" (*CFIDS Chronicle*, January/February 1989). One study by Dr. Levine provided encouraging results. Cognitive symptoms improved in six of ten CFS/ME patients treated with 5 mg naltrexone. No clinically significant side effects were observed.

Despite numerous studies on the immunological benefits of naltrexone, relatively few CFS/ME doctors have included LDN as part of their protocols. Dr. Klimas prescribes LDN to boost immune system responses and for pain. Dr. Enlander prescribes LDN, but remains "neutral" as to its benefits.

**PROTOCOL.** LDN dosage ranges from 3-5 mg. Patients who have taken LDN for several months report that it is better to start with half the lowest recommended dose (1.5 mg) and slowly work up to 3 mg a day. LDN is generally taken before bed, but may be taken during the day if sleep is disturbed.

**PROS AND CONS.** A number of patients have reported dramatic improvement in flu-like symptoms, energy, sleep and concentration. Some even claim that LDN has cured them of all their symptoms. Side effects are fairly mild and are usually transient: nausea, headaches, weakness, unusually vivid dreams and fatigue. Naltrexone seems to work best with patients who have had a viral onset, or who have significant flu-like symptoms (sore throat, low fever). Because

naltrexone is an opioid antagonist, it cannot be taken with any narcotic pain medication, or with corticosteroids.

**AVAILABILITY AND COST.** LDN is available by prescription through compounding pharmacies. The cost is approximately \$40 for a 30-day supply. Irmat Pharmacy in Manhattan supplies 30 capsules of 4.5mg LDN for \$38. Insurance coverage may vary, so check with your carrier.

SEE: Pain

#### FURTHER READING

*Very thorough review of the history and current uses of LDN written by Maija Haavisto. Also included are the patient's own experience with LDN*

<http://www.fiikus.net/?ldn>

*Phoenix Rising discussion of LDN for CFS/ME patients. Includes explanation of how the drug works:* <http://aboutmecfs.org.violet.arvixe.com/Trt/LDN.aspx>

*Biography of Dr. Zagon and general information:* <http://www.ldnscience.org/ldn-researchers/119>

*Where to find LDN*

[http://www.lowdosenaltrexone.org/index.htm#What\\_diseases\\_has\\_it\\_been\\_useful\\_for](http://www.lowdosenaltrexone.org/index.htm#What_diseases_has_it_been_useful_for)

*General information about LDN:* <http://www.lowdosenaltrexone.org/index.htm>

*Yahoo group for low dose naltrexone*

<http://health.groups.yahoo.com/group/lowdosenaltrexone/>

#### PATIENT REVIEWS

*CFS/ME patient reviews of naltrexone:* <http://www.revolutionhealth.com/drugs-treatments/rating/naltrexone-for-chronic-fatigue-syndrome-cfs-cfids-me>

*A patient's experience with naltrexone:* <http://livewithcfs.blogspot.com/2008/04/low-dose-naltrexone-treatment-for-cfs.html>

*Detailed information on how LDN affected the immune system of a CFS/ME patient over a two-year period. This blog is well worth reading:*

<http://www.users.on.net/~julian.robinson/cfs/naltrexone.htm>

#### RESEARCH

Younger J, Mackey S. "Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study." *Pain Med.* 2009 May-Jun;10(4):663-72.

<http://www.ncbi.nlm.nih.gov/pubmed/19453963> (Abstract)

#### NEXAVIR (formerly Kutapressin)

**DESCRIPTION.** Nexavir is a peptide and amino acid solution derived from porcine (pig) liver.

**BACKGROUND.** In the late 1920s, it was discovered that liver helped patients with acne vulgaris. As a result of this observation, attempts were made to isolate the active factor from liver. Not until the 1940s was a specially purified liver



fraction isolated. Subsequent refinements in the isolation of the active material led to the development of what was then called Kutapressin, a biological (as opposed to synthetic) medication which had anti-inflammatory properties. Over the following decade, Kutapressin was used to treat a variety of dermatological conditions, including poison ivy, hives, eczema, and severe sunburn. According to Dr. Thomas Steinbach, Kutapressin was used decades ago to treat neurasthenia, a condition that bore a remarkable resemblance to CFS/ME.

**USES IN CFS/ME.** Kutapressin's value as a CFS/ME treatment did not become generally known until Dr. Thomas Steinbach and Dr. William Hermann used Kutapressin successfully in the early 1980s to treat shingles and what was then referred to as Epstein-Barr virus reactivation (*CFIDS Chronicle*, Summer 1990). Dr. Steinbach had observed that Kutapressin's antiviral and anti-inflammatory properties made it an effective treatment for infectious mononucleosis. Because of Kutapressin's excellent safety record and the positive results in treating Epstein-Barr virus infection, they conducted an informal unblinded study of some 270 patients with CFS/ME.

The results were impressive. Of the study participants, 75% showed improvement, and in some cases marked improvement, after only 40 injections of Kutapressin. Even more promising was that many of these patients had been ill with CFS/ME for more than five years.

The study riveted the attention of CFS/ME clinicians, because no drug treatment to date had produced such impressive results. A second study published by Dr. Steinbach and Dr. Hermann demonstrated the same impressive results (presented at the International CFIDS Conference, Albany, N.Y., 1992). Of the 130 patients who participated in the second study, 85% reported notable or marked reduction of symptoms while receiving Kutapressin injections. Of 111 patients who reported significant reductions in symptoms, 103 noted results within six months of treatment. As a result of these studies, many CFS/ME clinicians began to incorporate Kutapressin in their treatment plans, particularly when there was evidence of viral activity (high titers of human herpesvirus 6 and high interferon levels).

Some researchers have theorized that Kutapressin must have had both antiviral and immunomodulatory properties to simultaneously curtail viral reactivation and the characteristic immune system upregulation typical in CFS/ME. Kutapressin's role in suppressing viral activity is fairly well documented. A study published by Dr. D.V. Ablashi and colleagues proved that Kutapressin was a potent inhibitor of herpesvirus 6 in vitro without causing cell damage (*In Vivo*, 1994). A later study conducted in 1996 by Dr. E. Rosenfeld and colleagues found that Kutapressin was also effective against Epstein-Barr virus (*In Vivo*, 1996). However, its role in immunomodulation remains speculative. Dr. Steinbach and Dr. Hermann postulated that Kutapressin may have acted to mediate the action of lymphokines, the immune system chemicals that are thought responsible for many of the symptoms characteristic of CFS/ME.

On the heels of these promising studies, the ownership of Kutapressin changed hands. The distributor, Schwartz Pharma, sold Kutapressin, along with its client list, to Nexco Pharma, a Texas-based company. The product was renamed Nexavir, and while patients and doctors were assured that it was identical to the original formulation, this turned out not to be the case. Nexavir contains preservatives as well as tyrosine, an amino acid to which many CFS/ME patients are sensitive. This prompted some doctors to switch to Hepapressin, a bovine liver alternative. According to Dr. Steinbach, Hepapressin is not nearly effective as the original formulation of Kutapressin (personal communication).

**PROTOCOL.** The original protocol developed by Dr. Steinbach and Dr. Hermann consisted of a daily intramuscular injection of 2 ml of Kutapressin for 25 days followed by 2 ml injections every other day for 25 days, followed by 2 ml injections three times a week for several months. This is the protocol currently followed for Nexavir.

When he was still using Kutapressin, Dr. Cheney prescribed lower doses (1 ml) working up to 4 ml daily for six months. A 23-gauge 1-inch-long needle is recommended for deep intramuscular injection.

Many doctors who include Nexavir in their protocols (or its counterpart, Hepapressin), combine it with other medications. Dr. Enlander combines Hepapressin with magnesium, B12, folic acid and minerals. Dr. De Meirleir combines Nexavir with B12. In Dr. De Meirleir's experience with this combination, 50% of patients are pain free within three months, and sleep often normalizes within three days.

**PROS.** Most patients who have benefited from it note an immediate cessation of sore throats, a reduction in flu-like feelings, pain, and fatigue, and improvement in energy level. Many others have reported decreased duration and severity of episodes of flu, increased energy and stamina, and a feeling of overall improvement with Nexavir. Although Nexavir is considered safe, it does produce a few minor side effects initially, but these usually pass quickly after the first few injections are given. In most patients, side effects subside within the first 20 days of treatment.

**CONS.** Nexavir, although effective for some patients, is not universally helpful. A small number of patients may even feel worse, particularly those who are sensitive to tyrosine. Nexavir can involve a lot of time and money, with little gain. To that end, patients often do not continue with it for the full six months if they have noted no results after three or four months. People with allergies to pork and women who are pregnant should not take Nexavir.

**AVAILABILITY AND COST.** Nexavir is available by prescription only. It costs about \$145 per 20 ml vial (10 injections). A full six-month course of treatment can cost upwards of \$2,000. Some insurance companies cover the cost. However, many companies consider Nexavir an experimental drug for off-label usage and will not cover the cost.

## FURTHER READING

*Detailed information about Nexavir*

<http://livingwithchronicfatiguesyndrome.wordpress.com/2010/10/25/nexavir-kutapressin-for-cfs/>

*Dr. Steinbach's groundbreaking 1996 study of Kutapressin in CFS/ME treatment:*

<http://www.me-cvs.nl/index.php?pageid=3423>

*Nice run-down of various CFS/ME doctors' Nexavir protocols:* [http://esme-](http://esme-eu.com/antivirals/nexavir-kutapressin-for-me-cfs-article447-135.html)

[eu.com/antivirals/nexavir-kutapressin-for-me-cfs-article447-135.html](http://esme-eu.com/antivirals/nexavir-kutapressin-for-me-cfs-article447-135.html)

**RESEARCH**

Ablashi DV, Berneman ZN, Lawyer C, Kramarsky B, Ferguson DM, Komaroff AL.

“Antiviral activity in vitro of Kutapressin against human herpesvirus-6.” *In Vivo*. 1994 Jul-Aug;8(4):581-6. <http://www.ncbi.nlm.nih.gov/pubmed/7893985> (Abstract)

Rosenfeld E, Salimi B, O'Gorman MR, Lawyer C, Katz BZ. “Potential in vitro activity of Kutapressin against Epstein-Barr virus.” *In Vivo*. 1996 May-Jun;10(3):313-8. <http://www.ncbi.nlm.nih.gov/pubmed/8797033> (Abstract)

**NITROGLYCERIN**

**DESCRIPTION.** Nitroglycerin is a nitrate commonly used to relieve angina.

**BACKGROUND.** Nitroglycerin is one of the oldest drugs in continual use, having been used for more than 100 years to treat angina pectoris, a condition in which a spasm of the coronary arteries causes oxygen loss (ischemia) to the heart. It is a vasodilator; that is, it causes relaxation of the blood vessels. This in turn increases the supply of blood and oxygen to meet the needs of the heart.

**USES IN CFS/ME.** Nitroglycerin has been used primarily to treat fibromyalgia-type pain in people with CFS/ME, although it has other uses as well. At the 1992 CFIDS conference in Albany, New York, Dr. Jay Goldstein reported that nitroglycerin not only relieved pain but often helped alleviate many other symptoms associated with low blood flow (hypoperfusion) in the brain. After initiating nitroglycerin treatment, Dr. Goldstein's patients reported a decrease in headaches, sore throat, irritable bowel-type symptoms, anxiety, and depression. They also noted increased energy and improved cognition. A point of great interest regarding nitroglycerin as a CFS/ME treatment is that some patients with concurrent multiple chemical sensitivities report improvement in symptoms.

Aside from Dr. Goldstein, very few doctors have investigated the effects of nitroglycerin on CFS/ME patients. In contrast, a number of doctors and researchers have pursued the possible benefits of nitroglycerin for those who suffer from fibromyalgia. A 2011 study by Cho et al found that in fibromyalgia patients, blood flow was restricted due to endothelial dysfunction (an imbalance between vasodilation and vasoconstriction in the inner lining of blood vessels). Nitroglycerin could potentially correct that problem.

Dr. Mark Reed, a podiatrist, prescribed nitroglycerin patches for use on the ankles of a patient with severe foot pain due to fibromyalgia. The patient reported a cessation of pain, and a return of normal skin color on her feet. The only side effect

was headache, which was relieved by cutting the patches into 1/8" segments. It is possible, given its vasodilating properties, that topical nitroglycerin can be used to alleviate localized ischemic pain in other areas of the body as well.

**PROTOCOL.** Because nitroglycerin affects the heart, it is best to determine a specific dose with your physician (individual requirements vary). Dr. Goldstein prescribed sublingual nitroglycerin, generally 0.04 mg (more information on Dr. Goldstein's protocol can be obtained by reading Dr. Goldstein's book, *Chronic Fatigue Syndrome: The Limbic Hypothesis*).

**PROS AND CONS.** In marked contrast to other CFS/ME medications, nitroglycerin acts very quickly. Improvement in symptoms can be noted within minutes, making the drug easy to evaluate. Benefits can be global; energy, pain, cognitive function, and mood may improve significantly. However, side effects are common.

The most frequent problems are reduced blood pressure, fainting, dizziness, and headache. For this reason, nitroglycerin is usually administered while the patient is sitting. Patients with migraine headaches should not take this drug because it will worsen the condition. An additional drawback to nitroglycerin is that it loses its effectiveness over time. Dr. Goldstein states, "The most vexing problem in my use of nitroglycerin has been the development of tolerance, which is sometimes extremely rapid, occurring even after the first dose" (*CFIDS Chronicle*, Summer 1993).

Concurrent use of any drug that lowers blood pressure or alcohol will exaggerate the hypotensive effect of nitroglycerin. Because it is a vasodilator, patients with syncope or hypotension should avoid nitroglycerin.

**AVAILABILITY AND COST.** Nitroglycerin is available by prescription, in pill or patch formulation. It can be purchased as a generic drug or any of more than two dozen brand-name drugs. Nitroglycerin is inexpensive; 100 sublingual pills cost less than \$30. The price of 10 patches is around \$10. Insurance usually covers the cost.

#### FURTHER READING

*Interesting article about the pain-relieving effects of nitroglycerin patches for peripheral neuropathy in a patient with FM:*

[http://www.fmaware.org/News2fa26.html?news\\_iv\\_ctrl=1&page=NewsArticle&id=9359](http://www.fmaware.org/News2fa26.html?news_iv_ctrl=1&page=NewsArticle&id=9359)

"Nitroglycerin: A Potential Mediator for Hypoperfusion in CFS." Jay Goldstein.

<http://www.me-cvs.nl/index.php?pageid=3022&printlink=true&highlight=cfs>

#### RESEARCH

Cho KI, Lee JH, Kim SM, Lee HG, Kim TI. "Assessment of endothelial function in patients with fibromyalgia--cardiac ultrasound study." *Clin Rheumatol*. 2011 May;30(5):647-54. <http://www.ncbi.nlm.nih.gov/pubmed/20957400> (Abstract)

OXYTOCIN (Pitocin, Syntocinon)

**DESCRIPTION.** Oxytocin is a hormone produced in the posterior lobe of the pituitary gland. It acts as a neuromodulator.

**BACKGROUND.** Oxytocin is a pituitary hormone that stimulates uterine muscle contraction and sensitizes nerves. It also controls microcirculation in the brain. Oxytocin is naturally produced in large quantities during childbirth, lactation, in response to certain stressors (hypoglycemia, exercise, hypothermia), and during sexual intercourse. Its most common medical use has been as an aid in stimulating contractions during labor. Oxytocin is also used to control postpartum uterine bleeding. The neurotransmitter dopamine stimulates oxytocin production.

Oxytocin is sometimes referred to as the “love” hormone. It produces feelings of calmness, trust and bonding while reducing anxiety and fear, all of which are important emotions to feel while caring for an infant. Oxytocin also has myriad other effects on the body. It reduces blood pressure and cortisol levels, improves pancreas and bowel function, and, of primary importance to CFS/ME patients, facilitates microcirculation in the brain. Catecholamines (adrenaline, noradrenaline) inhibit the release of oxytocin.

**USES IN CFS/ME.** CFS/ME clinician Dr. Jorge Flechas suggested that patients with CFS/ME might well have a deficiency in oxytocin (*CFIDS Chronicle*, Spring 1995). Dr. Flechas based his theory on the fact that CFS/ME patients have lower levels of two other hormones, corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which are coexpressed with oxytocin in the same region of the brain. He pointed out that many of the symptoms of CFS/ME (pain, loss of libido, sleep disturbances, low exercise tolerance, circulatory problems, and metabolic disorders) could be generated by oxytocin deficiency.

Several CFS/ME clinicians, including Dr. Flechas, Dr. Cheney and Dr. Jay Goldstein, have used oxytocin to treat CFS/ME symptoms. They have reported increased stamina, decreased pain, and improved cognitive function in those patients who have used it. In his book, *Betrayal by the Brain*, Dr. Goldstein also noted a decrease in fibromyalgia pain, anxiety, depression, and perhaps even food allergies.

Dr. Cheney has observed dramatic improvement in fatigue, pain, and short-term memory in his CFS/ME patients, which he attributes oxytocin's effects on microcirculation in the brain and deep tissues. Dr. Lapp also notes that oxytocin increases blood flow to the eyes, brain and muscles in CFS/ME patients:

“You think more clearly and you see more clearly. It can be remarkable. I can give the patient a shot of oxytocin in the hip and five minutes later they will say, “I haven’t seen this clearly, I haven’t felt this well in months.” It doesn’t work for everybody, but when it does, it is quite miraculous and can be a long-term therapy.”

Interestingly, several CFS/ME doctors have observed that when their patients become pregnant, their CFS/ME symptoms abate. Many attribute this improvement to an increase in oxytocin.

**PROTOCOL.** Oxytocin may be administered orally, sublingually, or as an intramuscular injection (IM). Dr. Cheney has used sublingual oxytocin at 10 units

up to three times a day. Dr. Teitelbaum recommends 10 units IM for patients in whom a deficiency is suspected (those with pallor and cold extremities). According to Dr. Teitelbaum, effects will begin within 45 minutes to an hour. He prescribes injections daily or on an “as needed” basis. Some specialists note the benefits of oxytocin after a single injection, while others believe it takes several injections to determine if oxytocin will have a positive effect.

Dr. Cheney has used a sublingual form of oxytocin at 10 to 20 units up to three times per day. Sublingual oxytocin has the advantage of being able to spit it out if a negative reaction occurs.

**PROS AND CONS.** Oxytocin has so many functions in regulating primary systems in the body that it may provide, as Dr. Lapp says, nearly “miraculous” results. But, it doesn't work for everybody. Because oxytocin is a hormone which can influence nearly every system in the body, side effects can be serious: nausea, irregular heartbeat, changes in blood pressure, convulsions, headache, weight gain, dizziness, difficulty breathing, and mental disturbances. Any side effects should be reported to your physician. Pregnant women should not take oxytocin.

**AVAILABILITY AND COST.** Oral oxytocin (Pitocin, Syntocinon) is available by prescription only. Injectable oxytocin can be expensive, \$50 for 10 ml. Nasal spray is less expensive. Belmar Pharmacy has also made available both a sublingual and oral form of oxytocin which may reduce the risk of side effects.

## SUPPLIER

Belmar Pharmacy

Website: <http://www.belmarpharmacy.com/oxytocin.htm>

## FURTHER READING

*Dr. Lapp's 1997 presentation on treatments, including oxytocin*

[http://www.prohealth.com/library/showarticle.cfm?id=2926&t=CFS/ME\\_FM](http://www.prohealth.com/library/showarticle.cfm?id=2926&t=CFS/ME_FM)

*Detailed discussion of oxytocin, primarily as it relates to FM*

[http://findarticles.com/p/articles/mi\\_m0FDL/is\\_3\\_14/ai\\_n27448236/](http://findarticles.com/p/articles/mi_m0FDL/is_3_14/ai_n27448236/)

*Very thorough explanation of the various functions of oxytocin by Dr. Jorge Flechas*

<http://cypress.he.net/~bigmacnc/drflechas/abstract1.html>

*How oxytocin is used for fibromyalgia and chronic pain*

[http://sacfs.asn.au/news/2011/01/01\\_25\\_oxytocin\\_may\\_offer\\_benefits\\_in\\_treatment\\_of\\_chronic\\_pain.htm](http://sacfs.asn.au/news/2011/01/01_25_oxytocin_may_offer_benefits_in_treatment_of_chronic_pain.htm)

## PATIENT REVIEWS

*Blog of one patient's unsuccessful treatment with oxytocin*

<http://livingwithchronicfatiguesyndrome.wordpress.com/2010/07/05/oxytocin-for-cfs/>

## PAIN RELIEVERS (ANALGESICS)

Aspirin, NSAIDs, Tylenol, Aleve, Ultram, Narcotics

*NOTE: Most analgesics are available over the counter, but it is still important to discuss dosage and side effects with your physician, especially if any of these medications are taken regularly.*

**DESCRIPTION.** Analgesics are agents that diminish pain.

**BACKGROUND.** Analgesics, or pain killers, work by blocking the body's production of hormones that send pain messages to the brain (prostaglandins) or by occupying the sites that receive those messages. The two general types of analgesics are non-narcotics, which block chemical production, and narcotics, which block reception in the brain. Non-narcotic pain killers include aspirin and other salicylates, acetaminophen (Tylenol), naproxen (Aleve) and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil, Motrin). Narcotic pain killers include the opiates and opioids, such as codeine, Darvon or Wygesic (propoxyphene), Demerol (meperidine), and morphine. Because narcotics are habit-forming, they are used on a short-term basis only. A number of prescription analgesics contain a combination of non-narcotic and narcotic pain killers. The most common combinations contain codeine and acetaminophen or aspirin. These drugs are used when pain persists or is not relieved by other non-narcotic or narcotic drugs.

#### ASPIRIN

**DESCRIPTION.** Aspirin is a salicylate, a group of drugs with many medicinal uses, including reduction of fever and inflammation, as well as exhibiting mild antibiotic properties. Aspirin blocks pain by inhibiting the enzyme cyclooxygenase (COX-1), which helps the body produce inflammation-causing prostaglandins. The main active ingredient in aspirin is acetylsalicylic acid, a chemical that was first derived from willow bark.

Aside from blocking pain, aspirin has a number of physiological mechanisms. It has been shown to prevent glutamate toxicity in the brain. Glutamate is a neuroexcitatory neurotransmitter which is frequently high in CFS/ME patients. Aspirin also reduces ATP storage pools, which increases bleeding time; increases extracellular adenosine, which is associated with short-term energy increase; and lowers inducible nitric oxide synthase activity (NO mediates vasodilation in blood vessels).

**USES IN CFS/ME.** Aspirin is recommended for those CFS/ME patients with continual or severe joint and muscle pain. In his book, *The Doctor's Guide to Chronic Fatigue Syndrome*, Dr. David Bell notes that aspirin is beneficial for CFS/ME patients with "prominent joint and muscle pain, headache, lymph node pain and general aching, and is less effective in patients with prominent fatigue, nausea, and neurologic symptoms."

**PROTOCOL.** Aspirin can be taken as needed to prevent or treat pain. Dr. Bell suggests that some patients with intractable pain may benefit from daily use of aspirin. To avoid stomach upset, aspirin should be taken with food. As with other drugs, it is best to begin with a small dose to assess tolerance.

**PROS.** For many patients, aspirin is an inexpensive, reliable analgesic. Some patients report an increase of energy after taking aspirin, probably due to the temporary increase of adenosine.

**CONS.** Although aspirin is generally regarded as safe, frequent use can lead to a number of side effects, including tinnitus (ringing in the ears), nausea, and heartburn. If aspirin is taken on a regular basis, an anti-ulcer medication (such as Cytotec, Zantac or Tagamet) may also be recommended to protect the lining of the stomach. Patients with a history of ulcers, gastroesophageal reflux, or other gastrointestinal problems should avoid aspirin. Some nutritionists recommend that patients with food sensitivities avoid salicylates. Aspirin should not be given to children because it can cause Reye's syndrome.

**AVAILABILITY AND COST.** Aspirin is available over the counter at any pharmacy and most supermarkets. It is quite inexpensive, often less than \$5 for a bottle of 300 tablets. Check the label carefully because some aspirin brands contain other potentially irritating ingredients, such as caffeine.

## RESEARCH

Crisanti P, Leon A, Lim DM, Omri B. "Aspirin prevention of NMDA-induced neuronal death by direct protein kinase C $\zeta$  inhibition." *J Neurochem*. 2005 Jun;93(6):1587-93.

<http://www.ncbi.nlm.nih.gov/pubmed/15935075?dopt=Abstract> (Abstract)

Czyz M, Watala C. [Aspirin--the prodigious panacea? Molecular mechanisms of the action of acetylsalicylic acid in the organism]. *Postepy Hig Med Dosw* (Online). 2005 Mar 23;59:105-15. <http://www.ncbi.nlm.nih.gov/pubmed/15928593> (Abstract)

## PATIENT REVIEWS

*A CFS/ME patient's review of Bayer aspirin*

<http://www.revolutionhealth.com/drugs-treatments/rating/bayer-aspirin-for-chronic-fatigue-syndrome-cfs-cfids-me>

## NSAIDs

Ibuprofen (Advil, Motrin), Naproxen (Aleve), Nabumetone (Relafen), Celecoxib (Celebrex), Meloxicam (Mobic), diclofenac (Arthrotec)

**DESCRIPTION.** Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting prostaglandin production by blocking both COX-1 and COX-2. Like aspirin, they reduce inflammation, pain, and fever. Unlike aspirin, which is cleared from the body quickly, NSAIDs have a long half-life and thus require less frequent administration. Their lower dosage leads to fewer side effects. There is also a class of strictly COX-2 inhibitors, of which Celebrex is the most common. These produce greater risks of side effects and should not be taken with other NSAIDs.



**USES IN CFS/ME.** NSAIDs are recommended to treat recurring pain in muscles and joints. Many patients with CFS/ME who have chronic acute pain prefer ibuprofen (Advil, Motrin) over other pain medications.

**PROTOCOL.** NSAIDs are generally taken as needed. Patients should start with a small dose to assess tolerance.

**PROS.** Some CFS/ME patients report that taking ibuprofen gives them an extra “boost.” Because NSAIDs actively work to reduce inflammation, they may work better on joint pain and stiffness than other analgesics.

**CONS.** Because all NSAIDs can produce gastrointestinal problems, caution must be exercised. Buffered or enteric-coated drugs help protect the stomach lining. The medication should always be taken with food. Finally, patients should be alert for signs of gastrointestinal distress (heartburn, reflux, pain). NSAIDs raise blood pressure, so patients with a history of hypertension should avoid taking them. NSAIDs are also contraindicated for patients with a history of kidney problems.

**AVAILABILITY AND COST.** NSAIDs are available over the counter. The most common is ibuprofen (Advil, Motrin). A bottle of 50 tablets of Advil (200 mg) costs around \$5.00. Prescription NSAIDs include Clinoril, Feldene, and Tolectin. Intramuscular Toradol may be prescribed for severe pain. NSAIDs are generally more expensive than aspirin or acetaminophen.

## PATIENT REVIEWS

*CFS/ME patient reviews of Advil:* <http://www.revolutionhealth.com/drugs-treatments/rating/advil-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Aleve:* <http://www.revolutionhealth.com/drugs-treatments/rating/aleve-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Arthrotec:* <http://www.revolutionhealth.com/drugs-treatments/rating/arthrotec-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Celebrex:* <http://www.revolutionhealth.com/drugs-treatments/rating/celebrex-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Mobic:* <http://www.revolutionhealth.com/drugs-treatments/rating/mobic-for-chronic-fatigue-syndrome-cfs-cfids-me>

*CFS/ME patient reviews of Naproxen:* <http://www.revolutionhealth.com/drugs-treatments/rating/naprosyn-for-chronic-fatigue-syndrome-cfs-cfids-me>

## ACETAMINOPHEN (Tylenol)

*CAUTION:* In January 2011, the FDA limited the use of acetaminophen-opioid combinations due to the risk of liver failure. These include hydrocodone with acetaminophen (Vicodin, Lortab), and oxycodone with acetaminophen (Tylox, Percocet).

**USES IN CFS/ME.** In contrast to NSAIDs, which work by inhibiting signals to the nervous system, acetaminophen (Tylenol) acts in the brain, where it blocks the perception of pain. As a consequence, acetaminophen is not of particular benefit

in treating joint or muscle pain due to inflammation. Its primary uses in CFS/ME are to relieve headache and generalized achiness, and to reduce fevers.

**PROS.** Acetaminophen does not cause stomach irritation, as do aspirin and other NSAIDs. However, a number of patients with CFS/ME find they can tolerate only low or infrequent doses.

**CONS.** A serious problem associated with acetaminophen is that high doses can lead to liver damage—as can any dose of this drug taken with alcohol. Acetaminophen also interacts in a similar fashion with opioids (narcotics). If signs of liver malfunction develop (jaundice or pain under the right side of the rib cage), acetaminophen should be discontinued immediately.

**AVAILABILITY AND COST.** Acetaminophen is available over the counter in brand-name and generic formulations. It is inexpensive. A bottle of 24 capsules costs less than \$6.00.

#### FURTHER READING

*Study linking acetaminophen to liver failure:* <http://www.masscfids.org/resource-library/3-research/61-increasing-number-of-fatal-acute-liver-failure-cases-linked-to-the-popular-painkiller-acetaminophen-tylenol>

#### PATIENT REVIEWS

*CFS/ME patient reviews of Tylenol:* <http://www.revolutionhealth.com/drugs-treatments/rating/tylenol-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### ULTRAM

**DESCRIPTION.** Ultram (tramadol) is a centrally acting synthetic opioid analgesic used for severe pain.

**BACKGROUND.** Tramadol was developed in the 1970s by the German company Grunenthal GmbH. Somewhat like narcotics, it is an opioid agonist, releasing serotonin and inhibiting the uptake of norepinephrine. Because tramadol is structurally similar to Effexor, it has been proposed as a treatment for mood disorders, phobias and anxiety, although physicians have not endorsed it for these uses.

**USES IN CFS/ME.** Ultram has been prescribed to treat muscle and fibromyalgia-type pain that has been resistant to other medications.

**PROS.** Some patients report that Ultram is the most effective medication for pain and that it also helps relieve insomnia and fatigue. Ultram acts quickly and does not seem to produce as many side effects as other pain medications.

**CONS.** Ultram is addictive. Withdrawal symptoms from extended use are more severe than for other opioids, and last for a longer period of time. This drug is contraindicated in patients with seizure disorders and those taking monoamine oxidase inhibitors (MAOIs) or other antidepressants.

**AVAILABILITY AND COST.** Tramadol is available by prescription. The generic is relatively inexpensive. Thirty tablets costs around \$20.

## PATIENT REVIEWS

*CFS/ME patient reviews of Ultram:* <http://www.revolutionhealth.com/drugs-treatments/rating/ultram-for-chronic-fatigue-syndrome-cfs-cfids-me>

## NARCOTICS

**USES IN CFS/ME.** The subset of CFS/ME patients with severe, burning, intractable pain that does not respond to other treatments may need stronger medications. In these cases, narcotics may be recommended. Although effective, narcotics are addictive and therefore should be used only when other pain treatments have failed to alleviate pain.

**PROS.** Narcotics offer immediate and sometimes total relief from certain types of pain. Some CFS/ME patients with fibromyalgia report that a single injection of Demerol may relieve pain for up to 6 months. The reasons for this are not clear, but for some patients breaking the cycle of pain reception in the brain seems to have long-term benefits.

**CONS.** Narcotics can be used only infrequently and in small doses because the risk of addiction is high. The most common side effects are drowsiness, mood changes, and constipation. Codeine also causes stomach upset. The higher the dose, the more serious the side effects. High doses, for example, may cause breathing problems; therefore, patients with a history of respiratory problems should exercise caution or avoid narcotics entirely.

## FURTHER READING

*CFIDS Association of America's list of commonly used analgesics and side effects*  
<http://www.cfids.org/resources/analgesic.asp>

*FDA limits use of acetaminophen-opioid combinations:*  
<http://www.fightingfatigue.org/?p=8933>

## PENTOXIFYLLINE (Trental)

**DESCRIPTION.** Pentoxifylline (Trental) is a hemorrheologic agent derived from xanthine. A number of stimulants, including caffeine, are derived from xanthine.

**BACKGROUND.** Pentoxifylline improves capillary blood flow by increasing the flexibility of red blood cells and lowering blood viscosity. This double action enables blood cells to squeeze through tiny capillaries with greater ease. Traditionally, pentoxifylline is used to treat vascular diseases, especially those that inhibit blood flow. Pentoxifylline is also used to treat the nausea and headaches associated with altitude sickness.

**USES IN CFS/ME.** Some clinicians have recommended pentoxifylline in CFS/ME to increase blood flow to the brain. Single-photon emission computed tomography (SPECT) scans consistently reveal lowered blood flow in patients with CFS/ME. In theory, pentoxifylline should resolve that problem.

Pentoxifylline may also address another blood problem common to CFS/ME. Dr. L.O. Simpson, a pathologist from the University of Otago Medical School in

Dunedin, New Zealand, discovered that patients with CFS/ME have irregularly shaped red blood cells, which makes it more difficult for blood cells to pass through capillaries. Dr. Simpson believes the decreased cerebral blood flow in CFS/ME is the consequence of abnormally shaped blood cells. Many of the symptoms of inadequate blood supply such as light-headedness, vertigo, and cognitive problems might be alleviated if blood flow is increased.

Apart from pentoxifylline's well-known effects on blood flow, it also has broad antiviral activity. A study conducted in 1993 by a team of Russian scientists found that trental [pentoxifylline] was an “effective broad spectrum virus inhibitor.” Pentoxifylline also has the ability to inhibit proinflammatory cytokines, which have been shown to be upregulated in CFS/ME patients.

**PROTOCOL.** The usual recommended dose for vascular problems is 400 mg three times a day, with meals. Patients with CFS/ME should begin with a lower dose (400 mg once a day) to assess sensitivity.

**PROS AND CONS.** CFS/ME patients who have benefited from pentoxifylline report dramatic improvement in cognitive function as well as a reduction in flu-like symptoms (sore throats, swollen glands, and malaise). Pentoxifylline should not be used by those who cannot tolerate stimulants. (Xanthine, from which pentoxifylline is derived, is closely related to caffeine.) Pentoxifylline is contraindicated in patients with peptic ulcers and those at risk for hemorrhage. The most commonly reported side effects are nausea, headache and flushing.

**AVAILABILITY AND COST.** Pentoxifylline is available by prescription. It is not expensive. Ninety tablets can cost as little as \$20.

#### FURTHER READING

*A very thorough discussion of one patient's experiences with pentoxifylline.*

<http://livingwithchronicfatiguesyndrome.wordpress.com/2011/09/05/pentoxifylline-for-me/>

*An excellent CFS Report on Les Simpson, blood flow and fatigue in CFS.*

<http://www.cfidsreport.com/Articles/researchers/lessimpson.htm>

#### RESEARCH

Amvros'eva TV, Votiaikov VI, Andreeva OT, Vladyko GV, Nikolaeva SN, Orlova SV, Azarova IA, Zgirovskaia AA. “New properties of trental as an inhibitor of viral activity with a wide range of activity.” *Vopr Virusol.* 1993 Sep-Dec;38(5):230-3.

<http://www.ncbi.nlm.nih.gov/pubmed/8284924> (Abstract)

#### PLAQUENIL

**DESCRIPTION.** Plaquenil (hydroxychloroquine) is an antimalarial drug. Chemically, it is classed as a 4-aminoquinoline compound.

**BACKGROUND.** Hydroxychloroquine is one of a number of drugs that have been used for many years in the treatment of malaria. It has also been used to treat a number of autoimmune and inflammatory disorders, including systemic lupus,

rheumatoid arthritis, and Sjögren's Syndrome. Hydroxychloroquine reduces the activation of dendritic cells, thus mitigating the inflammatory process.

**USES IN CFS/ME.** Hydroxychloroquine (Plaquenil) is prescribed to CFS and FMS patients if they have a high ANA level plus symptoms of Sjögren's syndrome, lupus, or other autoimmune diseases. Patients starting hydroxychloroquine therapy should have an ophthalmology exam every six months to monitor for retina toxicity.

**PROTOCOL.** As very few doctors use Plaquenil for CFS/ME, there is no protocol.

**PROS AND CONS.** Some patients report a decrease in pain and insomnia. The drawbacks, however, do not justify the benefits, which may be obtained through other less risky medications. As with all chloroquine medications, there are numerous serious side effects. People of African descent can develop severe anemia. In children, Plaquenil can be fatal.

Plaquenil diffuses rapidly into adipose (fatty) tissues, which are found abundantly in the nervous system and eyes. Permanent eye damage (retinal and corneal), including blindness, has been reported. Some patients experience psychosis (hearing voices, delusions, hallucinations, disorientation). The 4-aminoquinoline compounds are very rapidly and completely absorbed after ingestion, which means accidental overdoses, even at low doses, can occur. Toxic symptoms can occur within 30 minutes. These consist of headache, drowsiness, visual disturbances, cardiovascular collapse, and convulsions, followed by sudden and early respiratory and cardiac arrest (death).

**AVAILABILITY AND COST.** Plaquenil is available by prescription only.

#### FURTHER READING

*Patient thread on Plaquenil:* <http://forums.phoenixrising.me/showthread.php?3171-Plaquenil-hydroxychloroquine>

#### PATIENT REVIEWS

*One patient's review of Plaquenil:* <http://www.revolutionhealth.com/drugs-treatments/rating/hydroxychloroquine-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### PYRIDOSTIGMINE (Mestinon)

**DESCRIPTION.** Pyridostigmine (brand: Mestinon) is an acetylcholinesterase inhibitor. Pyridostigmine is poorly absorbed in the gut and does not cross the blood-brain barrier.

**BACKGROUND.** Pyridostigmine works by preventing the breakdown of acetylcholine (ACh) in nervous system synapses. This leads to an increase in acetylcholine, a neurotransmitter widely found in both the peripheral and central nervous systems. Acting as both an excitatory and inhibitory neurotransmitter, acetylcholine performs a variety of functions. Within the skeletal muscular system it contracts muscle, allowing for movement. It slows the heart, and promotes REM sleep. In the central nervous system, ACh is closely associated with learning, attention, and short-term memory.

Pyridostigmine is mainly prescribed for myasthenia gravis, an autoimmune condition in which acetylcholine is blocked, leading to profound muscle weakness. In spite of the fact that it does not cross the blood-brain barrier, pyridostigmine is also used to enhance memory in people with Alzheimer's disease. Pyridostigmine has been administered as a treatment for the paralysis caused by organophosphate pesticide poisoning. In a similar vein, the military administered pyridostigmine as a prophylactic to soldiers during the Gulf War to block potential exposure to Soman, a nerve gas which acts on acetylcholine in much the same manner as organophosphate pesticides. Recently, pyridostigmine has been used to treat orthostatic intolerance.

**USES IN CFS/ME.** In his book, *Betrayal by the Brain*, Dr. Jay Goldstein proposed that pyridostigmine can be used in CFS/ME with much the same results as in patients with myasthenia gravis: the alleviation of muscle weakness. Surprisingly, Dr. Goldstein found that even though pyridostigmine does not cross the blood-brain barrier it increased mental clarity in his CFS/ME patients. He noted that because pyridostigmine helps increase the secretion of growth hormone (GH), it might be of benefit to CFS/ME patients, who tend to have low levels of GH.

In 2003 a group of Japanese researchers published a study in which low-dose pyridostigmine was administered to three CFS/ME patients with dysautonomia and positive Epstein-Barr virus (EBV) titers. In all three cases, a one-month course of pyridostigmine relieved fatigue and muscle weakness. The authors speculated that EBV infection induces antibodies, which, through an inhibition of calcium influx at motor terminals, reduces acetylcholine release and causes muscle weakness and cholinergic autonomic dysfunction. The authors concluded that their case studies “strongly suggest therapy using a small dose (10 mg per day) of oral pyridostigmine in patients with CFS who have had more than a 40% amplitude increase in response to the RNS [repetitive nerve stimulation] test, positive anti-VCA IgG of EBV and mild impairment of autonomic functions.”

Based on findings that pyridostigmine increases growth hormone, a 2008 study of fibromyalgia patients in Portland, Oregon was conducted comparing exercise, diet and treatment with pyridostigmine. While the researchers did not find that either pyridostigmine alone or pyridostigmine plus exercise produced an improvement in most FM symptoms, they did find that pyridostigmine improved anxiety and sleep. The authors speculated that pyridostigmine may have improved vagal tone, thus alleviating sleep and anxiety symptoms.

**PROS AND CONS.** CFS/ME patients report a decrease in fatigue and post-exertional malaise. However, there are many side effects if taken at normal recommended doses. Common side effects include increased saliva, increased sweating, increased urination, watery eyes, stomach upset, stomach pain, nausea, warmth, tingling, and diarrhea.

**AVAILABILITY AND COST.** Pyridostigmine is available at most pharmacies with a prescription. A 30-day supply of generic 60 mg tablets costs about \$20. Insurance usually covers the cost.

## PATIENT REVIEWS

*FM patient reviews of Mestinon (pyridostigmine):*

<http://www.revolutionhealth.com/drugs-treatments/rating/mestinon-for-fibromyalgia-syndrome-fms>

## RESEARCH

Arvat E, Cappa M, Casanueva FF, Dieguez C, Ghigo E, Nicolosi M, Valcavi R, Zini M. "Pyridostigmine potentiates growth hormone (GH)-releasing hormone-induced GH release in both men and women." *J Clin Endocrinol Metab.* 1993 Feb;76(2):374-7. <http://www.ncbi.nlm.nih.gov/pubmed/8432781> (Abstract)

Jones KD, Burckhardt CS, Deodhar AA, Perrin NA, Hanson GC, Bennett RM. "A six-month randomized controlled trial of exercise and pyridostigmine in the treatment of fibromyalgia." *Arthritis Rheum.* 2008 Feb;58(2):612-22. <http://www.ncbi.nlm.nih.gov/pubmed/18240245> (Abstract)

Kawamura, Yasuo, Mikihiro Kihara, Kazuhiro Nishimoto, Mayumi Taki. "Efficacy of a half dose of oral pyridostigmine in the treatment of chronic fatigue syndrome: three case reports." *Pathophysiology* 9 (2003) 189-194. <http://www.cfids-cab.org/cfs-inform/Coicfs/kawamura.etal03.pdf>

## QUESTRAN (cholestyramine)

**DESCRIPTION.** Questran (cholestyramine) is a bile sequestrant; it attaches to bile in the intestines and removes it.

**BACKGROUND.** Bile is produced in the liver. When it is released via the gall bladder into the small intestine, it serves to break down fats. Bile is then reabsorbed by the ileum (the portion of the small intestine where it joins the large intestine). In some situations, such as GI surgery or Crohn's disease, the bile is not properly reabsorbed, resulting in a watery green diarrhea. Questran helps bind bile acids, reducing diarrhea. Questran's binding action is useful for the pruritus (itching) experienced by people with liver failure, and for reducing high levels of cholesterol in the bloodstream. Questran also binds to mold toxins, and is used by some alternative doctors to treat "sick building syndrome."

**USES IN CFS/ME.** The idea that CFS/ME patients suffer from neurotoxicity and oxidative stress is not a new one. Normally, CFS/ME physicians treat their patients with a combination of antioxidants (for oxidative stress) and nervous system down regulators, such as Klonopin (for neurotoxicity). However, it was Dr. Shoemaker's treatment of oxidative stress in mold toxicity, chronic Lyme and other bacterial infections with Questran that led to its use in CFS/ME.

**PROTOCOL.** The normal recommended dose of Questran is one packet (4 oz) of powder mixed into a beverage and drunk slowly. Dr. Cheney recommends that CFS/ME patients start with as little as ¼ teaspoon at bedtime. Be sure to drink plenty of water during the day as Questran is very constipating. Because Questran absorbs everything in your intestinal tract, you should not take Questran within an hour of taking other medications.

**PROS AND CONS.** Nothing will stop diarrhea faster than Questran, which is a boon to people who experience diarrhea often. Questran is a medication with a

good safety record and with few side effects. However, it is a stomach irritant. Because it binds to bile and fats, it not only can cause constipation, but can lead to deficiencies in fat-soluble vitamins. Questran contains sugar, which is not recommended for CFS/ME patients. Questran “Light” contains aspartame, which is also not recommended. Notwithstanding these drawbacks, some CFS/ME patients swear by it.

**AVAILABILITY AND COST.** Questran is quite expensive, but if you buy generic cholestyramine powder the price drops considerably. (A single dose of brand costs about \$2, whereas generic costs roughly 40 cents.) Insurance usually covers.

#### FURTHER READING

*Basic drug information about Questran:* <http://www.drugs.com/pro/questran.html>

*Summary of Dr. Cheney's protocol:* <http://www.dfwcids.org/medical/cheney.html>

*Dr. Teitelbaum's recommendations for how best to take Questran:*

<http://www.endfatigue.com/tools-support/Neurotoxins-Information-Sheet.html>

*CFS/ME patient reviews of Questran:* <http://www.revolutionhealth.com/drugs-treatments/rating/questran-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### RITUXIMAB

**DESCRIPTION.** Rituximab (trade names: Rituxan, MabThera) is a monoclonal antibody which acts against the protein CD20. Rituximab was first approved by the FDA in 1997 for the treatment of non-Hodgkin's lymphoma.

**BACKGROUND.** All cells have receptors on their surfaces which allow molecules to attach themselves and cause metabolic changes within the cell. One of these receptors, primarily found on the surface of B cells, is called CD20. Molecules that attach to CD20 can affect the growth and development of tumor cells, and, sometimes, cause the production of new tumor cells. Tests confirming the expression of CD20 antigens are important in diagnosing B-cell lymphomas and leukemia.

Rituximab was developed using cloning and recombinant DNA technology from human and murine (mice or rat) genes. It is believed that rituximab destroys tumors by attaching to the CD20 receptor on B cells, causing the tumor cells to disintegrate. In some non-Hodgkin's B-cell lymphomas, rituximab prevents the production of more tumor cells.

Rituximab is also used in the treatment of autoimmune disorders, such as rheumatoid arthritis and Wegener's granulomatosis. In these cases, rituximab works by temporarily depleting the total number of B cells, which are important in promoting inflammation. Rich Van Konynenburg has proposed that this is the reason rituximab may work for CFS/ME patients – by reducing B cells, rituximab reduces inflammation.

**USES IN CFS/ME.** The effect of rituximab on CFS/ME patients was discovered by accident. Two Norwegian doctors, Øystein Fluge and Olav Mella of Haukeland University Hospital, noticed that after treating a CFS/ME patient for



Hodgkin's lymphoma with rituximab, she recovered from CFS/ME. This led the doctors to initiate a small study of rituximab on CFS/ME patients.

Three CFS/ME patients were given rituximab in an open-label trial (that is, the patients knew they were receiving the drug). All three patients experienced significant improvement; two of them responded within six weeks and the third had a delayed response, occurring six months after treatment. The positive effects lasted for between 16 and 44 weeks. After relapse, the patients were administered another dose of rituximab, with the same positive results. The investigators hypothesized that B cells of the immune system might play a significant role in CFS, at least for a subset of patients, and that “CFS may be amenable to therapeutic interventions aimed at modifying B-cell number and function.”

The positive results of this, as well as a second open-label trial, led Drs. Fluge and Mella to conduct a larger study with a more rigorous design to test the effects of the drug. In 2009 they initiated a double-blind, placebo-controlled phase trial with 30 CFS/ME patients. As in the earlier open-label studies, the responses to rituximab were significant. Sustained overall improvements were noted in 67% of the patients (as opposed to 13% of the control group). Four of the rituximab patients showed improvement past the study period. The authors concluded that the delayed responses starting from 2–7 months after rituximab treatment, in spite of rapid B-cell depletion, “suggests that CFS is an autoimmune disease and may be consistent with the gradual elimination of autoantibodies preceding clinical responses.”

The result of this study not only generated headlines all over the world, but prompted an unprecedented apology from the Norwegian Directorate of Health. In a televised announcement, Deputy Director Bjørn Guldvog stated: “I think that we have not cared for people with ME to a great enough extent. I think it is correct to say that we have not established proper health care services for these people, and I regret that.”

#### FURTHER READING

“Rituximab Trial Shows Promise.” Kimberly McCleary. CFIDS Association of America. <http://www.research1st.com/2011/10/19/rituximab-trial/>

*ABC article on rituximab study:* <http://abcnews.go.com/Health/Wellness/chronic-fatigue-syndrome-study-supports-autoimmune-disease-theory/story?id=14801908>

“Norwegian research breakthrough can solve CFS mystery.” *English translation of first Norwegian news article on Rituximab:*

<http://www.tv2.no/nyheter/innenriks/english-version-norwegian-research-breakthrough-can-solve-cfsmystery-3615631.html>

“Will rituximab be a viable treatment option for ME/CFS.” *A thoughtful, clear analysis of the possible role of rituximab as a treatment for CFS/ME.*

<http://www.masscfids.org/resource-library/9/351>

*Cort Johnson's review of rituximab, including an interview with Dr. Olav Mella:*

<http://esme-eu.com/treatment/a-drug-for-me-cfs-the-rituximab-story-article468-110.html>

*Apology from the Norwegian Directorate of Health.* <http://www.euro-me.org/news-Q42011-003.htm>

*List of rituximab clinical trials.*

<http://www.clinicaltrials.gov/ct2/results?term=rituximab>

*Dr. Jamie-Deckhoff-Jones' fascinating blog. Scroll down for her explanation of how rituximab works in CFS/ME, as well as her personal critique. Both are quite good.* <http://treatingxmr.v.blogspot.com/2011/10/rituximab-big-guns-for-mecfs.html>

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Fluge, Øystein, Ove Brulan, Kristin Risa, Anette Storstein, Einar K. Kristoffersen, Dipak Sapkota, Halvor Næss, Olav Dahl, Harald Nyland, Olav Mella. “Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study.” <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0026358>

*Vandermeer's critique of Fluge et al double-blind study.*

<http://www.plosone.org/annotation/listThread.action?inReplyTo=info%3Adoi%2F10.1371%2Fannotation%2F43f3e6a8-cf7d-4438-8b97-b21b9c31bf5c&root=info%3Adoi%2F10.1371%2Fannotation%2F43f3e6a8-cf7d-4438-8b97-b21b9c31bf5c>

*Fluge and Mella's response to Vandermeer's critique. (This is well worth reading, as it lays the foundation for CFS/ME as an autoimmune disease.)*

<http://niceguidelines.blogspot.com/2011/10/dr-oystein-fluge-and-professor-olav.html>

## TRANSFER FACTOR

**DESCRIPTION.** Transfer factor, an extract from peripheral blood lymphocytes (white blood cells) of a healthy donor, facilitates the transfer of T cell-mediated immunity from one person to another.

**BACKGROUND.** Transfer factor has been used for more than 40 years to transfer immunity from a presumably healthy donor to a recipient. It has been used to treat viral, parasitic, and bacterial infections. Distinctive types of transfer factor may be used, depending on the condition being treated. Nonspecific transfer factor from a pool of healthy donors may be used for immune system modulation. Disease-specific transfer factor is used to treat a specific virus or infection, such as herpesviruses or human immunodeficiency virus (HIV). In addition, donor-specific or dedicated donor transfer factor can be obtained from a relative or other household member.

**USES IN CFS/ME.** Transfer factor, at least in theory, would appear to be valuable as a primary therapy in CFS/ME. Because the cause of CFS/ME is still

unknown, it has been difficult to find a universally effective treatment. Transfer factor is considered adaptogenic; that is, it can boost a deficient immune system or, conversely, can down regulate the immune system in certain autoimmune conditions. This makes it an ideal immunomodulator in CFS/ME. However, as the following data reveal, reports of the efficacy of transfer factor have been inconclusive.

- At the May 1994 CFIDS conference in Dublin, Ireland, information was presented regarding a study of 20 patients with CFS treated with oral transfer factor by Dr. Giancarlo Pizza and colleagues from Bologna, Italy. Of the 20 patients, improvement was noted in 12 and remission was observed in two. There were no significant side effects. This oral form of transfer factor was specific for Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and herpes simplex virus.
- Dr. Perry Orens of Great Neck, New York, reported a positive experience with transfer factor (*CFIDS Chronicle*, Fall 1993). With Dr. Hugh Fudenberg, a leading international expert on transfer factor, Dr. Orens used injectable, donor-specific transfer factor to treat symptoms of CFS in nine patients. The results were complete remission in two patients, marked improvement in two, partial improvement in two, and no improvement in three.
- In 1991 Dr. Denis Wakefield of Australia reported the results of an extensive double-blind study of transfer factor. Of 90 patients with CFS, 46 received the transfer factor and 44 received a placebo. Twenty-five patients received specific transfer factor donated by a family member and 21 received transfer factor from an unrelated donor (a healthy control). Follow-up three months later showed no difference in quality of life, immunological assessment, or activity levels. It was concluded that neither specific nor nonspecific transfer factor were of benefit. It is important to note that the treatment consisted of only eight injections, given over the course of a month. It is possible that the short duration of treatment affected the outcome.
- At the 2003 AACFS Conference held in Chantilly, Virginia, Dr. Brewer presented the results of a study in which 28 CFS patients were given a transfer factor (TF) preparation derived from bovine colostrum that has activity against HHV-6. Ten CFS patients (controls) received a similar TF preparation derived from bovine colostrum, except that it was devoid of any specific activity for HHV-6. Following the administration of the HHV-6 transfer factor preparation, improvements were noted in symptom scores in 68% and NK function in 75% of patients studied, as compared to 0% for both symptom score and NK function in the control group taking the TF preparation without HHV-6.

**PROTOCOL.** Transfer factor may be given in oral or injectable form. It may take at least six months before improvement is noted.

**PROS AND CONS.** Because transfer factor has not been widely tested as a treatment for CFS/ME, it is difficult to assess its efficacy. It is worth noting that

when transfer factor is effective, the results are global, with significant improvement of symptoms.

In his book, *The Type I/Type 2 Allergy Relief Program*, Dr. Alan Levin wrote of his extensive experience with transfer factor. After using it to treat severe allergic conditions in more than 300 patients, he reported a 68% success rate, with miraculous results in some patients. However, he pointed out some serious side effects, including heart or muscle malfunction, temporary or permanent brain damage, and aggravated vasculitis, and recommended that transfer factor should probably be used only in patients with incapacitating symptoms.

Other physicians have not shared Dr. Levin's success rate and a number of CFS/ME patients have reported not only lack of improvement but even a worsening of allergic-type symptoms, even after lengthy treatments with transfer factor. In fact, treatment surveys conducted by De Paul University and independent researchers have shown that about a third of those who try transfer factor consider it "harmful." Side effects of treatment may vary. Dr. Pizza notes that fatigue, sore throat, fever, and headache may occur within the first few days of treatment, but these resolve quickly. These side effects might be the result of immune system activation in response to transfer factor.

Few CFS/ME doctors currently use transfer factor, so it is difficult to assess its usefulness as a treatment. Dr. Cheney has used transfer factor, but to our knowledge, there are no other CFS/ME protocols that include transfer factor.

AVAILABILITY AND COST. Oral transfer factor is available through a number of online sources. ProHealth sells Transfer Factor Essentials for \$40 a bottle. Chisolm Biological Laboratory's ImmunFactor formulations cost \$140 for a bottle of 30 gel caps.

#### FURTHER READING

*Sloan Kettering's excellent review of transfer factor:* <http://www.mskcc.org/cancer-care/herb/transfer-factor>

*Patient thread discussing transfer factor:* <http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=1374195>

#### MORE INFORMATION

*Ordering information for transfer factor multi-immune:*

<http://www.forresthealth.com/search.php?page=1&q=transfer+factor&x=0&y=0>

*Ordering information for Chisolm Labs transfer factor:*

<http://www.forresthealth.com/chisolm-biological-laboratories/>

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Brewer, Joseph. "Administration of Transfer Factor for Human Herpesvirus 6 (HHV-6) in Patients with Chronic Fatigue Syndrome and HHV-6 Viremia."

*HHV6 News.* <http://hhv6.blogspot.com/2005/07/joseph-brewer-on-hhv-6-transfer-factor.html>

De Vinci, C, Levine, PH, Pizza, G, Fudenberg, HH, Orens, P, Pearson, G, Viza, D.  
“Lessons from a pilot study of transfer factor in chronic fatigue syndrome.”  
*Biotherapy*. 1996;9(1-3):87-90. <http://www.ncbi.nlm.nih.gov/pubmed/8993764>  
(Abstract)

## CHAPTER 5: NUTRITIONAL SUPPLEMENTS AND BOTANICALS

### INTRODUCTION

This section encompasses nutritional supplements, botanicals (herbs), and compounds that are naturally found in the body. Although some of these are also classed as pharmaceuticals, nearly everything in this section can be purchased without a prescription. (The exception is injectables.) We have not included each and every supplement that is available on the market, but have limited our selection to those for which there is relevant medical research, or which are in common use either by CFS/ME clinicians or by CFS/ME patients themselves.

Nutritional supplements are an essential component of any CFS/ME treatment protocol. Research has shown that people with CFS/ME are routinely deficient in many important nutrients (notably zinc, magnesium, and carnitine). These deficiencies, in and of themselves, can decrease the degree to which the body can absorb and make use of other nutrients. Even when there are no clinical nutritional deficiencies, the physiological demands of a chronic illness make it necessary to provide additional nutritional support – especially in light of the numerous GI problems prevalent in the CFS/ME population, which may lead to malabsorption. For these reasons, and because most CFS/ME doctors recommend supplements, this section attempts to be as inclusive as possible.

There is a method to taking nutritional supplements. As with pharmaceuticals, supplements should initially be taken in very small doses to test for sensitivity. Even if a supplement consists of something “natural” there is nothing natural about taking it in concentrated doses. Your body reacts to these as it would to any chemical. For that reason, it is wise to take supplements with food, unless instructed otherwise.

“Take with food” means eat a little first, then take the supplement, then eat some more. By sandwiching the supplement within a meal, you lower the risk of reactions, as the supplement is processed along with food. Sandwiching supplements also reduces the risk of heartburn. When a supplement is taken with water only it floats to the top of the stomach, where it can easily flow back into the esophagus, causing irritation.

New supplements should be taken one at a time. That is, don't start several supplements at once, even if they act synergistically. Take the new supplement for three or four days before introducing another. This allows you to evaluate the supplements for possible negative reactions or sensitivities.

Supplements can be quite expensive and are not usually covered by health insurance. But purchasing the cheapest brand is not always the wisest course to take. There is a wide range in quality when it comes to nutritional supplements. Some of the cheapest brands may not even contain the ingredients on the label. It is best to stick to well-known brands and to purchase from reputable suppliers. (See Appendix D: Mail Order Suppliers.) Purchasing online, rather than from retail outlets can cut the cost of expensive supplements in half. Whenever possible, we have included recommendations in each entry.

Most online suppliers include product label information on their websites, but for those who wish to compare the product labels of a supplement made by different manufacturers, or check into recalls or FDA notices for specific supplements, there are several helpful websites that will provide this information:

- The Dietary Supplements Labels Database. *This is a very useful website that allows searches for product labels by manufacturer and by product. From the website:* “The Dietary Supplements Labels Database offers information about label ingredients in more than 6,000 selected brands of dietary supplements. It enables users to compare label ingredients in different brands. Information is also provided on the "structure/function" claims made by manufacturers.” <http://dietarysupplements.nlm.nih.gov/dietary/index.jsp>
- Natural Products Foundation. *The NPF keeps an excellent database of supplements, as well as the medical conditions they are used for. From the website:* “The Dietary Supplement Information Bureau™ (DSIB™) was founded in 2001 to promote the responsible use of vitamins, minerals, herbs and specialty supplements. In June 2008 DSIB became part of the Natural Products Foundation, a not-for-profit organization whose mission is to promote and facilitate research and education related to natural products for the benefit of consumers and industry.” <http://www.naturalproductsinfo.org/>
- Consumer Healthcare Products Association. *The CHPA website provides a search for government warnings and decisions regarding most OTC medications and supplements. From the website:* “The Consumer Healthcare Products Association (CHPA), founded in 1881, is a member-based association representing the leading manufacturers and distributors of nonprescription, over-the-counter (OTC) medicines and dietary supplements.” <http://www.chpa-info.org/>

#### FURTHER READING

Dowson, David, MD. “Nutrition Toxicity and ME/CFS.”

<http://www.annhilltrust.org/nutrition-toxicity-and-me.html>

#### 5-HTP

**DESCRIPTION.** 5-Hydroxytryptophan (5-HTP) is a naturally occurring amino acid which serves as a precursor to the neurotransmitter serotonin.

**BACKGROUND.** 5-HTP is a precursor as well as a metabolic intermediate in the synthesis of serotonin and melatonin from tryptophan. Through the action of vitamin B6, 5-HTP is converted in the liver and nervous system to 5-HT (serotonin). Most commercially marketed 5-HTP is derived from the seeds of the *Griffonia simplicifolia*, a woody climbing shrub native to West Africa.

Serotonin is the most abundant neurotransmitter in the human body. In the brain it plays a crucial role in sleep, mood, learning, memory and appetite. However, the vast majority of serotonin, 90%, is produced in the lining of the intestines, which has led Dr. Michael Gershon, chairman of the department of anatomy and cell biology at Columbia University, to refer to the gut as the “second

brain.” This eponym is apt, for today gastroenterologists routinely prescribe serotonin enhancers for treating GI motility problems.

**USES IN CFS/ME.** Several studies have shown that 5-HTP is an effective overall treatment for fibromyalgia. For people with CFS/ME, 5-HTP is most often used as a sleep aid.

**PROTOCOL.** Dr. Rodger Murphree, a chiropractor and nutritionist who has been treating CFS/ME for over 15 years, recommends taking 5-HTP 30 minutes before bed, on an empty stomach, with four ounces of juice. Start with 100 mg, then go to 150 and then to 200. Don't go above 300 mg. It may take several nights to take effect. If it doesn't work in two weeks, Dr. Murphree suggests stopping and switching to melatonin. According to Dr. Murphree, patients who stay on 5-HTP for more than three months should take a broad-based amino acid supplement to balance out the other neurotransmitters.

**PROS AND CONS.** 5-HTP, like many antidepressants, can cause strange, vivid dreams. These dreams usually diminish over time. Excessively high serotonin levels can cause insomnia, hyperactivity, headache, and increased heart rate. CFS/ME patients who have a negative reaction to 5-HTP should either lower the dose or stop.

**AVAILABILITY AND COST.** 5-HTP is sold in most health food stores and by online distributors. A bottle of 60 tablets can cost as little as \$8.00.

**CAUTION:** High doses of 5-HTP can cause serotonin syndrome, a condition in which serotonin is raised to dangerous levels. Taking 5-HTP with serotonin-enhancing pharmaceuticals such as triptans (for migraines), antidepressants, Demerol, Rofitussin, and Ultram can also lead to serotonin syndrome.

#### FURTHER READING

*Good summary of 5-HTP as a CFS/ME treatment:*

<http://www.immunesupport.com/98wtr002.htm>

*Discussion of 5-HTP as a CFS/ME treatment:*

<http://aboutmecfs.org.violet.arvix.com/Trt/5-HTP.aspx>

*Dr. Teitelbaum on 5-HTP and other natural sleep aids:*

<http://www.healthy.net/scr/Column.aspx?Id=647>

*General information on 5-HTP:* <http://www.herbwisdom.com/herb-5-htp.html>

#### PATIENT REVIEWS

*CFS/ME patient reviews of 5-HTP:* <http://www.revolutionhealth.com/drugs-treatments/rating/5-htp-5-hydroxytryptophan-for-chronic-fatigue-syndrome-cfs-cfids-me>

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Caruso I, Sarzi Puttini P, Cazzola M, Azzolini V. “Double-blind study of 5-hydroxytryptophan versus placebo in the treatment of primary fibromyalgia



syndrome.” *J Int Med Res.* 1990 May-Jun;18(3):201-9.

<http://www.ncbi.nlm.nih.gov/pubmed/2193835> (Abstract)

Sarzi Puttini P, Caruso I, “Primary fibromyalgia syndrome and 5-hydroxy-L-tryptophan: a 90-day open study.” *J Int Med Res.*1992 Apr;20(2):182-9.

<http://www.ncbi.nlm.nih.gov/pubmed/1521674> (Abstract)

## ALPHA KETOGLUTARATE

**DESCRIPTION.** Alpha ketoglutarate (AKG) is an ionic form of alpha ketoglutarate acid, an intermediate in the tricarboxylic cycle (Krebs cycle, or citric acid cycle).

**BACKGROUND.** Alpha ketoglutarate (AKG) fulfills a vital role in the metabolism and utilization of carbohydrates, proteins, and long-chain fatty acids. Its best known function is as a component of a number of energy-producing cycles at the cellular level. The first of these, the Krebs cycle, breaks down and transforms citric acid through a series of enzyme-controlled reactions to produce adenosine triphosphate (ATP), a crucial energy source for many cell processes. AKG, as an early intermediate in the Krebs cycle, forms the basis for all further transformations. It is also required for catabolism of many amino acids, another process that generates energy.

Another important function of AKG involves the formation of nonessential amino acids (amino acids that are biosynthesized in the body), notably glutamate and, through its action, proline, alanine, aspartic acid, and asparagine. AKG is also one of the most important transporters of cellular nitrogen, combining with nitrogen in the cell to prevent an overload of ammonia in the body.

**USES IN CFS/ME.** AKG is used as a short-term energy enhancer and for Krebs cycle support in patients with CFS/ME. Because of its essential role in energy production and carbohydrate metabolism, it may be useful as a general CFS/ME treatment as well. AKG is also beneficial for the intestines. Many people with CFS/ME suffer from digestive problems, including food sensitivities, dysbiosis, slow transit time, small intestine bacterial overgrowth (SIBO) and a host of other disorders. AKG is converted in the intestines into glutamate, which regulates gastric emptying and provides an environment for healthy gut flora. AKG also prevents damage to the mucosal lining of the intestines by inhibiting oxidative stress.

**PROTOCOL.** The suggested dosage of AKG is one or two 300 mg capsules per day, which can be taken with meals. Because of its location in the Krebs cycle, alpha ketoglutarate is generally more effective if taken with other Krebs cycle supports such as vitamin C, B vitamins, essential fatty acids (evening primrose oil, borage oil, or fish oil), magnesium, nutritional supplements, and NAC (N-acetyl-L-cysteine).

**PROS.** Because alpha ketoglutarate is not a stimulant but works through natural metabolic pathways, it is a relatively risk-free source of energy. People who take alpha ketoglutarate usually do not "crash" afterward. It has no reported side effects at recommended doses. Patients with low levels of AKG (as confirmed by an

Organic Acids Test) have noted significant improvement in energy levels with alpha ketoglutarate supplementation.

CONS. Results tend to be less dramatic than those obtained with CoQ10, which may make this product less attractive to those who want a greater boost. Among its many function, AKG leads to production of nitric oxide (NO), which Dr. Pall has implicated in many CFS/ME symptoms. He has recommended that NO should be down regulated in people with CFS/ME. Because AKG is normally combined with excitatory amino acids, it can cause insomnia.

AVAILABILITY AND COST. Pure AKG is difficult to find. Most suppliers combine AKG with an amino acid, such as arginine or glutamine. Douglas Labs sells a 90-tablet bottle of AKG (300 mg) combined with vitamin B6, calcium and phosphorus for \$18.

#### FURTHER READING

*Benefits of AKG and its functions in the Krebs cycle:* <http://www.ei-resource.org/articles/general-environmental-health-articles/influencing-your-krebs-cycle/>

*A detailed description of Krebs cycle intermediaries, including AKG. Very technical.* <http://www.nutritionreview.org/library/krebs.php>

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#### ALPHA LIPOIC ACID

DESCRIPTION. Alpha lipoic acid, or lipoic acid, is a an organic compound derived from caprylic acid. It is both fat and water soluble.

BACKGROUND. Alpha lipoic acid (ALA) has been referred to as the "mother" of all antioxidants. This well-deserved epithet is due to the fact that not only does it act as a potent free radical scavenger, it can transform an oxidant into an antioxidant. Notably, when glutathione is oxidized, ALA can transform it back into its reduced form, thus increasing the pool of glutathione.

ALA is produced throughout the body through the biosynthesis of fatty acids. Although it is found in many foods (especially organ meats, yeast extract and leafy green vegetables), alpha lipoic acid is not readily available through dietary sources. As a consequence, all alpha lipoic acid supplements must be synthesized.

Alpha lipoic acid has been studied for its effects on many disease states, including treatment for cardiovascular disease, prevention of migraines, preventing organ dysfunction, slowing the progression of Alzheimer's disease, reducing inflammation, and the treatment of chronic diseases involving oxidative stress. A study conducted in 1999 by Kishi et al found that the reduced glucose uptake in diabetes was completely reversed with alpha lipoic acid, which not only corrected the deficit, but improved the peripheral neuropathy found in diabetics.

A detailed proposal submitted to the National Cancer Institute by the Chemical Selection Working Group (see below) indicates that ALA may work best when combined with acetyl L-carnitine. Acetyl-L-carnitine facilitates the movement of fatty acids into the mitochondria for energy and is also used to generate acetyl coenzyme A, while ALA is involved in mitochondrial ATP production and can recycle other antioxidants. The authors propose that the combination of acetyl L-carnitine and ALA may have significant synergistic effects – increasing energy and reducing oxidative stress.

**USES IN CFS/ME.** A number of CFS/ME clinicians and researchers, notably Martin Pall and Dr. Myhill, have pointed out that oxidative stress is a primary component in the cascade of CFS/ME symptoms. Oxidative stress can affect every system in the body, and has particularly deleterious effects on oxygen transport systems (blood). ALA has been shown to improve the integrity of red blood cells (which are often abnormal in CFS/ME patients) leading to elevated glutathione levels. Glutathione, one of the body's most potent antioxidants, is often diminished in CFS/ME patients.

**PROTOCOL.** The “R” form is the most bioavailable and stable form of alpha lipoic acid. (The “S” form deteriorates rapidly.) There is no set protocol for ALA. CFS/ME patients who have tried ALA recommend beginning at the lowest dose (100 mg) to avoid detox symptoms (headache, “hangover” feeling).

**PROS.** ALA has no documented side effects at low doses. Many people have noted an increase in energy, muscle strength, and mental alertness, particularly when taken with acetyl-L carnitine.

**CONS.** Too high a dose can cause insomnia and stomach upset. ALA lowers blood sugar, which may pose a problem for people with hypoglycemia. There is one study that suggests that ALA competes with biotin (vitamin B7) in rats, but the results have not been confirmed in humans. Those who take large quantities of lipoic acid may wish to independently supplement with biotin.

**AVAILABILITY AND COST.** ALA is widely available in health food stores and through online distributors. It is not expensive. A 60-capsule bottle of R-ALA (100 mg) can cost less than \$10.

#### FURTHER READING

*This article questions the necessity of supplementing lipoic acid with biotin.*

<http://www.geronova.com/content/lipoic-acid-biotin>

#### RESEARCH

Kishi, Yutaka, James D. Schmelzer, Jeffrey K. Yao, Paula J. Zollman, Kim K. Nickander, Hans J. Tritschler, and Phillip A. Low. “ $\alpha$ -Lipoic Acid: Effect on Glucose Uptake, Sorbitol Pathway, and Energy Metabolism in Experimental Diabetic Neuropathy.” *Diabetes*, VOL. 48, October 1999

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Mirjana M, Jelena A, Aleksandra U, Svetlana D, Nevena G, Jelena M, Goran P, Melita V. “Alpha-lipoic acid preserves the structural and functional integrity of

red blood cells by adjusting the redox disturbance and decreasing O-GlcNAc modifications of antioxidant enzymes and heat shock proteins in diabetic rats.” *Eur J Nutr.* 2011 Nov 18. <http://www.ncbi.nlm.nih.gov/pubmed/22094580> (Abstract)

“Acetyl-L-Carnitine/a-Lipoic Acid Supplements.” *This is a proposal prepared for the National Cancer Institute by the Chemical Selection Working Group (CSWG) on behalf of Technical Resources International, Inc. It contains a thorough and exhaustive account of the mechanisms of alpha lipoic acid.* [http://ntp.niehs.nih.gov/ntp/htdocs/chem\\_background/exsumpdf/carnliposupp.pdf](http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/carnliposupp.pdf)

## AMINO ACIDS

Carnitine, Glutamine, Lysine, Taurine

**DESCRIPTION.** Amino acids are nitrogen-containing chemical units (amines) that, bound together, make up protein.

**BACKGROUND.** The amino acids, in various combinations, form the hundreds of types of proteins present in every living organism. These proteins are essential for nearly all processes that induce cell growth and repair, as well as for continued maintenance of every body tissue, organ, and structure within the body. Amino acids link together to form tens of thousands of proteins and enzymes, each of which has a specific function. They can also perform as individual units. Single amino acids can act as neurotransmitters or as precursors to neurotransmitters in the central nervous system. Therefore, not only are they responsible for providing and maintaining the very substances of which we are made, but also for the communications system that enables us to plan, dream, think, feel, and direct our every action.

There are 20 primary amino acids. About 80% are produced in the liver and the remaining 20% must be obtained from food. Whether an amino acid can be produced within the body is what distinguishes the essential from nonessential amino acids. The essential amino acids (those which must be obtained from food sources) are arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Nonessential amino acids (those which can be produced within the body) include alanine, glutamine, asparagine, glycine, proline, and serine. Given the countless functions that amino acids perform, a protein shortage or congenital defect in amino acid synthesis can lead to problems that involve every system in the body.

Amino acids occur in two isomers: L and D. The L isomer is the form most commonly found in nutritional supplements.

**USES IN CFS/ME.** Specific amino acids, both essential and nonessential, have been recommended as treatments by a number of CFS/ME clinicians. Their applications include mediation of hyperactive nervous system responses, repair of

leaky gut and other intestinal disturbances, and regulation of the fundamental CFS/ME metabolic dysfunction that results in loss of cellular energy.

A number of researchers have documented imbalances in amino acid ratios among people with CFS/ME. In an article published in 1994, Dr. Alexander Bralley and Dr. Richard Lord noted that people with CFS/ME commonly have deficiencies in tryptophan, phenylalanine, taurine, isoleucine, and leucine. They also found lower than normal amounts of arginine, methionine, lysine, threonine, and valine in a smaller number of CFS/ME patients. It is significant that the most common deficiencies found by Drs. Bralley and Lord are of phenylalanine and tryptophan because these two amino acids are precursors to the catecholamines and serotonin, neurotransmitters that are closely involved with sleep function, stress responses, and regulation of pain and mood.

Dr. Scott Rigden has also noted that many of his patients with metabolic abnormalities have an imbalance in amino acid ratios. The implication is that, for these patients, amino acids may be either synthesized or utilized at a slower rate or appear in such disequilibrium that they no longer function together with full efficiency – perhaps giving a clue to the origins of the collagen formation problems and enzyme disturbances common in many patients with CFS/ME.

An extensive study published in 2005 by Jones et al compared organic acids in people with CFS/ME, major depression, and rheumatoid arthritis. The researchers found lower levels of taurine, GABA, histidine and tyrosine in the group with CFS/ME. The researchers also found low levels of histidine in plasma from rheumatoid arthritis patients, leading the team to speculate that a similar etiology might be involved for the two illnesses (i.e. inflammation).

A more recent study by Niblett et al confirms specific deficiencies in CFS/ME patients of asparagine, phenylalanine, leucine, isoleucine, valine, and the organic acid, succinic acid, as well as increases in 3-methylhistidine (an amino acid associated with protein loss) and tyrosine. The authors concluded that “urinary excretion and blood parameters data supported the hypothesis that alterations in physiologic homeostasis exist in CFS patients.”

In 2012 a team of Australian researchers identified low levels of glutamine and ornithine, along with other metabolites that participate in the urea cycle, in a group of CFS/ME patients. (CFS/ME patients are consistently low in uric acid.) The researchers suggested that a specific disturbance of amino acid and nitrogen metabolism was implicated in CFS/ME which might potentially serve as a biomarker.

Amino acid supplementation has received particular attention as a treatment for CFS/ME from nutritionists. Using an amino acid analyzer to measure specific imbalances, Drs. Bralley and Lord tailored a supplement to correct amino acid deficiencies. In a study of 25 CFS/ME patients, they found that correcting specific amino acid imbalances resulted in 50% to 100% improvement in symptoms (*Journal of Applied Nutrition*, 1994). The greatest effect was noted in energy levels. Two patients who had had CFS/ME symptoms for 15 years experienced dramatic

improvement. Patients also reported improvement in cognitive function and elimination of "brain fog."

It should be noted that single amino acids taken as dietary supplements may not be well tolerated by patients with serious metabolic disturbances. Also note that tyrosine, an amino acid often found to be deficient in CFS/ME patients, is seldom recommended. Tyrosine is a dopamine precursor which triggers symptoms in patients with inflammatory disorders such as migraine, interstitial cystitis, and rosacea. Dr. Bell has observed that in CFS/ME patients, dopamine precursors make the majority of CFS/ME patients feel much worse.

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Niblett SH, King KE, Dunstan RH, Clifton-Bligh P, Hoskin LA, Roberts TK, Fulcher GR, McGregor NR, Dunsmore JC, Butt HL, Klineberg I, Rothkirch TB. "Hematologic and urinary excretion anomalies in patients with chronic fatigue syndrome." *Exp Biol Med (Maywood)*. 2007 Sep;232(8):1041-9.

<http://www.ncbi.nlm.nih.gov/pubmed/17720950> (Abstract)

#### CARNITINE

**DESCRIPTION.** Carnitine (L-carnitine) is one of the methyl group donors. It is crucial for the transport of long-chain fatty acids into the mitochondria of cells, providing energy to skeletal and heart muscle. Carnitine also aids in reducing toxic buildup of organic acids which are a natural byproduct of cell metabolism. Carnitine deficiency produces fatigue, muscle weakness, malaise, exercise intolerance, heartbeat abnormalities, and tissue acidosis. Carnitine deficiency can result from congenital metabolic defects as well as the administration of antibiotics containing pivalic acid (e.g., Pondocillin).

USES IN CFS/ME. Japanese researchers have shown that CFS/ME patients have a deficiency in intracellular levels of acylcarnitine. They found no deficiency in serum levels of free carnitine, however, indicating the deficiency is not the result of lack of carnitine in the system but of its derivative, acylcarnitine. Acylcarnitine deficiency can be expected to produce not only the fatigue and weakness characteristic of interruption in mitochondrial processes but also the malaise typical of autointoxication. Dr. Hiroko Kuratsune and colleagues discovered that in their sample group of 38 CFS/ME patients, low levels of acylcarnitine covaried with the severity of the illness (*Clinical Infectious Diseases*, 1994). As symptoms improved, so did acylcarnitine levels. In a study comparing amantadine and carnitine, Dr. Audrius Plioplys and Dr. Sigita Plioplys found "statistically significant clinical improvement" after eight weeks of treatment with L-carnitine (*Neuropsychobiology*, 1997).

A subsequent study in 2004 by Okada et al, found secondary proof for acetyl-carnitine deficiency in CFS/ME patients. Using MRI imaging, they found that there was a reduction in gray matter in the prefrontal cortex of CFS/ME patients as compared to controls. The researchers concluded that their results were "consistent with previous reports of an abnormal distribution of acetyl-L-carnitine uptake, which is one of the biochemical markers of chronic fatigue syndrome, in the prefrontal cortex. Thus, the prefrontal cortex might be an important element of the neural system that regulates sensations of fatigue."

In a recent study conducted in 2011, researchers from the University of South Australia compared L-carnitine levels of 44 CFS/ME patients to 49 controls. They found that levels of acylcarnitine was 30-40% lower in CFS/ME patients. The authors hypothesized that the administration of omega-3 fatty acids in combination with L-carnitine would improve chronic fatigue syndrome symptomology.

PROTOCOL. Carnitine can be taken in liquid or pill form as an over-the-counter nutritional supplement. As a food supplement, the general recommended dosage is 1000 mg/day taken with a meal. The liquid is often better tolerated than the pill form although patients with chemical sensitivities should note that the liquid may also contain artificial flavors, colors, preservatives (methylparaben), and sucrose.

Dr. Teitelbaum has observed that in his experience acetyl-L-carnitine is much more effective than L-carnitine. This is due to the fact that acetyl-L-carnitine crosses the blood-brain barrier, as opposed to L-carnitine, which is too rapidly excreted by the kidneys to be adequately utilized by the brain. Dr. Teitelbaum recommends taking 500 mg of pure acetyl-L-carnitine 2-3 times a day. In low doses, acetyl-L-carnitine can mimic the effects of pyridostigmine and galantamine, increasing the availability of acetylcholine in both the peripheral and central nervous systems.

Because carnitine interferes with thyroid hormone production, thyroid levels (free T3 and T4, as well as TSH) should be taken before beginning supplementation. Even if thyroid hormone levels fall within the normal range, carnitine should not be

taken for more than a month. Signs of thyroid suppression are dry skin, low energy level, weight gain, excessive sleep, and hormonal disturbances.

**PROS.** L-Carnitine as a food supplement is widely available. Patients have reported increased muscle function, decreased weakness, and overall improved stamina and well-being after a few weeks of carnitine supplementation. In some cases, the benefits remain even after finishing the course of treatment.

**CONS.** Carnitine is not recommended for patients with low thyroid function, as it interferes with thyroid hormones. Excess amounts of carnitine can cause diarrhea and stomach upset, so start with low doses.

**AVAILABILITY AND COST.** A 12 oz bottle of the liquid nutritional supplement Mega L -Carnitine (Twin Labs) can be purchased online at Vitacost for \$10. At the recommended dosage of 1 tablespoon a day, the bottle will last for 1 month. A 30-capsule bottle of acetyl-L-carnitine costs around \$18. (There are many brands. Check Vitacost for a cost comparison.)

## FURTHER READING

*Dr. Teitelbaum's carnitine protocol:*

[http://www.endfatigue.com/health\\_articles\\_c/CFS\\_FM-acetyl-l-carnitine\\_for\\_cfs.html](http://www.endfatigue.com/health_articles_c/CFS_FM-acetyl-l-carnitine_for_cfs.html)

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## GLUTAMINE

**DESCRIPTION.** Glutamine is the most abundant nonessential amino acid in the body. It is a precursor to glutathione.

**BACKGROUND.** Glutamine plays an important role in many biological functions, including protein synthesis, providing cellular energy, and as a non-toxic transporter of ammonia in the bloodstream. When converted to glutamic acid, it acts as an excitatory neurotransmitter in the brain.

In the intestinal tract, glutamine strengthens the gut's function as an immune barrier by supporting the production of secretory immunoglobulin A (sIgA), which helps maintain the structure, metabolism, and function of the mucosal lining of the intestines. Glutamine can help heal injured gut mucosa after surgery and, in a high percentage (92%) of patients, completely heals ulcer damage. Glutamine is an important detoxifying agent for ammonia, a neurotoxin and one of the toxic by-products of protein metabolism. It is used to treat sugar craving, fatigue, ADHD,

peptic ulcers, and personality disorders. Dietary sources of glutamine include beef, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, and spinach.

**USES IN CFS/ME.** Because it is so important in gastrointestinal growth and function, glutamine is primarily used to treat leaky gut. Clinicians recommend taking 1000 mg of glutamine daily on an empty stomach, divided into equal doses (Patients with many sensitivities may want to test a very small amount of this amino acid before taking the full dose.)

**PROS.** A number of CFS/ME patients have noted improvement in gut function and increased food tolerance with this treatment as well as a decrease in “brain fog.” Side effects from this amino acid are relatively rare (but see below).

**CONS.** L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea. In patients with small intestinal bacterial overgrowth (SIBO) glutamine may actually worsen symptoms. Because glutamine is an excitatory neurotransmitter it may cause insomnia in individuals who do not tolerate stimulants. People who are sensitive to MSG should not take glutamine.

**AVAILABILITY AND COST.** Glutamine is available at health food stores and online in both powder and pill form. It is inexpensive. A 100-tablet bottle can cost as little as \$6. Glutamine is also available from some compounding pharmacies as enteric coated tablets which are formulated to bypass the stomach and increase bioavailability.

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## LYSINE

**DESCRIPTION.** Lysine is an essential amino acid. (It cannot be synthesized in the body.)

**BACKGROUND.** Lysine is needed for bone growth in children and to maintain nitrogen balance in adults. It also aids in the production of antibodies, hormones, and enzymes as well as helping in collagen formation, muscle building, and tissue repair. Lysine deficiency can result in hair loss, anemia, bloodshot eyes, loss of energy, and irritability. Food sources of lysine include meat, eggs, legumes and milk.

**USES IN CFS/ME.** Lysine is recommended chiefly because of its ability to inhibit reproduction of herpesviruses (herpes simplex virus, varicella zoster virus, human herpesvirus 6, and Epstein-Barr virus), which require arginine in order to reproduce. Lysine's structure is similar enough to arginine, however, that herpesviruses can be fooled into using lysine instead. Since the virus cannot use lysine for replication, the virus loses its ability to reproduce, effectively halting the spread of the infection. Some CFS/ME doctors recommend lysine to treat frequent outbreaks of cold sores (herpes simplex) or shingles (herpes zoster).

**PROTOCOL.** Dr. Charles Lapp recommends 1000 to 2000 mg of lysine, taken daily with meals. Foods high in arginine, such as chocolate, nuts, raisins, whole wheat, cereal, and brown rice, should be avoided.

**PROS.** Lysine appears to be a safe, effective treatment for cold sores.

**CONS.** Side effects of lysine can include dizziness, sweating, nausea, appetite loss, and difficulty swallowing. Lysine should be discontinued if these symptoms develop.

**AVAILABILITY AND COST.** Lysine is available in most health food stores and can be purchased inexpensively. Most brands retail for less than \$10 for a 100-capsule bottle (500 mg).

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## TAURINE

**DESCRIPTION.** Although taurine is usually classified as an amino acid, it is actually an organic acid, which is an organic compound with acidic properties but without a carboxyl group.

**BACKGROUND.** Taurine acts as a building block for all other amino acids and consequently is present in every cell in the body. It is a prime component of bile (thus aiding in fat digestion and vitamin absorption) and is found in high concentrations in heart muscle, skeletal muscle, white blood cells, and the central nervous system (CNS). Anxiety, hyperactivity, and poor brain function are related to taurine deficiency. Taurine can be synthesized in the body from cysteine, with the aid of vitamin B6.

Taurine is unusual in that it not only functions as a neurotransmitter, but as a potent antioxidant. When taurine interacts with the oxidant hypochlorous acid it forms taurine monochloramine, which inhibits the transcription iNOS gene as well as the expression of COX-2 protein, both of which are primary sources of inflammation. Taurine lowers NF-kappaB activity, which helps inhibit another important inflammatory pathway. It also acts to reduce intracellular calcium levels, thus lowering the production of nitric oxide. In its role as a neuromodulator, taurine stimulates the synthesis of GABA, the primary inhibitory neurotransmitter. It also stimulates glycine receptors, leading to a down regulation of excitatory NMDA receptors. (Glycine is also used in the biosynthesis of hemoglobin, which is very important in the maintenance of red blood cell integrity and oxygen transport.)

**USES IN CFS/ME.** Dr. Majid Ali, author of *The Canary and Chronic Fatigue*, makes extensive use of taurine as an antioxidant and has reported excellent results in treating fatigue and chronic constipation. Dr. Cheney has observed that taurine may also be of benefit in treating hyperactive nervous system responses. CFS/ME patients have been shown to have high amounts of glutamate in the brain, which

increases neuroexcitatory responses. Because taurine slows CNS impulses, it may help relieve symptoms such as insomnia, anxiety, and restlessness, especially when taken in conjunction with magnesium. Taurine is transported easily across the blood-brain barrier, allowing taurine supplements to work in the brain.

**PROTOCOL.** Dr. Ali recommends a dosage of 250 mg/day, along with magnesium and potassium. Dr. Cheney recommends ½ cc of injectable magnesium (250 mg) accompanied by ½ cc injectable taurine.

**PROS AND CONS.** Taurine has very few side effects, however, excess doses can cause GI upset (yellow diarrhea, gas, pale stools).

**AVAILABILITY AND COST.** Taurine can be purchased in most health food and vitamin stores and costs less than \$10 a bottle. Powdered forms can be purchased, for those who prefer to titrate dosage.

### FURTHER READING

*Very thorough discussion of the role of taurine:* <http://cfsmethylation.com/viewtopic.php?f=3&t=149>

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### ANTIOXIDANTS

**DESCRIPTION.** Antioxidants are a group of vitamins, minerals, and enzymes that help protect cells from free radical damage.

**BACKGROUND.** Antioxidants have long been used as preservatives because of their ability to retard the oxidation that causes oils to become rancid. However, they have garnered increased attention over the past few years for their medical value. The same process that allows them to prevent oils from becoming rancid also protects the body from damage caused by free radicals. Free radicals are atoms or groups of atoms that have lost an electron. These molecules containing unpaired electrons are highly unstable and can easily pick up other elements, causing volatile

reactions. When large numbers of free radicals are formed, whether from exposure to radiation, toxic chemicals or rancid oils, or because of prolonged illness and immune activation, significant damage can result. When dangerously high levels of free radicals are present, they can cause changes in protein structure. The body may identify the altered proteins as foreign elements and launch an immune system attack.

The body has its own defenses against excess free radical formation. The three most potent antioxidants produced in the body are superoxide dismutase (SOD), CoQ10, and glutathione peroxidase. However, the group of biochemicals known as antioxidants are also found abundantly in nature in the form of vitamins, minerals, and enzymes. Among the most widely used antioxidants are vitamins A, C, and E, alpha lipoic acid (ALA), gamma-linoleic acid (GLA), the amino acid cysteine, glutathione, taurine, the mineral selenium, CoQ10, and the bioflavonoids in pycnogenol, milk thistle, and ginkgo.

Antioxidants operate in concert to prevent free radical damage. A single antioxidant, once it has neutralized the free radical, can itself cause cell damage. The action of other antioxidants is necessary to return antioxidants to their reduced state, in which they can continue to scavenge free radicals. Therefore, antioxidants should be taken in combination rather than single forms. An article in the *New England Journal of Medicine* reports that heavy smokers in Finland who took very high doses of the antioxidant beta carotene had a higher rate of lung cancer than those taking a placebo (*CFIDS Chronicle*, Spring 1995). However, when beta carotene was combined with vitamin E, this was not the case.

Due to the potential of antioxidants to mitigate the more damaging effects of chronic illnesses (including cancer and diabetes) research on antioxidants is rapidly evolving. In 2004 Rezk et al proposed a new class of antioxidants based on the mechanism of vitamin E. In a study comparing the activities of different forms of vitamin E, the researchers discovered that vitamin E phosphate prevented the transfer of free radicals by forming a detergent barrier.

**USES IN CFS/ME.** Several studies have confirmed oxidative damage in CFS/ME patients. In 2000 a team of Italian researchers investigating the source of muscle pain found oxidative damage to DNA and lipids (fats) in the muscle tissue of CFS/ME patients. They also found significant differences in the composition of muscle membranes as compared to controls and patients with FM. The researchers concluded that their data “support an organic origin of CFS, in which muscle suffers oxidative damage.”

Patients with CFS/ME who experience depression also show evidence of free radical formation. In a 2001 study conducted by Maes et al, glutathione peroxidase levels were found to correlate with depressed mood and autonomic symptoms. The lower the glutathione levels, the greater the depression. The researchers recommended supplementation with glutathione, NAC and selenium.

Two studies conducted independently in 2000 and 2005 found that oxidative stress in CFS/ME patients could be measured through blood samples. In Australia, Richards et al measured methemoglobin in CFS/ME patients and controls.

Methemoglobin (pronounced “met-hemoglobin”) is an altered form of hemoglobin that does not bind well to oxygen, limiting the blood's ability to carry oxygen to tissues and organs. The formation of methemoglobin can be caused by various health problems and is a sign of oxidative stress. The study found that in CFS/ME patients, symptoms such as sleep disturbance, pain, and fatigue correlated with methemoglobin levels. They concluded that their data suggested that “oxidative stress due to excess free radical formation is a contributor to the pathology of CFS and was associated with symptom presentation.”

A second study by Kennedy et al. investigated free radical damage in CFS/ME symptoms using the “gold standard” of oxidative stress: isoprostanes. Isoprostanes are prostaglandin-like compounds which are formed after free radicals catalyze essential fatty acids. They have long been recognized as an accurate predictor of oxidative stress. Kennedy et al found that in CFS/ME patients, raised levels of isoprostanes correlated with post-exertional malaise. They postulated that in CFS/ME the excessive free radical formation could be due to persistent viral infection, to inflammation, or to metabolic abnormalities in mitochondria and lipids.

Antioxidants fall into many classes. The most commonly recommended antioxidants for CFS/ME patients are:

- Vitamins: A, C, E
- Vitamin co-factors: CoQ10
- Minerals: Manganese, selenium, zinc
- Hormones: Melatonin
- Flavonoids: Quercetin, pycnogenol, grape seed extract, Ecklonia cava
- Phenols: Silymarin
- Plant sources: Capsaicin, bilberry
- Enzymes: SOD
- Various Others: N-acetyl cysteine, alpha lipoic acid, essential fatty acids, glutathione, taurine

PROTOCOL. Most, if not all, CFS/ME doctors have included some form of antioxidant therapy into their protocols. Usually they recommend a broad-spectrum approach, as opposed to single-supplement therapy, accompanied in many cases by bioflavonoids such as pycnogenol (which is a potent antioxidant), grape seed extract, or “super foods” such as blue-green algae. Vitamin E, because it is the only fat-soluble antioxidant, is particularly good in combination with other antioxidants.

- Martin Pall, one of the leading researchers of oxidative stress in CFS/ME, recommends vitamin C, flavonoids, *Ecklonia cava* extract, B12, CoQ10, vitamin E, lipoic acid, as well as a host of other antioxidants to combat free radical damage.
- Dr. Cheney recommends daily doses of 2000-4000 mg vitamin C, 400-800 IU of Vitamin E, 200 mg of CoQ10, 100-300 mg of lipoic acid, omega-6 and omega-3 essential fatty acids and flavonoids. He stresses that because high doses of antioxidants can increase oxidative stress, flavonoids should be taken to mitigate potential free radical damage stemming from excessive antioxidant activity.

- Dr. Myhill recommends 300 mg of CoQ10 daily for three months, then reduced to 100 mg daily, 250 mg of glutathione daily together with 20 mcg of selenium as well as minerals to help produce the powerful free radical scavenger, superoxide dismutase. (Please see below for her discussion of antioxidants.)

## FURTHER READING

*Dr. Myhill's excellent discussion of antioxidants:*

<http://drmyhill.co.uk/wiki/Antioxidants>

Logan, Alan C. and Cathy Wong. "Chronic Fatigue Syndrome: Oxidative Stress and Dietary Modifications." *Altern Med Rev* 2001;6 (5): 450-459.

<http://www.altmedrev.com/publications/6/5/450.pdf>

*This article contains an excellent summary of research concerning oxidative stress in CFS/ME as well as a proposed list of antioxidant treatments.*

*Martin Pall's supplement list:* <http://esme-eu.com/supplements/supplements-in-me-cfs-by-prof-martin-pall-article276-139.html>

*Dr. Cheney's talk on CFS/ME treatments, including antioxidants:* <http://www.me-cfs.info/cheneyII3.pdf>

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brainstem under normal and ischemic conditions.” *Amino Acids.* 2008

Apr;34(3):429-36 <http://www.ncbi.nlm.nih.gov/pubmed/17665274> (Abstract)

## BETAINE HCl

**DESCRIPTION.** Betaine HCl is a synthesized chemical compound consisting of betaine, a methyl group donor, and hydrochloride, a salt.

**BACKGROUND.** Betaine is a vitamin-like substance that was originally derived from beets. For many years Betaine HCl was added to over-the-counter digestive aids, until in 1993 the FDA determined that it has not been proven “generally safe and effective.” At that point Betaine HCl began to be sold as a separate supplement.

Betaine HCl is still marketed as a digestive aid, particularly for the treatment of hypochloridia, a condition in which the stomach does not produce enough acid. Hypochloridia can occur after taking stomach acid suppressors (antacids, proton pump inhibitors), through *H. Pylori* infections (which interfere with stomach acid production), as well as any disease process that causes inflammation in the stomach lining. Stomach acid is often low in the elderly.

Lack of stomach acid can lead to the phenomenon known as “dumping,” in which the stomach's contents (chyme) are released into the small intestines before having been adequately broken down. The ability of the small intestines to further break down the chyme can result in poor absorption of nutrients, leading to deficiency states, particularly of minerals, which require acid to be absorbed. One of the most common symptoms of hypochloridia is reflux, which is frequently misdiagnosed as excess acid.

The most reliable test to determine hypochloridia is the Heidelberg Capsule test. The capsule contains a high frequency transmitter attached to a string. When the capsule is swallowed and drawn back up the esophagus, it gives an instant pH reading.

**USES IN CFS/ME.** A number of clinicians have proposed that low levels of stomach acid are responsible for many of the GI symptoms found in CFS/ME patients. Dr. Cheney routinely recommends Betaine HCl as a supplement to correct hypochloridia and prevent dumping. Dr. Myhill also maintains that people with CFS/ME chronically suffer from low levels of stomach acid.

**PROTOCOL.** Dr. Cheney recommends starting with a capsule (or ½ capsule) with meals. Paradoxically, too low a dose may actually increase reflux, as there still isn't enough stomach acid to trigger the opening of the sphincter that releases chyme into the intestines. The food that then returns through the esophagus contains not only normally occurring stomach acid, but the additional Betaine HCl as well. According to Dr. Cheney, increasing the dose will actually reduce reflux.

**PROS AND CONS.** Although Betaine HCl does not contain hydrochloric acid (the HCl, in this case, is a salt), some people report improved digestion. The



supplement does have mild acidifying properties, which is perhaps why people report having to take so many capsules with their meals (up to seven). It is quite possible that many of its benefits may actually come from the betaine, which acts as a liver support.

**AVAILABILITY AND COST.** Betaine HCl is easily available from health food stores and from online suppliers. It is inexpensive. Vitacost markets a 100-capsule bottle of Twinlab's Betaine HCl for about \$7.

#### FURTHER READING

*Dr. Sara Myhill's excellent discussion of hypochloridia:*

[http://www.drmyhill.co.uk/wiki/Hypochlorhydria - lack of stomach acid - can cause lots of problems](http://www.drmyhill.co.uk/wiki/Hypochlorhydria_-_lack_of_stomach_acid_-_can_cause_lots_of_problems)

*Basic information about Betaine HCl:* <http://www.encyclopedia.com/doc/1G2-3435100086.html>

*A good explanation of the Heidelberg capsule test and hypochloridia.*

<http://www.antiagingwellnesscenter.com/phcapsule.shtml>

*Dr. Paul Cheney on dumping, hypochloridia, and Betaine HCl supplementation.*

<http://www.prohealth.com/library/showarticle.cfm?libid=8037>

#### BIOFLAVONOIDS

Grape seed extract, Pycnogenol, Quercetin

**DESCRIPTION.** Bioflavonoids are glycosides (sugars) derived from citrus, paprika, and other plants, which serve to protect capillaries. Although formerly known as "vitamin P," bioflavonoids are not vitamins.

**BACKGROUND.** Bioflavonoids were first extracted from paprika in 1936 by a scientist who claimed that the substance had a greater effect than vitamin C in reducing capillary bleeding. It was later shown that the substance, or rather substances, helped maintain capillary strength by inhibiting permeability of the walls (rather than maintaining the actual structure, as does vitamin C). This may be because bioflavonoids inhibit oxidation of epinephrine (adrenaline), the hormone directly responsible for capillary wall integrity. Bioflavonoids enhance absorption of vitamin C and, when taken together, can help protect and preserve capillaries, increase circulation, prevent cataracts, and produce a mild antibacterial effect. Flavonoids have anti-allergic, anti-inflammatory and anti-microbial effects.

Dietary sources include buckwheat, black currants, peppers, and the white part of citrus peel. There are many bioflavonoids available for purchase through health food stores and online vitamin suppliers.

Bioflavonoids are rapidly absorbed in the system, and almost as rapidly excreted through the kidneys. Peak blood levels occur roughly two hours after ingestion, which means that to be effective, they should be taken throughout the day.

USES IN CFS/ME. Bioflavonoids are poorly absorbed, so for better utilization its best to take several. The most active intracellular free radical scavengers are lycopene, a carotenoid found in red fruits (except strawberries) and lutein, found in green leafy vegetables. Dr. Pall recommends FlaviNOx, which is a combination of standardized bioflavonoids derived from herbs (gingko, bilberry, milk thistle, grape seed extract, decaffeinated green tea extract, cranberry and hawthorn). The combination of antioxidants in FlaviNOx is designed to scavenge peroxynitrite and superoxide, two highly damaging free radicals.

AVAILABILITY AND COST. A 90-capsule bottle of FlaviNOx (Allergy Research Group) costs roughly \$35.

#### GRAPE SEED EXTRACT

DESCRIPTION. Grape seed extract is a polyphenolic compound derived from grape seeds.

BACKGROUND. Grape seeds contain polyphenols, procyanidins, and proanthocyanidins, which are antioxidants many times more powerful than vitamin C or E. Grape seed extract is reported to be a potent peroxynitrite scavenger, and therefore can protect the cells from intracellular damage. The effects of polyphenols are far-reaching, including the inhibition of skin cancer, reduction of inflammation, neuroprotective action, improvement of cerebral circulation, acceleration of wound healing, modulation of intestinal flora, repairing leaky gut, and immune system regulation.

USES IN CFS/ME. Grape seed extract is often used as a less expensive alternative to pycnogenol. Patients report that it helps with pain.

PROTOCOL. One 100 mg tablet taken with food.

AVAILABILITY AND COST. Grape seed extract is widely available in health food stores and through online distributors. A bottle of 120 capsules can cost as little as \$13. Grape seed extract is frequently combined with other bioflavonoids, such as green tea and resveratrol (found in grape skin) to increase its antioxidant effects.

#### FURTHER READING

*Sloan Kettering's review of the mechanisms of grape seed extract. Includes a list of studies.* <http://www.mskcc.org/cancer-care/herb/grape-seed>

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<http://www.ncbi.nlm.nih.gov/pubmed/22070681> (Abstract)

Vendrame S, Guglielmetti S, Riso P, Arioli S, Klimis-Zacas D, Porrini M. "Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the

human gut.” *J Agric Food Chem.* 2011 Nov 7.  
<http://www.ncbi.nlm.nih.gov/pubmed/22060186> (Abstract)

## PYCNOGENOL

**DESCRIPTION.** Pycnogenol (proanthocyanadin) is a bioflavonoid antioxidant derived from the bark of the French maritime pine tree.

**BACKGROUND.** Pycnogenol is a potent free radical scavenger. Studies have shown that, as an antioxidant, pycnogenol is up to 50 times more effective than other antioxidants to clear free radicals created from chemical sources (air pollution and food additives). It is 20 times more effective than vitamin C in scavenging superoxide, hydroxyl, and peroxide radicals. Pycnogenol is reported to enhance immune system function, increase energy, promote healing, and reduce allergic reactions. It is particularly effective in the brain.

**USES IN CFS/ME.** Pycnogenol has not been widely investigated for use in CFS/ME patients although it has been researched for other virally induced diseases. Some patients who have used pycnogenol report small increases in mental and physical energy and better resistance to bacterial and viral infections as well as stress.

**PROTOCOL.** The recommended dosage is 50 mg a day, taken with food. Some CFS/ME patients report that pycnogenol is more effective on an empty stomach.

**AVAILABILITY AND COST.** Pycnogenol can be purchased from health food stores and vitamin catalogs. Twinlab markets a 60-capsule bottle of pycnogenol (50 mg) for \$25 through Vitacost.

## FURTHER READING

*Sloan Kettering's excellent summary of the mechanisms of pycnogenol. Contains a list of research studies:* <http://www.mskcc.org/cancer-care/herb/pine-bark-extract>

Iravani S., and B. Zolfaghari. “Pharmaceutical and nutraceutical effects of *Pinus pinaster* bark extract.” PhD. *Res Pharm Sci.* 2011 Jan-Jun;6(1): 1–11.  
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*A thorough review of all research articles investigating pycnogenol.*

## RESEARCH

Feng WY, Tanaka R, Inagaki Y, Saitoh Y, Chang MO, Amet T, Yamamoto N, Yamaoka S, Yoshinaka Y. “Pycnogenol, a procyanidin-rich extract from French maritime pine, inhibits intracellular replication of HIV-1 as well as its binding to host cells.” *Jpn J Infect Dis.* 2008 Jul;61(4):279-85.

<http://www.ncbi.nlm.nih.gov/pubmed/18653969> (Abstract)

## QUERCETIN

**BACKGROUND.** Quercetin, a flavonol, is chiefly used to treat asthma and allergies. Quercetin has properties similar to that of the antihistamine disodium cromoglycate (found in Gastrocrom and Nasalcrom). It can inhibit mast cell

production and block histamine release, two functions that together can curb many allergic responses. In its antioxidant function, quercetin decreases the synthesis of pro-inflammatory leukotrienes, and inhibits free radical production and lipid peroxidation.

Quercetin is reported to help relieve muscle pain, particularly along the upper back and shoulders. It is commonly found in many food sources: green tea, apples, red onions, red grapes, citrus fruits, tomato, broccoli, leafy green vegetables, cranberries and raspberries, among others.

**USES IN CFS/ME:** An interesting study conducted in 2009 by Davis et al found that quercetin increased the genesis of mitochondria in mice, significantly improving exercise tolerance. The reason this study is important is that it was done *in vivo*. (Most studies on antioxidants are performed in test tubes.) As exercise intolerance is the hallmark symptom of CFS/ME, quercetin may play an important role in improving physical stamina among people with CFS/ME.

**PROTOCOL.** Because it is so poorly absorbed, quercetin needs to be taken with bromelain, an enzyme found in pineapple. Dr. James Balch, author of *Prescription for Nutritional Healing*, recommends 1000 to 2000 mg one to three times a day to prevent or lessen the severity of asthma attacks and allergies. CFS/ME patients are advised to start with much smaller doses, 200-1200 mg a day.

**PROS AND CONS.** Quercetin is the most widely used bioflavonoid among patients with CFS/ME. A number of allergy-prone patients with CFS/ME have noted that allergy symptoms subside with quercetin. For patients with many allergies, this may provide overall improvement because allergy symptoms can cause systemic problems. Some patients with interstitial cystitis have noted an improvement in symptoms after taking quercetin. The primary side effect is that high doses may cause diarrhea.

**AVAILABILITY AND COST.** Quercetin (with bromelain) is available from health food stores and online vitamin catalogs. A three-month supply may cost as little as \$8. ProHealth markets a 100-tablet bottle of a quercetin-bromelain combination (also containing vitamin C and magnesium) for about \$15.

#### FURTHER READING

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Pearce FL, Befus AD, Bienenstock J. "Mucosal mast cells. III. Effect of quercetin and other flavonoids on antigen-induced histamine secretion from rat intestinal

mast cells.” *J Allergy Clin Immunol*. 1984 Jun;73(6):819-23.

<http://www.ncbi.nlm.nih.gov/pubmed/6202731> (Abstract)

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## BUTYRIC ACID (BUTYRATE)

**DESCRIPTION.** Butyrates (butanoic, or butyric acid) are short-chain saturated fatty acids found naturally in the human intestine and in butter fat.

**BACKGROUND.** Short-chain fatty acids (volatile fatty acids) are produced in the colon as natural by-products of the bacterial fermentation of fiber. These fatty acids provide an energy source for the mucosal cells of the lining of the colon, enabling them to check the proliferation and establishment of pathogens (such as salmonella and Candida) and allowing greater absorption of magnesium and vitamin K. Deficiency of these fatty acids results in malabsorption, diarrhea, and, over the long term, colitis.

Of the three fatty acids found in all mammals – butyrate, acetate, and propionate – butyrate is the preferred energy substrate. It stimulates the normal proliferation of mucous cells, enabling greater efficiency of all colonic functions. Butyrates have been used successfully to treat Candida overgrowth (yeast infection), cancer, ulcerative colitis, and nonspecific inflammatory conditions of the colon. It is one of the treatments recommended for leaky gut and for alleviating food sensitivities.

**USES IN CFS/ME.** A significant number of people with CFS/ME suffer from gastrointestinal problems. According to Dr. Cheney, 90% of his CFS/ME patients have small intestinal bacterial overgrowth (SIBO), a condition in which bacteria from the large intestine migrate into the small intestines, interfering with fat and carbohydrate metabolism and causing a spate of GI symptoms. Rao et al found that 50% of CFS/ME patients meet the criteria for irritable bowel syndrome (IBS), a gut motility disorder. Butyrates, because they provide a substrate for beneficial intestinal flora, can be used in conjunction with probiotics to help restore gut mucosa damaged by SIBO as well as maintaining gut motility.

Although butyrates are primarily recommended for treating digestive disorders, it may also have a positive effect on some neurological problems associated with CFS/ME. Dr. Cheney proposes that an imbalance in the actions of the neuroexcitatory chemical NMDA (N-methyl-D-aspartate) and the neuroinhibitor GABA (gamma amino butyric acid) may lead to many of the troubling neurological symptoms experienced by patients with CFS/ME (insomnia, intolerance of sensory stimuli, seizure-like activity, pain) (*CFIDS Chronicle*, Spring 1995).

For many patients, down regulation of the NMDA receptors, accomplished with small doses of Klonopin (clonazepam), magnesium, Nimotop (nimodipine), melatonin, or calcium channel blockers, leads to general improvement of all

symptoms. Butyrate, because it forms a component of GABA, may also rectify some of this neurochemical imbalance by increasing the amount of neuroinhibitory action in the brain.

**PROTOCOL.** Butyrate is usually taken orally. The suggested dose is one or two capsules with each meal. It smells awful, so you may want to store it in the refrigerator.

**PROS AND CONS.** Butyrate is inexpensive, safe, and does not require a prescription.

**AVAILABILITY AND COST.** ButyrEn tablets, marketed by Allergy Research Group, are hypoallergenic, containing no yeast, wheat, corn, soy, dairy products, or artificial colors or resins. The tablets are buffered with calcium and magnesium. ButyrEn is available from online distributors and some specialized vitamin stores. One bottle of 100 capsules costs as little \$9 on amazon. PureFormulas markets a 90-capsule bottle of Cal-Mag Butyrate made by Ecological Formulas for \$10.50. Shipping is free.

#### FURTHER READING

*Life Extension is a bit pricier than other suppliers, but their website contains a very thorough description of the mechanisms of butyric acid.*

<http://www.lifeextensionvitamins.com/bualregr.html>

#### RESEARCH

Rao, A Venket, Alison C Bsted, Tracey M Beaulne, Martin A Katzman, Christina Iorio, John M Berardi and Alan C Logan. "A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome." *Gut Pathogens* 2009, 1:6.

<http://www.gutpathogens.com/content/1/1/6>

#### CHOLINE

**DEFINITION.** Choline is an amine (a nitrogen-containing compound) similar in function to B vitamins.

**BACKGROUND.** Choline is an essential nutrient, which means it cannot be synthesized by the body and must be obtained through food sources. Foods high in choline include egg yolk, liver, fatty meats, nuts and brown rice.

Choline performs three vital biological functions: 1) It is an important component of phosphatidylcholine, which forms cell walls and supports cellular function; 2) Choline serves as a precursor to acetylcholine, the neurotransmitter responsible for memory formation and muscle movement; 3) Choline is an important methyl donor, supporting the methylation cycle through its metabolite, trimethylglycine (betaine).

A deficiency in choline can lead to liver damage ("fatty liver") and a reduction in kidney function. Lack of choline in the diet can also cause infertility, growth impairment, bone abnormalities, and hypertension. Because choline plays such an important role in nervous system development, a deficiency in early life can lead to

neurological deficits. Vegans and athletes are particularly prone to choline deficiency.

**USES IN CFS/ME.** Because choline serves as a marker for certain types of brain damage, it is one of the compounds that is measured in magnetic resonance (MR) spectroscopy. For example, high amounts of choline accompanied by low amounts of creatine and N-acetyl aspartate (NAA) are indicative of stroke (cerebral ischemia and hypoxia). MR spectroscopy can also be used to monitor changes in tumors, stroke, epilepsy, metabolic disorders, infections, and neurodegenerative diseases.

In 2004 Chaudhuri and Behan used MR spectroscopy to assess brain chemistry in CFS/ME patients. They found that in CFS/ME patients, choline levels in the occipital cortex and basal ganglia were raised, but NAA and creatine were normal. The researchers concluded that in the absence of NAA and with no structural abnormalities, the increase in choline was probably due to increased phospholipase activity (the enzyme that breaks down the phospholipids that make up cell walls) rather than to inflammation. They theorized that viral activity could possibly contribute to the increased choline, as many viruses increase the activity of phospholipase.

While Chaudhuri and Behan concluded that inflammation in the brain was not indicated by their test results, further research indicates otherwise. Martin Pall has suggested that activation of NMDA receptors (due to oxidative stress) provides the missing inflammatory pathway that Chaudhuri and Behan were unable to identify. In fact, an increase in choline can be an early signal of an inflammatory process, even in the absence of NAA. The mechanism which induces release of choline was identified by Gasull et al as an inhibition of phosphatidylcholine synthesis rather than phospholipase degradation. The researchers found that the increase in extracellular choline was induced by NMDA receptor activation, which ties in with Martin Pall's theory. In addition, Gasull's group found that early choline release was directly related to excitotoxic cell death caused by glutamine.

**PROTOCOL.** Given the important role of choline in neuronal protection from oxidative stress, as well as the fact that it is a component of acetylcholine, choline comprises a valuable addition to any CFS/ME treatment plan. Dr. Cheney recommends taking 50 mg of choline bitartrate a day. Dr. Teitelbaum recommends the same dose, accompanied by vitamin C.

High doses (10 to 16 grams/day) of choline are not recommended. Side effects from excessive intake of choline have been associated with a fishy body odor, vomiting, salivation, and increased sweating. (The fishy body odor results from excretion of trimethylamine, a metabolite of choline.) Taking large doses of choline in the form of phosphatidylcholine (lecithin) does not generally result in fishy body odor. However, lecithin is not usually well-tolerated by CFS/ME patients.

**AVAILABILITY AND COST.** Choline bitartrate supplements are not widely available, so most people decide to purchase lecithin powder, which is inexpensive and easy to find. PureFormulas.com markets a bottle of 100 choline bitartrate capsules (235 mg) for roughly \$10. Purebulk.com sells a 100-gram container of

choline bitartrate powder for \$4.25. The powder may be a more viable option for most people as it allows for titration. Many B vitamin formulations contain choline, so check labels. It may be worthwhile to purchase a good-quality B-complex supplement that includes choline, as this will give you the proper balance of B vitamins as well.

#### FURTHER READING

*This Oregon University site provides excellent information about choline.*

<http://lpi.oregonstate.edu/infocenter/othernuts/choline/>

“What are Choline and Inositol?” (*Good overview*):

<http://www.livestrong.com/article/326852-what-are-choline-inositol/>

“Choline on the Brain? A Guide to Choline in Chronic Fatigue Syndrome.” Cort Johnson. Aug, 2005.

<http://aboutmecfs.org.violet.arvix.com/Rsrch/CholineBrain.aspx>

*Ray Sahelian's sensible advise on choline:* <http://www.raysahelian.com/cdp.html>

“Fundamentals of MR Spectroscopy.” John R. Hesselink. (*A nice summary of MR spectroscopy.*) <http://spinwarp.ucsd.edu/neuroweb/Text/mrs-TXT.htm>

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Doležal, Vladimír, Stanislav Tuček. “Activation of muscarinic receptors stimulates the release of choline from brain slices.” *Biochem Biophys Res Commun*. 1984 May 16;120(3):1002-7. <http://www.ncbi.nlm.nih.gov/pubmed/6732780> (Abstract)

Gasull, Teresa, Nuria DeGregorio-Rocasolano, Agustin Zapata and Ramon Trullas. “Choline Release and Inhibition of Phosphatidylcholine Synthesis Precede Excitotoxic Neuronal Death but Not Neurotoxicity Induced by Serum Deprivation.” First Published on March 28, 2000. *The Journal of Biological Chemistry*, 275,18350-18357. <http://www.jbc.org/content/275/24/18350.full>

#### COQ10 (UBIQUINONE, UBIQUINOL)

**DESCRIPTION.** CoQ10 (ubiquinone) is a fat-soluble coenzyme found in the mitochondria of most mammal cells.



**BACKGROUND.** CoQ10 was first discovered by R.A. Morton, a biochemist who gave it the name ubiquinone after its ubiquitous presence in nearly all living things. "Co" stands for coenzyme (a vitamin-like substance), "Q" for quinone (the group of organic chemicals to which CoQ belongs), and "10" for the number of isoprene units that characterize the particular coenzyme found in animal cells.

CoQ10 is vital for electron transport, the intracellular function that ultimately provides the energy necessary to sustain life. CoQ10 is also a powerful antioxidant and is important in immune system function. The Japanese have successfully used CoQ10 to treat gum disease, heart disease, and high blood pressure, and to enhance the effectiveness of the immune system. Research performed in Japan and elsewhere indicates that CoQ10 can be of benefit in treating allergies (owing to its ability to block the effects of histamine), asthma, candidiasis, obesity, diabetes, mental function diseases such as Alzheimer's disease, and can slow the aging process (CoQ10 levels decline with age).

High amounts of CoQ10 occur naturally in fatty saltwater fish, especially mackerel, salmon, and sardines.

**USES IN CFS/ME.** CoQ10 is one of the most frequently used supplements for the treatment of CFS/ME-related fatigue because of its importance in the production of adenosine triphosphate (ATP), the cellular source of energy. In addition to reducing fatigue, CoQ10 may alleviate muscle weakness and pain. It is also one of the few supplements that seems to reduce cognitive dysfunction. Its role as a free radical scavenger may lead to improvement in immune responses in patients with CFS/ME. Although its effects as a natural antihistamine have not yet been specifically explored in CFS/ME, patients with allergies may benefit from CoQ10.

There is also evidence that CoQ10 is deficient in CFS/ME patients. In 2009 Maes et al measured plasma CoQ10 in 58 CFS/ME patients. Compared to normal controls, the CFS/ME group had values significantly below the lowest recorded levels of the control group. Patients with very low levels of CoQ10 suffered significantly more from concentration and memory disturbances. The researchers concluded that lowered levels of CoQ10 play a role in the pathophysiology of ME/CFS and that "symptoms, such as fatigue, and autonomic and neurocognitive symptoms may be caused by CoQ10 depletion." Their results suggested that patients with CFS/ME would benefit from CoQ10 supplementation in order to normalize the low CoQ10 syndrome.

**PROTOCOL.** Nearly all CFS/ME physicians recommend supplementation with CoQ10. CoQ10 can be taken in a single dose or divided into two doses taken at different times during the day. There is evidence that dividing the dose is more effective than taking it all at once. The normal recommended dose is between 30 and 200 mg/day. Dr. Lapp and Dr. Klimas recommend 120 mg a day. Sublingual CoQ10, reputedly more effective against cognitive dysfunction, may be taken at higher doses. Oral CoQ10, although primarily absorbed by the digestive tract and liver, is also effective for some patients. The oral dosage varies, but is usually 25 to 50 mg/day. It may take up to eight weeks to see effects from oral CoQ10. Because

CoQ10 is fat-soluble, it should be taken with a meal that contains some kind of fat or oil.

**PROS.** Taken at lower doses, CoQ10 is a supplement with very few side effects. Patients report improvements in energy, stamina, light-headedness, and syncope (fainting). Dr. Lapp reports that half of his patients see improvement after taking CoQ10. A significant number of patients, particularly those with fibromyalgia, find that CoQ10 increases their energy over the course of the day.

**CONS.** Some patients report that CoQ10, while giving them an initial energy boost, also increases insomnia and causes jitters. Some people report, paradoxically, that CoQ10 produces exhaustion, although this effect may be more common in the acutely ill than in those with stable symptoms. CoQ10 lowers blood sugar levels, which may be problematic for patients with hypoglycemia. High doses can cause flu-like symptoms.

**AVAILABILITY AND COST.** CoQ10 can be purchased at most health food stores and from online distributors. There is a mind-boggling array of CoQ10 products. High-grade brands are preferred. (CoQ10 deteriorates rapidly when exposed to heat and light.) Because CoQ10 is fat-soluble, it should be purchased as a softgel (not capsule), preferably with a natural preservative (such as vitamin E).

Sublingual CoQ10 can be purchased from online sources without a prescription. Intensive Nutrition, Inc. markets a sustained-release sublingual CoQ10 for \$25 (80 mg, 30 count). Source Naturals sells sublingual CoQ10 for \$14 (30 mg, 120 count).

CoQ10 is also available by prescription as a gel. Unlike other forms of CoQ10, the gel is water soluble, and bypasses the GI tract completely. The gel is more easily absorbed than oral forms, so less CoQ10 needs to be taken. CoQ10 gel has been given orphan status by the FDA for treating mitochondrial dysfunction. (Orphan status means that a drug has been approved for the treatment of rare disorders.)

A more easily absorbed form of CoQ10, ubiquinol, is currently being marketed in the U.S. CoQ10 is converted in the body to ubiquinol, which is the active form of the enzyme, and therefore, more potent. Not only is ubiquinol more easily absorbed, it is longer acting than ubiquinone. Ubiquinol can be purchased from health food stores and online distributors. Vitacost sells a wide variety of ubiquinol products, ranging in cost from \$8 to \$74. (Read the labels carefully to confirm that the product contains pure ubiquinol.) Olympian Labs sells a bottle of 60 ubiquinol softgels (50 mg) with relatively few additives for \$27.62.

Oral CoQ10 is not usually covered by insurance, as it is classed as a supplement.

#### FURTHER READING

*Excellent summary of CoQ10 in CFS/ME:* [http://phoenixrising.me/?page\\_id=4759](http://phoenixrising.me/?page_id=4759)

*An interesting and useful site containing a discussion of ubiquinol, a comparison of ubiquinol to CoQ10, links and research:* <http://ubiquinol.org/what-is-ubiquinol>

*Website of the International CoQ10 Association:*

<http://www.icqa.org/ICQA/home.html>

*Ray Sahelian's informative site. Effects of CoQ10, studies and FAQs.*

<http://www.raysahelian.com/coq10.html>

*Compounding pharmacies that make CoQ10 troches:*

<http://www.mitoaction.org/blog/coq-10-update>

*Information on CoQ10 gel:* <http://www.epic4health.com/noname.html>

## PATIENT REVIEWS

*Patient reviews of CoQ10:* <http://www.revolutionhealth.com/drugs-treatments/rating/coenzyme-q10-coq10-for-chronic-fatigue-syndrome-cfs-cfids-me?sort=recent>

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<http://www.ncbi.nlm.nih.gov/pubmed/20010505> (Abstract)

## D-RIBOSE

**DESCRIPTION.** D-Ribose is a water-soluble simple sugar that is an important component of nucleic acids, vitamin B2, and various coenzymes.

**BACKGROUND.** Ribose was first identified in 1891 by Emil Fischer, a German chemist and recipient of the Nobel Prize in Chemistry. Fischer's primary work concerned sugars and the identification of their various functions. Ribose is an extremely important sugar in that it comprises the backbone of RNA, one of the three major macromolecules essential to all forms of life. Ribose is also a component of ATP, NADH and several other compounds that control the metabolism of carbohydrates, proteins, and fat.

**USES IN CFS/ME.** Mitochondrial defects that lead to low production of ATP, the principal source of cellular energy, have been thoroughly documented in people with CFS/ME. Low levels of ATP are responsible for the hallmark symptoms of CFS/ME, exercise intolerance and fatigue. However, direct supplementation with ATP seems to have no effect on either fatigue or stamina. This is due to the fact that ATP has a molecular weight of more than 500, which means that it is nearly impossible to absorb. Therefore, the mitochondrial defects leading to low ATP production must be addressed at a lower level in the metabolic chain.

The body makes ATP through the Krebs cycle, in which various enzymes convert citric acid into ATP. These enzymes are often deficient in people with CFS/ME, resulting in a lower production of ATP. The body can also make ATP from glucose, but the process involves first converting glucose into lactic acid, which then accumulates in the muscles, causing the familiar “burn” of over-exertion. This is also a longer and less efficient process than the Krebs cycle. D-Ribose cuts the time

required to produce ATP because the body can quickly convert D-Ribose into ATP without converting it first into lactic acid.

In a 2006 pilot study, Teitelbaum et al found that in 36 CFS/FM patients, 66% experienced improvement in energy, pain, sleep, mental clarity and overall well-being after treatment with D-Ribose. The average improvement in energy was 45%, while the global improvement was 30%. The researchers concluded that D-Ribose “significantly reduced symptoms in patients suffering from fibromyalgia and chronic fatigue syndrome.”

Apart from its uses in CFS/ME, D-Ribose is among the most popular nutritional supplements to have been recently patented. In 2010, Bioenergy Inc, the company which markets Corvalen (the brand recommended by Dr. Teitelbaum), achieved its highest revenue earnings in the history of the company.

**PROTOCOL.** The serving size recommended by Jarrow is 2 grams ( $\frac{1}{2}$  tsp/one scoop) up to three times a day. Dr. Teitelbaum recommends 5000 mg (5 grams) of D-Ribose three times a day for two to three weeks, then twice a day. Dr. Myhill also recommends 15 grams a day. Interestingly, she notes that the effects of D-Ribose can be enhanced by caffeine. She notes that D-Ribose has a short half-life, which is why it must be taken in small doses throughout the day. D-Ribose should be taken with food.

While initial doses of 15 grams are recommended by Drs. Teitelbaum and Myhill, it should be remembered that many CFS/ME patients are sensitive to supplements. Dr. Cheney has observed that fully one-third of his patients cannot tolerate D-Ribose. To test for sensitivities, an initial small dose (1 to 2 grams a day) is recommended.

**PROS.** D-Ribose appears to be generally well tolerated by people with CFS/ME. Patients usually notice improvement in energy levels within two or three days, although one patient commented that “within an hour, it was like a super thick fog bank had dissipated.” D-Ribose works particularly well with brain fog, daytime sleepiness and hypersomnia.

**CONS.** Some patients report that D-Ribose makes them sleepy, and that it saps them of energy. Those who take high doses (15 grams a day) have reported diarrhea, nausea, and headache. Because D-Ribose is derived from corn, those with corn allergies may not be able to tolerate this supplement. Although D-Ribose does not have the same properties as table sugar, it can be converted back to glucose, which may have an adverse effect on patients with Candida, as well as those with blood sugar problems. D-Ribose supplementation is not advised for diabetics. Nor is it recommended for those with gout, as it causes an increase in uric acid levels (which are usually low in people with CFS/ME).

**AVAILABILITY AND COST.** D-Ribose is widely available in health food stores and from online suppliers. Costs range from \$10 to \$75, depending on the brand. Corvalen, the brand Dr. Teitelbaum prefers, sells for roughly \$30 for a 280-gram container (56 servings, or roughly an 18-day supply at three scoops a day). Vitacost markets a 100-gram bottle made by Jarrow for about \$10 (45 scoops).

## FURTHER READING

*Dr. Teitelbaum addresses questions about D-Ribose:*

[http://www.endfatigue.com/web-newsletters/Newsletter\\_3\\_questions\\_d-ribose.html](http://www.endfatigue.com/web-newsletters/Newsletter_3_questions_d-ribose.html)

*Dr. Teitelbaum explains the functions and benefits of D-Ribose.*

[http://www.endfatigue.com/health\\_articles\\_d-e/D-ribose-powerful\\_body\\_energizer.html](http://www.endfatigue.com/health_articles_d-e/D-ribose-powerful_body_energizer.html)

Teitelbaum JE, JA St. Cyr, C Johnson. "The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study" *J Alternative and Complementary Medicine* 2006;12(9):857-862. <http://www.fibroandfatigue.com/files/d-ribose.pdf>

*Dr. Lapp's list of supplements, including D-Ribose:*

<http://www.prohealth.com/library/showarticle.cfm?libid=16109>

Myhill, Sarah, Norman E. Booth, and John McLaren-Howard. "Chronic fatigue syndrome and mitochondrial dysfunction." *Int J Clin Exp Med*. 2009;2(1): 1-16.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2680051/>

*(This is a very long paper. You may want to jump to the following site.)*

*A summary of the information in the previous paper:*

[http://www.drmyhill.co.uk/wiki/CFS\\_-\\_The\\_Central\\_Cause:\\_Mitochondrial\\_Failure](http://www.drmyhill.co.uk/wiki/CFS_-_The_Central_Cause:_Mitochondrial_Failure)

*Creatine and D-Ribose studies:* <http://www.vrp.com/energizers/mitochondrial-restoration-part-iii-d-ribose-and-creatine-increase-mitochondrial-energy-production>

*A patient's encouraging report of her experiences with D-Ribose.*

<http://www.healingwell.com/community/default.aspx?f=15&m=1253136>

## DIGESTIVE ENZYMES

**DESCRIPTION.** Gastrointestinal enzymes are secreted in the GI tract for the purpose of breaking down large food molecules into smaller molecules that are more easily absorbed.

**BACKGROUND.** Digestive enzymes are secreted in the mouth by salivary glands, in the stomach, in the pancreas and throughout the small intestine. Enzymes are classed into groups according to their function: proteases split proteins into amino acids, lipases split fat into fatty acids and glycerol, carbohydrases split sugars and carbohydrates into glucose, and nucleases split nucleic acids into nucleotides, which form RNA and DNA. Nucleotides also potentiate the production of ATP.

The mouth is where the digestive process is initiated. Enzymes which are released by salivary glands include lingual lipase, to start the digestion of fats; and amylase, which starts the conversion of carbohydrates into glucose; as well as immune system chemicals such as IgA to battle bacterial toxins, and R-factor which helps with the absorption of B12.

The main enzyme produced in the stomach is pepsin, which breaks down proteins. There are a number of other gastric secretions in the stomach which aid the process of breaking down food, the most important of which are hydrochloric

acid (HCl), which activates pepsin and destroys bacteria; intrinsic factor, which aids in the absorption of B12 by protecting it from HCl; and gastrin, the hormone which stimulates the stomach lining to produce HCl and intrinsic factor.

The pancreas produces trypsin, which further breaks down proteins into amino acids; pancreatic lipase, which breaks down fats; pancreatic amylase, which further breaks down carbohydrates into glucose; protease, for breaking down proteins; and several nucleases.

The small intestines, among many other chemicals, produce sucrase, to break down sugars; lactase, to break down lactose in milk; and maltase, which breaks maltose down into glucose.

**USES IN CFS/ME.** Given the broad range of GI disturbances in CFS/ME patients, as well as the importance of the GI tract in maintaining both nutritional health and immune system functioning, digestive enzymes can play a critical role in treatment. Dr. Cheney believes enzyme supplementation is essential for all CFS/ME patients.

**PROTOCOL.** Dr. Cheney recommends one or two tablets of Ultrazyme (made by Douglas Labs). Ultrazyme provides a broad spectrum of enzymes, including lipase, amylase, protease, ox bile extract, cellulase, pepsin and L-lysine. Dr. Myhill recommends Polyzyme Forte, a broad-spectrum enzyme supplement made by BioCare (available the U.K.). Enzymes are sensitive to temperature extremes. They should be taken with warm water or food. Enzymes are activated by moisture, so make sure you keep the tablets dry.

**PROS.** Many patients swear by enzymes, claiming that they help eradicate digestion problems as well as many food sensitivities.

**CONS.** Enzymes can be hard on the stomach. For those who are prone to reflux, or heartburn, enzymes may exacerbate these problems. Stomach problems can be mitigated by taking enzymes with food (rather than on an empty stomach).

**AVAILABILITY AND COST.** Enzymatic supplements are readily available at any health food store and from online suppliers. A 60-tablet bottle of Ultrazyme (Douglas Labs) sells for around \$15 on amazon.com. Enzymatic supplements can also be purchased in powder form. Plant-based enzymes, which are not degraded by stomach acid, should always be purchased.

## FURTHER READING

*Dr. Cheney discusses gut dysbiosis and CFS/ME symptoms:*

<http://www.cheneyclinic.com/gut-dysbiosis-modulates-significant-cfs-symptoms/247>

*Dr. Cheney discusses Betaine HCl and the function of enzymes. (Written by Carol Sieverling)* <http://www.prohealth.com/library/showarticle.cfm?libid=8037>

*Lots of articles about enzymes:* <http://www.enzymestuff.com/>

## DHEA

*NOTE: Not all CFS/ME patients have low levels of DHEA. Before embarking on a course of DHEA, make sure to have your DHEA level tested.*

**DEFINITION.** DHEA (dehydroepiandrosterone) is a naturally occurring adrenal hormone.

**BACKGROUND.** DHEA, a hormone produced in the adrenal cortex, generates the sex hormones estrogen and testosterone. It is the most common hormone in the blood and is found in greatest concentrations in the brain. Perhaps because DHEA levels decrease with age, it has been called "the fountain of youth." A substantial body of research has provided evidence that DHEA may help the elderly by strengthening bones and muscles, decreasing joint pain, and improving sleep and mood. In addition to influencing hormone production, DHEA has several effects on immune system function, not the least of which is the regulation of lymphokine production.

A study conducted in 1993 by researchers at the University of Tennessee showed that DHEA decreases the amount of circulating interleukin-6 (a potent bone resorber and pro-inflammatory cytokine) and enhances the function of natural killer cells. Another study conducted in 1998 confirmed an inverse correlation between DHEA levels and IL-6 (as DHEA drops, IL-6 increases). DHEA has also been used to treat osteoporosis. A twelve-month study conducted in Canada confirmed that in post-menopausal women the application of DHEA in the form of 10% cream stimulated bone formation.

**USES IN CFS/ME.** Inspired by mounting evidence of adrenal cortical hypofunction in CFS/ME, clinicians have tested for blood levels of DHEA in CFS/ME patients. Some have discovered lower than normal levels. Based on these results, low doses of DHEA have been administered in hopes of raising immune function and normalizing the metabolic and endocrine disturbances that commonly accompany CFS/ME. It is believed that DHEA could also act as an antiviral agent because testosterone, a DHEA derivative, has demonstrable antiviral effects.

**PROTOCOL.** The usual dosage of DHEA is 25 to 100 mg/day, although a number of clinicians report good results with smaller doses. Dr. Majid Ali states that he frequently prescribes DHEA in doses of 50 mg taken on alternating days for up to several months. In contrast, Dr. James McCoy found that smaller doses (10 mg or less) are equally, if not more, effective than larger doses (*CFIDS Chronicle*, Fall 1993). He recommended starting at one tenth the normal dose to minimize the chance of negative reactions. Many patients with CFS/ME confirm that smaller doses (10 mg) work well for them.

**PROS.** Patients with CFS/ME have reported weight loss, increased energy, improved cognitive function, and better immune system responses with DHEA.

**CONS.** A number of patients have reported heart palpitations, jitters, and altered mental and emotional states. Female patients have experienced hair loss and acne. Dr. Paul Cheney points out that DHEA is often most beneficial in mild CFS/ME. He notes that even in cases where DHEA deficiency can be documented, administration of this hormone has caused severe relapse in some of his more profoundly ill patients (*CFIDS Chronicle*, Spring 1995).

Researchers have noted side effects in older women given standard doses of DHEA (25-200 mg a day), including acne and hirsutism (facial hair growth). DHEA also lowers cortisol, an anti-inflammatory adrenal hormone responsible for raising blood sugar levels. It is important to remember that even though DHEA is a natural substance, it is still a powerful hormone. Hormones, because they are released directly into the bloodstream, produce profound metabolic effects, not all of which are intended. Like other steroid or hormone treatments, DHEA is not without some risk and must be approached with caution.

**AVAILABILITY AND COST.** DHEA can be purchased online and at most health food stores. It is inexpensive. Vitacost sells many brands for less than \$10. Mexican wild yam products containing diosgenin should be avoided, as the body cannot convert diosgenin to DHEA.

Although DHEA is sold as a supplement in the U.S., it cannot be purchased in the U.K. and Canada without a prescription. South Dakota and Missouri prohibit the sale of DHEA. Those under the age of 18 cannot purchase DHEA without a prescription. Most bottles of DHEA contain the warning: "Not for women under the age of 35."

One of the natural precursors to DHEA, pregnenolone, may be less risky than DHEA. Patients report increased energy, enhanced mental clarity, and general improvement after taking pregnenolone. The dosage is 10 mg every other day in patients younger than 50 years, and 20 mg every other day in patients over 50 years old. Pregnenolone can be purchased from online suppliers at roughly the same cost as DHEA. Pregnenolone carries the same warnings as DHEA.

#### FURTHER READING

*Very thorough overview of DHEA. Many studies are cited.*

[http://www.tidesoflife.com/dhea\\_basic\\_information.htm](http://www.tidesoflife.com/dhea_basic_information.htm)

*Dr. Cheney on DHEA and other supplements (1995).*

<http://www.immunesupport.com/news/95sum003.htm>

*Good article on the effects of DHEA on aging:* <http://www.anti-agingmd.com/dhea.html>

#### PATIENT REVIEWS

*CFS/ME patient reviews of DHEA:* <http://www.revolutionhealth.com/drugs-treatments/rating/dehydroepiandrosterone-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### RESEARCH

Casson PR, Andersen RN, Herrod HG, Stentz FB, Straughn AB, Abraham GE, Buster JE. "Oral dehydroepiandrosterone in physiologic doses modulate immune function in postmenopausal women." *Am J Obstet Gynecol.* 1993 Dec;169(6):1536-9. <http://www.ncbi.nlm.nih.gov/pubmed/8267058> (Abstract)

Labrie F, Diamond P, Cusan L, Gomez JL, Bélanger A, Candau B. "Effect of 12-Month Dehydroepiandrosterone Replacement Therapy on Bone, Vagina, and



Endometrium in Postmenopausal Women." *J Clin Endocrinol Metab.* 1997 Oct;82(10):3498-505. <http://jcem.endojournals.org/content/82/10/3498.short> (Abstract)

## ESSENTIAL FATTY ACIDS

Fish Oil, Flaxseed Oil, Evening Primrose Oil, Borage Seed Oil

**DESCRIPTION.** Essential fatty acids are fats (lipids) that are important in a number of physiological processes. They cannot be produced by the body and therefore must be obtained through dietary sources.

**BACKGROUND.** The two most important types of essential fatty acids are omega-3 and omega-6. Omega-3 fatty acids – alpha linolenic acid (ALA), docosahexanoic acid (DHA), and eicosapentaenoic (EPA) – are found in fish oil (especially cold water fish) and flaxseed oil. Omega-6 fatty acids (linoleic acid, LA) are found in many plant oils, including evening primrose oil, borage oil, and black currant oil.

Essential fatty acids are vital to a number of physiological processes, such as regulating cholesterol levels, keeping the skin moist and supple, and producing prostaglandins (hormone-like substances that affect a variety of body functions). Essential fatty acids are also indispensable in maintaining the structure and function of cell membranes. Most important, essential fatty acids, particularly those found in fish oil, can act as immune system modulators, enhancing immune system activity where needed, and inhibiting it when there is an upregulated immune response.

Several factors can affect fatty acid metabolism. Poor diet, stress, diabetes, excessive alcohol intake, radiation, and viral infections can disrupt the metabolism of essential fatty acids, making it difficult for the body to produce fatty acid metabolites in sufficient quantities. In such cases, supplementation may be necessary to prevent deficiency states. Supplementation with essential fatty acids has improved such diverse conditions as premenstrual syndrome (PMS), heart disease, rheumatoid arthritis, multiple sclerosis, hyperactivity in children, depression and mononucleosis.

**USES IN CFS/ME.** In 1987 Dr. Peter Behan, a professor of Clinical Neurology in Glasgow, Scotland, found that patients with CFS/ME have a disorder in fatty acid metabolism. Dr. Behan surmised that the disorder was the result of chronic viral infection much like mononucleosis, a prolonged illness that also produces abnormal serum fatty acid concentration. He conducted a double-blind trial using a fatty acid supplement (Efamol) containing both omega-3 and omega-6 fatty acids (*Acta Neurologica Scandinavica*, 1990). After 16 weeks of treatment, an astounding 85% of patients showed marked improvement, primarily in the areas of fatigue, dizziness, headaches, depression, and muscle pain.

In 1994, Gray and Martinovic hypothesized that the chronic immune system activation found in CFS/ME patients results in hyporesponsiveness of essential

fatty acid metabolites, which produces a state in which even minor stressors can disturb homeostasis. They tested their hypothesis by administering dietary essential fatty acids to a group of CFS/ME patients. After three months, 90% of the patients treated showed signs of improvement.

While the results of Behan's and Gray's studies were encouraging, not all studies have confirmed that the administration of EFAs significantly improves CFS/ME symptoms. It wasn't until specific EFAs were tested that some light was shed on the effects of EFA supplementation in CFS/ME.

In 2003 Liu et al measured specific EFAs in the red blood cells of CFS/ME patients. The researchers found that both DHA and ARA (arachidonic acid) levels were low, indicating a state of oxidative stress. The authors concluded that because ratios of EFAs are essential in maintaining signal transduction, the disruption in EFA ratios might induce an impairment in both circulation and immune system function. The authors stated that recurrent sore throat, tender lymph nodes, muscle aches, arthralgia, and headaches might be due to disruption in EFA signaling.

Puri's 2004 study of eicosapentaenoic acid (EPA) showed that it was the omega-3 fatty acids that produced the greatest improvement in CFS/ME symptoms. Four patients with chronic, intractable CFS/ME were treated with high doses (approx 1500 mg a day) of an over-the-counter high eicosapentaenoic acid fatty acid supplement (Equazen, Ltd., London). All four patients showed improvement in symptoms within 12 weeks of treatment. They reported a lessening of "brain fog," and an overall sense of well-being. The same patients when treated with a placebo did not note a similar improvement. While the cohort was small, the findings of this study were significant.

On the heels of this study, in 2005 Maes et al studied the ratios of fatty acids in CFS/ME patients. The researchers measured omega-6 and omega-3 fatty acid ratios in 22 CFS/ME patients and 12 controls. They found that CFS/ME patients, regardless of age or gender, had significantly higher levels of linoleic acid and arachidonic acid (omega-6) than controls. Both linoleic acid and arachidonic acid are implicated in the production of pro-inflammatory cytokines. They speculated that the low levels of circulating zinc found in CFS/ME patients (indicating an inflammatory response) might be due to the depletion of omega-3 fatty acids. The authors further hypothesized that the defects in T cell activation found in CFS/ME might also be attributed to a deficit in omega-3 fatty acids.

**AVAILABILITY AND COST.** EFAs are available at any health food store and through online suppliers. Many companies sell combinations of different EFAs for maximum effect. Because these are oils which are highly prone to rancidity, it is worth the price to buy a high quality product.

#### FURTHER READING

"The ABCs of EFAs." *CFIDS Chronicle*, Summer 2008.

<http://www.cfids.org/cfidslink/2009/040107.pdf>

*Good summary of essential fatty acids, their function, and their role as a treatment for CFS/ME.*

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## FISH OILS

**DESCRIPTION.** The oil derived from deep-sea fish (sardines, mackerel, salmon, and herring) is the richest source of omega-3 fatty acids (DHA and EPA). Four ounces of salmon can contain as much as 3600 mg of omega-3 fatty acids. Fish oil capsules have been particularly helpful in treating fibromyalgia, often providing immediate relief from pain. Fish oil is so effective that some physicians suggest it in place of Advil (ibuprofen) for pain from inflammation. Because of its anti-inflammatory properties, fish oil can also be used to treat arthritis and colitis.

**AVAILABILITY AND COST.** High-quality brands of fish oils are available from Kyolic and Cardiovascular Research Ltd. Plain cod liver oil is not recommended because the amount needed to provide sufficient fatty acids might lead to an overdose of vitamin A. Fish oils can range in price from \$5 to \$15 for a month's supply, depending on the brand, and can be purchased in health food stores or through online vitamin catalogs. The usual dose is one to four capsules a day.

For those who experience stomach upset with fish oil, the enteric-coated version, Fisol (made by Nature's Way), may be preferred. The enteric coating allows the capsules to pass through the stomach, dissolving only once they reach the intestines. One capsule of Fisol provides 500 mg of omega-3 fatty acids. Vitacost sells a 180-capsule bottle of Fisol for \$16.

## PATIENT REVIEWS

*CFS/ME patient reviews of fish oil:* <http://www.revolutionhealth.com/drugs-treatments/rating/fish-oil-omega-3-epa-dha-fatty-acids-for-chronic-fatigue-syndrome-cfs-cfids-me>

## FLAXSEED OIL

**DESCRIPTION.** Flaxseed (linseed) is a good plant source of omega-3 fatty acids. It is also high in magnesium and zinc, two important factors in fatty acid metabolism, as well as B complex vitamins, protein, and potassium. Flaxseed oil is low in saturated fat and calories and contains no cholesterol. It has a delicious nutty flavor and can be added to salad dressings or sprinkled over vegetables.

Flaxseed is high in alpha-linolenic acid (ALA), which the body converts to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two fatty acids found in fish oils. Some clinicians prefer flaxseed oil to fish oil because it is lower on the food chain and thus contains fewer fat-soluble contaminants. Fish oils, as opposed to vegetable oils, also contain large quantities of vitamin A, which can be toxic in excessive amounts.

**AVAILABILITY AND COST.** Flaxseed oil can be purchased in health food stores and is inexpensive. NOW markets a 24-ounce bottle of organic flaxseed oil for \$9. Flaxseed oil must be stored in the refrigerator to avoid rancidity. It should not be used for cooking. Gelcaps are also available.

## PATIENT REVIEWS

*CFS/ME patient ratings for flaxseed oil:* <http://www.revolutionhealth.com/drugs-treatments/rating/flax-seed-oil-omega-3-alpha-linolenic-acid-for-chronic-fatigue-syndrome-cfs-cfids-me>

## EVENING PRIMROSE OIL

**DESCRIPTION.** Evening primrose oil is one of the most popular and perhaps most effective of the omega-6 essential fatty acids. It comes from the evening primrose (*Oenothera*), a lovely yellow flower that grows wild along roadsides. The seeds contain large amounts of GLA (gamma-linolenic acid), a linolenic acid metabolite. Unlike other omega-6 fatty acids, GLA does not lead to increased production of pro-inflammatory cytokines, but has an anti-inflammatory effect. Evening primrose oil has been used to help alleviate the symptoms of premenstrual syndrome (PMS), menstrual cramps, and arthritis, often with dramatic results. It may even lessen the symptoms of endometriosis.

**PROS AND CONS.** Patients with CFS/ME have reported increased energy, improvements in skin disorders (eczema, acne, dry skin), and decreased mood swings. Side effects, although uncommon, include headache, nausea, mild intestinal discomfort, and, rarely, weight gain.

**AVAILABILITY AND COST.** Evening primrose oil capsules are relatively inexpensive. A bottle of 60 softgels can be purchased for under \$10 from online distributors.

## PATIENT REVIEWS

*CFS/ME patient ratings of evening primrose oil:*

<http://www.revolutionhealth.com/drugs-treatments/rating/vitamin-c-ascorbic-acid-for-chronic-fatigue-syndrome-cfs-cfids-me>

## BORAGE SEED OIL

**DESCRIPTION.** Borage seed oil, made from the borage plant, contains the highest GLA content of any currently available seed oil, up to four times more than the GLA content of evening primrose oil. Patients who have gained little benefit from or cannot tolerate evening primrose oil because of food sensitivities often take borage oil with good results. The recommended dose is lower than for evening primrose oil, only one to three capsules a day. As with all EFAs, it is best to purchase products that are high quality. Pureformulas.com markets a bottle of 30 softgels made by Allergy Research Group for \$14.

## FOS (Fructooligosaccharides)

**DESCRIPTION.** FOS (Fructooligosaccharides) are natural sugars derived from fruits and vegetables.

**BACKGROUND.** FOS is produced from the degradation of inulin, or polyfructose. It is roughly half as sweet as sugar. FOS has achieved popularity as a “prebiotic,” something that provides a necessary substrate for lower intestinal flora, particularly bifidobacteria. FOS also helps increase the absorption of calcium and magnesium.

**USES IN CFS/ME.** FOS is primarily used in conjunction with probiotics to aid in the promotion of friendly gut bacteria.

Opinions about FOS are mixed in the CFS/ME community. Dr. Cheney, for example, is not a fan of FOS. In a 1999 talk about CFS/ME patients with leaky gut, he likened FOS to “throwing fertilizer on a patch of weeds.” By this, he is referring to the fact that FOS, like other prebiotics, will nourish harmful bacteria as well as friendly bacteria. In the presence of a bacterial infection in the gut or SIBO (small intestine bacterial overgrowth), prebiotics such as FOS will only make the condition worse. Dr. Myhill, on the other hand, recommends supplementation for FOS to help replenish friendly flora.

**PROTOCOL.** The normal dose is ¼ to 1 teaspoon of powder, taken 2 -3 times daily, in divided doses, with or between meals. FOS is sweet, so it can be used in place of sugar.

**PROS AND CONS.** There is not much patient feedback on FOS. In small amounts it does not cause side effects. If too much is taken, it can cause gas. Because FOS provides a substrate for all bacteria, it should not be taken in the presence of intestinal bacterial infections (such as *C diff* or SIBO).

**AVAILABILITY AND COST.** FOS is available at health food stores and from online distributors. It can be purchased in capsules, tablets, or in a powder. Most health care practitioners recommend the powder, as it can be more easily titrated. PureFormulas.com markets a 100-gram container of FOS made by Pure Encapsulations for about \$14. (At 1 teaspoon a day, a 100-gram container will last a month.) There are many probiotic/FOS combinations on the market.

## GABA

**DESCRIPTION.** GABA (gamma aminobutyric acid) is the chief neuroinhibitory neurotransmitter in mammals. While GABA is commonly referred to as an amino acid, it is not incorporated into proteins.

**BACKGROUND.** Although GABA was first synthesized in the 19<sup>th</sup> century, it wasn't until 1950 that it was first discovered to be a central component of the nervous system of mammals. GABA is synthesized in the brain from glutamate, a neuroexcitatory neurotransmitter, through the enzyme L-glutamic acid decarboxylase in conjunction with the active form of vitamin B6. GABA's main function in the brain is to balance neuroexcitatory neurotransmitters by preventing nerves from excessive firing. There are many pharmaceuticals that act on GABA receptors, including anti-anxiety medications, anti-seizure medications, and pain medications. Valerian, skullcap, kava and L-theanine are supplements that act on GABA receptors.

**USES IN CFS/ME.** GABA has not been widely investigated in CFS/ME patients. Kowalski et al proposed that decreased activity of the enzymes which produce GABA may be the cause of several disorders, including CFS/ME. However, Murrough et al did not find any significant decrease in GABA itself among CFS/ME patients. In contradiction to Murrough's findings, McGregor et al found decreased beta-alanine (a GABA analogue) in CFS/ME patients, correlating with symptoms. However, Theodorsson et al found that while there was abnormal excretion of beta-alanine in CFS/ME patients, it did not correlate with symptoms. Notwithstanding this collection of contradictory evidence, it has long been proposed that people with CFS/ME suffer from neuroexcitatory states corresponding to an upregulated immune system.

Some CFS/ME doctors recommend GABA for their patients who experience anxiety and/or insomnia. Because GABA does not easily cross the blood-brain barrier, most physicians prefer to use pharmaceutical analogues such as Neurontin.

**PROTOCOL.** Dr. Rosenbaum recommends 500-1500 mg of GABA to his patients with insomnia.

**PROS AND CONS.** Given its inability to cross the blood-brain barrier, there is some doubt as to whether taking GABA supplements has any effect at all on the nervous system. But putting scientific skepticism aside, some patients report that it makes them jittery the day after using it for insomnia, which means it has some ability to affect the brain.

**AVAILABILITY AND COST.** GABA is sold in health food stores and from online suppliers. It is relatively inexpensive, and is available in pill, sublingual and

powder form. The sublingual form is supposed to provide the greatest calming effect.

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## GALANTAMINE

**DESCRIPTION.** Galantamine is a selective acetylcholinesterase inhibitor.

**BACKGROUND.** Galantamine has been used for decades in Eastern Europe for various central nervous system disorders, including post-polio paralysis and myasthenia gravis. It was originally derived from the *Galanthus Caucasicus* (Caucasian snowdrop), whose nodding white blooms are among the first to appear in the spring. Recently, a synthetic compound, galantamine hydrobromide (brand name: Razadyne), was approved by the FDA as a treatment for Alzheimer's disease. Because galantamine increases acetylcholine, it has also been used to block the effects of nerve gas and organophosphate pesticides, which operate by blocking acetylcholine.

Chemically, galantamine reduces the action of acetylcholinesterase (AChE), the enzyme that breaks down acetylcholine. Galantamine also modulates nicotinic cholinergic receptors, which acts to increase the release of acetylcholine.

**USES IN CFS/ME.** The first study to test galantamine as a treatment for CFS/ME was conducted in 1996 by a team composed of Dr. Ernir Snorrason, Dr. Arni Geirsson and Dr. Kari Stefansson. Their hypothesis was that a dysfunction of the cholinergic system lay at the heart of CFS/ME. The researchers tested their hypothesis by administering galantamine hydrobromide to 39 CFS/ME patients.

The results were impressive; 43% reported an 50% improvement in fatigue, pain and sleep. The authors noted that the improvement was stable, and that none of the patients who had reported 50% improvement relapsed after the cessation of the trial. Most dramatic was the improvement in sleep. More than 60% of the patients who finished the study reported a 70% improvement of sleep disturbances.

Given the striking results of this study, it is puzzling that there was so little follow-up. In 2009 Turan et al investigated the effects of galantamine on stress hormones in a group of CFS/ME patients. The study found that DHEAS/cortisol ratios normalized with galantamine treatment. But, while the findings confirmed a cholinergic deficit in CFS/ME, there have been no further treatment studies.

**PROTOCOL.** There is no protocol for galantamine. The Snorasson group used several different doses, but even at the lowest dose (5 mg) several patients developed severe nausea. High doses caused hallucinations, sweating, diarrhea, vomiting and confusion. Even though the side effects passed, Snorasson's group recommended starting with very low doses and close monitoring by a physician. They also recommended taking galantamine several hours before bed so as to reduce the risk of nightmares. Galantamine should be taken with choline.

**AVAILABILITY AND COST.** Galantamine is in the unusual class of medications that are both prescription drugs and supplements. (Even more confusing, nobody seems to know if there is a difference between the two.)

Galanta Mind, a blend of 4 mg galantamine hydrobromide, choline and B6 made by Life Enhancement, is available from such diverse sources as amazon.com, iHerb, and Sears. A 90-capsule bottle costs between \$40 and \$57, depending on the supplier. The manufacturer cautions that galantamine is for adults only. Instructions on the bottle read: "Start with one capsule each morning with breakfast for the first week. Add a second capsule with lunch, starting the second week. If desired, add another capsule to the breakfast serving the third week. Then, if desired, add another capsule to the lunch serving the fourth week, for a total of four capsules per day. If sensitivity occurs, reduce the amount used. If sensitivity continues, stop taking this supplement."

#### FURTHER READING

"If Only Galantamine Could Talk." *Great summary of galantamine's fascinating history as well as its medicinal properties:* [http://www.life-enhancement.com/article\\_template.asp?ID=973](http://www.life-enhancement.com/article_template.asp?ID=973)

"Can Galantamine Help Chronic Fatigue?" *Article on acetylcholine deficiency in CFS/ME patients.* [http://www.life-enhancement.com/article\\_template.asp?id=2224](http://www.life-enhancement.com/article_template.asp?id=2224)

*Ray Sahelian discusses galantamine:*

<http://www.raysahelian.com/galantamine.html>

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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2796068/>

## GLUCOSAMINE SULFATE

**DESCRIPTION.** Glucosamine sulfate is a mucopolysaccharide made up of the sugar glucose and the amino acid glutamine. It is the synthetic form of glucosamine, a naturally occurring amino acid compound found in the joints.

**BACKGROUND.** Glucosamine sulfate has been used for many years in Europe, Asia, and the Philippines to treat osteoarthritis. It appears to stimulate the synthesis of connective tissue and cartilage by aiding in the production of glucosaminoglycans and proteoglycans, the key building blocks of cartilage. Because glucosamine is also one of the main components of the synovial fluids that cushion joints and surrounding tissues, it has been used to treat degenerative joint diseases. It also may have anti-inflammatory properties, thereby lessening the need for anti-inflammatory pain medications.

**USES IN CFS/ME.** It is difficult to determine how useful glucosamine may be for people with CFS/ME. Its mode of action indicates that, in theory, it may be of benefit to patients with joint pain, fibromyalgia, or interstitial cystitis.

**PROTOCOL.** Dr. Jason Theodasakis, author of *The Arthritis Cure*, suggests taking glucosamine sulfate with chondroitin, another mucopolysaccharide, for maximum benefits. His daily dosage recommendations are based on patient weight:

- Less than 120 pounds: 1000 mg glucosamine sulfate plus 800 mg chondroitin
- 120 to 200 pounds: 1500 mg glucosamine sulfate plus 1200 mg chondroitin
- 200 pounds or more: 2000 mg glucosamine sulfate plus 1600 mg chondroitin

Other health care providers believe glucosamine sulfate is effective alone, although some recommend the addition of bromelain, an enzyme derived from pineapple, to help maximize its effects. Standard adult dosage as indicated by the manufacturer is one or two tablets three times a day. Health effects should be noticed within six to eight weeks. If no benefits are apparent by then, glucosamine sulfate should be discontinued.

**PROS AND CONS.** Glucosamine sulfate is generally considered safe and is well tolerated by most patients. However, some may be allergic to its source (usually crustacean shells). Patients taking blood thinners should consult with their physician before taking glucosamine sulfate because many of the mucopolysaccharides inhibit platelet formation.

**AVAILABILITY AND COST.** Glucosamine sulfate is available from health food stores and online distributors. A bottle of 120-tablets or capsules usually costs between \$12 and \$15. Glucosamine sulfate is also available in liquid form.

**FURTHER READING**

*Results of a comprehensive multi-center investigation of glucosamine chondroitin.*  
<http://nccam.nih.gov/research/results/gait/qa.htm>

## GLUTATHIONE

**DESCRIPTION.** Glutathione is a tripeptide composed of glycine, cysteine, and glutamic acid.

**BACKGROUND.** Glutathione is found in high concentrations in every tissue in the body. It is one of the three most powerful antioxidants and detoxification agents in the body, protecting tissues against damage from oxygen radicals such as hydrogen peroxide and superoxide. It also helps reduce injury caused by radiation, chemotherapy, heavy metals (mercury), and drugs (including cigarettes and alcohol). NAC (N-acetyl-L-cysteine), a precursor to glutathione, is an antidote to acetaminophen poisoning and helps deter the toxic effects of naphthalene, benzene, and anthracene. Low glutathione levels are associated with cataracts and muscle wasting diseases.

**USES IN CFS/ME.** A relationship between glutathione, muscle fatigue, low natural killer (NK) cell activity and CFS/ME was first proposed in 1997 by Droge and Holm, two scientists researching HIV in Heidelberg, Germany. Notably, Droge and Holm suggested cysteine supplementation as an adjunct to antiviral therapies to correct low glutathione. Expanding on their idea in 1999, two researchers at McGill University proposed that competition for glutathione between the immune system and skeletal muscles might be the cause of fatigue, muscle weakness, and pain in CFS/ME patients. More recently, Shungu et al found that glutathione levels were low in the cerebrospinal fluid of CFS/ME patients.

Dr. Patricia Salvato of Houston, Texas, reported in the *CFIDS Chronicle* (Jan/Feb 1998) that she had treated 276 CFS/ME patients with glutathione injections. Eighty-two percent of her patients experienced improvement in fatigue, 71 % reported improvement in memory and concentration, and 62% reported reduced pain. Natural killer cell function was also measured, with 187 people showing a two-fold increase. Some patients received the therapy for as long as 16 months. The only adverse side effects observed were palpitations in a few patients and a slight rash or itching around the site of injection.

Dr. Paul Cheney, who at one time stated that glutathione deficiency was universal among CFS/ME patients, has noted a striking improvement in his patients' symptoms, especially headache, within days of initiating glutathione treatment.

**PROTOCOL.** Because oral glutathione is poorly absorbed in the gut, Dr. Cheney recommends reduced glutathione (*CFIDS Chronicle*, Spring 1995). Initial doses are high, from 150 to 425 mg three times a day. After a short time, doses can be reduced to 75 to 150 mg three times a day and maintained at those levels. Glutathione can also be administered IV.

**AVAILABILITY AND COST.** There is no way of knowing how much, in any, glutathione is absorbed by mouth, so injectable forms are preferred. (These require a doctor.) Alternative forms of glutathione (suppositories and troches) may have

greater absorption rates. A pack of 30 Zetpil glutathione suppositories are available through Forrest Health for \$99. Glutathione troches are available through compounding pharmacies.

In part because glutathione is so difficult to administer effectively, a synthetic glutathione peroxidase mimic, ebselen, has been developed. Initial studies demonstrated that ebselen was effective in protecting against chemotherapy-induced hearing loss, renal injury and in recovery from stroke (if administered within 24 hours). Ebselen protects against manganese toxicity, inhibits *Candida* overgrowth, and performs a host of antioxidant activities. Ebselen has been licensed in the U.K. for treatment of ischemic stroke. It has not yet been approved by the FDA.

#### FURTHER READING

*Rich Van Konynenburg's excellent review of glutathione, including protocols, dosages, suppliers.*

<http://aboutmecfs.org.violet.arvix.com/Trt/TrtGlutathioneBuild.aspx>

*Another excellent discussion by Rich Van Konynenburg proposing glutathione depletion as a cause of CFS/ME:* <http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=1287095>

*A list of articles about glutathione written by Rich Van Konynenburg.*

<http://forums.phoenixrising.me/showthread.php?12927-Documents-by-Rich-Van-Konynenburg>

*An interesting, if somewhat convoluted, discussion of glutathione and its role in CFS/ME.*

<http://user.xmission.com/~total/temple/Soapbox/Articles/glutathione.html>

*Ray Sahelian discusses glutathione's role in various disease processes. Some good research citations.* <http://www.raysahelian.com/glutathione.html>

*Glutathione suppositories:* <http://www.forresthealth.com/reduced-glutathione-suppositories-30-count.html>

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## HERBS

Aloe vera, Astragalus, Chamomile, Echinacea, Garlic, Ginger, Gingko, Ginseng, Goldenseal, Gotu kola, Kava, Licorice, Lomatium, Milk Thistle, St. John's Wort, Uva ursi, Valerian

**DESCRIPTION.** Medicinal herbs are plants taken orally as teas or tinctures, or applied topically as poultices in order to heal the body.

**BACKGROUND.** Plants have always been used as remedies, which makes herbal treatment the earliest form of medicine. (The earliest human graves contain remnants of medicinal flowers.) Even animals eat certain plants when they become ill. Throughout the ages, people have used herbal remedies for an assortment of problems and, until the nineteenth century, herbs were the treatment of choice for most common ailments. Herbs have such a long history they are regarded as folk remedies. The contemporary medical world, as a consequence, has largely excluded them from scientific investigations, with the exception of the Chinese, who take herbs quite seriously. The government of China has funded a considerable amount research to study the chemical components, action, and efficacy of a number of herbs.

**USES IN CFS/ME.** A large number of patients with CFS/ME symptoms use herbs regularly, either as herbal substitutes for pharmaceuticals or as adjuncts to other therapies. Although many find that a particular herb is helpful for a specific symptom, most report that herbs have limited value in treating CFS/ME over the long term. It should be noted, however, that patients who have tried Chinese herbs (usually on the recommendation of an acupuncturist) generally report a higher rate of success.

**PROTOCOL.** Although herbalists recommend blending herbs for maximum effect, patients with CFS/ME frequently have had poor responses to multiple-herb blends (with the notable exception of Chinese herbs). For CFS/ME symptoms, herbs are best taken singly in teas or tinctures. Teas are prepared according to the part of the plant used. One teaspoon of herb leaves is steeped in two cups of boiling water for 15 or 20 minutes or ½ teaspoon of herb root or bark is boiled in two cups of

water. One to two cups of tea per day can be taken for up to two weeks. After that, the herb loses its potency. Tinctures are usually purchased from health food stores. Because they are quite strong, tinctures are usually taken a few drops at a time in water. For chronic symptoms, teas are advised. Short-term problems (flu, toothache, etc.) are best treated with tinctures.

*Note: Most tinctures are prepared in an alcohol medium. People with CFS/ME are advised to "flash off" the alcohol by adding the tincture to scalding hot water.*

**PROS AND CONS.** Herbs are inexpensive, safe, and readily available. However, it is always best to purchase them from a health food or specialty store. Culinary herbs from the grocery store are usually treated with chemical preservatives, seldom organic, and have little medicinal worth. The advantage of herbs for many people with drug and chemical sensitivities is that they can produce the desired therapeutic effects without as many side effects. This is not to say that negative reactions are not possible. People with bladder problems (interstitial cystitis), gastrointestinal symptoms, or migraine headaches may find that many herbs produce the same side effects as pharmaceuticals.

In general, patients with CFS/ME should avoid herbs classified as stimulants (ephedra, lomatium, and ginseng), because these can overtax the adrenal glands. Ephedra (*ma huang*), used to treat bronchial infections, is a powerful stimulant and can cause high blood pressure, palpitations, and even stroke. Ginseng and lomatium, although not as strong as ephedra, can produce similar reactions in the severely ill. Echinacea, because it is an immune system stimulant, might best be avoided by those with upregulated immune systems.

Some herbs such as goldenseal and St. John's Wort must be used with caution. St. John's Wort acts like a monoamine oxidase inhibitor (MAOI) and must be treated with the same care as the drug. (The newsletter of the Center for Specialized Immunology reported a serious reaction in a patient who took St. John's Wort concomitantly with an antidepressant.)

Chapparal and comfrey have caused liver problems in some people who took too high a dose. However, there are many other herbs that can provide temporary, safe relief from numerous CFS/ME symptoms. Those interested in pursuing herbal remedies should read about herbs before embarking on an herbal therapy program or should consult with an herbalist.

#### FURTHER READING

*Dr. Teitelbaum's herb recommendations for CFS/ME patients.*

<http://www.immunesupport.com/news/99spr012.htm>

*Nicely organized site about herbs. Herbs are listed alphabetically for easy access.*

<http://www.herbwisdom.com/>

#### BOOK

Castleman, Michael. *The Healing Herbs*. Emmaus, Pa.: Rodale Press, 1991

*This is a well-organized introduction to herbs and their uses.*

## ALOE VERA

Aloe vera is a succulent plant originating in Africa. Because it exudes a mucousy substance when cut, it has a long history as a topical treatment for minor burns. More recently, aloe juice has been promoted as an immune enhancer and as a treatment for cancer. Though research has not been able to substantiate these claims, aloe vera juice is recommended for people with a variety of immune system ailments.

While some people with CFS/ME have taken aloe and been pleased with the results, there are more negative than positive reviews. Although it is touted as a cure for IBS, aloe vera can cause diarrhea and intestinal irritation even in very small amounts.

## FURTHER READING

*General information about aloe vera:* <http://www.herbwisdom.com/herb-aloe-vera.html>

*CFS/ME patient reviews of aloe vera:* <http://www.revolutionhealth.com/drugs-treatments/rating/aloe-vera-aloe-barbadensis-for-chronic-fatigue-syndrome-cfs-cfids-me>

## ASTRAGALUS

Astragalus (*Astragalus membranaceus*) root has been popularized as an immune system modulator. It reputedly enhances immune system function when it is deficient and down regulates it when overactive. It is also thought to increase energy, stamina, and well-being and supports adrenal gland function. Some use it as a digestive aid. The effects of astragalus are not dramatic in most people, but some CFS/ME patients have noted increased energy after taking tincture of astragalus.

Recent research has shown that astragalus has measurable medicinal properties. A 2011 study by Cheng et al showed that astragalus may serve as a natural cholesterol-lowering agent. Astragalus has also been shown to enhance both humoral and cellular immune response (Th1 and Th2).

## FURTHER READING

*General information about astragalus*

<http://www.immunesupport.com/news/98spr007.htm>

*More general information about astragalus:* <http://www.herbwisdom.com/herb-astragalus.html>

## RESEARCH

Cheng Y, Tang K, Wu S, Liu L, Qiang C, Lin X, Liu B. "Astragalus Polysaccharides Lowers Plasma Cholesterol through Mechanisms Distinct from Statins." *PLoS ONE*. 2011;6(11):e27437. <http://www.ncbi.nlm.nih.gov/pubmed/22110652> (Abstract)

Du X, Chen X, Zhao B, Lv Y, Zhang H, Liu H, Chen Z, Chen Y, Zeng X. "Astragalus polysaccharides enhance the humoral and cellular immune responses of hepatitis B surface antigen vaccination through inhibiting the expression of transforming growth factor  $\beta$  and the frequency of regulatory T cells." *FEMS Immunol Med Microbiol*. 2011 Nov;63(2):228-35  
<http://www.ncbi.nlm.nih.gov/pubmed/22077226>

## CHAMOMILE

Chamomile (*Matricaria chamomila* [German chamomile]; *Anthemis nobilis* [Roman chamomile]) is a member of the daisy family. It is currently one of the most popular herbs in the United States and is widely used as an herb tea, in shampoos and soaps, and in skin-care products. Chamomile has been known as a sedative and antifever medicine since ancient times and was used by Greek and Roman physicians to treat a variety of ailments.

Contemporary herbalists recommend chamomile to treat digestive problems and ulcers, to prevent the spread of infections, and to reduce inflammation. Because chamomile is an antispasmodic, it has also been used to lessen the severity of menstrual cramps. Perhaps the most interesting effect of this herb is its ability to stimulate the immune system. British researchers discovered that chamomile increases macrophages and B lymphocytes.

**USES IN CFS/ME.** Patients with CFS/ME have chamomile tea before bedtime to help with insomnia and to alleviate gastrointestinal symptoms. Simply inhaling the steam is enough to produce a calming effect. (The sedative effects of the tea may be due to *apigenin*, a flavonoid that binds to benzodiazepine receptors.) In general, the herb is well tolerated. Chamomile tea should not be boiled because boiling makes the tea bitter. Those allergic to ragweed should avoid this herb.

## FURTHER READING

*General information about chamomile:* <http://www.herbwisdom.com/herb-chamomile.html>

## ECHINACEA

The roots of the purple coneflower (*Echinacea angustifolia*, *E. purpurea*) were used by Plains Indians as a cure for all kinds of infections. Although it has been relied on as a topical wound healer since Colonial times, echinacea's antibiotic properties have largely been unexplored until recently. Research conducted in Germany in the 1950s through the 1980s revealed that echinacea has broad antibiotic properties, much like penicillin, due to a substance (echinacein) that counteracts cell-penetrating enzymes. In this manner, echinacea works to strengthen individual cell defenses.

Echinacea also acts as an immune system stimulant. Echinacea boosts the macrophage's ability to destroy germs. It possesses antifungal as well as antibacterial properties. As an antiviral agent, echinacea has been used effectively to treat influenza and the common cold as well as to check herpesvirus infections.

USES IN CFS/ME. People with CFS/ME often use echinacea at the first sign of a cold or flu to help lessen the severity of the illness, and some even report lessening of all symptoms after using this herb. Echinacea tinctures are more effective than pills or capsules. An alcohol-free tincture should be used, however, because alcohol dramatically lessens the potency of this herb. Dry echinacea root can be purchased in health food stores and boiled to make a tea.

PROTOCOL. Dr. Teitelbaum recommends 300 to 325 mg taken three times a day. He recommends that patients take a break from echinacea for one week each month, or it will stop working. He suggests echinacea may also improve adrenal function. Other practitioners recommend starting at lower doses (200 mg). Alcohol-free tinctures can be taken at 15 to 20 drops a day.

Dr. Cheney is not a fan of echinacea. He believes that the immune-activating properties of the herb may pose problems for CFS/ME patients with upregulated immune systems.

#### FURTHER READING

*General information about echinacea:* <http://www.herbwisdom.com/herb-echinacea.html>

*CFS/ME patient reviews of echinacea:* <http://www.revolutionhealth.com/drugs-treatments/rating/echinacea-echinacea-spp-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### RESEARCH

See DM, Broumand N, Sahl L, Tilles JG. "In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients." *Immunopharmacology* 1997 Jan;35(3):229-35.

<http://www.ncbi.nlm.nih.gov/pubmed/9043936> (Abstract)

#### GARLIC

Garlic (*Allium sativum*) has a long history as a medicinal plant. The earliest medicinal description of garlic dates from 3000 BC. Garlic was even found in the tomb of King Tut. It has been used to treat headache, insect bites, menstrual disorders, intestinal worms, tumors, and heart disease. Garlic is a powerful antibiotic and antiprotozoan agent. It kills intestinal parasites, destroys the bacterium that causes tuberculosis, and can be used against various fungi, including *Candida albicans*. Daily ingestion of as little as half a clove of garlic can lower cholesterol. Garlic also lowers blood pressure, which means it may have a negative effect on people with hypotension. Some people with CFS/ME tend to be sensitive to garlic in both its raw and cooked forms. Enteric, deodorized garlic pills can reduce intestinal upset. A commonly recommended brand of deodorized garlic in capsules, Kyolic, is widely available from health food stores.

#### FURTHER READING



*General information about garlic:* <http://www.herbwisdom.com/herb-garlic.html>

*CFS/ME patient reviews of garlic:* <http://www.revolutionhealth.com/drugs-treatments/rating/garlic-allium-sativum-for-chronic-fatigue-syndrome-cfs-cfids-me>

## GINGER

Ginger (*Zingiber officinale*) was used by the ancient Greeks as a digestive aid. It is still used as an antidote for motion sickness, nausea, and numerous digestive disturbances. It soothes smooth muscles, making it useful for alleviating menstrual cramps, as well. Ginger can be taken in capsule form or boiled to make tea. Ginger root is available from grocery or health food stores. Ginger powder, however, as found in the spice section of a grocery store, should not be used as a medication because it is usually irradiated. Excessive amounts may cause mild headache. Some people with CFS/ME find ginger difficult to tolerate.

**USES IN CFS/ME.** Dr. Teitelbaum is a ginger enthusiast. He recommends it for relief of muscle and joint pain, nausea, migraines, motion sickness, and for raising blood pressure (for those with hypotension). The most common use among people with CFS/ME is for nausea, a symptom which can be utterly debilitating if unchecked.

**PROTOCOL.** Ginger is a food, so it can be taken on an as-needed basis. It can be purchased as a whole root, grated and added to food, or boiled to make a tea. For those with less tolerance for ginger's strong flavor, candied ginger may be eaten (or simply held under the tongue) as an alternative. Dry encapsulations are also available, although these tend to be less effective.

**PROS AND CONS.** A small amount of ginger goes a long way. CFS/ME patients find it especially effective for nausea and dizziness. It has an almost immediate effect. Dry ginger capsules may cause heartburn.

**AVAILABILITY AND COST.** Fresh ginger and candied ginger are available in health food stores, supermarkets and Asian specialty markets. Dried, encapsulated ginger can be purchased at health food stores and from online distributors. A 180-capsule bottle of Nature's Way dry ginger costs about \$5 from Vitacost.

## FURTHER READING

*CFS/ME patient reviews of ginger:* <http://www.revolutionhealth.com/drugs-treatments/rating/ginger-zingiber-officinale-for-chronic-fatigue-syndrome-cfs-cfids-me>

## GINGKO

Ginkgo (*Ginkgo biloba*) is the oldest species of tree on the planet. The Chinese have used its leaves for over 5000 years as an elixir to promote longevity. Studies have shown that ginkgo, by increasing blood flow to the brain, helps reduce the risk of stroke. It can also dramatically improve memory and reaction time. The neuroprotective effects of ginkgo are well documented. There is some evidence that

gingko modulates serotonin and dopamine, and may have antidepressant-like effects. Gingko also acts as a potent antioxidant, reducing oxidative stress by simultaneously scavenging peroxynitrite, nitric oxide and superoxide. In Europe, gingko is used as a conventional drug for treating short-term memory loss, headache, tinnitus, anxiety, vertigo, and depression.

**USES IN CFS/ME.** Alan Logan and Cathy Wong, in their comprehensive assessment of non-drug treatments for CFS/ME, state that because gingko has specific effects on cerebral blood flow, it may be useful for CFS symptoms related to hypoperfusion in the brain. Many CFS/ME doctors have recommended gingko to their patients, including Dr. Cheney and Dr. Teitelbaum.

**PROTOCOL.** For maximum effectiveness, gingko biloba should be taken as an extract (not a tea). Extracts are available in either pill or liquid form. In pill form, Dr. Teitelbaum recommends a 50:1 extract standardized to have 24% Glycosides (this will be indicated on the label). A 60-mg capsule can be taken once a day. The standard dose of liquid extract is 20 drops, up to three times a day. It may take up to six weeks to take effect.

**PROS.** For some people, gingko has been a “lifesaver,” allowing them to process information again. Many CFS/ME patients have reported that gingko helps cognitive function, memory, and “brain fog.” Some report a decrease in migraines and headache, as well as increased circulation to the legs.

**CONS.** Although gingko is usually well tolerated, some patients with CFS/ME have reported increased fatigue. Excessive doses can cause irritability, restlessness, nausea, and diarrhea. Gingko has mild blood thinning properties, which means it cannot be taken in conjunction with pharmaceutical blood thinners (e.g., Coumadin).

#### FURTHER READING

*General information about gingko:* <http://www.herbwisdom.com/herb-ginkgo-biloba.html>

*More general information about gingko:*

[http://www.altnature.com/gallery/Ginkgo\\_Biloba.htm](http://www.altnature.com/gallery/Ginkgo_Biloba.htm)

*CFS/ME patient reviews of gingko:* <http://www.revolutionhealth.com/drugs-treatments/rating/ginkgo-ginkgo-biloba-for-chronic-fatigue-syndrome-cfs-cfids-me>

Logan, Alan C., and Cathy Wong. “Chronic Fatigue Syndrome: Oxidative Stress and Dietary Modifications.” <http://www.thorne.com/altmedrev/fulltext/6/5/450.pdf>

#### RESEARCH

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<http://www.ncbi.nlm.nih.gov/pubmed/10886329> (Abstract)

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Schoenberger NE. “Ginkgo biloba extract: mechanisms and clinical indications.”

*Arch Phys Med Rehabil.* 2000 May;81(5):668-78.

<http://www.ncbi.nlm.nih.gov/pubmed/10807109> (Abstract)

Ihl R., Bachinskaya N., Tribanek M., Hoerr R. and Napryeyenko O. for the GOTADAY Study Group. "Efficacy and Tolerability of a Once Daily Formulation of Ginkgo biloba Extract EGb 761® in Alzheimer's disease and Vascular Dementia: Results from a Randomised Controlled Trial." *Pharmacopsychiatry.* 2011 Nov 15. <http://www.ncbi.nlm.nih.gov/pubmed/22086747> (Abstract)

Rojas P, Serrano-García N, Medina-Campos ON, Pedraza-Chaverri J, Ogren SO, Rojas C. "Antidepressant-like effect of a Ginkgo biloba extract (EGb761) in the mouse forced swimming test: role of oxidative stress." *Neurochem Int.* 2011 Oct;59(5):628-36. <http://www.ncbi.nlm.nih.gov/pubmed/21672588> (Abstract)

Woelk H, Arnoldt KH, Kieser M, Hoerr R. "Ginkgo biloba special extract EGb 761 in generalized anxiety disorder and adjustment disorder with anxious mood: a randomized, double-blind, placebo-controlled trial." *J Psychiatr Res.* 2007 Sep;41(6):472-80. <http://www.ncbi.nlm.nih.gov/pubmed/16808927> (Abstract)

## GINSENG

Ginseng (*Panax schinseng*; aka Chinese or Korean ginseng) is an ancient tonic and stimulant. It has been shown to possess anti-inflammatory, anti-diabetic, and antioxidant properties. Ginseng is frequently described as an "adaptogen," which means it can have normalizing metabolic effects, especially when homeostasis is disrupted. Although it possesses enormous therapeutic potential for common ailments, ginseng is usually not recommended to patients with severe CFS/ME. Ginseng stimulates the adrenal glands and can increase production of interferon. Because most patients with CFS/ME have excessive interferon production as well as endocrine abnormalities, *panax ginseng* may increase symptoms.

Siberian ginseng (*Eleutherococcus senticosus*), although it belongs to a different genus, has similar medicinal qualities to *panax ginseng*. (Though interestingly, Siberian ginseng appears to have the opposite effect of *reducing* inflammatory responses.) Siberian ginseng, marketed as Eleutherococcus Senticosus, is less expensive than *panax ginseng* and is often found in herbal ginseng formulations. (Check the label if you are looking for pure *panax ginseng*.)

Ginseng should not be used with estrogens or corticosteroids because of possible additive effects. It may affect the blood glucose levels of patients with diabetes mellitus.

## RESEARCH

Gaffney BT, Hügel HM, Rich PA. "Panax ginseng and Eleutherococcus senticosus may exaggerate an already existing biphasic response to stress via inhibition of enzymes which limit the binding of stress hormones to their receptors." *Med Hypotheses.* 2001 May;56(5):567-72.

<http://www.ncbi.nlm.nih.gov/pubmed/11388770> (Abstract)

Jung CH, Jung H, Shin YC, Park JH, Jun CY, Kim HM, Yim HS, Shin MG, Bae HS, Kim SH, Ko SG. "Eleutherococcus senticosus extract attenuates LPS-induced

iNOS expression through the inhibition of Akt and JNK pathways in murine macrophage.” *J Ethnopharmacol.* 2007 Aug 15;113(1):183-7.

<http://www.ncbi.nlm.nih.gov/pubmed/17644291> (Abstract)

See DM, Broumand N, Sahl L, Tilles JG. “In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients.” *Immunopharmacology.* 1997 Jan;35(3):229-35.

<http://www.ncbi.nlm.nih.gov/pubmed/9043936> (Abstract)

## GOLDENSEAL

Goldenseal (*Hydrastis canadensis*) is a North American herb known best for its antibiotic properties. Berberine, a substance found in goldenseal, kills many of the bacteria that cause diarrhea, as well as the protozoa that cause amoebic dysentery and giardiasis. It has been used against cholera bacteria and as a treatment for throat, sinus, and topical bacterial infections. Research has shown that goldenseal is also effective against some viral infections. People with CFS/ME generally use goldenseal to treat sinusitis and canker sores. It should be used with caution, however. Excessive or lengthy (more than 10 days) treatment can lead to neurological disturbances and gastrointestinal upset. The safest way to take goldenseal is externally as a poultice or paste spread directly over the sinuses or other affected area. Goldenseal should not be used during pregnancy because it stimulates uterine contractions.

## RESEARCH

Cecil CE, Davis JM, Cech NB, Laster SM. “Inhibition of H1N1 influenza A virus growth and induction of inflammatory mediators by the isoquinoline alkaloid berberine and extracts of goldenseal (*Hydrastis canadensis*).” *Int Immunopharmacol.* 2011 Nov;11(11):1706-14.

<http://www.ncbi.nlm.nih.gov/pubmed/21683808> (Abstract)

## GOTU KOLA

Gotu kola (*Centella asiatica*; *Hydrocotyle asiatica*), also known as sheep rot, Indian pennywort, marsh penny, and water pennywort, was originally used in Sri Lanka as a promoter of longevity. It is a member of the Umbelliferae family, which also includes carrots, parsley, dill, and fennel. Despite the similarity in name, gotu kola is not related to the stimulant kola. In small amounts, gotu kola is taken as a tonic, and in larger amounts as a sedative. Gotu kola traditionally has been used in the treatment of leprosy, but it is also noted for its ability to promote blood circulation. Gotu kola has been used to increase memory and mental function by increasing circulation to the brain.

## FURTHER READING

Shinomol G K, Muralidhara, Bharath M M. “Exploring the Role of “Brahmi” (Bocopa monnieri and *Centella asiatica*) in Brain Function and Therapy.”

*Recent Pat Endocr Metab Immune Drug Discov* 2011 Jan;5 1:33-49.  
<http://www.ncbi.nlm.nih.gov/pubmed/22074576> (Abstract)

## KAVA

Kava, or kava-kava (*Piper methysticum*) is a plant native to the Pacific. Traditionally, it has been used in the South Pacific in drinks. The roots of the plants have a sedative effect, making it a popular treatment for anxiety.

There has been a considerable amount of controversy surrounding the medicinal use of kava in recent years. In 2001, researchers discovered an apparent link to kava and liver toxicity which led European, British and Canadian authorities to ban kava sales in 2002. However, further research indicated that the toxic compounds were located in the stem peelings and leaves, which are parts of the plant not traditionally consumed. (Only the roots are used in Pacific cultures.) A study published in 2003 by Whitton et al found that modern extraction methods, using acetone or ethanol, were responsible for kava toxicity.

Kava is used primarily as a sleep aid and as an anxiolytic. In 1997 Volz et al found that an extract of kava was just as efficacious as benzodiazepines or antidepressants in reducing anxiety, and with none of the side effects. There is also some evidence that kava may be useful in treating ADD, which might help reduce the need for stimulant medications in children.

**PROTOCOL.** The recommended dose of kava extract for insomnia is 70 – 200 mg taken an hour before bedtime. For daytime anxiety, 70 mg may be taken one to three times a day. Kava is not sedating when taken at moderate doses. To avoid stomach upset, it's best to take kava with a little food.

## RESEARCH

Sarris J, Kean J, Schweitzer I, Lake J. “Complementary medicines (herbal and nutritional products) in the treatment of Attention Deficit Hyperactivity Disorder (ADHD): a systematic review of the evidence.” *Complement Ther Med*. 2011 Aug;19(4):216-27. <http://www.ncbi.nlm.nih.gov/pubmed/21827936> (Abstract)

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<http://www.ncbi.nlm.nih.gov/pubmed/9065962> (Abstract)

Whitton, Peter A., Andrew Lau, Alicia Salisbur, Julie Whitehouse, Christine S. Evans. “Kava lactones and the kava-kava controversy.” *Phytochemistry*, Volume 64, Issue 3, October 2003, Pages 673-679.  
<http://www.sciencedirect.com/science/article/pii/S0031942203003819>

## LICORICE

Licorice (*Glycyrrhiza glabra*) has long been known as one of nature's most potent healing herbs. It is a popular ingredient in many Chinese herbal remedies and has been used to treat cough, sore throat, ulcers, arthritis, herpes infections, and hepatitis. When combined with other herbs, licorice can increase their effectiveness.

**USES IN CFS/ME.** In CFS/ME, licorice is reputed to alleviate symptoms associated with adrenal insufficiency (intolerance to heat, cold, noise, and other stimuli, low blood pressure, faintness). Because the action of licorice's main active chemical, glycyrrhetic acid (GA), resembles that of the adrenal hormone aldosterone, licorice helps the body retain salt (and water) and ultimately may help raise blood volume and pressure. Because low blood pressure is a problem for many patients with CFS/ME, licorice could prove beneficial, especially for those who are sensitive to the drugs normally recommended to correct low blood pressure. In addition, licorice raises serum cortisol levels (often low in CFS/ME patients) and stimulates natural killer cell activity.

**PROTOCOL.** Dr. Riccardo Baschetti has used licorice for patients with low or low-normal plasma levels of cortisol. He claimed that dramatic improvement in CFS/ME symptoms could be seen after taking licorice for just three days (*New Zealand Medical Journal*, 1995). Baschetti recommends 2.5 gm of licorice root a day, in extract or capsules dissolved in milk. (Milk enhances the aldosterone-like effects of the licorice.)

Dr. Peter D'Adamo, a naturopath who also uses licorice to treat symptoms of CFS/ME, suggests taking ¼ teaspoon (2 gm) of solid licorice extract one to three times a day. He recommends his patients take 500 mg of the amino acid methionine and 99 mg of potassium supplement three times a day along with the licorice to counteract any potassium and sodium imbalances.

A number of physicians have recommended licorice for NMH (neurally mediated hypotension). NMH is a common problem for patients with CFS/ME, affecting up to 90% of the CFS/ME population. Many people with CFS/ME are sensitive to Florinef, the medication normally prescribed for NMH. Dr. Calkins, a member of the team at Johns Hopkins Medical Center that performed the initial investigations on NMH in adolescents, stated that "medicinal licorice is a good alternative for those sensitive to Florinef."

Dr. Cheney also endorses licorice for treating NMH. Dr. Cheney has found that Florinef forces potassium depletion, which further depresses the HPA (hypothalamus-pituitary-adrenal) axis in CFS/ME patients. Licorice can accomplish the same results as Florinef, without the side effects. He recommends two licorice root tablets with glycerizin two times a day. Dr. Cheney adds the caution, "Blood pressure must be monitored when taking licorice root!"

For optimal effect, licorice should be taken in the morning. (Cortisol levels in the body reach their peak at about 8AM.) It is important to note that licorice candies produced in the U.S. do not use licorice, but anise, as a flavoring. Doctors caution their patients to use pure licorice, not DGL. DGL (de-glycyrrhizinated

licorice ), a form of licorice in which glycyrrhizin has been removed. Glycyrrhizin is removed in DGL to prevent hypertension, however, it is the ingredient in licorice that treats NMH.

**PROS AND CONS.** Patients who have taken licorice report increased energy levels and improvement in symptoms of hypoglycemia, though some have noticed that its effectiveness wanes after a few months. Because of its steroid-like qualities, and due to its ability to help retain sodium, it is important to monitor licorice intake. Too much licorice, especially without potassium supplementation, can cause serious side effects. If high blood pressure, headaches, lethargy, and water retention develop, the dosage should be decreased immediately. Patients taking drugs that could interact with licorice, such as heart medications, MAOIs, or diuretics, should consult with their physician before embarking on a licorice protocol.

**AVAILABILITY AND COST.** Solid licorice extract is marketed by Allergy Research Group. A 4-oz container (½ tsp = 3 grams) sells for \$24 through PureFormulas.com (online). Douglas Labs sells a 60-capsule bottle of pure licorice (500 mg) for \$16 (also through PureFormulas.com).

#### FURTHER READING

*Good article on licorice:* <http://drholly.typepad.com/licorice/>

*Excellent summary of licorice as a treatment for CFS/ME:*

<http://www.encognitive.com/node/15023>

*General information on licorice root:* <http://www.herbwisdom.com/herb-licorice-root.html>

*Ray Sahelian on licorice:* <http://www.raysahelian.com/licorice.html>

Baschetti, R. "Chronic fatigue syndrome and liquorice" *N Z Med J.* 1995 Apr 26;108(998):156-7.

#### LOMATIUM

Lomatium is a North American herb reputed to have antiviral properties. It has been used to treat influenza, colds, and diseases such as measles. A number of patients who have tried lomatia extract have felt overstimulated. Some have experienced malaise, insomnia, and jitteriness after as little as one drop. Reports from the late 1980s stated that some CFS/ME patients have developed severe allergic reactions while taking this herb.

#### FURTHER READING

*Literally everything you need to know about lomatium:*

<http://www.naturalpedia.com/Lomatium.html>

#### MILK THISTLE/SILYMARIN

Milk thistle (*Silybum marianum*), also referred to as silymarin, appears to have a remarkable effect on the liver. There is a great deal of research showing that active ingredient in silymarin, silybin, stimulates liver cells to regenerate and is effective in treating jaundice, hepatitis C, and cirrhosis. Silymarin increases the

amount of liver glutathione, a tripeptide that activates liver enzymes. As a consequence, milk thistle helps protect the liver from toxins, including poisonous mushrooms, and various petrochemicals. In addition, silymarin has powerful antioxidant, anti-inflammatory, anti-cancer and cardioprotective properties. It also helps synthesize superoxide dismutase (SOD), an enzyme that increases mitochondrial function and can prevent oxidative stress both within and outside cell walls.

**USES IN CFS/ME.** Dr. Cheney has proposed that many people with CFS/ME have reduced liver function, and even subclinical hepatitis. For CFS/ME patients with mild liver dysfunction, milk thistle may provide some relief.

**PROTOCOL.** Milk thistle is poorly absorbed, so 150-300 mg a day is needed for basic liver support. Dr. Cheney recommends 150 mg silymarin/milk thistle taken twice a day. Siliphos, a more bioavailable form of silymarin, may be taken at lower doses. Some studies show that a silymarin-phosphatidylcholine complex may be absorbed more easily than regular standardized milk thistle. Phosphatidylcholine, a key element in cell membranes, helps silymarin attach easily to cell membranes, which may help in keeping toxins from getting inside liver cells.

**PROS AND CONS.** While milk thistle is generally well tolerated, common side effects are itching, indigestion and headache. Some patients have reported nausea and poor appetite on higher doses. People with allergies to plants in the aster family: daisies, artichokes, ragweed, chrysanthemums, marigolds, chamomile, yarrow, kiwi, and common thistle may also be allergic to milk thistle.

**AVAILABILITY AND COST.** Milk thistle, in liquid or capsule form, can be purchased at any health food store and through online vitamin suppliers. Standardized milk thistle extracts yielding 80% of the active ingredient in silymarin, silybin, are recommended. Jarrow, Metabolic Maintenance, Pure Encapsulations, and Douglas Labs all market standardized milk thistle. Prices range from \$13 to \$30 for a 100-capsule bottle. Siliphos is available from Vitacost and PureFormulas.com for roughly the same price.

## FURTHER READING

*Detailed information on silymarin:*

[http://www.salamresearch.com/html/milk\\_thistle\\_product.html](http://www.salamresearch.com/html/milk_thistle_product.html)

*Ray Sahelian on milk thistle. Includes dosage, research and medical uses.*

<http://www.raysahelian.com/silymarin.html>

## RESEARCH

Chen IS, Chen YC, Chou CH, Chuang RF, Sheen LY, Chiu CH. "Hepatoprotection of silymarin against thioacetamide-induced chronic liver fibrosis." *J Sci Food Agric.* 2011 Nov 18. <http://www.ncbi.nlm.nih.gov/pubmed/22102319> (Abstract)

Kalantari H, Shahshahan Z, Hejazi SM, Ghafghazi T, Sebghatolahi V. "Effects of silybum marianum on patients with chronic hepatitis C." *J Res Med Sci.* 2011 Mar;16(3):287-90. <http://www.ncbi.nlm.nih.gov/pubmed/22091246> (Abstract)



Rašković, A.; Stilinović, N.; Kolarović, J.; Vasović, V.; Vukmirović, S.; Mikov, M.  
 “The protective effects of silymarin against doxorubicin-induced cardiotoxicity and hepatotoxicity in rats.” *Molecules*. 2011 Oct 12;16(10):8601-13.  
<http://www.mdpi.com/1420-3049/16/10/8601>

## ST. JOHN'S WORT

St. John's Wort (*Hypericum perforatum*), a plant with anti-inflammatory, antiseptic and mood lifting properties, has been documented as a remedy for roughly two thousand years. Currently, it is a well-established treatment for depression. In Germany, St. John's Wort is widely prescribed for children and teens with depression as a safe alternative to antidepressants. The Cochrane Collaboration, an organization that reviews trials of health care treatments, found that in 29 studies with over 5,400 depressed patients St. John's Wort fared better than placebo.

Like most herbs, St. John's Wort has the potential to treat a variety of health problems. In 2011 Mozaffari et al found that St. John's Wort was useful for treating IBS (irritable bowel syndrome), a bowel motility condition for which antidepressants are sometimes prescribed. Studies have shown that St. John's Wort increases mitochondrial function, reduces inflammation, and inhibits nerve firing in epilepsy.

PROS AND CONS. St. John's Wort is generally well tolerated. However, it cannot be taken in conjunction with other antidepressants. Like any pharmaceutical antidepressant, it cannot be taken within two weeks of treatment with MAOIs. St. John's Wort decreases the effectiveness of many drugs, including benzodiazepines, oral contraceptives, beta blockers, statins, antiretrovirals, and theophylline.

## FURTHER READING

*Good general information about St. John's Wort:* <http://www.herbwisdom.com/herb-st-johns-wort.html>

*Cochrane Collaboration's summary of research on St. John's Wort for depression.*  
<http://summaries.cochrane.org/CD000448/st.-johns-wort-for-treating-depression>.

*A CFS/ME patient's review of St. John's Wort:*  
<http://www.revolutionhealth.com/drugs-treatments/rating/st-johns-wort-hypericum-perforatum-for-chronic-fatigue-syndrome-cfs-cfids-me>

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<http://www.ncbi.nlm.nih.gov/pubmed/21848657> (Abstract)

Woelk H. “Comparison of St John's wort and imipramine for treating depression: randomised controlled trial.” *BMJ.* 2000 Sep 2;321(7260):536-9.

<http://www.ncbi.nlm.nih.gov/pubmed/10968813> (Abstract)

## UVA URSI

A member of the Ericaceae family, uva ursi (*Arctostaphylos uva-ursi*) has been used for more than 100 years as a urinary tract antiseptic. Once in the urinary tract, the chemical (arbutin) found in uva ursi is transformed into an antiseptic agent, hydroquinone. This herb also contains diuretic chemicals (ursolic acid) and astringents. However, uva ursi is effective against urinary tract infections only if the urine is alkaline; therefore, citrus fruits (including tomatoes), vitamin C, and acidic foods should be avoided immediately before and after taking it.

Uva ursi is also used as an anti-Candida treatment and as an anti-bacterial.

PROS AND CONS. Some patients have reported “die-off” reactions from taking uva ursi.

## VALERIAN

Valerian (*Valeriana officinalis*) has long been used as a tranquilizer, and for treating epilepsy, nervousness, anxiety, insomnia, headache, and intestinal cramps. During World War I, it was routinely taken to relieve the “overwrought nerves” brought on by artillery bombardment. Valerian is used extensively in Germany, where it is the active ingredient in more than 100 over-the-counter sleep aids. The active ingredients in valerian are chemicals known as valepotriates, which are found in highest concentrations in the roots of the plant.

CFS/ME physicians recommend valerian primarily as a sleep aid. It can be taken as a tea or in capsule form, but because of its odor, capsules are usually preferred. Valerian should be taken with a little milk or food to prevent stomach upset. Valerian is often combined with other herbal sleep aids, such as passionflower, hops, and skullcap.

## FURTHER READING

Good summary of the uses of valerian: <http://www.herbwisdom.com/herb-valerian.html>

Several CFS/ME doctors discuss remedies for insomnia, including valerian. <http://www.prohealth.com/library/showarticle.cfm?libid=8563>

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- Taavoni S, Ekbatani N, Kashaniyan M, Haghani H. "Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial." *Menopause.* 2011 Sep;18(9):951-5. <http://www.ncbi.nlm.nih.gov/pubmed/21775910> (Abstract)

## HISTAME

**DESCRIPTION.** Histame is a dietary supplement containing the enzyme, diamine oxidase (DAO).

**BACKGROUND.** Diamine oxidase (also known as histaminase) is an enzyme found in large concentrations in the intestinal lining (mucosa) of all mammals. Its function is to break down histamine. Unlike antihistamines, Histame does not block histamine receptors, but acts directly on histamine itself.

In a study published in 1980, Luk et al found that after inducing damage to the intestines of rats, the amount of diamine oxidase was an accurate marker of intestinal integrity. The lower the amount of diamine oxidase, the greater the degree of damage. The researchers concluded that diamine oxidase was unique among intestinal mucosal enzymes in its ability to predict intestinal integrity.

In 2007 Maintz and Novak observed that people with low amounts of DAO can develop food sensitivities which symptomatically mimic food allergies (flushing, hypotension, diarrhea, headache, tachycardia, and itching). Although their symptoms match those of true allergies, these individuals do not test positive for IgE-mediated allergies. Low levels of circulating DAO prevent the breakdown of histamine in their intestines, causing allergic-type reactions, particularly to histamine-rich foods. Foods that are rich in histamine include all fermented and aged foods: cheese, alcohol, sauerkraut, canned fish (tuna, sardines), pizza, processed meats, as well as many fruits and chocolate. Nearly 100 drugs have been found to cause a decrease in DAO activity, including doxycycline, MAO inhibitors, cimetidine (Tagamet), and Verapamil (a calcium-channel blocker). DAO requires copper and Vitamins B2 and B6.

**USES IN CFS/ME.** Histamine intolerance is characteristic of CFS/ME patients. Aside from new allergies, many CFS/ME patients develop food sensitivities, as well as conditions such as migraines, rosacea and interstitial cystitis, which are provoked by tyrosine-rich foods. (Tyrosine is converted to tyramine, which is closely related to histamine.) Histame has been recommended by Dr. Kenny De Meirleir as part of treating gut dysbiosis in CFS/ME patients.

**PROTOCOL.** The makers of Histame recommend taking one or two tablets within 15 minutes of consuming histamine-rich food. The capsules can be opened and the contents swallowed, if preferred.

**AVAILABILITY.** Histame can be purchased from a number of online sources. Prices range from \$20-\$40 for a bottle of 30 capsules.

#### FURTHER READING

*Histame website:* <http://histame.com/>

*Patient thread on Histame:* <http://forums.phoenixrising.me/showthread.php?11967-90-cured-from-bed-bound-with-Histrelief-Histame-Daosin>

*Patient thread on histamine intolerance:*

<http://forums.phoenixrising.me/archive/index.php/t-1804.html>

*Comprehensive list of histamine-rich foods:* <http://histame.com/histamine-rich-foods-substances>

*An interesting study about histamine fish poisoning:*

<http://www.allergyclinic.co.nz/guides/63.html>

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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC371506/>

Maintz, Laura and Natalija Novak. "Histamine and histamine intolerance." *American Journal of Clinical Nutrition*, Vol. 85, No. 5, 1185-1196, May 2007

<http://www.ajcn.org/content/85/5/1185.full>

*In-depth medical study examining the effects of histamine on the gut, histamine intolerance, and the correlation of DAO levels with food intolerance.*

#### INOSINE/ISOPRINOSINE

**DESCRIPTION.** Inosine is a purine ribonucleoside (a nitrogen-containing compound combined with D-ribose). Isoprinosine (brand: Imunovir) is its pharmaceutical equivalent (now largely replaced by inosine).

**BACKGROUND.** Inosine is a naturally occurring chemical in the body which leads to the production of uric acid, a potent free radical scavenger. As a basic component of cells, uric acid is involved in a number of physiological processes including carbohydrate metabolism, insulin regulation, and protein synthesis. Uric acid levels are low in all inflammatory diseases, including CFS/ME. Pharmaceutical forms of inosine (inosine pranobex, or isoprinosine) have been used as immune system modulators. Currently, inosine is being investigated as a possible treatment for Parkinson's disease.

As a supplement, inosine is primarily used to enhance athletic performance. Manufacturers claim that because inosine is a precursor to adenosine, it facilitates the production of ATP (adenosine triphosphate). As a consequence, inosine should theoretically increase energy and endurance. Although there does not appear to be

any research to substantiate these claims, inosine is included in many sports supplements.

**USES IN CFS/ME.** Both Dr. Kenny De Meirleir and Dr. Cheney have largely replaced isoprinosine with inosine in their treatment protocols, under the assumption that the two are equivalent. Inosine, like its pharmaceutical counterpart, is supposed to modulate the immune system and act as an antiviral. However, inosine does not appear to possess the same antiviral properties as isoprinosine. The main function of inosine is as an antioxidant, which is linked to its ability to raise uric acid levels in the blood.

Dr. Klimas still uses isoprinosine (Imunovir) with her patients. The protocol is to alternate taking 3 and 6 pills daily, with weekends off, for three months. Over the next three months no Imunovir is taken. The physician decides how often to repeat this course of medication based on immune markers (as determined by blood tests).

**PROTOCOL.** The standard dosage of inosine is 500 mg three times a day for five days a week (allowing for weekend “drug holidays”). As always, CFS/ME patients are advised to start with low doses.

**PROS AND CONS.** Paradoxically, inosine seems to help with joint pain (gout is caused by an excess of uric acid, which is raised by inosine) and, to some degree, with energy. Although inosine functions as an antioxidant, the process of converting it to uric acid produces superoxide, a potent oxidant. Some patients report that inosine works fine for a while and then stops having an effect. Patients who were previously able to tolerate isoprinosine have reported headaches and insomnia while taking inosine.

**AVAILABILITY AND COST.** Inosine is a supplement, which means it can be purchased without a prescription at health food stores and from online distributors. Source Naturals markets a 120-tablet bottle of inosine (500 mg) for roughly \$20. Imunovir is currently registered outside the United States for the treatment of acute and chronic viral infections, including herpes and measles. It can be obtained in Canada.

## FURTHER READING

*Basic information on isoprinosine, including sources.*

<http://www.anapsid.org/cnd/drugs/isoprinosine.html>

*Manufacturer's description of Imunovir:*

[http://www.rivexpharma.com/products\\_imunovir.html](http://www.rivexpharma.com/products_imunovir.html)

*CFS/ME patient thread discussing isoprinosine and inosine:*

<http://www.prohealth.com/me-cfs/blog/boardDetail.cfm?id=1396515>

## INOSITOL

**DESCRIPTION.** Inositol is a carbocyclic polyol (a sugar alcohol) which forms an essential component of cell membranes.

**BACKGROUND.** Inositol, like choline, is an important component of phospholipids, the fatty substances which surround all cells in the body. Also like

choline, inositol helps with the transportation of fats, and prevents their accumulation in any one site (e.g., the liver). Because it is a key component of the myelin sheaths that surround nerves in the central nervous system, inositol performs a crucial role in maintaining the integrity of the nervous system.

Inositol also plays an important role in energy metabolism; its metabolites regulate bone mass and mediate amino acid signaling, acting as a “second messenger” for cell receptors. Inositol phosphates are important for a number of cellular functions, including cell growth, apoptosis (programmed cell death), cell migration, and cell differentiation. Inositol is found in the brain and nerves, muscles, bones, reproductive organs, stomach, kidney, spleen, liver and heart.

Because inositol is a second messenger of serotonin, it has been successfully used to treat several psychiatric conditions. (Second messengers are molecules that relay signals from neurotransmitters into the cell.) Medical uses of inositol include treatment of obsessive-compulsive disorder (OCD), anxiety, and depression. Inositol is also used for insomnia.

Inositol is produced in the gut in limited quantities by bacterial flora. Dietary sources include calf liver, cantaloupe, beans, dried beans, lentils, milk, nuts, oats, pork, rice, veal, wheat germ and whole-grain products.

PROTOCOL. Dr. Myhill recommends 500-2,000 mgs for low GABA activity. Dr. Teitelbaum recommends a slightly lower dose, 500-1,000 mgs a day. Maija Haavisto reports that 500 – 750 mg taken at bedtime improves insomnia.

PROS AND CONS. Inositol is safe and inexpensive. Some people report that they wake up at night with it. (This may be due to its SSRI-like effects.)

AVAILABILITY AND COST. Pure inositol (also known as myoinositol) can be purchased in powder form. PureFormulas.com markets a 250-gram container made by Pure Encapsulations for \$35 (at 500 mg a day, this will last approximately a year and five months). Inositol frequently comes combined with choline. Twinlabs, NOW, Solgar and Source Naturals all market inositol/choline combinations (500 mg) at less than \$10 a bottle. Inositol often is included in B complex supplements.

## FURTHER READING

*Ray Sahelian's informative page on inositol:*

<http://www.raysahelian.com/inositol.html>

*Links to useful articles about inositol:* <http://www.livestrong.com/inositol/>

*A nice summary of the functions of inositol in the body:* <http://www.diagnose-me.com/treat/T47006.html>

*Treatment of obsessive-compulsive disorder, panic attacks, and depression with inositol.*

[http://www.comprehensivepsychiatricresources.com/item.php?item\\_id=221&category\\_id=48](http://www.comprehensivepsychiatricresources.com/item.php?item_id=221&category_id=48)

*Maija Haavisto's excellent summary of treatments she has tried. Scroll down for inositol, or read them all:* <http://www.fiikus.net/?cfssupplements>

*Very interesting and informative patient thread about the use of inositol in OCD and its relationship with histamine:*

<http://www.stuckinadoorway.org/forums/archive/index.php?t-10476.html>

## RESEARCH

Gianfranco C, Vittorio U, Silvia B, Francesco D. "Myo-inositol in the treatment of premenstrual dysphoric disorder." *Hum Psychopharmacol*. 2011 Oct;26(7):526-30. <http://www.ncbi.nlm.nih.gov/pubmed/22031267> (Abstract)

## MALIC ACID

**DESCRIPTION.** Malic acid, an intermediate in the Krebs cycle, aids in the production of adenosine triphosphate (ATP).

**BACKGROUND.** Malic acid is found primarily in apples and pears, as well as other fruits. It is used primarily as a flavor enhancer and to lend tartness to food products. Malic acid helps in the breakdown and utilization of fats and glucose in muscle tissue, even in low oxygen conditions, and plays an important role in the production of ATP.

**USES IN CFS/ME.** Because of the prominent role malic acid plays in the energy-producing Krebs cycle, a deficiency can lead to inadequate breakdown of glucose in muscle tissue, with resulting buildup of lactic acid and other toxins. Increased amounts of malic acid should relieve many of the symptoms associated with tissue acidosis (spasms, cramps, and burning pain). A number of CFS/ME physicians recommend malic acid combined with magnesium to treat fibromyalgia symptoms. Dr. Guy Abraham, Dr. J. E. Michalek, Dr. Jorge Flechas, and Dr. I. Jon Russell observed improvement in pain among CFS/ME patients taking Super Malic, a combination of 200 mg of malic acid and 50 mg of magnesium (*Journal of Rheumatology*, 1995). The researchers noted that low doses of Super Malic were not effective, and recommended six tablets a day for two months.

**PROTOCOL.** As with other supplements, physicians recommend starting with the lowest dose, one tablet daily taken with food and water, to check for possible sensitivities. The dosage can be increased gradually to between 6 and 12 tablets daily, depending on tolerance. If gastrointestinal problems develop, the dosage should be decreased. Although results may be experienced within a few days, most physicians recommend a trial of several months.

**PROS.** As a dietary supplement, malic acid is relatively risk free. People with CFS/ME report increased energy, less muscle pain and more stamina. One patient reported a complete cessation of leg spasms, allowing her to rest better.

Surprisingly, a patient with kidney stones reported that they decreased after taking malic acid for ten days.

**CONS.** Some patients report nausea and stomach cramps (on 400 mg a day). Others find malic acid to be too stimulating, resulting in insomnia. The stimulating effects can be reduced by combining malic acid with magnesium.

**AVAILABILITY AND COST.** Malic acid is available from most health food and vitamin stores. Malic acid supplements are inexpensive. PureFormulas.com

sells a bottle of 90 capsules (600 mg) made by Ecological Formulas for \$12. Super Malic has been discontinued. However, various combinations of magnesium and malic acid are still available. Allergy Research Group markets a 120-tablet bottle of Magnesium Malate Forte (124 mg magnesium, 500 mg malic acid, with 10 mg B2) for roughly \$20 (through PureFormulas.com).

#### FURTHER READING

*Patient thread on malic acid:*

<http://www.chronicfatiguetreatments.com/forums/vitamins-for-chronic-fatigue-f7/topic593.html>

#### RESEARCH

Russell IJ, Michalek JE, Flechas JD, Abraham GE. Treatment of fibromyalgia syndrome with Super Malic: a randomized, double blind, placebo controlled, crossover pilot study." *J Rheumatol.* 1995 May;22(5):953-8.

<http://www.ncbi.nlm.nih.gov/pubmed/8587088> (Abstract)

#### MELATONIN

**DESCRIPTION.** Melatonin is a hormone produced by the pineal gland.

**BACKGROUND.** Melatonin is a naturally occurring hormone produced in the pineal gland, the brain's "master gland." It is derived from serotonin, one of the brain's most important neurotransmitters. Serotonin, a neurochemical derived from the amino acid tryptophan, is converted by enzymes sensitive to the diurnal cycle of darkness and light into melatonin. Melatonin, because it is produced in the part of the brain that regulates diurnal rhythms, is essential for maintaining normal sleep patterns. Large amounts of melatonin are produced in children, which is one reason why young people sleep so much. As we age, melatonin levels decrease, making it more difficult for the elderly to sleep through the night.

Disruption of both melatonin and serotonin production has been implicated in seasonal affective disorder, the treatment of which involves increasing melatonin levels through exposure to full-spectrum light early in the day. Low melatonin and serotonin levels have also been implicated as contributing factors to depression. Currently, physicians are exploring the use of melatonin as an anti-aging factor. It is possible that supplementation with melatonin in the elderly may help correct the disturbed sleep, poor immune response, and diminished capacity for tissue repair typical of the aging process.

Melatonin may also help correct insomnia in the young. Studies released by the Massachusetts Institute of Technology showed that it took less than half the time for volunteers given melatonin to fall asleep than those given a placebo. Subjects given melatonin also tended to sleep about twice as long as those given placebo and woke without the "hangover" normally associated with sleeping pills. The results of this study are encouraging to those with sleep disorders. However, the effectiveness of melatonin depends on a number of other factors.



Benita Middleton and her colleagues at the University of Surrey tested the effect of melatonin in conjunction with body temperature. They discovered that in subjects whose body temperature rose later in the day, melatonin had a negative effect on sleep, producing extremely fragmented sleeping and waking patterns. Although melatonin is produced in the pineal gland, it is regulated by a part of the hypothalamus, the suprachiasmatic nucleus, which acts as the body's "clock" by tracking the length of the day. The hypothalamus also controls body temperature, so it is not surprising that the body's internal clock is linked to core temperature. Middleton concluded that while melatonin plays an important role in circadian sleep cycles, the effects are highly individualized.

Melatonin also regulates the "gut clock." About 400 times more melatonin is produced in the gut than in the brain. The reason for this vast production of melatonin is that digestion is regulated by circadian rhythms. Bile flow increases at night, as do other digestive secretions. Melatonin functions not only to set the circadian rhythms of the digestive system, but to harmonize them with immune and endocrine functions. When these rhythms are disrupted, digestive disturbances result.

It is known that people with severe insomnia are prone to irritable bowel syndrome (IBS), peptic ulcers, fatty liver, GERD, and dyspepsia. In an interesting study of the use of melatonin for treating IBS conducted by Lu et al in 2005, 88% of the patients reported significant improvement of their GI symptoms after 8 weeks of treatment with melatonin over placebo. Oddly enough, the patients experienced no difference in sleep between melatonin and placebo.

**USES IN CFS/ME.** Sleep disturbance is one of the primary symptoms of CFS/ME. Many patients experience persistent insomnia throughout the illness. Even after a full night's rest, patients with CFS/ME awaken tired. Many clinicians believe that treating the CFS/ME sleep disorder is of primary importance because it reduces the severity of many other symptoms. However, owing to the prevalence of drug and chemical sensitivities in the CFS/ME population, it is not always easy to find a safe, effective means of obtaining a good night's rest. Melatonin may offer an alternative.

In 2006 van Heukelom et al explored the use of melatonin on CFS/ME patients with Dim Light Melatonin Onset (DLMO) later than 11:30 PM. DLMO is when the body begins its own production of melatonin. In healthy people, it occurs roughly two hours before bedtime, provided the light is dim. Van Huekelom's group found that in people with CFS/ME the delayed onset of DLMO was rectified by administration of 5 mg of melatonin five hours before DLMO. After three months, fatigue, energy, and concentration were significantly improved. The researchers concluded that melatonin was an effective therapy for those CFS/ME patients with significantly delayed sleep onset.

Although many CFS/ME physicians use melatonin, there is no clear evidence from the literature that melatonin levels are actually deficient in CFS/ME patients. In a study of 13 adolescents with CFS/ME, Knook et al found that melatonin levels were actually higher in the CFS/ME group than in controls.

There is a possible explanation for why some CFS/ME patients might be high in melatonin. Researchers have found that melatonin increases the release of cytokines, immune system chemicals that act as messengers to initiate various immune responses. In 1997 Garcia-Maurino et al found that melatonin increased the production of IL-2, IL-6 and gamma interferon, enhancing the effectiveness of Th1 (cellular) immunity (the type of immune function that combats viruses).

A previous study by Ben-Nathan et al found that injecting virus-infected mice with melatonin significantly reduced mortality rates. The implication for at least some people with CFS/ME is that the excess melatonin might be a response to reactivated viruses, providing a hormonal route to immune activation. In light of melatonin's role in enhancing cellular immunity, which is deficient in people with CFS/ME, this is an area which warrants further investigation, especially given the strong association between mono and CFS in teens.

**PROTOCOL.** Dr. Lapp uses melatonin with patients who have “phase shifted.” That is, they can't fall asleep until 1 or 2AM, and then sleep all day (indicating that the body's “clock” needs to be reset). He recommends starting with as little as 0.1 mg taken a half-hour before bedtime and increasing the dose until the desired effect is achieved. He also has observed that synthetic (not from animal sources) and sublingual forms of melatonin are safest and most effective (*MEssenger*, 1997). Dr. Lapp does not recommend melatonin for children younger than the late teens.

While product labels usually recommend one to two tablets (3 to 6 mg) taken before bedtime, studies at the Massachusetts Institute of Technology indicate 0.3 mg daily is sufficient to raise blood levels to normal. MIT researcher, Dr. Richard Wurtman, claims that serious side effects can be produced by taking standard doses, which can raise blood levels to more than 10 times the norm. Dr. Teitelbaum also agrees that the standard dose of 3 mg is too high. He recommends taking no more than 0.5 mg.

**PROS.** A number of CFS/ME patients have reported that melatonin has given them their best night's sleep in years. Melatonin works quickly. For people who become insomniacs while taking beta blockers, melatonin supplementation may provide considerable relief. (Beta blockers can deplete the body of melatonin.)

**CONS.** Melatonin can lose its effectiveness over time. After working beautifully for a few weeks or months, it can suddenly stop providing the desired results. Some people report paradoxical reactions, such as feeling more awake or experiencing partial or light sleep states. The reason melatonin works for some but not for others may have to do with individual biorhythms (see above). It is possible that patients with CFS/ME whose temperatures rise in the evening due to immune activation may not respond well to melatonin treatment.

Excessive doses of melatonin can cause jitters and headaches. Female patients may experience hormonal disturbances (early onset of periods). Interactions with antidepressant drugs such as Prozac, Elavil, or Zoloft and the pain medication, Ultram, have been reported. People taking antidepressants should

discuss the risks and benefits of melatonin with their physicians. Preexisting depression as well as orthostatic intolerance may be worsened by melatonin.

**AVAILABILITY AND COST.** Although it is a hormone, melatonin is currently considered a nutritional supplement. Consequently, it can be purchased over the counter from most health food stores and vitamin catalogs. A 100-tablet bottle of melatonin (3mg) can cost less than \$5. Those who wish to start with lower doses should order the liquid.

#### FURTHER READING

“Sleep and Snake Oil.” Rachel Preiser. *Discover Magazine*. March 1997.

<http://discovermagazine.com/1997/mar/sleepandsnakeoil1082>

*Cort Johnson's informative page about melatonin in CFS/ME.*

<http://aboutmecfs.org.violet.arvixe.com/Trt/TrtMelatonin.aspx>

*Dr. Lapp on melatonin and other sleep medications.*

<http://www.prohealth.com/library/showarticle.cfm?libid=8563>

*Melatonin safety assessment by the Mayo Clinic.*

[http://www.mayoclinic.com/health/melatonin/NS\\_patient-melatonin/DSECTION=safety](http://www.mayoclinic.com/health/melatonin/NS_patient-melatonin/DSECTION=safety)

*CFS/ME patient forum on melatonin:*

<http://forums.phoenixrising.me/archive/index.php/t-12516.html?s=8dd572918a1b8e25a023bda45d398c90>

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<http://www.ncbi.nlm.nih.gov/pubmed/7710351> (Abstract)

Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. “A review of the multiple actions of melatonin on the immune system.” *Endocrine*. 2005 Jul;27(2):189-200.

<http://www.ncbi.nlm.nih.gov/pubmed/16217132> (Abstract)

Garcia-Maurino S, MG Gonzalez-Haba, JR Calvo, M Rafii-El-Idrissi, V Sanchez-Margalet, R Goberna and JM Guerrero. “Melatonin enhances IL-2, IL-6, and IFN-gamma production by human circulating CD4+ cells: a possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes.” *The Journal of Immunology*, Vol 159, Issue 2 574-581, 1997.

<http://www.jimmunol.org/content/159/2/574.abstract> (Abstract)

Guerrero JM, Reiter RJ. “Melatonin-immune system relationships.” *Curr Top Med Chem*. 2002 Feb;2(2):167-79. <http://www.ncbi.nlm.nih.gov/pubmed/11899099> (Abstract)

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van Heukelom RO, Prins JB, Smits MG, Bleijenberg G. "Influence of melatonin on fatigue severity in patients with chronic fatigue syndrome and late melatonin secretion." *Eur J Neurol.* 2006 Jan;13(1):55-60.

<http://www.ncbi.nlm.nih.gov/pubmed/16420393> (Abstract)

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<http://www.ncbi.nlm.nih.gov/pubmed/12423324> (Abstract)

## MINERALS

Calcium, Magnesium, Selenium, Colloidal Silver, Zinc

### CALCIUM

**BACKGROUND.** Calcium is the most abundant mineral in the human body. A 150-pound adult's body contains about three pounds of calcium, 99% of which is found in the skeletal bones. The small portion of calcium found in soft tissues and body fluids is essential for maintaining a number of important biochemical functions, including regular heartbeat and transmission of nerve impulses. Calcium also prevents muscle cramps and is vital for the formation of healthy teeth and strong bones.

There are two main forms of calcium: inorganic and organic. The inorganic forms (sulfate, carbonate, and phosphate) are poorly absorbed. The organic forms (citrate, lactate, gluconate, orotate, aspartate, ascorbate and various chelates) are better absorbed. Once calcium is metabolized through the action of stomach acid, it passes into the small intestine where the ionized (liquified) calcium is absorbed into the bloodstream. Ionized calcium is the most important physiological component of calcium. In fact, because calcium is so easily bound to other compounds, blood measurements of total calcium are useless for determining the amount of calcium actually available in the body. Only ionized calcium gives an accurate picture as to how much calcium is actually available to maintain physiological functions.

**USES IN CFS/ME.** CFS/ME patients often take calcium at night to alleviate insomnia. It is also useful for treating muscle spasms. Those ingesting high amounts of protein or phosphorus may want to supplement their intake of dietary

calcium because both protein and phosphorus increase calcium excretion from the body. Good natural sources of calcium are dairy products and green leafy vegetables.

**PROTOCOL.** Dr. Lapp recommends 1,000 mg to 1,500 mg daily. Calcium intake should not exceed 2500 mg a day. Calcium cannot be properly absorbed and assimilated unless vitamin D and trace minerals are present (chromium, boron, copper, iron, manganese, phosphorus, silicon, strontium, and zinc). It is important to supplement with these trace minerals while taking calcium, because calcium competes with other minerals for absorption in the intestines. It is also important to supplement with magnesium. (Magnesium prevents plaque buildup from unabsorbed calcium.)

Liquid ionic calcium is more easily absorbed and utilized than other forms of calcium. For example, only 10% of either calcium carbonate (Tums) or calcium citrate is absorbed. This means you get 100 mg of usable calcium for every 1,000 mg consumed. (You'd have to eat over 30 Tums to get 1000 mg of calcium.) Calcium lactate, found in milk, fares a little better at 33%. In contrast, calcium aspartate is 85% absorbed and calcium orotate is 90-95% absorbed. Ionic calcium is nearly 100% absorbed.

CFS/ME patients taking verapamil (a calcium channel blocker) to treat cognitive dysfunction need to be aware that calcium supplements may interfere with the effects of this medication. People with a history of kidney disease or kidney stones should not take calcium supplements, because the additional calcium may exacerbate the condition.

**PROS AND CONS.** Calcium is inexpensive and generally well tolerated. Calcium supplements can interfere with the absorption of both iron and zinc (but not magnesium), so if you are supplementing with either of these minerals, be sure to take them at least two hours after (or before) taking calcium.

**AVAILABILITY AND COST.** There is a wide variety of calcium supplements available at supermarkets, drug stores, health food stores, and from online distributors. Mineral Life sells an 8-oz bottle of liquid ionic calcium for \$20 (60-day supply). Pure Essence markets Ionic Fizz (a blend of ionic trace minerals and vitamins) for \$16 through Vitacost. Advanced Research markets a 100-tablet bottle of calcium orotate combined with magnesium for about \$20 (through amazon.com). Advanced Research also markets a 100-tablet bottle of calcium aspartate for the very affordable price of \$7.

#### FURTHER READING

*Good overview of calcium, including rates of absorption for different calcium compounds.* [http://www.uswellnessmeats.com/Calcium\\_Myth\\_and\\_Facts.pdf](http://www.uswellnessmeats.com/Calcium_Myth_and_Facts.pdf)  
*Brief interview with Dr. Spreen about the different forms of calcium and their bioavailability.* <http://www.alkalizeforhealth.net/Lcalcium.htm>  
*Ionic calcium supplier:* <http://www.mineralifeonline.com/pd-calcium-8oz-60-day-supply.cfm>

“When Is It *Appropriate* to Order an Ionized Calcium?” Laura M. Calvi and David A. Bushinsky. *JASN* July 1, 2008 vol. 19 no. 71257-1260.

<http://jasn.asnjournals.org/content/19/7/1257.full>

*Good medical article about the importance of measuring ionic calcium in the bloodstream.*

## MAGNESIUM

**BACKGROUND.** Magnesium is one of the six major minerals classified as essential for the functioning of the human body. The average human body contains about 25 grams of magnesium salts, about half of which is stored in the bones and one-fourth in muscle. Only about 2% circulates freely in the blood. The rest is located within the cells. Blood levels of magnesium are controlled by the kidneys.

Magnesium is necessary for relaying nervous system impulses and for normal metabolism of calcium and potassium. Much like a vitamin, magnesium functions as a coenzyme, aiding in enzyme systems, storage and release of energy generated from carbohydrates, and synthesis of proteins and DNA. Magnesium deficiency can result in anorexia, nausea, learning disabilities, personality changes, weakness, exhaustion, and muscle pain.

According to the USDA, a staggering 68% of Americans do not consume the daily recommended intake for magnesium. In a forward-looking article written in 1990, Kubena et al outlined the effects of chronic marginal intakes of magnesium, including “abnormalities in reproduction, growth, and development and disorders of neuromuscular, cardiovascular, renal, and immune function.” In addition, the authors pointed out that problems related to the use of pharmacological agents or trace metals, such as aluminum (which has been implicated in the development of Alzheimer's disease), may be worsened with a low intake of magnesium. Dr. Pall has speculated that, given the likelihood that people with CFS/ME are marginally deficient in magnesium before falling ill, magnesium deficiency may contribute to the pathogenesis of the illness.

**USES IN CFS/ME.** Magnesium is an indispensable supplement for people with CFS/ME. Nearly every CFS/ME physician includes either injectable or oral magnesium as part of their protocol. In early 1991, I.M. Cox, M.J. Campbell, and D. Dowson published a preliminary study on magnesium levels in CFS/ME patients (*Lancet*, 1991). All 22 patients studied had reduced levels of serum magnesium.

They followed up their findings with a randomized clinical study in which 15 of the patients received intramuscular injections of magnesium sulfate every week for six weeks and 17 received a placebo. Of the 15 patients receiving magnesium, 12 reported improvement in symptoms. Although subsequent studies have not confirmed low serum levels of magnesium to be universal among CFS/ME patients, magnesium is still the most frequently recommended mineral supplement for patients with CFS/ME.

In his book, *Explaining “Unexplained Illnesses,”* Dr. Martin Pall presents a compelling argument implicating oxidative stress in the etiology of CFS/ME. An important part of the ongoing oxidative stress typical of multisystem illnesses like

CFS/ME, FM and Gulf War Syndrome is the chronic excitability of NMDA receptors, which results in a hyperactive nervous system (along with cell damage, inflammation, and lowered production of ATP). Magnesium is one of the principal inhibitors of NMDA activity, which makes it a valuable treatment for any illness involving chronic oxidative stress.

Dr. Myhill believes that low magnesium levels in CFS/ME patients is a symptom of mitochondrial failure. When mitochondria fail, calcium leaks into cells and magnesium leaks out. According to Dr. Myhill, this leakage explains why it is useless to test serum levels of magnesium. As she puts it, "Serum levels are maintained at the expense of intracellular levels. If serum levels change this causes heart irregularities and so the body maintains serum levels at all cost. It will drain magnesium from inside cells and indeed from bone in order to achieve this." Dr. Myhill's explanation not only accounts for why serum levels of magnesium are inconsistent in CFS/ME, but why magnesium supplementation is effective.

**PROTOCOL.** Magnesium can be administered orally or by injection. Because oral magnesium is difficult to absorb, the forms most frequently recommended are magnesium citrate and magnesium glycinate. Magnesium citrate will dissolve in water, which makes it more bioavailable than most other forms of magnesium. However, Dr. Cheney has observed that magnesium glycinate causes the least intestinal upset and is the most easily absorbed. The usual recommended dosage is 200 to 400 mg/day taken with food, although CFS/ME patients are cautioned to start with a smaller dose and increase it gradually. Intramuscular injections of 1 cc of magnesium sulfate (50%) or magnesium chloride can be administered once or twice a week. Because of magnesium's effect on heart function, the first injection should be performed in a physician's office.

**PROS AND CONS.** Most people who take magnesium, whether oral or injected, report increased stamina and energy. Many include better sleep as an additional benefit (most likely due to magnesium's muscle-relaxing effects). The main drawback of injected magnesium is that the injections are painful. The simultaneous administration of vitamin B12 or lidocaine helps relieve the pain of the injection. Because magnesium is a cathartic, high doses can cause diarrhea. In patients prone to gastrointestinal upset, a low dose is normally recommended.

**AVAILABILITY AND COST.** Oral magnesium is readily available from health food stores, online vitamin suppliers, and most drugstores. It is inexpensive. A bottle of 120 tablets of either magnesium glycinate or magnesium citrate (400 mg) costs \$12 from Vitacost. Topical magnesium creams are also available. PureFormulas.com markets a 4-ounce jar of magnesium cream made by Kirkman for \$16. (Or you can make your own cream using Epsom salts.) Magnesium can be purchased as a powder and mixed into a beverage for easier assimilation. Magnesium sulfate injections usually cost \$16 to \$20 per injection.

#### FURTHER READING

*Excellent summary of magnesium's effects on the body from the Linus Pauling Institute.* <http://lpi.oregonstate.edu/infocenter/minerals/magnesium/>

*Dr. Myhill discusses magnesium deficiency and treatment in CFS/ME patients.*

[http://www.drmyhill.co.uk/wiki/Magnesium - treating a deficiency](http://www.drmyhill.co.uk/wiki/Magnesium_-_treating_a_deficiency)

*USDA statistics on nutrient consumption by state and nationally.*

<http://www.ars.usda.gov/Services/docs.htm?docid=11197>

“Review and Hypothesis: Might Patients with the Chronic Fatigue Syndrome Have Latent Tetany of *Magnesium* Deficiency.” Mildred Seelig, MD, MPH

<http://www.mgwater.com/clmd.shtml>

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*Journal of Chronic Fatigue Syndrome*, Vol. 4(2) 1998

<http://www.mgwater.com/clmd.shtml>

## SELENIUM

**BACKGROUND.** Selenium is a trace mineral found in the soil, and in foods such as lobster, tuna, shrimp, oysters, fish, brown rice, garlic, whole grains, sesame seeds, and mushrooms. Although it is needed in only small amounts, selenium performs an important role in kidney, spleen, pancreas and liver function, as well as in reproduction. In men, about half of the body's selenium is concentrated in the testes. Selenium forms a component of glutathione peroxidase, the body's most prolific antioxidant. Deficiencies in selenium can lead to infertility, arthritis, hypothyroidism (selenium is essential for making T3), loss of energy, immune system deficiency, and, in children, cardiac problems.

Apart from its many metabolic functions, selenium performs an important role in the functioning of the immune system. In a 1994 study performed at New York University, subjects who received a 200 mcg daily supplement of selenium for eight weeks showed an enhanced immune response to foreign antigens, including an increase natural killer cell activity. Research also indicates that selenium up-regulates IL-2 and increases activation of T helper cells. Selenium supplementation



may also down regulate abnormally high levels of the inflammatory cytokines IL-8 and TNF alpha.

It is because of selenium's dual function as an antioxidant and as an immune system enhancer that attention has recently been drawn to its possible role in the creation of "superbugs," such as the Ebola virus. In the mid-1990s two researchers, Melinda Beck, a virologist at the University of North Carolina, and Orville Levander, a nutritional chemist with the USDA, set about to investigate the effects of selenium deficiencies on mice infected with Coxsackie virus. They discovered that not only did the mice develop virally induced heart disease, but that the virus itself had mutated into a more virulent strain.

Subsequent studies by Beck and colleagues confirmed that a host deficient in selenium not only has a poor immune response, but also can influence the genetic makeup of the virus, producing a more deadly strain. In an enormously understated conclusion, the authors stated that "this latter finding markedly changes our concept of host-pathogen interactions and creates a new paradigm for the study of such phenomena." For those who have suffered for decades from the long-term effects of viral infections, the implications of this study are ominous.

**USES IN CFS/ME.** In CFS/ME, selenium is used primarily as an antioxidant. Selenium helps form glutathione peroxidases (which eliminate peroxide oxidants in the cell), as well as acting as a peroxynitrite scavenger. Both of these properties make selenium an important adjunct in antioxidant therapy. Selenium's role in thyroid hormone production also make it an essential supplement for people suffering from borderline hypothyroidism (a common finding in CFS/ME, due to disturbances in the endocrine system). Selenium has been identified as a mood enhancer as well.

In an interesting study of the psychological impact of selenium, Benton observed that "the metabolism of selenium by the brain differs from other organs in that at times of deficiency the brain retains selenium to a greater extent." Benton proposed that this preference indicates that selenium is important in psychological function, particularly mood. In his article, Benton cites five studies that have associated low selenium intake with poorer mood. These studies seem to bear out independent reports from CFS/ME patients who have successfully taken selenium in place of antidepressants.

**PROTOCOL.** Dr. Pall recommends selenium methionine as the best form of selenium. Unless there is a verified selenium deficiency, low doses are recommended (50 mcg).

**PROS AND CONS.** Selenium is toxic at high levels, and overdoses can cause numerous symptoms: hair loss, tooth decay, brittle nails, nausea, vomiting, poor appetite, metallic taste in the mouth, loss of feeling in the hands and feet, and changes in skin pigmentation. (A garlic smell on the breath is an indication of excessive selenium intake.) Selenium is often produced as a yeast, which is problematic for people with Candida overgrowth and mold allergies, so check the label carefully.

**AVAILABILITY AND COST.** Selenium is widely available at health food stores and from online suppliers. PureFormulas.com markets a bottle of yeast-free seleno-methionine capsules (200 mcg) made by Douglas Labs for \$26.40 (250 capsules). Capsules can be divided for a lower dose.

#### FURTHER READING

*Detailed information about selenium from the Linus Pauling Institute.*

<http://lpi.oregonstate.edu/infocenter/minerals/selenium/>

“Is Selenium Deficiency Behind Ebola, AIDS and Other Deadly Infections?”

[http://infonom.com.ar/task/html/selenium\\_deficiency\\_behind\\_tod.html](http://infonom.com.ar/task/html/selenium_deficiency_behind_tod.html)

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#### COLLOIDAL SILVER

*NOTE: Some of the colloidal minerals distributed by multilevel marketers contain arsenic and lead, which are toxic even in small doses. Caution should be exercised. Read labels carefully!*

**DESCRIPTION.** Colloidal silver solution is composed of ultrafine, non-soluble particles of silver suspended in a liquid medium such as water.

**BACKGROUND.** Colloidal silver has long been used as a germicide. In the early twentieth century, colloidal silver was used in place of antibiotics. Silver was used orally, intravenously, and intramuscularly (as an injection), as a throat gargle, and in eyedrops. Colloidal silver has been used to treat such varied maladies as tonsillitis, cystitis, ringworm, and dysentery. Over the course of this century,

antibiotics have replaced silver as drugs of choice, although silver nitrate is still used to prevent eye infection in newborn infants.

**USES IN CFS/ME.** Some patients with CFS/ME report that colloidal silver helps control recurring infections, particularly in the mouth. Research has shown that colloidal silver may be of benefit in treating oral infections, sinusitis, sore throat, and canker sores.

**PROTOCOL.** Dosage varies, depending on the concentration of the product used.

**PROS AND CONS.** It appears that low doses of silver are fairly safe. However, argyria (grayish skin discoloration) may develop when excessive doses of silver are ingested. Because most studies evaluating the antimicrobial properties of silver are not conducted on people, patients are cautioned to exercise judgment before choosing silver over a medication whose mode of action and recommended dosage are better known.

**AVAILABILITY AND COST.** Colloidal silver may be purchased from most health food stores and online distributors. It costs \$12 to \$25 for a 4-oz bottle, depending on the brand. Some companies make a spray colloidal silver for oral use. Stick to reputable brands such as Source Naturals when purchasing.

## RESEARCH

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## ZINC

**BACKGROUND.** Zinc is a remarkably versatile mineral. It plays an important role in the more than 70 enzyme systems that regulate most metabolic processes. It stimulates digestion, aids in extracting stores of vitamin A from the

liver, helps maintain the mucous lining of the mouth, throat, stomach, and intestines, is vital for the normal growth of hair, skin, and nails, controls sexual maturation and fertility (zinc deficiency in men can lead to infertility), and aids in the healing of wounds. Zinc is necessary for the utilization of vitamin B6, a vitamin which is crucial for nervous system function. It also helps improve immune responses, although excessive intake of zinc (more than 50 mg) can suppress immune function. (High doses of zinc also deplete copper.)

**USES IN CFS/ME.** Many CFS/ME patients take zinc to help relieve sore throat and other viral symptoms. In a 2005 study published by Maes et al, 33 CFS/ME patients were examined for serum zinc deficiencies. The researchers found that serum levels of zinc were lower in CFS/ME patients than in controls. In addition, low serum zinc status was related to signs of inflammation and defects in early T cell activation pathways. Since zinc is a strong antioxidant, the results of this study support the findings that CFS is accompanied by increased oxidative stress. The researchers concluded that “the results of these reports suggest that some patients with CFS should be treated with specific antioxidants, including zinc supplements.”

**PROTOCOL.** The recommended daily allowance for zinc is 15 mg. The most bioavailable form is high-zinc yeast. This is a form of yeast that has a high zinc content. Unfortunately, it is not available in the U.S. (Lalmin Zn, a high-zinc yeast supplement using *Saccharomyces cerevisiae*, is produced in Denmark.) Zinc picolinate is well-absorbed, as is zinc citrate. Zinc carnosine, a combination of zinc and the amino acid carnosine, is reported to be well absorbed, as well as providing support for the mucosal lining of the stomach and gut.

**AVAILABILITY AND COST.** Zinc is available from health food stores, vitamin catalogs, and some drugstores. As with other mineral supplements, it is not expensive. A 100-tablet bottle of zinc picolinate (25 mg) made by Country Life costs less than \$5 on Vitacost. Zinc should be taken with food to avoid stomach upset. Zinc is found naturally in pumpkin seeds, liver, egg yolks, and seafood (especially oysters).

#### FURTHER READING

*Essential reading about zinc:* <http://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>

*Article discussing zinc bound in yeast:*

<http://www.nutraingredients.com/Research/Zinc-bound-in-yeast-promotes-superior-bioavailability-claims-study>

*Interesting study of high-zinc yeast in rats:* [http://www.beta-glucan-info.com/pdf/Zinc\\_Bioavailability.pdf](http://www.beta-glucan-info.com/pdf/Zinc_Bioavailability.pdf)

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## MONOLAURIN

**DESCRIPTION.** Monolaurin is a mono-ester formed from glycerol and lauric acid.

**BACKGROUND.** Monolaurin is a fatty acid found in human breast milk. Lauric acid, a closely related compound, is found in coconuts. It has broad anti-microbial properties. In *in vitro* studies, monolaurin was able to destroy several strains of bacteria. *H. Pylori* is particularly susceptible – which may be why coconut water is traditionally used as a treatment for dyspepsia in tropical countries.

Other *in vitro* studies have shown that monolaurin can kill viruses by destroying their lipid membrane. (Laurates are commonly found in soap.) Some of the viruses inactivated by these lipids are measles, herpes simplex, hepatitis C, and cytomegalovirus (CMV). A number of fungi, yeasts, and protozoa are also inactivated or killed by monolaurin. These include ringworm, *Candida albicans*, and the protozoan parasite *Giardia lamblia*. Among the many benefits of monolaurin is the fact that it can destroy harmful bacteria without affecting beneficial intestinal flora.

**USES IN CFS/ME.** Monolaurin is an antiviral, antifungal and anti-Candida treatment. It is used as a safe alternative to pharmaceutical antivirals and antifungals, which often have harmful side effects.

**PROTOCOL.** Physicians advise starting with very low doses (¼ scoop of Lauricidin) to prevent Herxheimer, or “die-off,” reactions. The makers of Lauricidin recommend starting with one pellet a day (approx 30 mg) in order to avoid Herxheimer reactions. Do not chew the pellets. (They taste like soap.) Monolaurin capsules can be taken with greater frequency. Dr. Teitelbaum recommends taking 9 capsules (300 mg) once a day on an empty stomach for 1 week, followed by 6 capsules once a day for 20 days. He recommends taking lysine 1500 mg twice a day while on monolaurin.

**PROS AND CONS.** Patients report that monolaurin helps ward off colds and flus. One patient wrote that at high doses (500 mg) it helped shingles. However, most patients report that monolaurin will cause “die off” (Herxheimer-like) reactions. Some fibromyalgia patients have reported an increase of pain on even very low doses of Lauricidin. Other side effects include acid reflux and a general “sick” feeling.

**AVAILABILITY AND COST.** Patients recommend purchasing pure monolaurin (Lauricidin). An 8-oz container of Lauricidin pellets can be purchased for around \$30 on amazon.com. Ecological Formulas markets two monolaurin

combinations (one with magnesium, and one with lysine) for roughly \$13 for a 90-capsule bottle (through PureFormulas.com online).

#### FURTHER READING

*A Review of Monolaurin and Lauric Acid. Shari Lieberman and Harry Preuss.*

<http://www.easihealth.co.za/wordpress/wp-content/uploads/downloads/2011/02/trials/Monolaurin.pdf>

*Patient thread on monolaurin:* <http://www.prohealth.com/mefcs/blog/boardDetail.cfm?id=428991>

*Manufacturer's information on Lauricidin:* [http://lauricidin.com/tech\\_data/](http://lauricidin.com/tech_data/)

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<http://www.ncbi.nlm.nih.gov/pubmed/19895490> (Abstract)

#### MUSHROOM EXTRACTS

LEM (shiitake), Maitake, Cordyceps

Mushroom extracts have become increasingly popular in recent years for their broad medicinal properties. Research has shown that mushroom extracts have anticancer, anti-diabetes, antibacterial, antifungal, and immune stimulating properties. Although many varieties of mushroom extracts are currently marketed for their medicinal effects, the two mushroom extracts most widely used for CFS/ME are the shiitake (LEM) and maitake.

In 2002 Dr. Peter R. Rothschild conducted a 120-day study to observe therapeutic responses to RM-10 (a combination of 10 mushroom extracts) for the reduction of symptoms in 33 CFS/ME patients. The researchers found that 60% of the participants reported a reduction of symptoms by 40%, with 33% totally asymptomatic by the end of the trial period. All participants reported some degree of improvement. Dr. Rothschild stated, "We had highly significant results with the multi-mushroom formula, brand named RM-10 [TM]. For affected patients, there was a remarkable percentage of remissions and a quite noticeable improvement in symptomology overall."

#### FURTHER READING

*Good general information about mushroom extracts.*

<http://www.nammex.com/MedicinalMushroomBooks.html>

*Report on RM-10 mushroom extract administered to CFS/ME patients.*

[http://findarticles.com/p/articles/mi\\_m0ISW/is\\_2002\\_August-Sept/ai\\_90794449/](http://findarticles.com/p/articles/mi_m0ISW/is_2002_August-Sept/ai_90794449/)  
*Description of RM-10:* [http://www.healthfoodemporium.com/garden-of-life/rm\\_10.html](http://www.healthfoodemporium.com/garden-of-life/rm_10.html)

## SHIITAKE (LEM)

**DESCRIPTION.** LEM (*Lentinus edodes mycelium*) is an extract made from the immature shiitake mushroom.

**BACKGROUND.** Although shiitake mushrooms have long been used in the East for culinary purposes, they have recently gained attention for their medicinal value. Numerous studies, mostly conducted in Japan, have demonstrated that LEM increases immune system function by stimulating production of lymphocytes and macrophages, the immune system's defense against bacteria, viruses, and tumor cells. LEM may also interfere with the action of reverse transcriptase (an enzyme that aids in viral replication) and block cell receptor sites of viruses. Owing to these properties alone, LEM shows promise in treating cancer, diseases related to immune system dysfunction, and viral infections.

**USES IN CFS/ME.** Most patients with CFS/ME use LEM as a general treatment for lethargy, weakness, and exhaustion, three primary symptoms of CFS/ME. A number have reported improvement in stamina, energy, and strength, decreased diarrhea, and increased white blood cell count after taking LEM.

**PROTOCOL.** Shiitake extract is usually sold in liquid or tablet form. The suggested dose is 40 drops of liquid, taken twice daily. Up to eight tablets may be taken a day. As with other medications, patients with CFS/ME should start with smaller doses and gradually increase to the full dose.

**PROS AND CONS.** LEM is one of the few botanical products that affects CFS/ME as a whole. A number of patients report general improvement and lessening of some of their worst symptoms. LEM may provoke a severe allergic reaction in patients with allergies to mushrooms, molds, and other fungi. Those with recurring yeast infections, athlete's foot, or thrush should probably delay trying LEM until these problems are resolved.

**AVAILABILITY AND COST.** Shiitake extracts are widely available in health food stores and through internet suppliers. Vitacost sells a 2-oz bottle of pure shiitake extract made by Planetary Herbals for \$12. Source Naturals markets a bottle of 40 tablets for about \$15.

## FURTHER READING

“Mushroom Extracts: Exciting News for Good Health.” *Neenyah Ostrom's article on LEM and CFS/ME.* <http://www.immunesupport.com/news/93fal003txt.htm>  
*Sloan Kettering's very thorough review of shiitake extract:*  
<http://www.mskcc.org/cancer-care/herb/shiitake-mushroom>

## MAITAKE EXTRACT

**BACKGROUND.** The maitake (*Grifola frondosa*) is a large mushroom that resembles Elizabethan neck ruffles. It grows in clusters at the base of oak trees in

Japan and North America. Maitake mushrooms are used in Asian cuisine, and because of their size (up to 50 pounds) are known as the “king” of mushrooms. Maitake mushrooms are rich in nutrients, including B vitamins, magnesium, potassium, and calcium.

In the late 1980s an active constituent in maitake, a beta-glucan compound, was found to enhance immune activity. Studies have shown that whole maitake also has the ability to regulate blood sugar and blood pressure, as well as insulin, lipids and cholesterol. Recent research has shown that maitake also has antioxidant and anticancer properties.

**USES IN CFS/ME.** People with CFS/ME use maitake extract as an immune system stimulator, particularly of NK (natural killer) cells. (Low NK cell activity has been well documented among CFS/ME patients.)

**PROTOCOL:** Maitake capsules should be taken on an empty stomach. The standard dose for 300 mg capsules is one to three capsules taken twice daily.

**AVAILABILITY AND COST.** Iherb.com markets a full spectrum maitake extract made by Mushroom Science for \$24 for a bottle of 90 capsules.

#### FURTHER READING

*Extensive list of many maitake extracts:* <http://www.vitasprings.com/maitake.html>

#### RESEARCH

Yeh JY, Hsieh LH, Wu KT, Tsai CF. “Antioxidant properties and antioxidant compounds of various extracts from the edible basidiomycete *Grifola frondosa* (Maitake).” *Molecules*. 2011 Apr 15;16(4):3197-211.

<http://www.ncbi.nlm.nih.gov/pubmed/21499220> (Abstract)

#### CORDYCEPS

**BACKGROUND.** Cordyceps is a fungus that grows on the larvae of the caterpillar, *Hepialus armoricanus Oberthuer*, found in China and Tibet. (Traditionally, the product contains both the fungus and its caterpillar host.) Cordyceps has been used in China to treat a wide range of conditions including fatigue, sexual dysfunction, and coughs. It is an adaptogen and immune stimulant.

Cordyceps has also been found to increase red blood cells, and to stimulate the production of testosterone (which is perhaps why it is used for sexual dysfunction). Research conducted primarily in China has also found cordyceps beneficial in increasing cellular oxygen absorption, protecting the liver, enhancing the immune system (by increasing natural killer cell activity), and improving shortness of breath and fatigue in patients suffering from chronic heart failure.

**PROS AND CONS.** CFS/ME patients have reported that cordyceps gives them a boost. It also reduces “air hunger” and increases stamina.

#### MORE INFORMATION

*Sloan-Kettering's page on cordyceps:* <http://www.mskcc.org/cancer-care/herb/cordyceps>



“Dr Oz: Chronic Fatigue Syndrome, Cordyceps & D5 Ribose Sweetener.”

<http://www.drozfans.com/dr-ozs-advice/dr-oz-chronic-fatigue-syndrome-cordyceps-d5-ribose-sweetener/>

“Cordyceps Chinensis.” *Everything you could possibly want to know about Cordyceps.* <http://mdidea.com/products/herbextract/cordyceps/data06.html>

“Mushroom remedy 'makes you fit' A Chinese mushroom improves the fitness of middle-aged and elderly people, research suggests.”

<http://news.bbc.co.uk/2/hi/health/3638543.stm>

NAC (N-acetylcysteine )

DESCRIPTION. N-acetylcysteine (NAC) is a derivative of cysteine, an amino acid.

BACKGROUND. NAC acts as an antioxidant, and is a precursor to glutathione. Clinically, it has been used to treat acetaminophen (paracetamol in Britain) overdose. It has also been used to reduce the viscosity of mucus in pulmonary conditions such as pneumonia, bronchitis, emphysema and tuberculosis. NAC is commonly used in patients with renal impairment. It is being explored as a possible treatment for both schizophrenia and bipolar disorder. NAC's ability to counteract glutamate hyperactivity in the brain also make it a good candidate for treating obsessive-compulsive disorder. NAC is also a chelating agent for mercury, and can be used for mercury toxicity.

USES IN CFS/ME. NAC can inhibit muscle fatigue after exercise. Reid et al, in a 1994 study, showed that pre-treatment with NAC improved performance of muscles during exercise. They suggested that “oxidative stress plays a causal role in the fatigue process” and that NAC “may be useful clinically.”

Research on NAC has shown that it is effective in reducing depletion of glutathione. People with CFS/ME are demonstrably low on glutathione. However, direct supplementation with glutathione is problematic because glutathione is rapidly broken down in the gut. Taking glutathione precursors, such as NAC, allows the body to synthesize glutathione on its own.

PROTOCOL. Martin Pall has speculated that because NAC rapidly releases cysteine, it may cause neural excitotoxicity. He recommends using NAC at low doses.

PROS AND CONS. NAC is generally well tolerated. However, in those who are sensitive to stimulants, it can cause insomnia and headaches. NAC is contraindicated for people with kidney stones.

AVAILABILITY AND COST. NAC is available at health food stores and from online suppliers. It is inexpensive. A 60-capsule bottle of Carlson NAC (500 mg) costs about \$8 (through Vitacost).

#### FURTHER READING

Kelly GS. “Clinical applications of N-acetylcysteine.” *Altern Med Rev.* 1998 Apr;3(2):114-27. <http://www.ncbi.nlm.nih.gov/pubmed/9577247> (Abstract)

Kerksicki, Chad and Darryn Willoughby. "The Antioxidant Role of Glutathione and N-Acetyl-Cysteine Supplements and Exercise-Induced Oxidative Stress." *Journal of the International Society of Sports Nutrition* 2005, 2:38-44.

<http://www.jissn.com/content/2/2/38> (This is a review of research into glutathione and NAC in exercise-induced muscle fatigue.)

Reid MB, Stokić DS, Koch SM, Khawli FA, Leis AA. "N-acetylcysteine inhibits muscle fatigue in humans." *J. Clin. Invest.* 1994 Dec;94(6):2468-74.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC330079/>

## NADH (ENADA)

**DESCRIPTION.** NADH is the reduced form of nicotinamide adenine dinucleotide (NAD), also called ubiquinone reductase. It is found in all living cells.

**BACKGROUND.** NADH was first discovered in the 1930s by an American scientist who observed that NADH played an essential role in the energy production of cells. It was not until more than 60 years had passed, however, that Dr. Georg Birkmayer, a biomedical researcher from Vienna, Austria, developed a stable oral form of NADH. Since then, a growing body of research has documented that NADH not only acts as a driving force in the production of cellular energy, but also is a potent antioxidant, is a key component of DNA repair and cellular regeneration, and stimulates the production of the neurotransmitters dopamine, noradrenaline, and serotonin. Ongoing research in the United States and abroad may help define the role of NADH in treating such degenerative neurological conditions as Alzheimer's disease and Parkinson's disease.

**USES IN CFS/ME.** NADH may be of great benefit in treating CFS/ME. When NAD is oxidized (NAD<sup>+</sup>) in the cell's mitochondria, energy is released. This energy is preserved in the form of adenosine triphosphate (ATP), a substance required by all energy-absorbing processes in the body.

Researchers have proposed that NADH may help correct the metabolic defect in CFS/ME that inhibits the production of ATP. Because low ATP production means less energy, clinicians believe NADH may alleviate CFS/ME-related exhaustion and may also improve cognitive function. The three neurotransmitters stimulated by NADH serve critical functions in the central nervous system: dopamine is important for short-term memory; noradrenaline contributes to alertness; and serotonin has a pronounced effect on mood and regulates sleep.

In 1999 Forsyth et al conducted a trial of NADH (as ENADA, a stable, bioavailable form of NADH) on 26 CFS/ME patients. Thirty-six percent of the CFS/ME patients taking NADH responded favorably, as opposed to 8% on placebo. No adverse effects were noted. In a longer term, open-label phase of the study, Birkmayer reports that "72% of the patients continued to report an improvement of their symptoms after six months of taking 10 mg ENADA daily. After approximately one year of taking ENADA the research doctors are reporting up to 81 percent of the patients continue to benefit from ENADA. These findings suggest that long-term ENADA therapy can lead to continued improvements, especially in energy and mental/ cognitive status."

While these results looked promising, there has been little follow-up on the initial trial with ENADA. Dr. Myhill lists ENADA as one of the CFS treatments “not worth trying” (along with graded exercise, CBT, and cold baths). As Dr. Myhill puts it, “It is the old story - single interventions are highly unlikely to result in worthwhile improvements because CFS is a complex problem - it is the combined approach that gets the results.”

**PROTOCOL.** Although Forsyth et al used 10 mg a day, the suggested starting dosage of NADH is 5 mg/day, (though some people report taking as much as 15 mg). The dosage is dependent on weight. Heavier people will need a higher dose to see an effect. NADH should be taken first thing in the morning on an empty stomach (about 20 minutes before your first meal).

Dr. Lapp recommends NADH in combination with acetyl-L-carnitine for his patients with severe “brain fog.” He observes that it can take three to six months to produce a response. Dr. Lapp recommends a dosage of 10 to 20 mg per day.

Patients note that sublingual NADH tablets are more effective than oral forms.

**PROS AND CONS.** Some patients report that NADH is moderately to mildly helpful, “making bad days somewhat less bad and good days somewhat better” (*CFIDS Chronicle*, Summer 1996). The majority of patients who take NADH note that it helps with cognitive symptoms more than fatigue.

**AVAILABILITY AND COST.** NADH is classified as a supplement and therefore does not require a prescription. Source Naturals sells a 60-tablet bottle of reduced Enada-NADH (5 mg) for \$40 through Vitacost. PureFormulas.com sells a 30-tablet (10 mg) pack made by Physiologics for \$38.50. Vitacost's own brand of sublingual NADH (10 mg) costs \$20 for a packet of 30 tablets. A 30-tablet box of 5 mg ENADA costs \$22.25 through the official ENADA website.

## MORE INFORMATION

*The official ENADA site, containing product and brand information:*  
<http://www.enada.com/>

## FURTHER READING

*Dr. Birkmayer's review of ENADA, including summaries of trials, and recommended dosage.* <http://www.encognitive.com/node/5059>

*Patient thread on NADH. Includes references to several studies, responses and dosage.* <http://forums.phoenixrising.me/archive/index.php/t-5096.html>

## RESEARCH

Forsyth LM, Preuss HG, MacDowell AL, Chiazzie L Jr, Birkmayer GD, Bellanti JA.

“Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome.” *Ann Allergy Asthma Immunol.* 1999 Feb;82(2):185-91.

<http://www.ncbi.nlm.nih.gov/pubmed/10071523> (Abstract)

## PROBIOTICS

**DESCRIPTION.** Probiotic bacteria, primarily *Lactobacillus acidophilus* and *Bifidobacterium bifidus*, aid in many digestive processes and help maintain balance in the intestines.

**BACKGROUND.** Digestive tract bacteria (intestinal flora) have evolved within humans to aid in completing the breakdown and absorption of many foods. Without the thousands of "friendly" bacteria that inhabit the intestines, malnutrition would develop no matter how much food was eaten. These bacteria not only aid in digestion, but are responsible for manufacturing many nutrients that are essential to survival, such as the B vitamin complex. Some bacteria, such as *bifidus*, live in the large intestine; others, such as *acidophilus*, live in the small intestine.

As long as the intestinal flora are working well, a minimum of digestive problems can be expected. However, once the function of friendly flora is upset, harmful bacteria can proliferate, causing bloating, stomach upset, poor digestion, constipation, gas, and malabsorption problems. The most common sources of flora upset are recurrent use of antibiotics, oral contraceptives, aspirin, corticosteroids, poor diet, stress, and *Candida* infections. In these cases, it may be necessary to use a probiotic supplement to reestablish a healthy balance of intestinal flora.

A number of studies have shown that intestinal flora are effective for treating intestinal problems. In a review of probiotic treatments for diarrhea, Guandalini found that several strains of probiotics, including *Lactobacillus GG*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium ssp*, *Streptococcus ssp*, and the yeast *Saccharomyces boulardii*, were effective in combating diarrhea due to antibiotics, *C. difficile* and viruses. Two strains, *Lactobacillus GG* and *Saccharomyces boulardii* were particularly effective. Researchers have also found probiotics helpful in treating irritable bowel syndrome and inflammatory bowel disease, suggesting a possible link between these two conditions.

**USES IN CFS/ME.** Patients with gastrointestinal symptoms or recurring yeast infections, or who regularly take antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, or cortisone are advised to use a probiotic supplement. Products that contain *bifidus* seem to help with leaky gut.

Generally, people with CFS/ME appear to suffer from a deficiency in friendly flora. According to a study by Butt et al in Australia, the colonic bacterial population in CFS/ME patients is deficient in *Bifidobacterium* and *E. Coli*. In contrast, the lactic acid bacteria, *Enterococcus*, is significantly higher – 28.7% of the total aerobic flora in CFS/ME patients – than in the healthy subjects (3-5%).

Remarkably, the researchers found that specific changes in gastrointestinal flora were associated with CFS/ME symptoms. A high enterococcal count positively correlated with neurological and cognitive functions: nervousness, memory loss, forgetfulness, confusion, and "mind going blank." Similarly a high aerobe/anaerobe ratio significantly correlated with poor colonic functions, poor digestion, and malabsorption of the gastrointestinal tract. The implications of this study are that the composition of bacterial flora has a significant impact on both digestion and the nervous system, and that in people with CFS/ME the two are linked.

In an interesting paper published in 2003, Logan et al proposed that probiotics might serve to enhance immune function in people with CFS/ME. The authors pointed out that people with CFS/ME have marked alterations in intestinal flora as well as oxidative stress. They state that “lactic acid bacteria (LAB) have the potential to influence the immune system in CFS patients by supporting . . . cellular immunity and may decrease allergies. In addition LAB are strong antioxidants, may improve EFA status, can enhance absorption of micronutrients by protecting the intestinal epithelial barrier.” The authors suggested that lactic acid bacteria might have a therapeutic role in the treatment of CFS/ME.

Probiotics may be useful for other reasons as well. Due to disruptions in the balance of neurotransmitters which are responsible for maintaining gut motility, people with CFS/ME often have motility problems. When motility is slowed, the bacteria from the large intestine can travel upward, where they colonize the small intestines. This leads to a condition known as SIBO (small intestinal bacterial overgrowth). Once established in the small intestines, the bacteria interfere with the breakdown of fats and carbohydrates. According to Dr. Cheney, a significant percent of the CFS/ME population suffers from SIBO. The standard treatment for SIBO is antibiotics, which, ironically, are also the primary cause of SIBO. Many gastroenterologists recommend treatment with probiotics, in particular *Lactobacillus GG* for SIBO in order to restore beneficial flora after antibiotic treatment.

**PROTOCOL.** Probiotics are sold in different forms. Each should be taken according to directions. Enteric-coated tablets, for example, need to be taken only once a day and can be taken with food, because the enteric coating protects the bacteria from being destroyed by stomach acids. Patients with altered intestinal flora as a result of taking antibiotics need to take a probiotic supplement for a least two weeks after finishing the treatment to repopulate the intestines. Single-strain varieties are reported to be more effective than multiple strains.

**PROS.** Most patients with CFS/ME who regularly take probiotics report easing of gastrointestinal symptoms (especially gas and bloating) and overall improvement in digestion. One of the main advantages of probiotics is that they can be taken daily for months, or even years, without causing any adverse effects or loss of benefits. They rarely cause side effects and are safe for children.

**CONS.** Probiotics are not without risk. There is some concern in the medical community about the safety of probiotic supplements (which is why it is important to purchase reputable brands). Probiotics should be used to caution in individuals with an abnormal gastrointestinal mucosal barrier (leaky gut), due to the risk of the bacteria penetrating the intestinal wall. Some people with CFS/ME who have been diagnosed with SIBO sometimes report experiencing flares and “brain fog” after taking probiotics, especially if the initial infection has not been eradicated.

**AVAILABILITY AND COST.** Many good brands of probiotic supplements can be purchased from health food stores and vitamin catalogs. Vitacost sells a package of 30 capsules of Culturelle (*Acidophilus GG*) for \$15. Vitacost sells a 50-capsule

bottle of *Saccharomyces boulardii* made by Allergy Research Group for about the same price.

Acidophilus can also be found in foods such as yogurt and kefir, although these are more effective at maintaining intestinal balance once it has been corrected. Foods such as miso and tofu can enhance bifidus growth, as can a number of vegetables that provide intestinal substrate (fructo-oligosaccharides (FOS) and inulin) in which the bacteria can flourish.

#### FURTHER READING

*CFS/ME forum discussing some of the risks of probiotics.*

<http://forums.phoenixrising.me/archive/index.php/t-8976.html>

“Intestinal Flora.” *Very good website with research and specific information on intestinal flora.* <http://www.probiotic.org/intestinal-flora.htm>

“Probiotics in Clinical Practice: An Update.” *Good general information about the clinical use of probiotics:* <http://www.ecologyhealthcenter.net/node/839>

“An Emerging Trend of High Dose Probiotic Use in Clinical Practice- A Brief Survey.” October 2011.

<http://www.pointinstitute.org/resources/Point+Inst.+High+Dose+Probiotics+Oct.+2011.pdf>

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#### RESEARCH

Butt H. L., Dunstan R. H., McGregor N. R., Roberts T. K. “Bacterial colonosis in patients with persistent fatigue.” *Proceedings of the AHMF International Clinical and Scientific Conference*; 2001 Dec 1–2; Sydney, Australia.

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Gibson GR, Beatty ER, Wang X, Cummings JH. “Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin.” *Gastroenterology*. 1995 Apr;108(4):975-82.

<http://www.ncbi.nlm.nih.gov/pubmed/7698613> (Abstract)

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<http://www.ncbi.nlm.nih.gov/pubmed/21992955> (Abstract)

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<http://www.cfids-cab.org/cfs-inform/Hypotheses/logan.etal03.pdf>

Ku WH, Lau DCY, Huen KF. "Probiotics Provoked D-lactic Acidosis in Short Bowel Syndrome: Case Report and Literature Review." *HK J Paediatr* (New Series) 2006;11:246-254. <http://hkjpaed.org/details.asp?id=577&show=1234>

### PIRACETAM (Nootropil, Lucetam)

**DESCRIPTION.** Piracetam is a derivative of GABA (gamma-aminobutyric acid), the brain's primary neuroinhibitory amino acid.

**BACKGROUND.** Piracetam is a nootropic, or "smart drug." It has been used for a wide range of neurological impairments, including seizures, dementia, focal lesions in the brain, and concussions. There is also evidence that it can enhance cognitive performance among the healthy. In a study by Dimond and Brouwers, administration of piracetam for 14 days improved verbal memory in a group of college students. Piracetam appears to work not just by acting on cholinergic receptors, but by decreasing the viscosity of blood, which, in turn, enhances the delivery of oxygen to the brain.

**USES IN CFS/ME.** Piracetam is used more widely in Europe than in the U.S., where the FDA has determined that because it is not a vitamin, mineral, amino acid, herb, botanical, or other dietary substance, it is therefore not a supplement. Nor is it approved as a drug, which puts piracetam in the odd category (along with galantamine) of having no clinical status. As a consequence, there has not been a great deal of research done on piracetam for CFS/ME.

There is, however, a small but significant body of research that seems to indicate that piracetam would be appropriate for the treatment of cognitive impairment in CFS/ME patients. In one such study, researchers in Brazil found that piracetam protected the hippocampus (the part of the brain associated with the formation of new memories) during alcohol withdrawal. It has been widely noted that CFS/ME patients have difficulty forming new memories, which is crucial to learning.

Of even greater interest to CFS/ME patients is a study conducted in 2002 by Gabryel et al, in which piracetam was shown to protect the brain against hypoxic injury. Not only did the drug prevent cell damage, it stimulated mitochondrial function, increasing intracellular ATP. Given the growing body of evidence that people with CFS/ME not only experience lowered oxygenation of brain tissues, but loss of brain matter, this finding could point the way to effective treatment.

**PROTOCOL.** Dr. Teitelbaum recommends 1200 mg twice a day for 2 weeks, and then 2400 mg twice a day for 2 weeks to treat brain fog. He recommends that piracetam be taken with hydergine, a dopamine-stimulating nootropic. CFS/ME patients may wish to start with the recommended dosage, which is 400-800 mg a day. Those with insomnia and sensitivities to stimulants should begin at an even lower dose – 50 mg.

**PROS AND CONS.** There are very few reported side effects, but large doses can cause headache, restlessness and insomnia. Patients report good effects at very low doses (50 mg a day). Effects are similar to caffeine – a feeling of alertness, greater focus, and "being awake."

**AVAILABILITY AND COST.** Piracetam is available online. Amazon.com sells 60-capsule bottle of piracetam (800 mg) for \$23.42. This amounts to roughly \$1 for 2 grams. If the product works for you, bulk purchase is much less expensive.

#### FURTHER READING

“Living With Chronic Fatigue Syndrome” blog entry on piracetam.

<http://livingwithchronicfatiguesyndrome.wordpress.com/2011/04/04/piracetam-for-mecfs/>

*Patient experiences with piracetam*

<http://forums.phoenixrising.me/archive/index.php/t-9408.html>

#### RESEARCH

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<http://www.ncbi.nlm.nih.gov/pubmed/7639963> (Abstract)

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<https://www.ncbi.nlm.nih.gov/pubmed/826948> (Abstract)

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Waegemans T, Wilsher CR, Danniau A, Ferris SH, Kurz A, Winblad B. "Clinical efficacy of piracetam in cognitive impairment: a meta-analysis." *Dementia and geriatric cognitive disorders*. (2002)13 (4): 217–24.

<https://www.ncbi.nlm.nih.gov/pubmed/12006732> (Abstract)

Winblad, B. "Piracetam: a review of pharmacological properties and clinical uses." *CNS Drug Reviews* (2005)11 (2): 169–82.

[www.ncbi.nlm.nih.gov/pubmed/16007238](http://www.ncbi.nlm.nih.gov/pubmed/16007238) (Abstract)

#### ROYAL JELLY

**DESCRIPTION.** Royal jelly is a thick, milky substance secreted by young nurse honeybees to nourish the young larvae in a colony, especially the queen larvae.

**BACKGROUND.** Royal jelly is one of nature's most potent foods. It is rich in B vitamins (especially pantothenic acid), biotin, folic acid, and inositol. It also contains vitamins A, C, D, and E, seven minerals, 18 amino acids, fatty acids, enzymes and hormones, and is the only natural source of acetylcholine, the neurotransmitter that aids in memory. Health-enhancing properties attributed to royal jelly range from reducing cholesterol levels to healing skin disorders.

In 2011 a group of researchers found that royal jelly exerted a protective effect on the liver and kidneys of rats which had been given cisplatin, a cytotoxic agent used for chemotherapy. The beneficial effects of royal jelly were attributed to



a reduction of oxidative stress and apoptosis (cell death). Oxidative stress and increased cell apoptosis are commonly found in CFS/ME patients. Further research has indicated that royal jelly may be effective in reducing inflammation.

**USES IN CFS/ME.** Although CFS/ME doctors do not routinely prescribe royal jelly, it has been used by CFS/ME patients for decades. Royal jelly is a natural source of acetylcholine, a neurotransmitter some researchers believe is deficient in CFS/ME, which may be why it is effective in reducing muscle weakness some patients. Its anti-inflammatory properties make it well suited to mitigating pain. Royal jelly also provides an easily tolerated form of B vitamins. Many patients with CFS/ME who need B vitamins cannot tolerate yeast-based vitamin B products.

Steve Wilkinson, author of *Chronic Fatigue Syndrome: A Natural Healing Guide*, claims that royal jelly can help provide increased stamina and energy, greater mental alertness, and relief from muscle problems. He states that in his case the improvement in muscle pain was "dramatic" after just a few weeks of taking royal jelly.

In a pilot study conducted in England with ME patients, approximately 40 of the participants noted an improvement in energy and stamina. Twelve patients reported a decrease in muscle and joint pain. Another forty noted a decrease in depression. Eighty of the 109 participants said that royal jelly was beneficial.

**PROTOCOL.** Y&S Eco Bee Farms recommends taking ¼ teaspoon of royal jelly once or twice daily on an empty stomach, followed by a small amount of chilled water. Royal jelly can be taken for months. Some patients need two to three months before its benefits can be felt. Pure royal jelly (not mixed with honey) requires refrigeration because it spoils easily. Royal jelly should not be mixed into or consumed with anything hot.

**PROS.** Royal jelly is a safe, inexpensive supplement that provides some necessary nutrients, as well as acting as immune modulator. As the only natural source of acetylcholine (ACh), it is one of the safer treatments for the ACh deficiency posited in CFS/ME patients.

**CONS.** Allergic reactions to royal jelly are not unknown. Patients with a history of pollen allergies should be cautious in using royal jelly. Patients with allergies should be sure the royal jelly has not been mixed with other products (ginseng, bee pollen, honey) to avoid possible allergic reactions to these additives.

**AVAILABILITY AND COST.** Pure royal jelly is available as a thick liquid or in capsules. Ebeehoney.com sells a 2 oz jar of pure royal jelly for \$13. (Shipped with an ice pack.) Because royal jelly loses its potency when improperly handled or processed, it may be worthwhile to buy the purest form available. The refrigerated section of health food stores usually contains the most potent royal jelly products.

## FURTHER READING

*A pilot study of Irena Royal Jelly conducted on 109 ME patients:*

<http://www.irenesteinrj.com/files/ME%20REPORT.pdf>

*Suppliers of Y&S pure royal jelly:*

<http://www.yahwehsaliveandwell.com/ysroyaljelly.html>

*Online site for purchasing pure royal jelly:*

<http://www.ebeehoney.com/royaljelly.html>

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<http://www.ncbi.nlm.nih.gov/pubmed/14745176> (Abstract)

Yanagita M, Kojima Y, Mori K, Yamada S, Murakami S. "Osteoinductive and anti-inflammatory effect of royal jelly on periodontal ligament cells." *Biomedical Research*. 2011;32(4):285-91. <http://www.ncbi.nlm.nih.gov/pubmed/21878736> (Abstract)

## SAMBUCOL

**DESCRIPTION.** Sambucol is an extract made from the fruit of the European black elder tree (*Sambucus nigra L*), a member of the Adoxaceae family.

**BACKGROUND.** Black elderberry berries have long been used in Europe to make jams, jellies, soft drinks, and aromatic wines. In addition to its pleasant taste, elderberry is valued as a rich source of B vitamins and bioflavonoids, as well as minerals such as calcium and phosphorus. Medicinal use of black elderberry has been documented as early as the fifth century BC, when the ancient Greeks described it as a remedy for colds, flu, and upper respiratory tract infections. In the mid-1980s, researchers found that two of the active ingredients in elderberry inhibited the replication of the influenza virus by preventing the virus from entering cells.

In a continuation of that research, in 1992 a group of Israeli scientists and physicians formulated a black elderberry syrup that acted successfully against the influenza virus in a laboratory setting. Soon afterward, a double-blind, placebo-controlled study was conducted in patients with influenza in southern Israel. The results of that study indicated that black elderberry effectively reduced the duration and severity of influenza infections. Flu symptoms (fever, cough, and muscle pain) significantly improved in 20% of the patients within 24 hours, compared with 8% of the control group. Within three days, more than 90% of the patients were symptom free, compared with six or more days for the control group.

In 2011 a group of researchers from the Institute of Medical Biology in Germany found that standardized extract of elderberry inhibited viral replication of influenza A and influenza B. They also found that the extract possessed

antimicrobial activity against both gram-positive and gram-negative bacteria in liquid cultures. Another group of researchers in Austria found that a fraction of elderberry produced broad anti-inflammatory effects and supported “the traditional use of extracts and preparations of *Sambucus ebulus L.*, rich in ursolic acid, for the treatment of chronically inflammatory processes.” Results of further studies have also shown that elderberry extract can act against herpes virus and Epstein-Barr virus.

**USES IN CFS/ME.** The fact that Sambucol has such a wide range of antiviral effects may make it particularly useful for the many patients with CFS/ME who have frequent colds and flu. It may also be valuable for those who demonstrate reactivation of Epstein-Barr virus and other latent viruses, the effects of which can lead to many of the symptoms typical of CFS/ME. Many CFS/ME patients taking Sambucol have noted overall improvement (*Mass CFS/ME Update*, Fall 1995).

**PROTOCOL.** The recommended dosage of Sambucol syrup is 4 tablespoons daily in adults and 1 tablespoon daily in children younger than 12 years. Patients with CFS/ME should probably start with a smaller dose to check for tolerance. Sambucol should be taken on a full stomach. Dairy products should be avoided for 30 minutes before and after to avoid stomach upset. The manufacturers recommend refrigeration after opening.

**PROS.** Sambucol is an all-natural product, which is an advantage for patients with chemical and drug sensitivities. There are no reported side effects or contraindications associated with its use. Those who have tried it claim that it hastens recovery from flu and colds, and lessens general malaise. Sambucol is also safe for children, which is good news for parents of children with CFS/ME, because so few effective pediatric medications are currently available.

**CONS.** Some patients report allergy-type reactions (congestion, headache, dizziness) to elderberry. As fresh elderberry leaves and bark are poisonous (but not the berries), always purchase processed elderberry extracts with high flavonoid content from a reputable company. Do *not* make your own tea.

**AVAILABILITY AND COST.** Sambucol is currently marketed in the United States, Europe, Israel, and South Africa through health food stores and drugstores. The liquid extract contains glucose and honey for sweetening and raspberry extract to enhance flavor. If a glucose-free product is desired, Sambucol is available in lozenge form and as a liquid sweetened with sorbitol. Vitacost sells 4 oz bottle of liquid Sambucol for between \$10 and \$15. Lozenges in packs of thirty cost about \$7. Prices at retail outlets are generally considerably higher.

## FURTHER READING

*Complete information about the composition, effects and clinical research of elderberry extract.* <http://www.drugs.com/npp/elderberry.html>

## RESEARCH

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## SAMe

**DESCRIPTION.** SAMe (S-Adenosyl methionine), is a primary methyl group donor that is involved in the synthesis of neurotransmitters.

**BACKGROUND.** SAMe (pronounced "Sammy") was first discovered in Italy in 1952. It is a cornerstone in the methylation cycle, which is the biochemical process through which amino acids are transformed into neurotransmitters. (SAMe's contribution of its methyl group (CH<sub>2</sub>) is what converts an amino acid into a neurotransmitter.) It should not come as a surprise that SAMe plays a key role in mood, nervous system regulation, and maintaining energy levels, since all of these are regulated by neurotransmitters.

The first studies of SAMe's use in depression were conducted in Italy in the 1970s. Because SAMe is a primary methyl group donor, the authors concluded that depression could be linked to the methylation cycle. Since that time, there have been dozens of studies confirming the efficacy of SAMe in treating depression.

**USES IN CFS/ME:** Rich Van Konynenburg has proposed that in CFS/ME there is a partial block of the methylation cycle. This would cause a depletion of ATP, as well as reductions in neurotransmitters, detoxing agents such as glutathione, and impairment of normal immune system function. Because SAMe is a vital component of the methylation cycle, Dr. Myhill recommends it as an all-round support.

**PROTOCOL.** SAMe should be taken on an empty stomach. Low doses, ranging from 50 to 100 mg/day are recommended. (Ray Sahelian advises taking half of a tablet, and storing the rest for the next day.) Because SAMe can produce insomnia, it is best taken in the morning. SAMe is highly unstable, and should be stored in a cool, dry place to prevent deterioration. SAMe should be taken with vitamin B6, B12 and folic acid as adjuncts.

**PROS AND CONS.** SAMe appears to have few side effects. But as with any product that affects the central nervous system (even indirectly), care should be exercised. While most people feel an immediate improvement in mood and focus,

some sensitive individuals can experience side effects typical of stimulants (jitters, insomnia, headache, anxiety). SAME raises levels of all neurotransmitters, so it is difficult to predict how any individual person may respond.

**AVAILABILITY AND COST.** SAME is available in health food stores and from online suppliers. A package of 20 foil-wrapped enteric-coated tablets (200 mg) costs \$10 through Vitacost.

SEE: Van Konynenburg/Yasko Methylation Protocol

#### FURTHER READING

*Ray Sahelian on SAME:* <http://www.raysahelian.com/sam-e.html>

*Dr. Myhill discusses the methylation cycle:* [http://drmyhill.co.uk/wiki/CFS -  
The Methylation Cycle](http://drmyhill.co.uk/wiki/CFS_-_The_Methylation_Cycle)

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#### VITAMINS

Vitamin A, Beta-Carotene, Vitamin B12, Vitamin B6, Vitamin B Complex, Vitamin C, Vitamin D, Vitamin E and Tocotrienols

**DESCRIPTION.** Vitamins are organic (carbon-containing) substances needed in tiny amounts to promote biochemical reactions within living cells.

**BACKGROUND.** Vitamins, as independent biochemical agents, were discovered around the turn of the century when an English biochemist proposed that diseases such as rickets and scurvy were most likely caused by a lack of "accessory food factors" in the diet. After observing that these diseases could be corrected by adding certain foods (whole rice, which is high in vitamin B, to cure rickets; and oranges, an easy source of vitamin C, to cure scurvy), scientists began to search for chemical compounds in these foods that could produce such extensive changes in the body. When these accessory food factors were finally isolated in food, the name "vita-mine" was proposed (from the Latin *vita*, necessary for life, and *amine*, a chemical substance containing nitrogen). Later, when it was discovered that not all vitamins were amines, the final "e" was dropped.

There are thirteen known vitamins, all of which act as catalysts, or more specifically, coenzymes; that is, they initiate or speed chemical reactions in cells while remaining unchanged themselves. They accomplish their task mainly by

combining with a protein-containing apoenzyme (vitamins contain no protein) to form a complete enzyme. The completed enzyme performs the role of biochemical catalyst, enabling most of the body's vital cell functions to occur in an orderly and efficient manner. Without vitamins, many essential cell functions would cease, resulting in any number of vitamin deficiency-related diseases and problems. Most vitamins must be obtained from food because the body rarely manufactures them in adequate amounts (vitamin K is the exception).

**USES IN CFS/ME.** Most CFS/ME physicians and clinicians include vitamin supplementation as a part of a general treatment protocol. The reasons vitamin supplementation is considered such a central part of CFS/ME treatment are threefold. First, the ill body consumes vitamins much faster than the healthy body. Patients, particularly those with long-term illnesses, need vitamins in amounts that exceed those which can be derived from food, especially when (as in CFS/ME) the illness causes certain metabolic defects.

Second, at least 50% of patients with CFS/ME have absorption problems (leaky gut, low stomach acid production, or other gastrointestinal difficulties). When food is improperly digested, vitamins are not extracted efficiently, necessitating some kind of supplementation.

Third, as has been pointed out by a number of researchers, the particular nature of CFS/ME immune system activation prevents some vitamins from working properly. The excess cytokine production that blocks vitamin C function, for example, is justification enough for supplementation.

The most frequently recommended vitamin supplements are vitamin C and B12, but general wide-spectrum supplements are also important. Benefits of vitamin supplementation generally are not apparent for several weeks, but some undernourished patients notice significant effects within a few hours. Many CFS/ME patients report an overall improvement in vitality, energy level, and stamina with vitamin supplementation. Few report any adverse effects (and these are usually remedied by switching brands).

**AVAILABILITY AND COST.** Vitamins are easily obtained from supermarkets, health food stores, pharmacies, and online suppliers. Vitacost markets a good multi-vitamin/mineral supplement made by Carlson for \$8.50 (90 gelcaps).

Care should be taken to purchase high-grade vitamins because the excessive heat and poor handling to which low-grade vitamin products are exposed often cause fat-soluble vitamins to become rancid and can considerably reduce the efficacy of water-soluble vitamins. Excess filler also makes some cheaper vitamins difficult to dissolve. (A good test for vitamin tablets is to place one in a small glass of lemon juice. If it doesn't dissolve in the lemon juice, it won't dissolve in your stomach.) With the exception of vitamin E, synthetic vitamin preparations are as effective as natural vitamins.

In addition to a wide-spectrum vitamin supplement, many CFS/ME physicians recommend taking extra amounts of specific vitamins for the purposes of

providing added antioxidant protection, for immune system enhancement, or to compensate for the functional deficits common to the illness.

#### FURTHER READING

*General information about vitamins (and other) supplements for CFS/ME patients.*

<http://www.cfids.org/archives/2004/2004-1-article04.asp>

#### VITAMIN A

**DESCRIPTION.** Vitamin A (retinol) plays a variety of roles in human metabolism. It helps maintain the health of the skin and all mucous linings of the body (stomach, intestines, bladder, mouth, nose, throat, windpipe, and other air passages). It is essential for vision. Vitamin A also increases resistance to infections and is involved in the maintenance of the adrenal cortex, where cortisol is formed.

**USES IN CFS/ME.** Vitamin A is primarily used to help maintain mucous membranes, which are often compromised in CFS/ME. Patients prone to intestinal, respiratory, or ear infections also take vitamin A to boost immune system efficiency. There have been attempts in the past to redefine vitamin A as an "anti-infective agent." However, because its protective capacity is limited to bacterial infections of the mucous membranes, these have been abandoned.

The recommended daily allowance for vitamin A is 5000 IU a day. Because vitamin A is fat soluble, it can be stored in the liver, which means it can be taken less frequently in larger doses. A physician or nutritionist should be consulted before taking larger doses, however, to prevent possible overdosing. Loss of appetite, irritability, widespread itching, headaches, and mouth ulcers are all signs of vitamin A toxicity. People with low thyroid function must take vitamin A supplements, as the thyroid is responsible for converting beta-carotene into vitamin A.

**AVAILABILITY AND COST.** Vitamin A is available from health food stores, many pharmacies, and some supermarkets. The form of vitamin A most easily absorbed is micellized A, a liquid suspension sold in health food stores. The best natural sources of vitamin A are animal products (liver, whole milk, butter, and cheese). Fish liver contains huge amounts of vitamin A (200,000 to 1 million IU, depending on the type). Pregnant women should not take more than 5000 IU of vitamin A, because higher doses have been associated with birth defects.

#### BETA-CAROTINE

**DESCRIPTION.** Beta-carotene is the precursor to vitamin A. When foods containing beta-carotene (yellow or orange vegetables) are ingested, the liver converts the beta-carotene to vitamin A. However, unlike vitamin A it cannot be stored in the body and therefore entails far fewer risks of toxicity, although its function remains largely the same. Like vitamin A, beta-carotene strengthens mucous membranes. It also helps protect against skin and lung cancer and improves the functioning of the thymus gland (where T cells are produced). There is no recommended daily allowance for beta-carotene, but people who take large

amounts often notice that certain areas of their skin, particularly the palms and around the fingernails, turn yellowish orange. This condition is called carotenemia and, while benign, is a sign that too much beta-carotene is being consumed. Patients with diabetes or hypothyroid conditions should avoid taking beta-carotene because they cannot convert it to vitamin A.

**USES IN CFS/ME.** Beta-carotene is one of the vitamins mentioned by clinicians as having particular value in CFS/ME. Dr. Burke Cunha proposed that one of the chief benefits of beta-carotene for CFS/ME patients lies in its ability to stimulate the production of natural killer cells (*CFIDS Chronicle*, Fall 1993). He found that among the majority of his patients who tested low in natural killer cells, high doses of beta-carotene resulted in an increase in the number of these cells. He also found less fatigue in these patients. (Patients with normal numbers of natural killer cells before therapy showed less improvement, however.)

Dr. Cunha postulated that by increasing natural killer cell production, beta-carotene may serve as an effective antiviral agent. He recommended a high dose (25,000 to 50,000 IU/day, depending on the patient's needs), but cautioned that high doses of beta-carotene should not be taken for more than three weeks to prevent carotenemia and vitamin A toxicity. Most clinicians recommend a daily dose of 5000 to 10,000 IU in combination with other antioxidants to prevent carotenemia.

#### FURTHER READING

*Dr. Cunha on beta-carotene supplementation for CFS/ME patients.*

<http://www.immunesupport.com/94wtr007.htm>

*CFS/ME patient ratings of beta-carotene:* <http://www.revolutionhealth.com/drugs-treatments/rating/beta-carotene-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### VITAMIN B12

**DESCRIPTION.** Vitamin B12 (cobalamin) is a member of the B vitamin complex. It is naturally found in animal products and is required for proper digestion, food absorption, protein synthesis, metabolism of carbohydrates and fats, myelin synthesis, nerve function, and activation of folic acid (used in the formation of red blood cells). Its name is derived from cobalt, the mineral to which this vitamin is bound. When cobalamin is ingested, contact with stomach enzymes splits it apart, freeing it to join with a special protein called "intrinsic factor," which is secreted by the stomach lining. Only when vitamin B12 combines with intrinsic factor – which converts the cobalamin into methylcobalamin – can it be absorbed by the body. Because vitamin B12 is highly unstable outside the body, cyanocobalamin, a synthetic form of B12, is normally used in supplements. Oral vitamin B12 cannot be absorbed in malabsorptive states such as pernicious anemia.

**USES IN CFS/ME.** Although the traditional use for vitamin B12 injections has been limited to the treatment of anemia, Dr. Charles Lapp and Dr. Paul Cheney have observed that such injections are highly beneficial to their CFS/ME patients, even in the absence of vitamin B12 deficiency or any sign of anemia. They report



that some 50% to 80% of their patients demonstrate improved stamina and energy with vitamin B12 therapy (*CFIDS Chronicle*, Fall 1993).

Dr. Cheney was first motivated to include vitamin B12 in his general treatment plan after seeing evidence that vitamin B12 injections had been helpful in a number of nonanemic neuropsychiatric patients. These patients had demonstrated some of the symptoms common to CFS/ME (paresthesia, sensory loss, loss of coordination, and mood swings), all of which improved with vitamin B12 injections. Dr. Cheney theorized that vitamin B12 injections work so well among CFS/ME patients because the elevated rate of cytokine production in CFS/ME may be effectively blocking vitamin B12 function in the body. In this case, massive amounts of vitamin B12 would be needed to overcome the functional deficiency brought about by excess cytokine production.

Vitamin B12 may also help correct the red blood cell abnormalities in CFS/ME patients discovered by New Zealand researcher Dr. Leslie O. Simpson (*CFIDS Chronicle*, Fall 1995). Dr. Simpson observed that hydroxocobalamin injections corrected this defect by increasing production of disc-shaped cells. About 50% of the patients in this group felt better with B12 injections.

Dr. Myhill, in her explanation of the benefits of B12 in CFS/ME patients, observes that B12 is a powerful free radical scavenger, particularly of nitric oxide. (People with CFS/ME have high levels of nitric oxide.) In addition to mitigating the harmful effects of nitric oxide, B12 also helps correct one of the immune system abnormalities found in CFS/ME patients. According to Dr. Cheney, CFS/ME patients experience a shift from Th1 (cellular) to Th2 (humoral) immunity. In essence, the immune system is skewed in favor of B cells (which search for pathogens in the bloodstream) rather than searching for pathogens within cells. This imbalance allows for the proliferation of viruses within cells. According to Dr. Bell, vitamin B12 is one of the most effective means of re-orienting the immune system back to Th1 (cellular) immunity.

**PROTOCOL.** The dosage Dr. Cheney recommends is 2000 to 5000 ug/ml (in a 0.5 to 1.0 cc syringe) administered subcutaneously or intramuscularly every two or three days. Other physicians generally recommend 1000 to 2000 ug (1 to 2 cc syringe) one to three times a week. Dr. Myhill starts with ½ mg (500 mcgms) daily by subcutaneous injection. Dr. Lapp says that to obtain a “continuous and satisfactory level of improvement,” 3000 mcg of cyanocobalamin every two to three days should be administered.

High doses of vitamin B12 must be accompanied by a multivitamin that includes the entire vitamin B complex to avoid B vitamin imbalances. This dosage can be tolerated over long periods, although benefits can wane. In that case, a short period without vitamin B12 injections (1 to 2 weeks) is usually enough to reestablish its efficacy. Most physicians prefer cyanocobalamin to hydroxocobalamin because it is the most stable form of vitamin B12. However, some patients who cannot tolerate cyanocobalamin prefer the more bioavailable, and longer acting, hydroxocobalamin.

**PROS.** Most patients who take vitamin B12 injections report favorable results. Common benefits include increased energy, mental clarity, and stamina, usually lasting for several days after a single administration. Because benefits may not be felt for the first three to six weeks, a month's trial is generally recommended.

**CONS.** Although vitamin B12 is fairly innocuous, some patients report side effects. The most common side effect is lassitude. Some patients also report local rashes, which diminish when dosage is reduced, and various allergic reactions (including diarrhea) to the preservatives used in the solution. To avoid potential allergic reactions, a patch test should be performed first. Administration of the first injection in a physician's office is also recommended in highly allergic individuals.

**AVAILABILITY AND COST.** The most effective form of B12 is injectable vitamin B12, available by prescription. After injections, the most easily absorbed form of B12 is via nasal spray, also available by prescription. For those who do not have a doctor willing to prescribe B12, there are both sublingual and oral spray forms that are fairly well absorbed. (Don't waste your money on oral tablets and capsules. They are very poorly absorbed.) Perque markets activated sublingual hydroxocobalamin (2000 mcg) for about \$30 (100 lozenges). (Take one a day.) PureFormulas.com markets B12 spray (with B6 and folic acid) made by NOW for \$12.59.

#### FURTHER READING

*Dr. Lapp's B12 recommendations:* <http://www.cfids.org/archives/1999/1999-6-article03.asp>

*Dr. Myhill's excellent explanation of why B12 works in CFS/ME patients.*  
[http://www.drmyhill.co.uk/wiki/B12\\_-\\_rationale\\_for\\_using\\_vitamin\\_B12\\_in\\_CFS](http://www.drmyhill.co.uk/wiki/B12_-_rationale_for_using_vitamin_B12_in_CFS)

*B12 Basics – very detailed:* <http://forums.phoenixrising.me/showthread.php?11522-Active-B12-Protocol-Basics/>

*Informative patient thread on the uses of B12 for treating CFS/ME.*

<http://www.prohealth.com/fibromyalgia/blog/boardDetail.cfm?id=1318273>

#### RESEARCH

van Asselt, D Z B, F W H M Merkus, F G M Russel, and W H L Hoefnagels. “Nasal absorption of hydroxocobalamin in healthy elderly adults.” *Br J Clin Pharmacol.* 1998 January; 45(1): 83–86.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1873990/>

#### VITAMIN B6

**DESCRIPTION.** Vitamin B6 (pyridoxine, pyridoxal, and pyridoxamine), is one of nature's busiest vitamins. It is involved in more than one hundred essential chemical reactions in the body, including making amino acids and neurotransmitters, metabolizing energy, balancing hormones, and supporting the immune system. High doses of B6 have been shown to decrease colorectal cancer rates. Vitamin B6 is also used to prevent heart disease by lowering cholesterol, to

treat the nausea and vomiting associated with morning sickness, and, because of its importance in nervous system function, to treat various CNS conditions, including depression, schizophrenia and ADD.

**USES IN CFS/ME.** A study published in 1999 by a group of British researchers found that CFS/ME patients had reduced functional status of B vitamins, particularly B6. Because B6 is vital to so many neuroendocrine reactions, a deficiency can result in impaired sleep (due to B6's role in converting glutamate to GABA), hypoglycemia (due to the role of B6 in neoglucogenesis), and neuropathy (damage to the peripheral nervous system). A classic sign of vitamin B6 deficiency is skin eruptions resembling seborrheic dermatitis, a common symptom in acute stages of CFS/ME. CFS/ME patients have found that B6 is useful for treating pain, especially carpal tunnel syndrome.

**PROTOCOL.** As high doses can cause imbalances in other B vitamins, a low dose is recommended. The minimum requirement is 1.5 mg. (The maximum dose is 100 mg.) The active, and therefore most effective, form of B6 is pyridoxal phosphate (also known as P5P). P5P is well tolerated and is easily absorbed in oral form. High doses of B6 (200 mg) can cause symptoms of nerve damage (loss of feeling in the legs, loss of balance). These effects are reversible once the dosage is lowered. Supplementation with zinc is advised if there is a deficiency of either B6 or zinc, as B6 cannot be utilized without zinc.

#### FURTHER READING

*The University of Maryland's informative page on vitamin B6.*

<http://www.umm.edu/altmed/articles/vitamin-b6-000337.htm>

#### RESEARCH

Heap LC, Peters TJ, Wessely S. "Vitamin B status in patients with chronic fatigue syndrome." *J R Soc Med.* 1999 Apr;92(4):183-5.

<http://www.ncbi.nlm.nih.gov/pubmed/10450194> (Abstract)

#### VITAMIN B COMPLEX

**DESCRIPTION.** Many patients with CFS/ME benefit from taking a vitamin B complex formulation, either in accompaniment to single B vitamins (to prevent imbalances) or alone. CFS/ME patients have reported improvement in energy levels, symptoms of premenstrual syndrome (PMS), mood, and sleep disorders after taking vitamin B complex. Most vitamin B complex formulations include vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine, pyridoxal, and pyridoxamine), B7 (biotin), B9 (folic acid), and B12 (cobalamin). People with allergies, Candida infection, or digestive symptoms should avoid yeast-based formulations, which may be poorly tolerated.

**AVAILABILITY AND COST.** Nature's Life and Source Naturals both sell a 100-capsule yeast-free bottle of B complex for about \$7 (available online). Vitacost sells its in-house brand of yeast-free liquid vitamin B complex for \$15 (will last three months).

## VITAMIN C

**DESCRIPTION.** Vitamin C (ascorbic acid) is a water-soluble antioxidant found in most raw fruits and vegetables. It serves a number of vital functions in the body, including connective tissue repair (especially collagen), maintaining healthy teeth and bones, promoting the synthesis of anti-inflammatory hormones in the adrenal glands, helping to produce the neurotransmitters serotonin and norepinephrine, healing wounds, maintaining capillaries, healthy adrenal glands, and ovaries, absorbing iron into the bloodstream, promoting efficient white blood cells, and maintaining cholesterol balance. It is widely touted as a preventive for the common cold, perhaps because vitamin C increases the production of interferon, an antiviral cytokine.

Animal experiments have shown that vitamin C has other immune system-enhancing effects as well, increasing the body's ability to fight off bacterial infections and promoting general immunity. Patients with allergies may want to take special note of vitamin C's function as a natural antihistamine. A research team led by the co-discoverer of vitamin C, Professor Charles Glen King of Columbia University, demonstrated as early as 1940 that it can both prevent and moderate allergy symptoms. In addition to its other beneficial properties, vitamin C is also a natural chelator, helping to remove heavy metals and toxins from the body.

Vitamin C is not stored in the body, as are fat-soluble vitamins, and thus must be constantly replenished. Smoking, drinking (alcohol), illness, and physical or emotional stress all cause rapid depletion of vitamin C.

**USES IN CFS/ME.** Vitamin C is the most widely used of all vitamins for CFS/ME patients, not just because of its role as an antioxidant and free radical scavenger, but also because of the numerous other vital functions it performs. Of particular relevance to patients with CFS/ME is the role of vitamin C in maintaining healthy capillaries. A number of researchers have remarked on the poor circulation in patients with CFS/ME, resulting in corollary illnesses such as Reynaud's phenomenon. Even more critical in CFS/ME is reduced blood flow to the brain, which is especially dependent on capillary action for its blood supply. This function alone helps to place vitamin C at the forefront of any vitamin therapy. However, its role in collagen formation and tissue repair, its importance in immune system function, and its place as an adrenal gland support do much to explain why it is one of the most frequently recommended CFS/ME nutritional treatments.

**PROTOCOL.** Most nutritionists recommend taking vitamin C to tolerance; that is, until the patient begins experiencing diarrhea or burning urine. Considering the broad spectrum of sensitivities among CFS/ME patients, tolerance can vary considerably. CFS/ME clinicians generally recommend anywhere from 2000 – 6000 mg/day (taken in small divided doses) up to tolerance.

Dr. Martin Pall recommends doses on the order of 500 to 1000 mg/day, taken several times per day. Vitamin C can act to regenerate tetrahydrobiopterin (BH4) and, therefore, may act to lower oxidative stress. High doses of vitamin C can be

useful in scavenging peroxynitrite ( $\text{ONOO}^-$ ), the most central element in his NO/ONOO<sup>-</sup> cycle hypothesis.

For those who are intolerant to vitamin C, it is worthwhile to administer it topically. It is very easy to make an ointment. Put a small amount of hand lotion into a small bowl (only as much as you intend to use). Add 1/8 teaspoon of pure ascorbic acid powder (about 500 mgs) to the lotion. Mix with your finger and apply immediately to the skin. The mixture cannot be stored, so be sure not to make too much. About 10% of the vitamin C you use can be absorbed via this method. (Over a period of time, the mixture will yellow your nails. This is because the vitamin C turns yellow when exposed to moisture. The effect goes away when you stop topical applications.)

**PROS AND CONS.** Vitamin C is inexpensive, easy to take and usually well-tolerated. Patients report that on low doses (500 – 1000 mg), they catch fewer colds. Some CFS/ME patients are quite sensitive to vitamin C and can only tolerate small amounts.

**AVAILABILITY AND COST.** Vitamin C is one of the least expensive vitamins and is widely available at most pharmacies, health food stores, online suppliers, and supermarkets. Unfortunately, vitamin C is quite unstable. It degrades quickly when exposed to light and heat, and has a short shelf life, which means most commercial tablets and pills contain very little usable vitamin C. In addition, Vitamin C degrades when exposed to moisture, which means drinks with added vitamin C share the same drawbacks as tablets.

The best form of Vitamin C is pure vitamin C powder (ascorbic acid). Because it is a powder, it can be titrated (taken in very small doses). Ascorbic acid is very sour, so most people prefer mixing it with a bit of juice. Allergy Research sells a 120-gm bottle of pure ascorbic acid powder for roughly \$10 through Vitacost. At ½ teaspoon a day (2000 mg) a bottle will last two months.

For those with gastrointestinal symptoms, acid-free C powder may be more tolerable. Ascorbic acid can be buffered with magnesium carbonate, calcium carbonate and/or potassium carbonate to reduce acidity. Oral buffered vitamin C in small doses is extremely safe, with virtually no side effects.

Intravenous (IV) drip is another form of vitamin C therapy used in CFS/ME. Administering vitamin C directly into the bloodstream not only increases the rate at which it is absorbed but enhances its role as a chelating agent. A number of health care practitioners use vitamin C as an essential component of CFS/ME therapy.

Intravenous drip therapy should not be administered daily and requires monitoring by a physician. The charge for an intravenous drip is \$70 to \$125, depending on locale. Insurance usually does not cover the cost.

## FURTHER READING

*Good overview of vitamin C supplements.*

<http://www.electroherbalism.com/Naturopathy/Therapies/Supplements/Vitamins/VitaminC/index.htm>

*Detailed overview of the Krebs cycle and its role in CFS/ME.*

<http://www.nutritionreview.org/library/krebs.php>

*CFS/ME patient ratings of vitamin C:* <http://www.revolutionhealth.com/drugs-treatments/rating/vitamin-c-ascorbic-acid-for-chronic-fatigue-syndrome-cfs-cfids-me>

## VITAMIN D

**DESCRIPTION.** Vitamin D is a unique vitamin in that the body can synthesize it when exposed to sunlight. There are two forms of vitamin D, ergocalciferol (D2) and cholecalciferol (D3). The difference between the two forms is that D2 is derived from ergosterol (a chemical compound produced by phytoplankton, invertebrates, and fungi) while D3 is produced by ultraviolet light irradiation.

Vitamin D has come under increasing scrutiny over the past few years due to its functions in bone maintenance and immune system function. Physicians have known for decades that cod liver oil is an effective treatment for rickets, a childhood condition in which bones and teeth become soft. Ultimately, it was discovered that rickets was caused by a deficiency of vitamin D. As a consequence, vitamin D is added (actually, produced via exposure to ultraviolet light) to all milk. Aside from rickets, deficiencies in vitamin D have been linked to gingivitis, inflammatory bowel disease, depression, fatigue, and heart disease. Vitamin D is also recommended for women at risk for osteoporosis.

Vitamin D's role in the immune system is no less important. One of its most important functions is to activate T cells, in particular the T cells that identify and attack invading pathogens. Without vitamin D, T cells remain dormant or "naive."

**USES IN CFS/ME.** In a 2009 study, Berkovitz et al found that vitamin D levels were moderately to severely low in CFS/ME patients as compared to the general population. The researchers recommended vitamin D supplementation. More recently, in 2011 a group of pediatric researchers at the Mayo Clinic discovered that adolescents with CFS/ME and orthostatic intolerance (OI) had low levels of both ferritin (a protein that stores and releases iron) and vitamin D.

The question for some researchers is whether low vitamin D levels are a cause of the illness or a result of it. CFS/ME is characterized by a shift from Th1 (cellular) to Th2 (humoral) immunity. Basically, the immune system in a person with CFS/ME spends too much effort identifying and attacking foreign invaders (Th2) and too little effort focusing on pathogens within cells (Th1). This allows for a proliferation of viruses that multiply within cells. The argument is that Vitamin D, because it is crucial for the production of macrophages (the immune system components that "eat" extracellular pathogens), may become depleted as a result of the shift to Th2.

**PROTOCOL.** In the presence of low serum D levels, dosage is determined by the physician. For those who wish to supplement, and who are getting adequate sun exposure, low doses are advised (1000 – 2000 IU).

**AVAILABILITY AND COST.** Vitamin D is inexpensive and widely available at any health food store, supermarket, drug store and from online distributors. It is a fat-soluble vitamin, so gencaps or drops are more easily assimilated. But, for those who are sensitive to gencaps, there are dry forms of vitamin D as well. (Although some form of oil or fat must be in the intestines for proper absorption.) If you are already taking fish oil, supplementation with vitamin D may not be necessary.

**TESTING:** There are two tests for determining blood levels of vitamin D. The most commonly used test is for 1,25 (OH)<sub>2</sub> vitamin D (1,25 dihydroxy vitamin D). This test measures a form of vitamin D that has a long half life (about three weeks) and therefore will only give your doctor an overall picture of your vitamin D. A more specific test, 25OH vitamin D (25-hydroxy vitamin D), will tell your doctor how much vitamin D is currently in your bloodstream. Of the two tests, the second is more useful for determining actual vitamin D levels.

#### FURTHER READING

*List of articles concerning vitamin D deficiency:*

<http://www.vitaminCouncil.org/about-vitamin-d/vitamin-d-deficiency/>

*CFS/ME patient reviews of vitamin D:* <http://www.revolutionhealth.com/drugs-treatments/rating/vitamin-d-for-chronic-fatigue-syndrome-cfs-cfids-me>

#### RESEARCH

Antiel RM, Caudill JS, Burkhardt BE, Brands CK, Fischer PR. "Iron insufficiency and hypovitaminosis D in adolescents with chronic fatigue and orthostatic intolerance." *South Med J.* 2011 Aug;104(8):609-11.

<http://www.ncbi.nlm.nih.gov/pubmed/21886073> (Abstract)

Berkovitz S, Ambler G, Jenkins M, Thurgood S. "Serum 25-hydroxy vitamin D levels in chronic fatigue syndrome: a retrospective survey." *Int J Vitam Nutr Res.* 2009 Jul;79(4):250-4. <http://www.ncbi.nlm.nih.gov/pubmed/20209476> (Abstract)

#### VITAMIN E

**DESCRIPTION.** Vitamin E (tocopherol) is a fat-soluble vitamin found in butterfat, meats, vegetable oils, and particularly wheat germ oil, from which this vitamin was first isolated in 1936. It is made up of four tocopherols (alpha, beta, gamma, delta) and four tocotrienols (alpha, beta, gamma, delta). Like other antioxidants, vitamin E serves to protect cell linings from damage caused by oxidation. It helps to maintain red blood cell membranes and other cell tissues (even the walls of the tiny structures within cells), ensures normal muscle metabolism, and protects essential unsaturated fatty acids and vitamin A from destruction from oxidation. Vitamin E has protective activity against methyl mercury toxicity and increases the activity of glutathione. Zinc is needed to maintain proper levels of vitamin E in the blood; thus, zinc deficiency can lead to low vitamin E levels.

**USES IN CFS/ME.** In a 2003 study conducted in Italy, researchers found that CFS/ME patients exhibited significantly lower antioxidants (vitamin E among others) in serum samples as compared to controls. The CFS/ME group also had lower pain thresholds than controls in all muscle sites tested. The researchers

correlated levels of vitamin E concentration to the degree of muscle pain — the lower the vitamin E levels, the greater the pain. While the researchers did not offer treatment suggestions, their findings indicate that supplementation would be beneficial.

In 2009 Miwa and Fujita also found low serum levels of vitamin E in CFS/ME patients. They concluded that the reduction in vitamin E was due to oxidative stress. In a later study, Miwa and Fujita found that low serum levels of vitamin E in CFS/ME patients correlated with flares. They concluded that the “low level of serum alpha-tocopherol was ameliorated during the remission phase as compared with the exacerbation phase in the patients with chronic fatigue syndrome, suggesting that increased oxidative stress may be involved in the pathogenesis of chronic fatigue syndrome and might also be directly related to the severity of the symptoms of chronic fatigue syndrome.” This conclusion is very much in line with research demonstrating oxidative stress in people with CFS/ME, and leads to a specific course of supplementation. Vitamin E reduces oxidative stress by mitigating the effects of lipid peroxidation. Vitamin E can also reduce chronic inflammation by down-regulating the NF-kappaB inflammatory pathway.

In keeping with these findings, and numerous other studies linking oxidative stress to CFS/ME symptoms, vitamin E is used chiefly for its properties as an antioxidant. Its ability to strengthen cell walls and protect other vitamins and fats from destruction makes it highly desirable as an adjunct to other vitamin therapies.

**PROTOCOL.** Because it is fat-soluble, only minimal amounts are needed to produce antioxidant benefits. The optimal dosage, 200 IU of natural vitamin E (mixed tocopherols), taken daily with the largest meal is usually recommended for patients with CFS/ME. Vitamin E acts as a blood thinner, so do not take it with other blood thinners, or before surgery.

Recently, research has been focused on tocotrienols, which are closely related to the tocopherols. Tocotrienols, like tocopherols, are found in some vegetable oils, wheat germ, barley, saw palmetto, and certain varieties of nuts and grains. The reason for the high interest generated by tocotrienols is that they have been shown to protect against brain cell damage and cardiovascular disease, prevent cancer, reduce cholesterol and combat oxidative stress to the skin produced by UV exposure. Dr. Pall has pointed out that tocotrienols can penetrate tissues with saturated fatty layers more efficiently than tocopherols, making tocotrienols, particularly delta tocotrienols, powerful antioxidants.

**AVAILABILITY AND COST.** Vitamin E is available at any drug store, health food store, and from online suppliers. Look for a good brand of natural Vitamin E. Vitacost sells natural vitamin E for between \$8 and \$17 a bottle. Delta tocotrienols are available in health food stores and online through PureFormulas.com and Vitacost for roughly \$13 to \$25 a bottle.

#### FURTHER READING

*CFS/ME patient reviews of vitamin E:* <http://www.revolutionhealth.com/drugs-treatments/rating/vitamin-e-for-chronic-fatigue-syndrome-cfs-cfids-me>



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- Yam ML, Abdul Hafid SR, Cheng HM, Nesaretnam K. "Tocotrienols suppress proinflammatory markers and cyclooxygenase-2 expression in RAW264.7 macrophages." *Lipids*. 2009 Sep;44(9):787-97. <http://www.ncbi.nlm.nih.gov/pubmed/19655189> (Abstract)

## WHEY PRODUCTS

Colostrom, Udenatured Whey, Probioplex

## COLOSTRUM

**DESCRIPTION.** Colostrum is the first milk produced by the mother in late pregnancy and just after birth.

**BACKGROUND.** Because babies are born with immature digestive systems, colostrum delivers important nutrients – proteins, vitamins, and sodium – in a concentrated form. Colostrum also helps the newborn to clear excess bilirubin from its system, which prevents jaundice. Most important, colostrum contains antibodies, such as IgA, IgG, and IgM, three major components of the immune system. Colostrum also contains cytokines, interleukins, and tumor necrosis factor as well as a number of growth factors. The antibodies in colostrum provide immunity, while growth factors stimulate the development of the GI system, which together provide the newborn with its first protection against pathogens.

**USES IN CFS/ME.** Gut problems (including leaky gut, small intestine bacterial overgrowth (SIBO), irritable bowel, and motility problems) are endemic in CFS/ME patients. Colostrum may be beneficial for all these conditions. Many allergists believe that colostrum helps food intolerance and allergies.

**PROTOCOL.** Dr. Teitelbaum recommends three capsules of colostrum three times a day for six to nine months. Then stop, or use the lowest dose needed for symptoms. If nausea or indigestion occurs, lower the dose to a comfortable level for one or two weeks until symptoms pass. Take first thing in the morning on an empty stomach.

**PROS AND CONS.** Some patients report increased energy after taking colostrum for a few weeks. As with other milk-based products, however, many patients are sensitive to colostrum.

**AVAILABILITY AND COST.** Colostrum is available from health food stores and from online distributors. Symbiotics sells a 60-capsule bottle of Colostrum Plus (950 mg) for around \$10 through Vitacost. Jarrow and Source Naturals also market colostrum capsules for roughly the same price.

#### FURTHER READING

*Colostrum and leaky gut:*

[http://www.carttonic.com/files/file\\_download.php?fi\\_id=684](http://www.carttonic.com/files/file_download.php?fi_id=684)

#### RESEARCH

Hanson LA, Ahlstedt S, Andersson B, Carlsson B, Fällström SP, Mellander L, Porras O, Söderström T, Edén CS. "Protective factors in milk and the development of the immune system." *Pediatrics*. 1985 Jan;75(1 Pt 2):172-6.  
<http://www.ncbi.nlm.nih.gov/pubmed/3880886> (Abstract)

#### UNDENATURED WHEY

**DESCRIPTION.** Undenatured, or non-denatured, whey is a form of whey (the liquid part of milk after it has curdled) which has not been subjected to high temperatures.

**BACKGROUND.** Undenatured whey has been used primarily for protein supplementation. It contains all the amino acids in their natural unoxidized forms. Undenatured whey helps control unfriendly bacteria in the gut, and supports the immune system. The unoxidized cysteine is easily absorbed by the liver, and can be used to make glutathione.

In 1991 Bounous and Gold found that when mice were fed undenatured whey, their glutathione levels rose. (These findings were confirmed by later studies by Pacheco et al.) Further research has shown that undenatured whey's effect on glutathione levels can ameliorate liver disease, asthma, and diabetes.

**USES IN CFS/ME.** In CFS/ME patients, undenatured whey has been used to increase glutathione levels in patients who do not respond to direct glutathione supplementation. Dr. Cheney found that in his patients, results with reduced glutathione and with glutathione precursors (e.g., NAC) were "modest." He began

using a weakly hydrolyzed whey protein and noted positive results. This prompted Dr. Cheney to embark on a six-month trial using ImmunoPro on a small subset of patients. At the end of the study, the patients were tested for bacterial and viral titers. He found that *chlamydia pneumoniae*, *mycoplasma incognitus*, and *mycoplasma penetrans* were eradicated after six months. Dr. Cheney did not find similar results with viral levels, but cautions that the study was not large enough to draw conclusions.

**PROTOCOL.** Dr. Cheney's study patients were given two packs a day (10 mg, or 1.75 tablespoon per pack) of undenatured whey (ImmunoCal), but he reports that patients can take more as results are dosage dependent. (The higher the dose, the greater the effect.) Undenatured whey should be taken on an empty stomach with a bit of water or milk (not juice).

**PROS AND CONS.** Those who respond to undenatured whey report a marked increase in energy. Unfortunately, a number of CFS/ME patients report “die-off” type reactions (sore throats, swollen glands and flu-like symptoms) at even the smallest doses. According to Richard Van Konynenburg, the lack of tolerance could be due to a reaction to casein, or (and this is most likely) to the fact that when glutathione is raised, it stimulates the immune system. Immune system stimulation is often mistaken for “die-off.”

**AVAILABILITY AND COST.** ImmunoPro, the brand Dr. Cheney currently recommends, can be purchased from online distributors. Amazon.com markets a 10.6-oz (300 gm) container for \$33. At one scoop a day, the container will last for two months. Swanson and ProHealth sell good quality undenatured whey for a similar price.

## FURTHER READING

*Patient thread on nondenatured whey, including an excellent explanation of how these products work by Rich Van Konynenburg*

<http://forums.phoenixrising.me/showthread.php?9596-Whey-powder-any-CFS-issues-benefits>

*Information about whey and lactoferrin:* <http://www.wellwisdom.com/pages/Whey-Facts.html>

*Dr. Cheney talks about whey protein and glutathione*

<http://www.wellwisdom.com/pages/Whey-Facts.html#10tharticle>

*Carol Sieverling's article about whey, Cheney and glutathione.*

<http://www.prohealth.com/library/showarticle.cfm?libid=8874>

*Detailed information on whey and glutathione*

<http://www.nutritionadvisor.com/glutathione.html>

## RESEARCH

Bounous G, Gold P. “The biological activity of undenatured dietary whey proteins: role of glutathione.” *Clin Invest Med.* 1991 Aug;14(4):296-309.

<http://www.ncbi.nlm.nih.gov/pubmed/1782728> (Abstract)

Chitapanarux T, Tienboon P, Pojchamarnwiputh S, Leelarungrayub D. "Open-labeled pilot study of cysteine-rich whey protein isolate supplementation for nonalcoholic steatohepatitis patients." *J Gastroenterol Hepatol*. 2009 Jun;24(6):1045-50. <http://www.ncbi.nlm.nih.gov/pubmed/19638084> (Abstract)

Pacheco MT, Sgarbieri VC. "Effect of different hydrolysates of whey protein on hepatic glutathione content in mice." *J Med Food*. 2005 Fall;8(3):337-42. <http://www.ncbi.nlm.nih.gov/pubmed/16176144> (Abstract)

## PROBIOPLEX

**DESCRIPTION.** Probioplex is a whey-derived product that concentrates the active globulin (immune) proteins in cow milk.

**BACKGROUND.** Probioplex is a source of secretory IgA, the immunoglobulin found in mucosal secretions. Secretory IgA is produced in the mucous lining of the intestines and is essential both for maintaining the gut barrier and for "tagging" unfriendly organisms in the gastrointestinal tract. It is used in the treatment of leaky gut, ulcers, and damage to gut mucosa. Secondary benefits include increased immune system efficiency, reduction of yeast overgrowth, and control of enteric viral and bacterial infections.

**USES IN CFS/ME.** Probioplex is recommended for treating digestive tract problems, particularly leaky gut, irritable bowel syndrome, gas, and food sensitivities. It may serve as a substitute for L-glutamine for those who cannot tolerate amino acids, as it performs a similar function. Probioplex also stimulates the growth of helpful bacteria in the intestines, making it a useful corollary treatment for Candida overgrowth, which is common in CFS/ME. The secondary benefits of improving immune system function are also highly relevant for patients with CFS/ME.

**PROTOCOL.** Probioplex is a powder that can be mixed with water or juice. Nutritionists recommend ½ teaspoon two to three times a day for 3 to 4 weeks. After that, the dosage should be reduced to ¼ teaspoon once or twice a day and discontinued when benefits are no longer noticeable. Reported benefits include reduced abdominal pain due to gas, reduced bloating, relief of constipation, reduced food reactivity, and improved sleep.

**PROS AND CONS.** Probioplex is safe, easy to use, relatively inexpensive, and is available without prescription. It resists digestion in the stomach and small intestine and so may be taken with meals. However, because it is a whey product, persons with milk allergies or sensitivities may not be able to tolerate it. Probioplex also contains rice maltodextrin, which may limit its value for those with rice allergies.

**AVAILABILITY AND COST.** Probioplex is available from specialized vitamin stores and from online suppliers. A 90-gm container (a one-month supply) costs about \$30 from PureFormulas.com.

## ACUPRESSURE

**DESCRIPTION.** Acupressure (or G-Jo) is a Chinese technique for the immediate treatment of minor ailments based on the same principles as acupuncture (see Acupuncture).

**BACKGROUND.** Acupressure was developed to provide a fast remedy for various symptoms and ailments. Much like acupuncture, it relies on stimulation of certain points on the surface of the body to release *chi*, or life energy. Instead of needles, the fingertips are used to apply pressure. Usually, light pressure is exerted for only a few seconds with the tip of the thumb. Most points are located by placing the fingers along easily identifiable body landmarks. Distance between points is measured in finger widths. The technique is easy to learn and requires relatively little exertion.

**USES IN CFS/ME.** Acupressure can be used for short-term relief of mild to moderate CFS/ME symptoms, such as minor aches and pains, insomnia, anxiety, shortness of breath, nausea, headache, eyestrain, and tension.

### *FOR NAUSEA, INSOMNIA, INDIGESTION, AND NERVOUSNESS*

#### *Inner Wrist Point (P6)*

Place your three middle fingers crosswise along the inside of your wrist. The third finger should align with the first crease that separates your hand from your wrist. The inner wrist point is located directly under the index finger, in the middle of your arm.

### *FOR INDIGESTION*

#### *Bottom Of Abdomen (CV6)*

CV6 is two finger widths under the belly button. Wait for two hours after eating before using this points. Do not massage for longer than two minutes.

### *FOR GERD*

#### *Midline Of The Body (CV12)*

The point CV12 is on the midline of the body, halfway between your breastbone's base and your belly button. CV6 is two finger widths under the belly button. CV12 specifically treats heartburn. Wait for two hours after eating before using this point. Do not massage for longer than two minutes.

### *FOR SHORTNESS OF BREATH, CHEST TENSION, COUGHING, AND CONGESTION*

### *Inner Shoulder Point*

This point is located on the outer part of the chest near the shoulder, four finger widths above the armpit and one finger width toward the chest.

*FOR GENERAL MUSCLE TENSION, ANXIETY, LEG SPASMS, AND INSOMNIA*

This point is located at the base of the spine, approximately at the top of the hip bone, four finger widths from the spine.

*FOR FATIGUE, WEAKNESS, AND PAIN*

### *Foot Points*

The Chinese believe that the lines of *chi*, which run throughout the body, end in the feet. For this reason, the feet are a rich source of acupressure points for all kinds of problems. Many people with CFS/ME find that exerting pressure with the tip of the thumb over the entire bottom of the foot provides relief from generalized achiness.

### FURTHER READING

*General information about acupressure, including pressure points:*

<http://www.acupressure.com/>

*Acupressure points for GERD:* <http://www.livestrong.com/article/191417-acupressure-point-for-gerd/>

*Video showing acupressure point for anxiety, panic attacks and palpitations. (There are several youtube videos demonstrating acupressure points.):*

<http://www.youtube.com/watch?v=7ZTHjjGtuDA>

*Acupressure point finder.* <http://pointfinder.org/>

### BOOK

Blate, Michael. *The Natural Healer's Acupressure Handbook*. Falkynor Books, 1983.

### ACUPUNCTURE

**DESCRIPTION.** Acupuncture is a therapeutic technique in which small needles are inserted under the skin at *chi* points to promote the repair and healing of major organs, regulate body metabolism, and correct physical ailments that result from imbalances in the flow of *chi*.

**BACKGROUND.** The Chinese invented acupuncture sometime in the third millennium BC, but it was not systematized until 200 BC, when the *Hungdi Neiging* Suwen (*The Yellow Emperor's Classic of Internal Disease*) was written. Acupuncture is based on the concept of *chi*, which is life energy. In the Chinese conceptual system, *chi* flows along channels throughout the body, which can be felt

at specific points. When a person is ill, these points become tender. The acupuncturist can discern the nature of the illness and treat it by finding the tender points and stimulating them with small needles inserted just under the surface of the skin. Many years of rigorous training, as well as considerable talent, are required to be able to locate these acupuncture points.

Because the concept of vital energy, or "life force," is entirely absent in European conceptions of illness, it is difficult to say how acupuncture works. The system of meridians does not correspond to the central nervous system (CNS) or any other physiological system, insofar as anatomists can determine. There has been speculation that some of the effects produced by acupuncture may result from localized stimulation of cortisol or perhaps a kind of "distraction" of the CNS utilizing electrical fields or endorphins; the mechanism, however, is still not readily explained using the European model of the body.

Acupuncture produces distinct effects in about 80% of patients, whereas 20% note no effect. In China, acupuncturists use acupuncture to treat any condition that is reversible. They also use it to block pain. Since the late 1950s, more than 600,000 operations have been performed in China using acupuncture analgesia. Acupuncture has also been used successfully to treat animals.

**USES IN CFS/ME.** Several dozen studies investigating the use of acupuncture for CFS/ME have been published. Unfortunately for non-Chinese speakers, most of these have not been translated. (Although the abstracts of many of them can be viewed on PubMed.) The vast majority of these studies have shown that CFS/ME patients experience a reduction in symptoms, particularly pain, fatigue, and brain fog.

**PROTOCOL.** During acupuncture, the patient lies on a table while the acupuncturist places small sterile needles under the skin. (Needle insertion is painless.) Usually, the acupuncturist will first "pulse" you, that is, measure the flow of *chi*. The effectiveness of the treatment is determined by the size of the bore of the needle, how long it is left in place, the depth of penetration, how much it is moved, and how often the treatment is repeated. Sometimes one treatment is all that is needed to achieve the desired effect. For complicated or severe problems, sessions may be needed two or three times a week.

Acupuncturists are also trained in Chinese herbal medicine. Certain Chinese herbs may be recommended as part of the acupuncture therapy. Moxa (herbal incense) is also used to provide localized heat. Many people with CFS/ME, particularly those with chemical sensitivities, cannot tolerate the odor of Moxa. Be sure to discuss any sensitivities with your acupuncturist before Moxa treatments.

**PROS.** Acupuncture provides an alternative to drug treatment. Patients note improvements in generalized pain, eye pain, overall well-being, mental clarity, and energy. Positive results are most often obtained when the treatment focuses on specific problems, such as pain, insomnia, loss of appetite, or nausea.

**CONS.** Negative results in many cases are due to the acupuncturist's mistaken idea that people with CFS/ME have depressed immune systems and, as a

consequence, require immune system stimulation. In severely ill CFS/ME patients, immune system stimulation can cause a profound exacerbation of symptoms.

**AVAILABILITY AND COST.** Acupuncture is available in most urban centers in the United States and is becoming increasingly more so. Fees vary, but most acupuncturists charge \$70 to \$95 per treatment. Insurance in some states covers the cost, especially if the acupuncturist is also a physician. Make sure to check the acupuncturist's credentials, how long he or she has been practicing acupuncture, and whether he or she has any experience with CFS/ME. If possible, talk to another person with CFS/ME who has been a patient.

#### FURTHER READING

*This is a good general article about acupuncture for CFS/ME:*

<http://www.cfids.org/archives/1999/1999-5-article03.asp>

*Acupuncturists talk about treating CFS/ME. The article includes specific points and meridians.* <http://www.chirofind.com/mpacms/at/article.php?id=30188>

*Detailed summary of several acupuncture studies performed in China. Results are analyzed and discussed:* [http://findarticles.com/p/articles/mi\\_m0ISW/is\\_265-266/ai\\_n15688805/](http://findarticles.com/p/articles/mi_m0ISW/is_265-266/ai_n15688805/)

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<http://www.ncbi.nlm.nih.gov/pubmed/20862932> (Abstract)

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Wang JJ, Song YJ, Wu ZC, Chu XO, Wang XH, Wang XJ, Wei LN, Wang QM. [A meta analysis on randomized controlled trials of acupuncture treatment of chronic fatigue syndrome]. *Zhen Ci Yan Jiu*. 2009 Dec;34(6):421-8. <http://www.ncbi.nlm.nih.gov/pubmed/20209981> (Abstract)

#### AROMA THERAPY

**DESCRIPTION.** Aroma therapy involves use of the distilled essential oils naturally found in plants for healing and cosmetic purposes.

**BACKGROUND.** For centuries, aromatic oils have been recognized for their medicinal properties. In biblical times, oil of myrrh, which is a powerful antiseptic, was revered for its power to quickly heal surface wounds (hence the significance of the gift of the Magi). When Tutankhamen's tomb was opened in 1922, scent pots of frankincense were found. The range of uses for essential oils appears limitless.

Essential oils can be used to induce sleep (e.g., jasmine), calm the nerves (e.g., valerian, clary sage), clean wounds (e.g., lavender), reduce aches and pains (e.g., rosemary), relieve gas pains (e.g., peppermint), and open respiratory airways (e.g., basil). The mode of action of aromatic oils is complex. A single oil can produce



a number of different, and even opposing, effects. Lavender, for example, sedates in small quantities but stimulates in larger quantities.

It is not known how plant oils produce these effects in people, but it has been theorized that smell, our most primordial sense, stimulates a complex set of central nervous system (CNS) reactions that can culminate in emotional and physiological changes. It is well known that the ketones, esters, aldehydes, and alcohols found in plant oils can serve as insect repellents, fungicides, and bactericides. Many oils also have hormone-like properties (for example, hops, fennel, and anise contain estrogens).

Production of essential oils is a long, arduous process involving oil-based extraction and repeated distillation (alcohol is never used). It takes many pounds of flowers, leaves, or bark to produce 1/3 oz of concentrated essential oil, which is why only a drop or two produces the desired effect.

**USES IN CFS/ME.** Aroma therapy may hold promise for the alleviation of some CFS/ME symptoms, because odors readily cross the blood-brain barrier. Because the olfactory bulbs tie in directly to the limbic system (that part of the brain that processes emotion), essential oils may be useful in alleviating emotional symptoms such as anxiety, anger, and fear. Essential oils can also be effectively used to relieve insomnia and muscle aches. A number of patients who have tried aroma therapy have reported good results in treating anxiety, "jitters," and insomnia, with no negative side effects.

To relieve chronic, severe stress, Valerie Worwood, author of *The Complete Book of Essential Oils and Aromatherapy*, recommends use of hypnotics such as narcissus for hyperactivity, jonquil for anxiety, jasmine for depression, carnation or valerian for insomnia, and vanilla for general stress. Oils that can help relieve muscle fatigue include rosemary, thyme, and marjoram. To treat insomnia, a blend of sandalwood, clary sage, lemon, and chamomile may be helpful. Lavender has been shown to act as an anticonvulsant.

In *Chronic Fatigue Syndrome: A Natural Healing Guide*, Steve Wilkinson recommends the following oils to treat symptoms of CFS/ME: lavender (for tension), lemon (to calm the mind, night sweats), peppermint (for fever, night sweats, digestive disorders), basil or orange (to lift the spirit), rosemary (for lethargy), clary sage (for invigoration), and geranium (for sluggishness and emotional upset).

**PROTOCOL.** Essential oils are always used by the drop. Measurements are precise, so you should have a "recipe." (See some of the sites below.) The oils are not meant to be taken internally. They can be rubbed on the skin (after thorough cleansing), inhaled, or floated in a bath. When applied directly to the skin, they must be mixed with vegetable oil. To make a rub for the skin, slightly warm two tablespoons of pure vegetable oil (corn, safflower, sunflower, peanut, or soy oils are all readily obtained and make good mediums) and add four or five drops of essential oil (or one each of several oils if you are making a blend).

You can also add the oils to bathwater before getting into the tub. One or two drops of lavender is all you need for a relaxing bath. To treat insomnia, try placing one or two drops of clary sage, jasmine, or any of the hypnotics on a handkerchief

and place it near your pillow. The oils are strong, so not much is needed. Breathing the vapor from a single drop of peppermint oil floated in a cup of hot water can relieve gas pain instantly, and help clear the sinuses, too!

**PROS AND CONS.** Essential oils are benign when used externally and in small amounts. Aroma therapy can prove particularly useful for treating gastrointestinal disturbances because the oils are not processed through the GI tract. Oils can be a good therapy option for those who are sensitive to synthetic chemicals, because they generally do not provoke reactions. Because the oils work synergistically, you may want to do some investigation online for the most effective blends. Follow your nose to choose the oils that are best for you. (If it smells bad to you, don't buy it.) Those with MCS, multiple allergies or hypothyroidism may not be able to tolerate essential oils.

**AVAILABILITY AND COST.** Essential oils can be purchased at health food stores and online. They are usually sold in 1/3-oz bottles. Given the tiny doses, one bottle can last for years. Aura Cacia is one of the better known suppliers. The common oils are not expensive. A bottle of peppermint oil costs about \$4.

#### FURTHER READING

*Essential oil blends for enhancing mood:*

[http://www.aromatherapy.com/mood\\_blends.html](http://www.aromatherapy.com/mood_blends.html)

*Comprehensive aromatherapy recipes:*

<http://www.aromaweb.com/recipes/default.asp>

*Aromatherapy for CFS/ME (with recipes):*

<http://www.dreamingearth.com/chronicfatigue.html>

*Excellent list of essential oils useful for CFS/ME patients.*

<http://aboutmecfs.org.violet.arvixe.com/Trt/AromatherapyEssentialOils.aspx>

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<http://www.ncbi.nlm.nih.gov/pubmed/19962288> (Abstract)

#### BACH REMEDIES

**DESCRIPTION.** Bach remedies are herbal essences principally derived from flowers used to remedy specific physical or psychological complaints.

**BACKGROUND.** Bach remedies were devised by Dr. Edward Bach, a British bacteriologist, in the 1930s. In the 1920s, he proposed the theory that altered mental and emotional states were brought about by disharmonies that could be corrected with the use of plant essences. Dr. Bach collected these essences, at first, by gathering the dew that had collected on the underside of leaves and flower petals. Because this method proved arduous, he later tried putting plant parts in a bowl of pure spring water, which he left in the sun for a few hours. He then preserved the water in alcohol. To make his remedies, he took a few drops from the

bottled essence and added them to an ounce of pure water. He administered four drops in a little water four times a day.

By the time of Dr. Bach's death in 1936, he had discovered 38 such herbal remedies. Dr. Bach claimed that his flower remedies cured various common physical ailments, but primarily the remedies were used to treat emotional problems. For example, he treated fearfulness with mimulus, obsessional thoughts with white chestnut, lack of faith with gentian, and general ailments with a blend of five of the essences, which he called "Rescue Remedy."

**USES IN CFS/ME.** Although there is no scientific evidence proving the effectiveness of Bach remedies, some people with CFS/ME report good results. Aspen is reputedly effective for fear. Patients report success using scleranthus to control night sweats. Given the low risk associated with Bach remedies, scleranthus might be worth trying if night sweats are severe or resistant to other treatment. Rescue Remedy, a blend of several essences that alleviates many symptoms simultaneously, is popular among those who use Bach remedies to relieve stress and improve sleep.

**PROTOCOL.** Standard dosage is three to seven drops placed under the tongue, or in a small glass of water, taken four times a day.

**PROS AND CONS.** Bach remedies are generally well tolerated. Patients who are highly reactive, severely ill, or have multiple allergies may wish to start with one drop. Keep in mind that the more essences you use, the less effective the mixture will be. Try to focus on one or two problems rather than several.

**AVAILABILITY AND COST.** Bach remedies can be purchased at most health food stores and online. They generally cost about \$7 a bottle.

## FURTHER READING

*A list of all Bach Flower remedies and what they are used for.*

<http://www.bachcentre.com/centre/remedies.htm>

## BED REST

**DESCRIPTION.** Bed rest is lying down, with your eyes shut, and *resting*.

**BACKGROUND.** Resting was an integral part of daily life until the last generation. The Spanish siesta, the dinner hour, teatime, the evening cigar, and afternoon snooze all acknowledged the need to take a break from long periods of activity. Rest charges our batteries, so to speak. Bed rest was an essential part of treatment for every illness until the middle part of the twentieth century. Conscientious physicians, and mothers, have recognized throughout the ages that the body needs adequate rest to recover from daily wear and the insults of infectious disease. Given the frequent occurrence of serious infectious diseases that characterized life in the earlier part of this century, the sickbed was a place where everyone would no doubt spend time at some point during a lifetime.

Since the discovery of antibiotics, however, we have become overconfident. When we get sick, we take a pill and keep going. In contemporary society, resting is regarded as a luxury rather than a necessity, much to the detriment of our health.

We seem to have forgotten that the human body is fundamentally material and, like any material object, it wears down with continual use.

**USES IN CFS/ME.** Views on bed rest in CFS/ME are somewhat divided. More than a few (misguided) physicians are under the impression that resting makes CFS/ME patients more tired. This attitude reflects what one might call the “buck up and take it like a man” school of treatment. However, virtually every CFS/ME physician recommends bed rest as an essential part of coping with the illness, as do nearly all patients. As one patient points out, “Nothing cures better than rest.” Resting seems obvious when you are tired, but all too many times we ignore what our bodies are telling us. Patients with CFS/ME learn very quickly that pushing past their limits exacerbates symptoms. Both those who are well into recovery and those who are recently ill learn this lesson over and over again: Rest is essential to recovery.

**PROTOCOL.** There is a method to resting. Simply lying down is not enough. In order for your body to rest, your mind must rest, too. No single part of the human body consumes more calories than the brain. If you use your rest time to study, or do taxes, or some other task, you will not reap the benefits of rest.

When you rest, lie as comfortably as you can. Listen to soothing music or do relaxation exercises. Breathe. Do nothing else. The important thing is to allow your body some time for self-repair. Resting may be considered “doing nothing” in our achievement-oriented world, but as far as your body is concerned, it is “work.” Your body needs rest to reestablish a normally functioning metabolism and immune system. If you are severely ill or relapsed, you will need to rest all the time. Even if you are nearly fully recovered, include rest time during the day. Remember: Rest time is not wasted time; it is healing time.

#### FURTHER READING

*How to pace your energy with rest:* <http://cfidselfhelp.org/library/3-reducing-symptoms-with-planned-rest>

*More on pacing:* <http://www.cfidselfhelp.org/library/4-nurture-yourself-with-pre-emptive-rest>

*Michael Sharpe and Simon Wessely's infamous advice to “buck up.”*  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1112768/>

#### BIOFEEDBACK

**DESCRIPTION.** Biofeedback is a technique in which physiological processes are monitored by a computer to enable a person to exercise control over previously unconscious body functions.

**BACKGROUND.** Biofeedback is a relatively new technique, although the concept of using the mind to control the body is an ancient one. Tibetan lamas and Indian yogis achieve tremendous control over unconscious functions through the practice of simple meditation techniques. In biofeedback, the patient actually sees or hears a representation of brain waves using a computer. Different brain wave patterns can be represented by fish swimming, abstract designs, or music. The

object is to change the pattern—make it grow or shrink, make the fish swim faster, make the music play louder— through the power of concentration.

Biofeedback has been a topic of great interest in the medical community since the 1950s. Biofeedback devices have been used to help patients regulate heartbeat, eliminate migraine headaches, and control elevated blood pressure. Ultimately, any medical problem that is affected by stress hormones can be influenced by biofeedback techniques. In CFS/ME, biofeedback may be useful in reducing symptoms exacerbated by a dysregulation of the hypothalamus-pituitary-adrenal axis because adrenal hormones are sensitive to brain wave output.

**USES IN CFS/ME.** There is no doubt that the nervous system plays an important role in generating, or exacerbating, the fatigue and cognitive impairment experienced by CFS/ME patients. A number of studies have reported abnormalities in EEG (brain wave) patterns in CFS/ME patients.

In 1997, researchers at the University of West Florida compared the EEGs of a group of 28 CFS/ME patients with age- and gender-matched controls. They found that the CFS/ME subjects displayed greater impairment than non-controls in that they generated higher microvoltage activity in the lower frequencies (5-7 Hz, the stage of light sleep, also known as theta waves). The authors concluded that “the increased microvolt levels found in the lower frequencies in CFS subjects may be indicative of deficits in information processing speed, psychomotor activity, attention, retrieval of information from semantic memory, and logical reasoning.” Basically, this means CFS/ME patients are functionally asleep while in the waking state.

More recently, in 2011 Duffy et al used EEG patterns to differentiate between patients with CFS/ME, patients with depression and healthy controls. The researchers found that EEGs correctly identified unmedicated patients with CFS/ME and healthy control subjects without misclassifying depressed patients as having CFS/ME. This study provides concrete evidence that CFS/ME patients demonstrate brain physiology that is not observed in healthy normals or patients with major depression.

In 1993, Michael Tansey, a researcher in Somerville, New Jersey, successfully used neurofeedback techniques to reduce cognitive confusion, pain, headaches, and cold extremities in a CFS/ME patient who had had severe symptoms for 2 ½ years (*CFIDS Chronicle*, Fall 1993). He placed sensors along the top of the skull, just above the supplemental motor area (SMA) of the brain, with the idea that because that area controls limbic outflow and the flow of sensory information, resolution of abnormal brain waves in the SMA would result in cessation of cognitive, verbal, and motor control problems.

Three years later, James and Folen, two psychologists in Hawaii, published a case report in which they measured a CFS/ME patient's response to neurofeedback using a standardized tool (the Wechsler Adult Intelligence Scale). The results revealed improvements in the patient's cognitive abilities, functional skill level, and quality of life.

Myra Preston, Ph.D., a biofeedback therapist practicing in Charlotte, North Carolina, has patented a neurofeedback technique that in some patients has resulted in a significant decrease in cognitive problems (*CFIDS Chronicle*, Winter 1996). She uses the basic biofeedback apparatus together with an EEC to correct the excess delta wave (slow wave) anomaly found in people with cognitive difficulties. Dr. Preston argues that when the brain wave pattern reverts to normal, many central nervous system (CNS) symptoms will recede, including difficulty in concentrating, headaches, and insomnia.

Preston's theories were supported by a study published in 2001, in which a young woman with sudden onset CFS/ME was treated with neurofeedback and self-hypnosis. Her EEG showed excessive theta wave activity (characteristic of light sleep) in the left frontal lobe. After being treated with neurofeedback and self-hypnosis, the patient experienced considerable improvement in fatigue, vigor, and confusion. Most important, the majority of the changes were maintained at five-, seven-, and nine-month follow-up testing.

**PROS AND CONS.** As a treatment modality, biofeedback is completely safe. Patients with CFS/ME have successfully used biofeedback to treat cognitive problems, headache, anxiety, cold hands, and for general relaxation. Because the technique is noninvasive and seems to address one of the core CFS/ME problems, it may hold great promise for those with severe CNS and cognitive problems. The main drawback of biofeedback is that it requires frequent training sessions and daily practice. Many of the more seriously ill CFS/ME patients may not feel up to the time commitment.

**AVAILABILITY AND COST.** Biofeedback has become so popular in recent years that finding a clinician who uses it is not difficult. In general, clinicians who use the technique are psychologists. To find a certified specialist check the Association of Applied Psychophysiology and Biofeedback's website. The cost of biofeedback depends on the hourly fees charged by the practitioner. Sometimes insurance covers the cost, but check with your carrier first.

#### FURTHER READING

“Neurotherapy: Rehabbing the CFS/ME brain.” *Winter 2003 CFIDS Chronicle article discussing the benefits of neurotherapy for CFS/ME:*

<http://www.cfids.org/archives/2003/2003-1-article07.asp>

*The Association of Applied Psychophysiology and Biofeedback maintains a very useful consumer section. The section contains a list of disorders, information on how biofeedback works, efficacy information, research and how to find a provider:* <http://www.aapb.org/consumers.html>

*Biofeedback Research Institute's website. Click on “What is Biofeedback” for a detailed description of a biofeedback session:* <http://www.7hz.com/>

*A very thorough account of one patient's experience with biofeedback. Includes photos.* [http://fibrofriends.typepad.com/fibro\\_friends/2010/05/biofeedback-therapies-for-cfs-fms.html](http://fibrofriends.typepad.com/fibro_friends/2010/05/biofeedback-therapies-for-cfs-fms.html)

*Myra Preston's site:* <http://www.siberimaging.com/index.html>

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<http://www.ncbi.nlm.nih.gov/pubmed/11790917> (Abstract)

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<http://www.ncbi.nlm.nih.gov/pubmed/8879459> (Abstract)

## CHELATION THERAPY

**DESCRIPTION.** Chelation therapy involves use of intravenous EDTA (ethylene diamine tetra-acetic acid) to bind and remove metal molecules from the body.

**BACKGROUND.** Chelation was developed in the late 1940s to treat lead poisoning. It had been discovered about a decade earlier that EDTA, a synthetic amino acid compound, had the ability to bind with calcium. (As a consequence, EDTA is classified as a calcium channel blocker.) The resulting calcium combinations then bind with heavy metals in the bloodstream and remove them by way of the kidneys and bladder. Although the only approved use of chelation in the United States is to treat heavy metal poisoning (chiefly lead, arsenic and iron), chelation therapy has also been used to treat chronic degenerative diseases such as diabetes, stroke, cataracts, senility, Parkinson's disease, and osteoporosis. Currently, chelation is being tested for treatment of coronary artery disease.

**USES IN CFS/ME.** Not many CFS/ME physicians have included chelation in their protocols, though, in theory, chelation could offer considerable benefit to patients in whom CFS/ME was triggered by exposure to pesticides or other toxic chemicals. In these cases, chelation would remove toxins and heavy metals which continue to cause symptoms and exacerbate immune system irregularities.

In 1994 Dr. Boergman of South Africa reported a 100% improvement rate in 16 CFS/ME patients using EDTA chelation (*CFIDS Chronicle*, Summer 1994). One of Dr. Boergman's patients recovered totally after 10 infusions. The others reported 60% to 90% recovery from physical and mental symptoms. However, it is important to note that Dr. Boergman's study was quite small and has not been replicated. Other physicians have not substantiated Dr. Boergman's findings.

There is a subset of health practitioners who believe that mercury amalgams are responsible for CFS/ME. They routinely advise patients to have the amalgams replaced, followed up by chelation therapy to remove mercury from the body. While some people have gone through this costly process, most have not found relief from CFS/ME symptoms.

**PROTOCOL.** EDTA chelation can be administered by intravenous drips, suppositories, and orally. The recommended frequency of treatment is once a week. Daily chelation is not advised. The main chelating ingredient used in IV therapy is EDTA, but other chelators such as vitamin C, vitamin A, heparin, and selenium may be added to the infusion to boost the chelating power of the mixture. Suppositories can be taken up to three times a week. A less expensive, and less risky, form of chelation can be accomplished orally with natural chelating agents such as vitamin C (4000 mg/day) and lipoic acid.

**PROS AND CONS.** Side effects of chelation include decreased blood pressure, hypoglycemia, joint pain, fatigue, weakness (due to potassium depletion), and peeling of the skin (due to decreased zinc and vitamin B6 levels). Because the chelated compounds are excreted through the kidneys, chelation can damage those organs. Chelation is contraindicated in patients with a history of kidney, liver, or bladder disease (such as interstitial cystitis).

Chelation also depletes the body of vitamin B6 and minerals such as potassium, zinc, magnesium, calcium, and chromium. In patients with low concentrations of these vitamins and minerals, a long course of chelation therapy can cause considerable damage. Before starting chelation therapy, nutritional status should be checked and corrected if necessary. In any case, nutritional supplementation is necessary during chelation therapy. (Be sure your physician is familiar with the American College of Advancement in Medicine protocol before chelation therapy is started.) Chelation can cause sudden cardiac arrest resulting from hypocalcemia. At least thirty deaths have been attributed to chelation therapy.

**AVAILABILITY AND COST.** Each chelation treatment costs around \$100, depending on where it is performed (costs are higher on the east and west coasts) and whether other supporting therapies are included. With additional tests and supporting treatments, an entire course of treatment may cost well over \$2000. Insurance companies usually require a predetermination for this treatment to establish "medical necessity," so check with your carrier first. Suppositories are less expensive at \$8 a day, but like IV chelation, should be supervised by an experienced physician.

#### FURTHER READING

*This is a commercial site, but it contains a good summary of different forms of chelation.*

[http://www.chelationhealthproducts.com/why\\_kelatox\\_suppositories.php](http://www.chelationhealthproducts.com/why_kelatox_suppositories.php)

*CDC report of deaths related to chelation therapy.*

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a3.htm>



"Why the NIH Trial to Assess Chelation Therapy (TACT) Should Be Abandoned."

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2438277/>

*This is a lengthy, well-documented report written by a team of doctors about the hazards of chelation therapy. It reports 30 deaths resulting from chelation therapy.*

## CHIROPRACTIC

**DESCRIPTION.** Chiropractic is the technique of manipulating the spinal column and body joints to alleviate back or joint pain.

**BACKGROUND.** Although hands-on manipulation of the joints and spine was practiced in ancient Egypt and Assyria, the technique was not popularized in the United States until the late 1800s, when D. D. Palmer founded the practice. The central premise of traditional chiropractic is that subtle deviations of the spinal column, called subluxations, can interfere with nerve transmissions, causing various health problems. The chiropractor, by manipulating the vertebrae back into their normal position and giving recommendations about exercise and posture improvement, can remove irritation to the nerves that may be causing pain.

**USES IN CFS/ME.** Chiropractic is normally used to treat back and joint pain, although it also helps alleviate a broad range of related symptoms such as insomnia, headaches, and sciatica.

**PROTOCOL.** Most chiropractors prefer to see their patients two or three times a week. It may take up to 12 sessions to note improvement.

**PROS AND CONS.** Results in CFS/ME are mixed. Some patients claim relief from headaches and muscle pain, which, in turn, has helped them sleep. An equal number say chiropractic worsens their pain. The muscles and other tissues surrounding the spine are exquisitely sensitive. The traditional form of chiropractic, in which the spine is abruptly "popped" with a sharp hand movement, may place too much strain on these tissues, causing injury. (Neck manipulations carry the risk of stroke, and should be avoided.) The pain generated by such treatment may last for days, sometimes weeks. Patients interested in trying chiropractic for the first time might want to try a more gentle form of chiropractic, such as Network Chiropractic.

**AVAILABILITY AND COST.** Chiropractic adjustments average \$65 per visit. Initial visits, which may include taking a history and x-ray examination, may cost more. Many insurance companies cover the cost of chiropractic treatment.

## MORE INFORMATION

*The Association for Network Chiropractic website.*

<http://www.associationfornetworkcare.com/whatisnsa.shtml>

*Database for locating chiropractors:*

<http://www.chirofind.com/mpacms/dc/locator/home.php>

## COGNITIVE BEHAVIORAL THERAPY (CBT)

**DESCRIPTION.** Cognitive Behavioral Therapy (CBT) is a psychotherapeutic approach used by psychologists to treat dysfunctional behaviors.

**BACKGROUND.** In a departure from traditional psychotherapy, which focuses on events of the past, CBT focuses on present behaviors and problems and seeks practical solutions.

CBT was primarily developed through an integration of behavior therapy, a form of therapy that utilizes behavioral conditioning, and cognitive therapy, a form of therapy developed in the 1960s that helps patients overcome dysfunctional beliefs. CBT is primarily used for psychological disorders that are rooted in the patient's basic concepts, ones that he or she may not be aware of. Through a partnership with the therapist, the patient learns to recognize and eliminate ideas which are contributing to dysfunctional behaviors.

CBT is best used for conditions in which dysfunctional behavior has a psychological or cognitive basis, such as bulimia, phobias, obsessive-compulsive disorder, post traumatic stress disorder, social phobia, generalized anxiety, and some forms of depression. It is particularly effective for eating disorders. CBT has not been shown to be effective for schizophrenia, bipolar disorder, addictions, or major depression.

**USES IN CFS/ME.** According to its proponents, CBT is a safe, effective treatment because “patients gradually shift their fixed ideas that they are helpless against the fatigue that dominates their lives and move to the perception that fatigue is only one negative experience among many positive ones.” Because CFS/ME is classed as a mental illness in the U.K., CBT has been officially endorsed as a CFS/ME treatment in Great Britain. Numerous studies, conducted primarily in the U.K., have appeared to support the efficacy of CBT for treating CFS/ME. However, these studies have not been replicated elsewhere.

In a special edition of the *Journal of Chronic Fatigue Syndrome* (Vol 11, (1) 2003), an article written by a panel of eleven CFS/ME physicians discussed the results of several CBT studies. The authors concluded that the U.K. studies were inherently flawed. According to the Oxford case definition of CFS/ME (which was the case definition used in most of the British CBT studies), the only criterion for CFS/ME is six months of unexplained fatigue. None of the other symptoms specified by the U.S. and Canadian case definitions (sore throats, sleep disturbance, pain, exercise intolerance, etc.) are required.

This very broad case definition allows patients with other disorders, such as depression, to be included under the designation of CFS/ME. The authors of the article noted that “a systematic review of prognosis studies show that the less stringent the clinical criteria, the better the prognosis.” In short, studies demonstrating the efficacy of CBT for CFS/ME patients tend to yield much better results when subjects without CFS/ME are included. The authors concluded that “to ignore the demonstrated biological pathology of this illness, to disregard the patient's autonomy and experience and tell them to ignore their symptoms, all too often leads to blaming patients for their illness and withholding medical support and treatment.”

Even in the face of rising criticism, the proponents of CBT have maintained their position. But in 2008 a meta-analysis of 15 studies (1043 CFS/ME

participants) conducted by Price et al found that CBT might be more effective in reducing fatigue symptoms *only when compared with other psychological therapies*. The researchers noted that there were very few follow-up studies, and these showed inconsistent findings. The authors concluded that “there is a lack of evidence on the comparative effectiveness of CBT alone or in combination with other treatments.”

A year later, two Dutch researchers, Twisk and Maes, reviewed CBT and GET (graded exercise therapy) as treatments for CFS/ME/ME. The authors determined that the success claim for CBT was “unjust” and that CBT was hardly more effective than no care at all. They concluded that “it is unethical to treat patients with ME/CFS with ineffective, non-evidence-based and potentially harmful “rehabilitation therapies,” such as CBT/GET.”

Finally, in 2011 a randomized controlled trial comparing CBT/GET with usual care (exercise counseling and pharmacological treatment) conducted by Núñez et al found that after twelve months the CBT/GET group showed no improvement in health-related quality of life and actually declined in physical function and bodily pain.

**PROTOCOL.** A typical CBT course consists of between twelve and sixteen hour-long sessions. (Note that a therapist's “hour” is 50 minutes.) A typical cognitive therapy program may involve keeping an “energy diary” in which the patient reports any psychological or social factors, such as losing a job, which might be making the fatigue worse. Patients also use the diary to track peaks and troughs in energy levels. After reviewing the diary, patients adjust their schedules in order to rest during low-energy periods, while reserving high-energy times for important activities. Because energy peaks and troughs are unpredictable, patients are encouraged to be flexible and to prioritize, dropping the least important tasks while focusing on the tasks that are essential. Patients are encouraged to set limits, manage impaired concentration, and to accept relapses. Throughout this re-training of the mind, patients are taught to reverse “negative beliefs.”

**PROS AND CONS.** Although many patients find some form of counseling helpful, there appears to be no evidence supporting the use of CBT as a CFS/ME treatment. Dr. Myhill has included CBT on her list of treatments “not worth trying,” noting that it makes her patients feel worse. It might be of benefit to mildly ill patients, but that group has not been included in CBT studies, and the moderately ill cohort in well-structured studies appears to suffer a decline after treatment. In a survey conducted by the 25% Severe ME Group (for severely ill CFS/ME patients), 93% of the respondents indicated that CBT was not helpful.

**AVAILABILITY AND COST.** CBT is practiced by many psychologists. The cost is the practitioner's hourly rate. Insurance usually covers.

#### FURTHER READING

*Basic information about CBT in CFS/ME:* <http://www.cfids.org/resources/patient-ed-cbt-fsheet.asp>

“Cognitive behavioural therapy for ME/CFS sufferers: How strong is the evidence?” <http://www.mereseearch.org.uk/research/reviews/cbt.html>

*Historical review of all CBT studies.*

[http://www.mecfsforums.com/wiki/Cognitive\\_Behavioral\\_Therapy](http://www.mecfsforums.com/wiki/Cognitive_Behavioral_Therapy)

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## EXERCISE/GET

**DESCRIPTION.** Exercise includes any systematic program of body movement that is designed to strengthen, tone, or stretch muscles.

**BACKGROUND.** Exercise has been an important component of school health programs since the early 1960s when President Kennedy called for a new era of "vigor." Since then, exercise has become a perpetual preoccupation for health-conscious Americans, many of whom incorporate jogging, running, swimming, and regular visits to a health club into busy work schedules. Moderate exercise produces many health benefits, such as increased strength and sense of well-being, lowered risk for heart disease, reduced arthritic pain, increased mental alertness, and improvements in digestion and metabolism. For most people, exercise is indeed "good for what ails you."

The three basic types of exercise are aerobic, subaerobic, and anaerobic. Aerobic exercise induces systemic changes. In concrete terms, aerobic exercise is any exercise that lasts at least 12 minutes, involves deep breathing, and uses major muscle groups (thighs and buttocks). Jogging and hiking are good examples of aerobic exercise because they affect heart rate and breathing, and utilize major muscle groups. Some metabolic changes that occur as a direct result of aerobic exercise are increased utilization of oxygen, increased production of ATP (adenosine triphosphate), and increased utilization of the Krebs cycle (tricarboxylic, or citric acid cycle).

Subaerobic exercise, such as walking, golfing, nonstrenuous hiking, light weight lifting, and swimming, is what most clinicians mean by "gentle" exercise. All of these can be done without pushing the heart rate past 50% of its maximum capacity. None of these forms of exercise will produce metabolic changes unless the person is out of shape or is ill. However, they help build muscle strength and endurance. Subaerobic exercise also elevates mood, improves cognition, enhances immune system function, and improves circulation.

Anaerobic exercise is any form of aerobic exercise that pushes heart rate to its limit. A runner who reaches a point of breathlessness is exercising anaerobically. Metabolic changes induced by anaerobic exercise include increased production of lactic acid (causing burning pain in muscles), lowered ATP production, and decreased dependence on the Krebs cycle.

**USES IN CFS/ME.** One of the ongoing debates among CFS/ME clinicians, as well as their patients, is whether exercise is good or bad for patients with CFS/ME. The Centers for Disease Control and Prevention (CDC) maintains that patients with CFS/ME need to maintain a steady, low-impact exercise regimen to avoid becoming deconditioned. Indeed, some physicians recommend exercise as one of their chief CFS/ME therapies. Other clinicians disagree, noting that exercise is contraindicated in viral illnesses (e.g., poliomyelitis). They point out that exercise intolerance is a hallmark symptom of CFS/ME and that symptoms invariably worsen after any form of exercise.

According to Dr. Charles Lapp, exercise is the proverbial "double-edged sword." On the positive side, people mention that exercise increases their strength and helps keep them mentally alert. It also seems to have beneficial effects on the immune system. Some physicians believe gentle exercise can help reverse some of the immune system malfunction of chronic CFS/ME. Dr. Benjamin Natelson, of the New Jersey CFS Center, points out that natural killer cells decline with inactivity (*CFIDS Chronicle*, Winter 1996). He contends that with a "very, very gentle training program," immune markers may improve.

On the negative side, single-photon emission computed tomographic (SPECT) scans have shown that in CFS/ME patients who exercise, brain blood volume is reduced one to three days after exercising. In patients who are acutely or seriously ill, this could have profoundly deleterious effects on immune and endocrine system regulation. In patients with CFS/ME, exercise also lowers cortisol levels, which makes it more difficult for the body to control inflammation.

In addition, exercise in this population increases erratic breathing and leads to a rapid progression to anaerobic metabolism, which produces ammonia and lactic acid. (These results are the opposite of what would normally be expected in a healthy population.) Given the results of the Peckerman studies on cardiac insufficiency in CFS/ME patients, it would be quite risky for those who are severely ill to embark on any kind of exercise program.

In short, a simple answer to the exercise question is: if you are severely or acutely ill, exercise will only make matters worse. The time to discuss an exercise program with your physician is when clear signs of recovery are noted.

**PROTOCOL.** Most CFS/ME clinicians advise a very gradual reintroduction of exercise. Subaerobic exercise, that is, exercise that does not cause the body to heat up or increase heart rate, is often recommended once a patient is showing a return of overall health. (On a scale of 1-10, this would be a 5.) This form of exercise helps keep muscles conditioned, increases stamina, and helps with blood circulation. It also puts little strain on ATP production, making it appropriate for people with CFS/ME-induced metabolic disturbances. Walking and swimming are probably the best forms of exercise for this purpose.

A good measure of readiness to exercise is when daily household activities (e.g., sweeping, washing dishes, doing laundry) are no longer a challenge. Once you can function normally in your home, you can begin to walk. The amount of time spent walking can be increased in gradual increments over weeks or months (not days). When you are able to walk for six or seven minutes without feeling short of breath, you can consider gentle stretching, yoga or "weightless" weight training to strengthen specific sets of muscles. (Some CFS/ME patients have had success using weight-lifting equipment set at zero to help tone muscles.)

Once you begin to exercise, it is important to remember that you are not in a contest. How fast you go, how many laps you swim, how many blocks you walk, or how much weight you lift is not only irrelevant, but can be counterproductive. As Dean Anderson, a former ski racer put it, "Most important was learning to enjoy exercise without succumbing to the urge to 'train,' which meant I had to give up on any idea of progressing—of doing more push-ups or of jogging farther or faster . . . Had I set training goals, as healthy people do, I would have invited not only a succession of relapses, but also discouragement and perhaps demoralization" (*CFIDS Chronicle*, Winter 1996). In other words, learn your limits, which may very well fluctuate from day to day, and stick to them.

**PROS AND CONS.** As with most treatments, CFS/ME patients respond differently to exercise. But, in this case, the sub-groups sort out rather neatly. Those who are severely ill invariably get much worse from exercise, while those who are mildly ill seem to benefit. The moderately ill group (on a 1 to 10 scale: 5-7) seems to do well with gentle stretching, swimming and walking. While a number of physicians promote the idea that prolonged lack of exercise will worsen CFS/ME by leading to "deconditioning" there is little evidence to support this. In fact, research suggests the opposite.

In one of the few longitudinal studies of CFS/ME patients, Matthews and Komaroff found that physical capacity was not only undiminished, but had improved in 99 CFS/ME patients over a 10-year period. There is plenty of anecdotal evidence from CFS/ME patients themselves that even long periods of inactivity do not worsen the illness, and that once recovery is under way the body regains its strength fairly quickly.

SEE: Cardiovascular symptoms

#### FURTHER READING

*General information about CFS/ME and exercise:*

<http://www.cfids.org/archives/2000rr/2000-rr4-article02.asp>

*Interesting article about responses to exercise in CFS/ME patients.*

<http://www.research1st.com/2011/06/02/exercise-challenge-reveals-potential-cfs-biomarkers/>

#### RESEARCH

Matthews, Rosalind M., Anthony L. Komaroff. "Changes in Functional Status in Chronic Fatigue Syndrome Over a Decade: Do Age and Gender Matter?" *Journal of Chronic Fatigue Syndrome*, Vol. 14(1) 2007

#### GET (GRADED EXERCISE THERAPY)

**DESCRIPTION.** GET is a training program that increases exercise in small increments on a day-to-day basis. It is usually accompanied by CBT (cognitive behavioral therapy), a psychotherapeutic program designed to correct "illness beliefs."

**USES IN CFS/ME.** GET was developed in Great Britain as a therapy for CFS/ME. It is based on the idea that CFS/ME is fundamentally a psychological condition that manifests itself as an avoidance of activity. The underlying concept of GET is that maintaining the habit of avoidance perpetuates CFS/ME symptoms.

Needless to say, the GET program has been met with a great deal of criticism. Both patient groups and researchers have pointed out that exercise intolerance is *the* hallmark symptom of CFS/ME and that a program of systematic exercise will inevitably cause relapse. Researchers who have investigated the mitochondrial defects and resultant cardiac insufficiencies that are common in CFS/ME patients have added that it may, in fact, be dangerous to force severely ill CFS/ME patients into any kind of exercise regime.

The supporters of GET answered this flood of criticism with an extensive randomized trial comparing GET, CBT, Pacing and specialist medical care in 641 CFS/ME patients. Predictably, the PACE trial, as it was called, concluded that GET and CBT could be added to specialized medical care to improve outcomes, but that Pacing (which limits physical activity and requires resting) is not effective.

Almost immediately after the PACE trial publication, the CFIDS Association of America responded with a five-page analysis, in which they pointed out that the

cohort selected for the study was skewed. The PACE Group selected their subjects on the basis of the Oxford Criteria for CFS/ME, which only requires six months of fatigue for a diagnosis. This allows for the inclusion of patients with depression and other disorders.

In addition, the CFIDS Association pointed out that the conclusions drawn by the PACE study were biased, not just in the diagnostic criteria used, but on the basis of patients selected. The PACE study excluded severely ill or homebound patients. Nor did it include patients who had been ill longer than six years. In addition, the cohort was relatively young, with a mean age of 38. After a careful analysis, the CFIDS Association concluded that the only concrete result of the study was that a program of graded exercise might be somewhat beneficial to young, moderately or mildly ill patients with non-specific “fatigue” of short duration.

While the heated debate surrounding GET and CBT has most often centered on the basic argument of whether CFS/ME is a biological (American camp) or psychological ailment (British camp), one cannot help but wonder whether the bottom line in the GET debate isn't the bottom line. CBT and GET are cheap to implement. Doubtless, there is strong economic incentive in Great Britain, where medical care comes out of the national budget, for cutting corners on diagnosing CFS/ME (which in the U.S. requires many specialized tests), as well as for treating such a long, costly illness.

**PROTOCOL.** Typically GET begins with active stretching, followed by range-of-motion contractions and extensions, done for only a few minutes a day for a completely inactive individual. Exercise is increased daily following a schedule until normal activity is resumed.

**PROS AND CONS.** According to the 2010 treatment survey conducted by the M.E. Association, GET is one of the least successful, if not directly harmful, CFS/ME treatments. While CFS/ME doctors in the U.S. encourage gentle exercise in patients who are well on the road to recovery, they do not endorse graded exercise programs. In addition, most (non-British) studies have concluded that GET has a negative impact on CFS/ME patients. Numerous CFS/ME patients have reported relapses, flares, and a general worsening of symptoms after starting the GET program.

## FURTHER READING

*Review of GET studies:*

[http://www.mecfsforums.com/wiki/Graded\\_Exercise\\_Therapy](http://www.mecfsforums.com/wiki/Graded_Exercise_Therapy)

“Falling Off the PACE.” *An analysis of the PACE trial by the CFIDS Association of America.* <http://www.cfids.org/pdf/lancet-analysis.pdf>

*101 Reasons why it is wrong to provide CBT and GET to ME patients.*

<http://niceguidelines.blogspot.com/2011/08/101-reasons-why-it-is-wrong-to-provide.html>

## RESEARCH



- Bjørkum T, Wang CE, Waterloo K. [Patients' experience with treatment of chronic fatigue syndrome]. *Tidsskr Nor Laegeforen*. 2009 Jun 11;129(12):1214-6. <http://www.ncbi.nlm.nih.gov/pubmed/19521443> (Abstract)
- Núñez M, Fernández-Solà J, Nunez E, Fernandez-Huerta JM, Godás-Sieso T, Gomez-Gil E. "Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year of follow-up." *Clin Rheumatol*. 2011 Mar;30(3):381-9. <http://www.ncbi.nlm.nih.gov/pubmed/21234629> (Abstract)
- White P D, K A Goldsmith, A L Johnson, L Potts, R Walwyn, J C DeCesare, H L Baber, M Burgess, L V Clark, D L Cox, J Bavinton, B J Angus, G Murphy, M Murphy, H O'Dowd, D Wilks, P McCrone, T Chalder, M Sharpe. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet*, Volume 377, Issue 9768, Pages 823 - 836, 5 March 2011 [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(11\)60096-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext)

## HOMEOPATHY

**DESCRIPTION.** Homeopathy (from the Greek *homeos*, similar, and *pathos*, suffering) is a system of medicine based on the principal that "like cures like"; that is, substances that produce symptoms similar to those manifested by the illness will act as remedies for that illness.

**BACKGROUND.** The basic principles of homeopathic medicine date from the fourth century BC, when Hippocrates first articulated the idea that a remedy which produces specific symptoms in a healthy person will cure the same symptoms in a sick person. It was not until 1810, however, that homeopathic remedies achieved wide popularity in Europe and America.

In the early part of the nineteenth century a young German physician, Dr. Samuel Hahnemann, discovered that chinchona bark gave him malaria-like symptoms. What surprised him was that chinchona bark was used to treat malaria. Over the years, Dr. Hahnemann experimented with a number of other plant extracts, drugs, and chemicals that produced symptoms of various illnesses. He discovered that minute quantities of these substances served to cure the illnesses whose symptoms they mimicked. Larger quantities of these plants were poisonous, so Hahnemann devised a system of repeated dilutions, or titrations, to preserve effectiveness without injury to the patient.

Homeopathic remedies are so diluted as to leave no perceivable trace of the original plants from which they are derived. The effectiveness of the substance, even in molecular traces, is due to its ability to stimulate the body's natural healing mechanisms along certain specific lines, the symptoms produced by the remedy acting as a set of instructions to the immune system.

An exploratory study performed in Great Britain in 2006 attempted to isolate the active ingredients of homeopathic remedies. The researchers found that about

one-third of patients experienced a major improvement in their health over the study period, a third had some improvement and a third had no improvement. However, given the extensive consultations, the in-depth investigation of patient complaints, and the empathy provided by homeopaths themselves, it was impossible to separate the influence of the homeopathic remedies from the positive effects of lengthy consultations with empathetic practitioners.

**USES IN CFS/ME.** In 2004 a group of researchers from the University of Sheffield in Great Britain studied the effects of homeopathy on a group of 92 CFS/ME patients. The researchers found that homeopathic remedies scored slightly higher than placebo. However, the study used the Oxford Criteria (which defines CFS/ME simply as fatigue lasting for six months) for establishing their patient cohort. As a consequence, the results cannot be considered applicable to the general population of CFS/ME patients.

In a study performed twelve years earlier using the modified Holmes criteria (which includes symptoms other than fatigue), six CFS/ME patients were treated with homeopathic remedies and herbs for three weeks. The researchers found that homeopathy did not affect any of the immunological markers characteristic of CFS/ME patients. The researchers acknowledged that larger studies would be required to verify the effectiveness of herbal and homeopathic remedies, but did not think they were warranted.

**PROTOCOL.** Classical homeopathic remedies are usually taken either all at once or over a short time. Because they are incompatible with allopathic, or pharmaceutical, remedies, you must make a choice as to which approach you think will work best for you. Homeopathic remedies and drugs cannot be taken at the same time, although they can be taken serially. The decision as to which remedy is best is based on careful, lengthy evaluation of symptoms by a homeopath, who must choose wisely, because in classical homeopathy only a single remedy is prescribed. Often the remedy will provoke a "healing crisis" or worsening of symptoms, after which the homeopath will reassess the situation and recommend a different remedy if necessary.

Although classical homeopathy includes only a limited number of remedies (about 20), "eclectic" homeopathy can make use of hundreds of solutions. Homeopathic blends and remedies for specific problems can also be purchased in health food stores. (Although these tend to be less reliable than consulting a homeopath.) The dosage is usually "as needed" or as indicated on the package. This type of homeopathic remedy may be taken in conjunction with pharmaceutical agents, which is an advantage for patients who must take certain medications on a regular basis. Homeopathic remedies are taken on an empty stomach in pill, liquid, or sublingual form.

**PROS AND CONS.** Although homeopathic remedies have come under fire by physicians, many CFS/ME patients have found them effective, particularly for treating specific or acute problems such as headache, sinusitis, or insomnia. Homeopathic remedies are generally less expensive (especially single-dose remedies) than drugs and are usually regarded as having fewer side effects.

(Homeopaths refer to these remedies as "suggestions" that the body may take or ignore.) The drawback is that classical homeopathy requires patients to discontinue pharmaceuticals. Because many CFS/ME patients rely on pharmaceuticals to manage their symptoms, even a short lapse can make symptoms worse. Consult with a trained homeopath before embarking on this type of therapy.

**AVAILABILITY AND COST.** Homeopathic remedies range from \$6 to \$15, although imported remedies (usually German) can cost more. Office visits are comparable to those to a physician and sometimes include the cost of the remedy. As some homeopaths are also M.D.s, insurance may cover the cost of a consultation.

#### FURTHER READING

*Good general guide to homeopathy:* <http://nccam.nih.gov/health/homeopathy/>  
*A critical, but fair examination of homeopathy:* <http://www.skeptdic.com/homeo.html>

#### RESEARCH

Leyton, Edward and Hugh Pross. "Chronic Fatigue Syndrome Do herbs or homeopathy help?" *Can Fam Physician*. 1992 September; 38: 2021–2026. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2145466/>

Thompson TD, Weiss M. "Homeopathy--what are the active ingredients? An exploratory study using the U.K. Medical Research Council's framework for the evaluation of complex interventions." *BMC Complementary and Alternative Medicine*. 2006 Nov 13;6:37. <http://www.ncbi.nlm.nih.gov/pubmed/17101037> (Abstract)

Weatherley-Jones E, Nicholl JP, Thomas KJ, Parry GJ, McKendrick MW, Green ST, Stanley PJ, Lynch SP. "A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome." *J Psychosom Res*. 2004 Feb;56(2):189-97. <http://www.ncbi.nlm.nih.gov/pubmed/15016577> (Abstract)

#### HYDROTHERAPY

*CAUTION: Some naturopathic physicians use hot water hydrotherapy to artificially create a fever (102 degrees). This form of hydrotherapy is contraindicated in CFS/ME patients. Most CFS/ME patients have some form of dysautonomia, which will only be made worse by exposure to heat. In addition, those patients with upregulated immune systems run the risk of relapse by inducing a fever. Patients with tachycardia or any other cardiac symptoms should avoid all forms of heat exposure as heat places a strain on the heart.*

**DESCRIPTION.** Hydrotherapy is the use of water for healing.

**BACKGROUND.** The idea of using water to heal the body is not new. For centuries, people have immersed themselves in therapeutic baths as a means to prevent and cure illness. The ancient Romans and the Incas built sumptuous tiled baths, which to this day stand as proofs of the importance these civilizations placed

on the restorative powers of water. Healing waters can be found all over the world, from Lourdes in France to the Ganges River in India. Spas and hot springs have long been popular in the United States as well. Saratoga Springs, New York, and Hot Springs, Arkansas, still enjoy a reputation for restoring health and vigor.

Although spas are no longer as popular as they were a century ago, the effects of water on the body should not be underestimated. The human body is, after all, 70% water. Water, in one form or another, supplies most of the nutrients our bodies need to maintain life. Our permeable skin allows substances in mineral-rich water to pass into our bodies. And various water temperatures and pressures can have a profound effect on the way our metabolism and immune system function.

**USES IN CFS/ME.** Warm-water baths can help reduce pain associated with lactic acid buildup in muscle tissues. This is the pain so often experienced by patients with fibromyalgia symptoms. The water temperature should be at about body temperature. Many people have reported that warm-water baths help loosen tight muscles, reduce leg pains, and in general create a feeling of relaxation.

Immersion in cold water has been beneficial for some patients. One woman reported that a daily 20-minute bath at a very cool 61° F (16° C) helped her feel better overall. The effectiveness of this strategy is most likely due to the fact that the body, when immersed in cold water, automatically shuts down the blood supply to the skin, shunting it instead to vital organs. The additional blood supply to the brain, liver, and other organs affected by CFS/ME could theoretically have a profound impact on reducing symptoms. Dr. Myhill, however, cautions against cold water baths. She theorizes that cold water works because it gives the adrenal glands a huge “kick.” If the adrenal glands are not working properly, as in CFS/ME, then the patient will feel awful. (To avoid the adrenal “kick,” those who wish to try cold water therapy should do so while swimming.)

Both Dr. Paul Cheney and Dr. Charles Lapp have used tepid-water hydrotherapy with good results. Vertical immersion up to the neck in water at about the temperature of a heated swimming pool has reduced symptoms in a number of Dr. Cheney's patients.

The rationale behind this novel form of hydrotherapy is that the increased pressure at the feet forces lymphatic flow to reverse itself, up the body to the thoracic duct (just below the left clavicle), where it is infused into the bloodstream. The presence of the extra lymph tissue signals the immune system that cytokines are already circulating, and the immune system automatically down regulates. In patients experiencing the effects of excess cytokine production, down regulation of immune system chemicals can provide tremendous relief. The increased pressure also forces blood into vital organs.

Whether due to the additional blood supply provided to vital organs or to down regulation of the immune system, this form of hydrotherapy may offer considerable benefits to a number of people with CFS/ME.

**PROTOCOL.** Dr. Cheney's hydrotherapy protocol requires almost complete immersion in water at 80° to 86° F (swimming pool temperature). For the process to work, it is important that the patient remain vertical and immersed up to the neck,

which means a flotation device is necessary. Initially, immersion time is fifteen minutes, increasing slowly to a half hour. The entire treatment plan calls for 16 weeks of hydrotherapy, with three sessions per week.

**PROS AND CONS.** Dr. Cheney's hydrotherapy program may be a particularly good treatment option for people with pain because it appears to have a positive effect in relieving fibromyalgia symptoms. It seems to have minimal side effects, although some severely ill patients have experienced temporary worsening or relapse of symptoms, no doubt due to the increased concentration of cytokines in the bloodstream. These symptoms decrease over time. Patients who stopped treatment before the 16-week period have had relapses. Once you embark on this treatment, you are committed to finish it. Another problem that could occur is chilling. Dr. Cheney recommends that if you start to shiver, get out of the pool, but do not take a hot shower. If necessary, purchase a wetsuit to help maintain body heat.

**AVAILABILITY AND COST.** Most forms of hydrotherapy are not expensive. A membership to a facility with a pool (such as a club or a community center) may be necessary to follow Dr. Cheney's hydrotherapy program, however. For his program, you will also need to purchase a flotation device to rest on while you are in the water.

For those who do not have access to a pool, Dr. Lapp finds that a bathtub may be equally effective.

## HYPNOSIS

**DESCRIPTION.** Hypnosis involves inducing a trance-like state, somewhere between sleep and wakefulness, to produce greater suggestibility in a patient.

**BACKGROUND.** Although the technique of producing physiological and psychological effects by means of deep trances has been used by yogis, mystics, and oracles since earliest times, it was not until the eighteenth century that Europeans regarded the hypnotic trance as useful for medical purposes.

In the 1760s, Franz Anton Mesmer popularized hypnosis in Europe via a series of theatrical demonstrations of what he called "animal magnetism." Mesmer believed that illness was the direct result of an imbalance in animal magnetism and that hypnosis could correct these imbalances. Because Mesmer's subjects did rather silly things while "mesmerized," hypnosis initially acquired the reputation as a form of entertainment rather than as a therapy.

The current practice of hypnosis has discounted Mesmer's theory of animal magnetism and eliminated the theatrical aspects of hypnosis in order to provide a unique means of influencing normally inaccessible physiological functions, namely those controlled by the autonomic nervous system. By accessing the body's ability to produce heat, dilate or constrict blood vessels, speed or slow metabolism, and so forth, the hypnotist can utilize the body's own mechanisms to control pain, reduce anxiety, relieve phobias, and cure addictions.

**USES IN CFS/ME.** Hypnosis can be beneficial in reducing the effects of anxiety and stress brought on by illness. It can also help alleviate headaches, pain,

insomnia, and some cognitive problems. Most people with CFS/ME describe hypnosis as "very relaxing."

**PROTOCOL.** A standard visit to a hypnotist involves evaluation of a particular problem (e.g., insomnia, pain, anxiety). After assessing the problem, the hypnotist will ask you to sit back in a reclining chair and focus your eyes on a point on the ceiling or a light while he or she speaks to you in a low, monotonous voice. After a short time, your body will relax, and the hypnotist will suggest that you close your eyes. While your eyes are closed, the hypnotist will read from a script specifically designed for your particular problem. After listening, you will be asked to open your eyes on the count of ten and come back to the office setting. The hypnotist may ask you what you felt or "saw." The visit usually lasts one hour.

**AVAILABILITY AND COST.** Licensed hypnotists generally charge \$50 - \$95 per hour session, depending on their degree of training. Hypnotherapists holding an advanced degree in psychology may charge more.

#### FURTHER READING

*This site provides a hypnotherapy script for CFS/ME.*

[http://www.brooksidecenter.com/hypnosis\\_and\\_chronic\\_fatigue\\_syn.htm](http://www.brooksidecenter.com/hypnosis_and_chronic_fatigue_syn.htm)

#### MASSAGE

Craniosacral Massage, Lymphatic Drainage, Myofascial Release, Perrin Technique, Reflexology, Shiatsu

*CAUTION: Vigorous massage is contraindicated in patients with osteoporosis, hypertension, inflammation, arthritis, varicose veins, thrombosis, aneurysm, skin, muscle, or bone disease, unhealed bone fracture, torn ligaments, tendons, or muscles, diabetes, tumors, frostbite, and in pregnant women.*

**DESCRIPTION.** Massage therapy involves manipulation of soft tissue by rubbing, stroking, kneading, compressing, or vibration.

**BACKGROUND.** Massage techniques are as old and as varied as the cultures that originally devised them. As a consequence, it is almost impossible to make a general description of massage therapy. Some techniques, such as Swedish massage, are vigorous and cover the entire body. Others, such as shiatsu, apply pressure to specific areas.

All massage techniques share the principle that the body can be healed through mechanical means. Massaging the body can produce profound metabolic changes. A vigorous massage stimulates the sympathetic nervous system, which speeds up the metabolism, increasing blood circulation, heart rate, respiration, and surface temperature. A light massage, especially over the lower back, stimulates the parasympathetic nervous system, decreasing heart rate and blood pressure and increasing digestive action. Any relaxation of muscle knots and spasms enhances the ability of the vascular system to cleanse the lymphatic system and to clear

stagnant tissue fluid, toxins, and the excess lactic acid buildup that causes acidosis and muscle pain.

**USES IN CFS/ME.** Most CFS/ME patients use massage to relieve muscle pain, headaches, and muscle spasms. A number of patients have reported that a firm massage of the soles of the feet has a profound beneficial effect throughout the body.

**PROS AND CONS.** While it may seem like the logical therapy for pain, a vigorous massage can paradoxically make pain worse. The reason for the aggravation of pain is probably due to the practice of placing excessive pressure on nerve endings to relieve knotty muscles. Nerve compression only exacerbates the pain created by an already irritated nervous system. Vigorous massage will also release accumulated toxins into the system. According to Dr. Cheney, this may lead to malaise in CFS/ME. On the other hand, gentle massage is often beneficial. Those who want to try massage to treat chronic or severe pain may want to consider starting with some of the gentler techniques.

**AVAILABILITY AND COST.** Massages generally cost \$40 to \$60 per hour. If performed by a licensed physical therapist, the cost of massage may be covered by insurance (usually a physician's referral is required).

## CRANIOSACRAL MASSAGE

Craniosacral massage (also called cranial osteopathy) is a gentle form of massage focusing on the spinal cord and skull. It was developed in the 1970s by an American osteopath, John Upledger, who noticed that spinal fluid made rhythmic pulsations as it traveled up the spinal column. He speculated that alterations in the pulses could be used for diagnosis and devised a system by which illnesses could be treated by subtle readjustments. Craniosacral massage is used to treat head injuries, migraines, balance disorders, hyperactivity, whiplash, ear and eye problems, fibromyalgia, and temporomandibular joint (TMJ) syndrome.

Although there have not been any studies confirming the clinical efficacy of craniosacral massage, it continues to be employed by CFS/ME and fibromyalgia patients for temporary relief of pain.

## FURTHER READING

*Website of the Craniosacral Therapy Association (U.K.):*

<http://www.craniosacral.co.uk/>

*Website of the Biodynamic Craniosacral Therapy Association of North America.*

[http://www.craniosacraltherapy.org/CSTA\\_home.html](http://www.craniosacraltherapy.org/CSTA_home.html)

*Craniosacral Therapy:* <http://www.beatcfs.info/osteopathy.html>

Hartman, Steve E. and James M. Norton. "Interexaminer Reliability and Cranial Osteopath." *Sci Rev Alt Med* 6 (1): 23–34. 2002.

<http://faculty.une.edu/com/shartman/sram.pdf>

## LYMPHATIC DRAINAGE

The Vodder method of manual lymphatic drainage is a gentle, rhythmic European massage technique designed to increase and accelerate the movement of lymphatic fluid through the body. It was developed in France in the 1930s to treat a variety of conditions that might be caused or aggravated by congested lymph, including sinusitis, acne, edema, inflammation, and arthritis.

Lymphatic drainage uses several techniques. In the first, light circular motions are directed towards the heart to facilitate the return of the lymph to the circulatory system. Therapists may also focus on the face and neck, using the same circular motions. In the “pump technique” the therapist presses the back of the client while moving the fingers and thumbs in slight oval movements towards the heart. At the end of the session, a twisting motion is used to “wring out” the client’s lymph nodes. According to practitioners, when the massage is complete, clients should feel relaxed, with decreased swelling in the lymph nodes.

#### FURTHER READING

*Lymphatic drainage techniques:*

<http://www.mesupport.co.uk/index.php?page=lymph-drainage-massage>

*General information about lymphatic drainage.*

<http://www.healthguidance.org/entry/11584/1/Lymphatic-Drainage-Massage.html>

*Worldwide directory of lymphatic drainage specialists:*

[http://www.vodderschool.com/find\\_a\\_therapist](http://www.vodderschool.com/find_a_therapist)

#### MYOFASCIAL RELEASE

**DESCRIPTION.** Myofascial release is a form of massage that involves exerting sustained pressure. It was originally designed by Andrew Taylor Still, the founder of osteopathy. The basis of osteopathic medicine is that the body is a self-regulating unit with the power to heal itself. Traditional osteopathic techniques involve manipulation of fascia (soft tissue) in order to reduce pain, increase lymphatic drainage, and improve blood flow.

There are two methods of myofascial release. In direct myofascial release practitioners use their knuckles, elbows, or other tools to exert a strong pressure that slowly stretches the restricted soft tissue. The practitioner moves slowly through the layers of soft tissue until the deep tissues are reached.

Indirect myofascial release utilizes a gentle pressure, which allows the fascia to simply “unwind” without causing undue stress on the tissue. The indirect method involves lightly contacting the fascia and slowly stretching the fascia for approximately three to five minutes. The slow stretching results in an increase of blood flow to the affected area, which, in turn, reduces pain.

**USES IN CFS/ME.** In 2011 a study was conducted on myofascial release for the treatment of fibromyalgia. The researchers found that “immediately after treatment and at 1 month, anxiety levels, quality of sleep, pain, and quality of life were improved in the experimental group over the placebo group.” However, the results were not sustained six months after the cessation of treatment, which



suggests that myofascial release, like other forms of massage, provides benefits only in the short term.

#### FURTHER READING

*John Barnes' website for myofascial release. Includes directory of practitioners.*

[http://www.myofascialrelease.com/fascia\\_massage/public/whatis\\_myofascial\\_release.asp](http://www.myofascialrelease.com/fascia_massage/public/whatis_myofascial_release.asp)

*Directory of myofascial release practitioners:* <http://www.advanced-trainings.com/directory.html>

Castro-Sánchez, A.M., Matarán-Peñarrocha, G.A., Granero-Molina, J., Aguilera-Manrique, G., Quesada-Rubio, J.M., Moreno-Lorenzo, C. “Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia.” *Evid Based Complement Alternat Med.* 2011;2011:561753. <http://www.ncbi.nlm.nih.gov/pubmed/21234327> (Abstract)

#### PERRIN TECHNIQUE

The Perrin Technique is a form of lymphatic massage that is practiced in Great Britain, and, to a limited extent, in Europe. It was developed exclusively for treating CFS/ME by Dr. Raymond Perrin, a British osteopath.

According to Dr. Perrin, people with CFS/ME suffer from a build-up of toxins in the fluid around the brain and spinal cord. CFS/ME symptoms are the result of the congestion of these toxins. In the Perrin Technique, the spine is manipulated so that soft tissues in the head, neck, back and chest can direct the toxins out of the lymphatic system and into the blood, where they are eventually detoxified in the liver. Dr. Perrin states that “with no poisons affecting the brain, the sympathetic nervous system begins to function correctly, and providing the patients do not overstrain themselves their symptoms should gradually improve and in time some patients become totally symptom free.”

While claims that the Perrin Technique can actually cure CFS/ME are exaggerated, about 50% of the respondents to the 2010 ME treatment survey in Great Britain reported that the Perrin Technique provided them with some improvement. The other half reported no change or a worsening of symptoms.

#### FURTHER READING

*Website of the Perrin clinic:* <http://www.theperrinclinic.com/>

*Patient thread on the Perrin Technique:*

<http://forums.phoenixrising.me/showthread.php?8526-Perrin-lymph-drainage-massage-makes-sense-or-not>

*Another patient thread on the Perrin Technique:*

<http://forums.phoenixrising.me/showthread.php?11258-The-Perrin-Technique-Does-it-help>

Perrin, Raymond N., DO. “Lymphatic Drainage of the Neuraxis in Chronic Fatigue Syndrome: A Hypothetical Model for the Cranial Rhythmic Impulse.” *Journal of*

*the American Osteopathic Association.* 2007  
<http://www.jaoa.org/content/107/6/218.full>

## REFLEXOLOGY

Although foot massage has been practiced for centuries, it wasn't until the early 20<sup>th</sup> century that it was introduced in the United States as a medical treatment. In 1913 William Fitzgerald, an ear, nose and throat specialist, found that applying pressure on one part of the body produced an anesthetic effect on other areas of the body. In the 1930s, Eunice D. Ingham (1889–1974), a nurse and physiotherapist, expanded on Fitzgerald's observation, identifying the feet and hands as especially sensitive. Ingham then mapped the entire body, identifying corresponding zones on the feet.

Modern reflexology is based Ingham's idea that reflex points (or zones) located on the hands and feet correspond to every organ in the body. Steady, even pressure applied by the fingers to these zones is said to remedy any imbalances in the corresponding organs. Reflexology is supposed to promote improved circulation and contribute to a sense of relaxation and well-being. Because reflexology may be practiced easily on one's own feet and hands, it is an ideal form of self-massage

Several studies have shown that reflexology may be beneficial for some conditions. In 2010 a group of Japanese researchers found that reflexology improved cold intolerance. A 2009 Korean study found that self-administered reflexology improved fatigue, stress and blood circulation.

While there are no systematic scientific studies confirming the efficacy of reflexology in treating any specific medical condition, it remains a very popular form of massage.

## FURTHER READING

Ernst E. "Is reflexology an effective intervention? A systematic review of randomised controlled trials." *Med J Aust.* 2009 Sep 7;191(5):263-6.  
<http://www.ncbi.nlm.nih.gov/pubmed/19740047> (Abstract)

Jang SH, Kim KH. [Effects of self-foot reflexology on stress, fatigue and blood circulation in premenopausal middle-aged women]. *J Korean Acad Nurs.* 2009 Oct;39(5):662-72. <http://www.ncbi.nlm.nih.gov/pubmed/19901496>

Zhang W, Takahashi S, Miki T, Fujieda H, Ishida T. "A pilot study exploring the effects of reflexology on cold intolerance." *J Acupunct Meridian Stud.* 2010 Mar;3(1):43-8. <http://www.ncbi.nlm.nih.gov/pubmed/20633515> (Abstract)

## SHIATSU

Shiatsu is an ancient form of Japanese massage closely related to acupuncture that dates to the third millennium BC. The basic technique consists of the application of pressure by the fingers over some 600 neural trigger points located on lines (meridians) throughout the body. The points are said to be places where lymph vessels tend to congregate. By releasing the point with gentle

sustained pressure, energy blocks are removed and the body can better eliminate waste products such as lactic acid that have accumulated in body tissues.

In Japan, where Shiatsu is recognized as a formal branch of medicine, Shiatsu practitioners must undergo a three-year course of training and be licensed with the Ministry of Health and Welfare. Western nations, because they do not recognize Shiatsu as a medical treatment, do not require a license. Nevertheless, Shiatsu is an established form of massage not just in Asia, but in most Western countries.

In 2011 a meta-analysis of 1714 publications regarding acupressure and shiatsu was conducted by members of the Allied Health Sciences Department of London South Bank University. While there was evidence supporting acupressure's efficacy in moderating pain, nausea, and insomnia, the investigators found that research of Shiatsu was too scant to come to an overall conclusion.

As with other forms of gentle massage, CFS/ME patients report that Shiatsu is helpful with managing pain.

#### FURTHER READING

*General discussion of Shiatsu in CFS/ME:* <http://www.beatcfs.info/shiatsu.html>  
Robinson N, Lorenc A, Liao X. "The evidence for Shiatsu: a systematic review of Shiatsu and acupressure." *BMC Complement Altern Med.* 2011 Oct 7;11:88.  
<http://www.ncbi.nlm.nih.gov/pubmed/21982157> (Abstract)

#### MEDITATION/AMYDALA RETRAINING PROGRAM

**DESCRIPTION.** In meditation, a calm state of consciousness is achieved by means of concentration, contemplation, or visualization techniques.

**BACKGROUND.** Meditation is an ancient practice that has been used throughout the ages to reach an inner state of quiet. Meditation techniques form the backbone of Buddhism, one of the world's major religions. Because meditation was, and still is, practiced to achieve an altered or "higher" state of consciousness (a drawing closer to a divine state of being), the practice of meditating is less a therapy than a way of life.

Meditation is as much a mode of looking at the world as it is a technique, as much a philosophy as a practice. In meditation, the means and the ends are as one. One meditates for its own sake, not to achieve a specific goal but to let go of all goals. In the process of letting go, a different person emerges. A different body may emerge, as well. Those who meditate have been known to achieve lowered blood pressure, relief from pain and migraine headaches, and greater mental clarity and alertness through the simple act of gazing within.

**USES IN CFS/ME.** In the 2010 M.E. Association's survey of treatment modalities, nearly 54% of respondents indicated that meditation and relaxation techniques were helpful. Those who meditate on a regular basis report an increased feeling of calm and improved outlook on life. Meditation is also effective in controlling the pain generated by an over-reactive nervous system. Like rest, meditation seems to cause no damage and results only in a general sense of

improvement. Patients with CFS/ME, especially those who find themselves plagued by depression, anxiety, fear, and anger, can benefit greatly by the practice and philosophy of "letting go."

**PROS AND CONS.** There is no "right" way to meditate, but some practitioners may try to convince you there is. Of the many meditative traditions, not all are conducive to healing long-term illnesses. Zen, for example, was developed for healthy, young, Japanese monks. Sitting for several hours staring at a blank wall (and getting roused by a sharp rap on the head when you drift off to sleep) is perhaps not the best meditation technique for ill people. When you begin to meditate, especially if you are quite ill, do it your own way. Lie down in the comfort of your own bed, and listen to your favorite relaxing music. Then breathe. Remember, meditation is a state of mind. How you get there is up to you.

**AVAILABILITY AND COST.** You can meditate at home for free or you can join a meditation group. Classes in meditation and yoga centers are not usually expensive. You can teach yourself to meditate easily and painlessly by listening to various CDs made for that purpose or by reading a book on meditation techniques. There are many videos of guided meditations posted on youtube.

#### FURTHER READING

*For those who wish to understand the philosophy of meditation, anything written by Thich Nhat Hanh will be helpful.*

*The Mayo Clinic's excellent overview of meditation and its benefits.*

<http://www.mayoclinic.com/health/meditation/HQ01070>

*Margaret Fergusson's personal account of her recovery from CFS/ME (in which meditation played a prominent role):*

<http://www.cfidsselfhelp.org/library/physical-and-psychological-recovery-cfs>

*"Meditation and the Course of Chronic Fatigue Syndrome."* William Collinge.

<http://www.collinge.org/Fri.htm>

*Living with CFS/ME. "Meditation for Peace of Mind."* CFIDS Chronicle, Summer 2000. <http://www.cfids.org/archives/2000/2000-3-article09.asp>

*Phoenix Rising page on meditation:* <http://phoenixrising.me/treatments-3/treating-chronic-fatigue-syndrome-mecfs-meditation>

#### AMYGDALA RETRAINING PROGRAM

The Amygdala Retraining Program (ARP) is a combination of meditation, visualization and self-guided therapy techniques developed by Ashok Gupta. Gupta's theory is that CFS/ME is caused by trauma to the amygdala, which is the part of the limbic system most closely associated with learning and fear responses.

According to Gupta, during the acute physical stage of the illness, the amygdala "learns" to be hyper-reactive to any symptoms detected in the body. Once the amygdala become hyper-reactive, it overstimulates the sympathetic nervous system, the hypothalamus, the HPA axis, and the immune system, creating the cascade of symptoms experienced by people with CFS/ME.

Ashok Gupta makes the claim that his program is the first world-wide “100% cure for CFS/ME,” which automatically rouses suspicions in most people with the illness. (If there really were a 100% cure out there, you would not be reading this book.) However, many of the methods Gupta employs are based on time-honored meditation techniques. These include halting circular thoughts (which are a sign that the brain is in overdrive), visualizing well-being, breathing exercises, and mindfulness meditation. During the ARP, these techniques are practiced for 30 minutes a day. The entire program takes six months.

The Amygdala Retraining Program is available through Ashok Gupta's clinics in Great Britain and from ARP coaches in France, Germany and Israel. A set of 12 DVDs that will guide you through the program can be purchased for \$200 (U.S.) with a full money-back guarantee.

#### FURTHER READING

*ProHealth interview with Ashok Gupta, in which he explains his theory and describes how his program works:*

<http://www.prohealth.com/library/showarticle.cfm?libid=14508>

*Cort Johnson's interview with Ashok Gupta about controlling the stress response.*

<http://phoenixrising.me/archives/495>

*Amygdala Retraining from a psychologist's perspective.*

<http://alwayswellwithin.com/2010/05/11/retraining-the-brain-for-cfs-fms-mcs-ptsd-gws/>

*Detailed critique of Gupta's hypothesis:*

<http://forums.phoenixrising.me/showthread.php?4191-Amygdala-retraining-fact-from-fiction>

*Informative discussion of the amygdala and fear responses:*

<http://serendip.brynmawr.edu/exchange/node/1749>

*Ashok Gupta's website:* <http://www.guptaprogramme.com/default.asp>

#### PACING

**DESCRIPTION.** Pacing is a system in which CFS/ME patients learn to stay within their limits.

**USES IN CFS/ME.** At first glance, pacing is no more than the exercise of common sense. It was developed as an extension of the advice CFS/ME doctors usually give their patients: Don't push it. Although this may seem logical, many moderately or recently ill CFS/ME patients are deceived by the waxing and waning pattern of their symptoms. As a consequence, they attempt to resume “life as usual” long before they have recovered. These efforts are almost always followed by a crash. Pacing is merely the formalized means by which a patient learns to find his or her limits.

**PROTOCOL.** There are three basic tenets of pacing: 1) stay within your envelope – only do 70% of what you think you can do, 2) schedule rest times – even on “good days” lie down for at least 15 minutes, at least twice a day, 3) keep a diary of symptoms – if they follow a pattern (and sometimes they do!), plan your activities

accordingly. For example, if you find that you “crash” in the afternoon (many people with CFS/ME slump at that time), schedule meetings, shopping, etc. for the morning. Do one important errand, not four minor ones. If you are doing a task at home, don't try to finish before you lie down. Take breaks and rest frequently during work time. Last of all, procrastinate – never do today what you can put off for tomorrow.

#### FURTHER READING

*A patient discusses how she uses Pacing to manage CFS/ME.*

<http://www.cfidsselfhelp.org/library/how-i-use-pacing-manage-cfs>

#### TENS

**DESCRIPTION.** TENS (transcutaneous electrical nerve stimulation) is the topical application of an electrical stimulus to a peripheral nerve in order to control pain.

**BACKGROUND.** The TENS machine was developed after the "gate" model of pain was developed. Pain researchers believed that when nerves are overstimulated, the pain message stops (the assumption being that the brain cannot process sensory input from so many "gates"). The stimulation from TENS is supposed to "drown out" the pain felt in a nerve. Some have also proposed that the reason TENS works is not because the nerve is overstimulated but because the electrical stimulation prompts the release of pain-killing endorphins. Whether the relief is through nerve overstimulation or chemistry, the result is the same—pain is relieved.

Several studies have found that TENS is useful for treating pain in post-operative patients, for arthritis, and chronic back pain. An equal number have not found evidence of efficacy beyond placebo. What needs to be remembered is that pain is a purely subjective experience; it cannot be measured by any objective means (e.g., blood tests, CT scans). Moreover, people have varying pain thresholds; what is painful for one person, may not be for the next. This makes it difficult to measure the effectiveness of any pain treatment.

**USES IN CFS/ME.** TENS has been recommended for patients with fibromyalgia pain, that is, pain generated by trigger points and nerve irritation.

**PROTOCOL.** The TENS unit is a small machine that generates electrical current which is conveyed along wires to small rubber-tipped electrodes. The unit can be worn on a belt. The electrodes are placed on specific sites on the skin by a physician or physical therapist and are held in place with adhesive tape. The amount of stimulation is regulated by the physician.

**PROS AND CONS.** TENS is nonaddictive, has no damaging side effects, and, in many cases, is an effective form of pain control. However, it does require a visit to the physician's office and can be expensive if many treatments are required.

**AVAILABILITY AND COST.** TENS units are expensive to purchase (\$650), and rental can cost \$50 a month. Inexpensive home units are available for much less, but may not have the capacity of larger units. However, it is best to receive

TENS treatments in the office of a health care practitioner who monitor the level of stimulation. The cost of treatment varies, depending on the supervising clinician. When TENS is ordered by a physician, insurance may cover the cost.

#### FURTHER READING

*Detailed explanation of how TENS works:* <http://www.patient.co.uk/health/TENS-Machines.htm>

Bjordal JM, Johnson MI, Ljunggreen AE. "Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain." *Eur J Pain*. 2003;7(2):181-8.

<http://www.ncbi.nlm.nih.gov/pubmed/12600800> (Abstract)

#### VISUALIZATION AND IMAGERY

**DESCRIPTION.** Visualization (guided imagery, creative visualization, creative imagery, or mental imagery) is the use of mental images to produce changes in the body.

**BACKGROUND.** The use of imagery for healing first drew attention in the 1950s when a cancer patient went into remission after visualizing the disappearance of a tumor. This case fueled a great deal of interest in the medical community and eventually led to the development of visualization techniques geared specifically to certain diseases. While visualization has enjoyed a reputation as a "miracle cure," it should be remembered that spontaneous remissions are possible with any illness. Those who question the curative powers of visualization point out that its healing powers are coincidental at best. Despite its limitations, visualization can serve as a useful coping technique.

Visualization is thought to work by mobilizing the immune system, which is not normally under conscious control, through the efforts of higher brain functions. The act of voluntarily creating images (as opposed to hallucinations or dreams) is controlled by the cortex, whereas the immune system is regulated, at least in part, by structures in and around the limbic system, notably the hypothalamus. Since the nerve fibers that connect the limbic system to the cortex flow through the hypothalamus, allowing for a two-way interchange between thought and autonomic nervous system and, hypothetically, immune system function, it is argued that thought can also direct the outcome of illness.

**USES IN CFS/ME.** Visualization techniques can be helpful in maintaining a sense of calm. This can be useful for patients who are severely ill or are experiencing a relapse. Some have reported that, much like hypnosis and meditation, visualization helps them control pain and anxiety.

**PROTOCOL.** To visualize, you must begin by relaxing. Get comfortable, take three or four deep breaths (if you practice meditation or self-hypnosis, you can use any of those techniques), and concentrate on the desired images. For CFS/ME, images that have been suggested include the following:

- Imagine you are surrounded by a bubble of pink light through which nothing can pass. You are completely protected.
- Breathe in light through the crown of the head. Feel that the light's energy is going through every cell and every tissue, bringing feelings of love and well-being to every part of your body.
- See the light perfectly balancing your immune system and restoring it to the way nature intended.

If "seeing" does not work for you, try kinetic imagery. Kinetic, or motion, imagery techniques are more primal than techniques that rely on vision alone. As a consequence, they may be more useful to patients who are acutely ill or cannot make a visual image. Some patients have imagined they are gently rocking in a boat, floating down a stream, or traveling around a sideways figure of eight. These movement-oriented images are useful to alleviate headaches, panic, vertigo, and episodes of nonlocalized pain.

**PROS AND CONS.** Visualization is inexpensive – all you need is a book to explain the theory and you can invent your own images – and it may help you feel more in control. Visualization, however, does not seem to work against the disease process itself. Patients who are led to believe that skillful use of imagery will rid them of all their ills are invariably disappointed. However, if your goal is short-term alleviation of pain, anxiety, or stress-related symptoms, guided imagery, like hypnosis or meditation, can serve a purpose.

#### FURTHER READING

*Bruce Campbell's relaxation and visualization techniques:*

<http://www.cfidsselfhelp.org/library/stress-reduction-five-practical-techniques>

#### BOOK

Collinge, William. *Recovering From Chronic Fatigue Syndrome*. New York: The Body Press/Perigee Books, 1993.

*Includes many guided imagery techniques.*

#### YOGA

**DESCRIPTION.** Yoga is a physical, mental, and spiritual discipline that was developed in India as a form of meditation.

**BACKGROUND.** The practice of yoga is thousands of years old. Like other forms of meditation, it was originally intended for the purpose of achieving a higher state of consciousness in which the material world is left behind. In Indian Buddhism, yoga is considered to be the path to enlightenment.

Yoga, along with other forms of Eastern philosophy, was popular in the counter-cultural movement of 1960s. But it didn't hit the mainstream until the 1980s, when Dr. Dean Ornish disconnected yoga from its Buddhist origins and related it to health. Dr. Ornish is well known as an advocate of life-style changes for improving health, particularly heart disease. By now, his health recommendations of low-fat diets, exercise, and cessation of smoking have become standard in the



medical community. Dr. Ornish is also a firm advocate of meditation and yoga. In the United States, where achieving spiritual enlightenment is not a strong motivation for adjusting one's lifestyle, the promise of reducing the risk of heart attack was enough of an incentive to spur the growth of yoga centers across the country.

There are several different schools of yoga. Hatha yoga is the most familiar to most Westerners. In Hatha yoga the focus is on adopting postures (*asanas*) while maintaining slow, meditative breathing. Iyengar yoga is a more athletic form of yoga which uses belts, cushions, benches, blocks, and straps to maintain *asanas*. Tantric yoga is a form of mysticism that utilizes *prana* (energy, particularly sexual energy) to achieve ecstatic states.

**USES IN CFS/ME.** The most beneficial form of yoga for people with CFS/ME is hatha yoga. Most yoga studios have special hatha yoga classes designed for people who have medical conditions. These allow for resting periods and don't require excessive physical exertion. The *asanas* are confined to those which gently stretch muscles in the torso and limbs.

**PROTOCOL.** Yoga sessions usually last 45 minutes to an hour. Typically, yoga instructors begin with a relaxation exercise designed to quiet the mind. This is done lying down. (Studios usually provide mats). Then the instructor describes how to do the first *asana* and gently reminds the class to coordinate their breathing. After allowing the class to rest, the instructor proceeds to the next *asana*, until the set is finished. The atmosphere of a yoga studio is calm and relaxing.

**PROS AND CONS.** As a non-aerobic form of exercise, yoga tones muscles without increasing heart rate. People who are well into recovery (those who would rate themselves at a 5) tend to do well with a course of gentle yoga. People with moderate to mild CFS/ME report that yoga helps lower stress and anxiety, and provides a sense of well-being. However, like other forms of exercise, severely ill patients should avoid yoga, as it will only increase pain and fatigue.

**AVAILABILITY AND COST.** Yoga studios can be found in most urban centers. Many offer drop-in classes for \$7 or \$8. Frequently, yoga classes are offered through community colleges.

#### FURTHER READING

“Yoga: Stretching Away Your Stress.” *CFIDS Chronicle*, Spring 2003.

<http://www.cfids.org/archives/2003/2003-2-article06.asp>

## COPING AND MANAGEMENT STRATEGIES

### INTRODUCTION – PACING YOURSELF

Coping with chronic illness presents quite a challenge. A patient with diabetes, cancer, multiple sclerosis, allergies, high blood pressure, or any other condition that does not resolve by itself has to make lifestyle adjustments. Some illnesses require constant accommodation, while others may require fewer changes in thinking and behavior. For example, for those with high blood pressure, changes in medication and diet may be the only adjustments the patient has to make. CFS/ME, unfortunately, does not fall into that category. Patients with CFS/ME must make profound adjustments in the way they see themselves in the world, and modify the way they live accordingly.

The keys to coping with CFS/ME consist of first acknowledging the illness, and then adjusting to its limitations. Acknowledging the illness must be the first step. If you cannot accept that you have an illness, making the necessary practical adjustments will be difficult indeed.

Acknowledgment and acceptance of CFS/ME are formidable tasks for most patients. The majority of people diagnosed with CFS/ME had been healthy, leading normally productive lives until they contracted the illness. As a consequence, the diagnosis invariably comes as a shock, in spite of the time and effort most patients spend seeking it. And once the diagnosis is made, the process of accepting it may take years.

Dean Anderson, a former skier and manager of renewable energy projects in the United States, conveys the process of acceptance eloquently:

In America we are taught from early childhood that succeeding in life is important and that striving is the key to achievement. I initially viewed the healing process as one in which I would succeed through determination and hard work... I believe today that a certain kind of acceptance may be important to recovery. It is not a resignation to one's fate as a sick person. Rather, it is an acceptance of the reality of illness and of the need to live a different kind of life (*CFIDS Chronicle*, Winter 1996).

Acceptance of the reality of one's illness implies that this new life is going to be quite different from one's former life—a scary thought for most individuals. In this new reality all the rules are different. They are also unknown. CFS/ME, unlike better researched ailments, is new territory for clinicians as well as patients, making expert advice difficult to obtain. The rule book for living with CFS/ME is yet to be written, for even after the illness has been diagnosed and acknowledged, there still remains the task of figuring out how to live with it.

Dr. Paul Cheney has observed that "patients with this disease must, for many of them for the first time, place limits on their workstyles and lifestyles. Proper limit-setting, which is always individualized, is the key to improvement in this syndrome" (*CFIDS Chronicle*, March 1991). This comment comes after close observation of thousands of patients, many of whom denied their illness for extended periods of time before adjusting to its limitations. Dr. Cheney has seen not only the successes inherent in making these adjustments, but the failure that

results from attempting to ignore them. But first, we must address the question of what is meant by "proper limit-setting."

To set proper limits, we must start with a basic awareness of how CFS/ME affects the body and the mind. CFS/ME affects the ability to maintain homeostasis; that is, once the illness is established, it alters the body's ability to adjust to changes in the environment. For example, when a person with CFS/ME climbs a set of stairs he or she may feel like he or she has just climbed Mount Everest. The out-of-breath, depleted feeling is the result of an impaired output of the heart, which, in CFS/ME, either does not respond in time, or responds inadequately to the greater demands for oxygen required by exertion. As a result, not enough oxygen is available, and a person with CFS/ME will feel winded after even minimal strain.

This type of sluggish reaction also results from temperature changes. People with CFS/ME often remark that when they become cold, "it takes forever to warm up." Heat intolerance is also common in CFS/ME patients. In fact, any sudden change in temperature will produce symptoms as the body attempts to adjust. Coping, in this case, means avoiding, what are now, extremes.

People with CFS/ME often comment that they are either "on" or "off." Once they stop, they can't get going again; and once they start, they can't stop. In *The Clinical and Scientific Basis of ME/CFS*, Dr. Byron Hyde, a well-known clinician and researcher of myalgic encephalomyelitis (ME) describes taking a walk with one of his patients. Dr. Hyde noticed that when he stopped to look in a store window, his companion kept going. When asked why, Dr. Hyde's companion replied that if he stopped, he would never get going again.

Conversely, once embarking on a project, a task, or a plan, it is difficult to stop. Even when performing formerly effortless activities such as taking a walk or balancing a checkbook, patients with CFS/ME often pass the point of endurance without even realizing it, and symptoms rapidly develop as a result. In this case, coping requires stopping an activity while you still feel able to continue.

Learning when we are "overdoing it" is how we define our own particular limits. This takes awareness, skill, and practice. Each person has limits that are defined by the severity of the illness. For a person who is bedbound, limits will be very different from those of someone who is able to work. Patients who are bedbound may find that extended telephone conversations, standing in the shower, or tackling stressful tasks such as filling out disability application forms produce exhaustion and a general exacerbation of symptoms. These patients may find that sitting in a plastic chair while showering, limiting conversations to ten minutes, and resting before and after doing necessary paperwork are ways to conserve energy. A patient who is mildly ill and able to work may wish to cut back on work hours, take naps, and forgo activities that place excessive or inflexible demands on the body (such as team sports or other activities that do not allow the participant to "listen" to the body).

A former airline pilot refers to limit setting as living in a box. "As long as I'm in the box, I do alright. If I cross the margins of this box, I don't do very well" (*CFIDS Chronicle*, March 1991). Defining the limits of your own particular box is

the key to developing good coping strategies. Whatever produces symptoms on any particular day or at any particular hour is where you should define your limits, not by an abstract assessment of what you think you should be doing or a comparison with former capacities. Dean Anderson sees this process as a form of discipline:

It is the discipline to recognize and adhere to one's known limitations and to follow a strict regimen without lapsing. It is the discipline not to succumb to family or societal pressures to get back into the rat-race. It is the will to protect oneself, to not over-do and to find ways to be productive and find fulfillment under unfamiliar and difficult circumstances.

By setting limits and staying within them, a person can learn to live with, and in spite of, CFS/ME.

Chapters 7 through 9 discuss some of the main pitfalls of CFS/ME in three of the areas that require considerable adjustment: coping with stress, the home environment, and dietary limitations. Each offers a series of useful coping suggestions based on the experiences of patients with CFS/ME and related conditions, as well as those of the clinicians who specialize in these areas.

Children and adolescents with CFS/ME present a special challenge. Chapter 10 offers some suggestions for helping children and their families cope with the unique problems CFS/ME creates for children and adolescents.

## STRESS REDUCTION AND ELIMINATION

One of the most common observations made by CFS/ME patients is that stressful situations become harder to handle after becoming ill. Difficulty coping with stressful situations arises as one of the earliest symptoms of CFS/ME and, depending on the circumstances, can be one of its more problematic aspects. Many people with CFS/ME remark that a stressful job or home environment during the early stages of the illness contributed to the severity of the illness at onset. Indeed, patients often notice that an inability to handle stress *preceded* their onset of CFS/ME by several months. Patients in the recovery phase often note that emotional stress can trigger flares; and those who are severely ill experience profound exacerbation of symptoms when placed in stressful situations or environments.

The relationship between stress and relapse is striking enough to have garnered the attention of psychologists and therapists who specialize in CFS/ME. In 1994 Fred Friedberg, a psychologist who has both researched and treated CFS/ME for the better part of his professional life, conducted an investigation of relapse triggers in CFS/ME. In a study group of 300 CFS/ME patients, he found that in the majority, physical or emotional stress was likely to trigger a relapse.

The controversy surrounding the relationship between stress and the exacerbation of CFS/ME symptoms has generated considerable discussion among researchers. The proposed correlation between prolonged stress states and certain physiological problems has led a number of health care professionals to conclude that prolonged stress can produce CFS/ME. This, in essence, is the origin of the epithet "yuppie flu" in the 1980s, when journalists promoted the idea that CFS/ME resulted from the hectic lifestyle and inflated expectations of young, upwardly mobile professionals. At the time, the treatment recommendation for "yuppie flu" was to "take it easy," with the assumption that once the stress was removed the body would return to normal.

For patients with CFS/ME, taking it easy, while helpful, does not fix the problem. Inexperienced physicians treating this puzzling illness, though quick to recommend "taking a break," have been at a loss to understand why their patients do not bounce back after a week or two of vacation. The reason a little distraction or a vacation does not bring a complete restoration of body and mind is because CFS/ME is not a stress-induced illness. Rather, it is a *stress-sensitive* illness; that is, stress does not cause CFS/ME, but it can prolong, or intensify, the disease process – as it does with most illnesses. This is the real obstacle faced by most patients with CFS/ME, for nobody can live a stress-free life.

The many negative consequences of stressful situations make managing stress one of the most important of the coping and lifestyle changes that a CFS/ME patient can make. Most CFS/ME clinicians recommend reducing or eliminating stress as part of their general CFS/ME treatment plan. Stress, however, is an unavoidable fact of life. Whether it's losing a job or a loved one, moving to a new home, being injured, having a baby, or becoming ill, everyone experiences stress during the normal course of a lifetime. It is difficult to plan for such life events, let

alone avert them. However, numerous other stressful situations are predictable and can be effectively controlled. This chapter explains how stress control can be accomplished with a minimal amount of effort, through methods that have withstood the test of time.

### THE STRESS RESPONSE: A BRIEF OVERVIEW

The study of the physiology of stress did not gain significant attention in the medical world until Hans Selye popularized the term in the 1930s. At that time, Selye, a young endocrinologist studying ovarian hormones, discovered that when rats were subjected to various environmental stresses (prolonged heat or cold, rough handling, forced exercise), they developed peptic ulcers, adrenal enlargement, and atrophy of the immune system. Selye concluded that the physiological effects of prolonged stress cause damage to the endocrine system and, consequently, the immune and nervous systems. He formalized this concept with the term "general adaptation syndrome." This syndrome is characterized initially by enlargement of the adrenal glands, to compensate for an increased stress response, followed eventually by shrinking of adrenal tissue, leading to an inability to handle stress.

Although Selye's perceptive conclusions have since been modified – most researchers no longer believe that stress causes adrenal gland atrophy – stress remains an area of medical interest. Physicians are well aware that prolonged stress can increase the risk of heart disease, hypertension, chronic headache, and numerous other conditions. Stress exacerbates the effects of many illnesses. The reason stress has such far-reaching effects is that its mechanisms are complex, diffuse, and involve nearly every system in the body. Stress affects the vascular system, digestive system, endocrine system, central nervous system, and most metabolic processes. It also affects the immune system in ways that are sometimes subtle or contradictory, but which, nevertheless, have profound consequences.

What happens when a person experiences stress, such as news of illness in the family, or experiences a near accident on the highway? In response to emotional stressors, the cortex (the part of the brain responsible for thinking and reasoning) signals the limbic system (the part of the brain that governs raw emotions) that danger is imminent. The limbic system recognizes the threat and produces the appropriate emotions of fear and anxiety. The hypothalamus, located in the center of the limbic system, sends chemical messages to the pituitary gland to speed up metabolism. The pituitary gland signals the adrenal glands to release stress hormones – specifically the catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) – and the physiological effects of stress become manifest.

As stress hormones are released throughout the system, certain changes occur that enable a person to respond to a potentially dangerous situation. This is called the "fight-or-flight" response, which is governed by the sympathetic nervous system. After the sympathetic nervous system is aroused, the heart rate increases to supply extra blood to major muscle groups. The heart may pound and the chest may feel constricted as breathing control shifts from the diaphragm to the upper

chest. Catecholamines as well as glucocorticoids (cortisol) are released from the adrenal glands. These release stored glucose from the liver, raising blood sugar levels and providing extra energy to muscles. The additional norepinephrine in the brain increases alertness and the ability to focus in order to make quick responses.

In addition to speeding up the endocrine system, the stress response slows all competing systems to maximize the amount of energy available for either fighting an enemy or fleeing. Because digestive processes utilize a lot of blood and energy, appetite is suppressed, and digestion and salivation are slowed. During stressful events, a dry mouth and difficulty swallowing may be experienced, as well as "butterflies" in the stomach. Production of the reproductive hormones, estrogen and testosterone, is inhibited and metabolic processes involving cell repair and growth are halted, as these are taxing in terms of energy requirements. The net result of all these changes is that the body is now at its maximum readiness to face danger.

What happens when the danger does not require the numerous physiological changes necessary for the fight-or-flight response? Say a person is driving a car during rush hour, or dealing with a grouchy boss, or coping with a difficult domestic situation. The final outcome could be a stress response that goes awry, or what Hans Selye termed the "stress syndrome," a set of physiological responses that, if left unchecked over time, create havoc. The prolonged arousal of the sympathetic nervous system can lead to high blood pressure, increased sensitivity to environmental changes, and various gastrointestinal disorders.

To complicate matters, the continued release of cortisol can lead to depression of the immune system (paving the way for opportunistic infections and increasing susceptibility to a host of transmissible diseases), followed in short order by cortisol depletion, resulting in low blood sugar levels, low blood pressure, muscle weakness, and depression. Whereas short bursts of stress hormones can be beneficial and, indeed, may be crucial in circumstances in which running from a tiger will guarantee survival, the long-term results can be disastrous. This is part of the problem patients with CFS/ME encounter when their stress response triggers symptoms.

## THE STRESS RESPONSE IN CFS/ME

In CFS/ME there is ample proof that something is amiss in the processes through which the body normally handles stress. In early 1990, Dr. Peter Behan, a neurologist and professor at the Institute of Neurological Sciences in Glasgow, Scotland, observed that patients with CFS/ME seemed to have abnormal endocrine responses. Although he found that many symptoms, and even test results, were similar to those of Addison's disease (a disorder in which low tolerance to heat, cold, and other stressors result from decreased production of adrenal hormones), the symptoms did not resolve with administration of adrenal hormones (e.g., steroids), as they do with patients with Addison's disease. Dr. Behan suggested that these abnormal adrenal responses indicated some subtle problem in brain regulation.

The interesting puzzle of adrenal function was considered again two years later when a research team headed by Dr. Mark Demitrack published the results of

a study concerning the production and response to cortisol, adrenocorticotrophic hormone (ACTH), and corticotropin-releasing hormone (CRH) in 30 CFS/ME patients and 72 healthy volunteers (*Journal of Clinical Endocrinology and Metabolism*, 1991). It is the orchestrated release of each of these hormones that provides adequate responses to environmental stress.

Cortisol, a glucocorticoid steroid produced in the adrenal cortex, helps reduce inflammation, inhibits immune system activity, and serves a variety of systemic functions, including blood sugar regulation. The adrenal cortex is stimulated by the pituitary gland to release cortisol through pituitary ACTH. The hypothalamus, by releasing CRH, stimulates the pituitary gland to release ACTH. Primary adrenal insufficiency (such as Addison's disease) reflects a defect in the adrenal gland's ability to respond to ACTH, no matter how much ACTH is released. In secondary adrenal insufficiency, the problem lies not with the adrenal glands but with the glands that control it—the pituitary and hypothalamus.

Dr. Demitrack and colleagues found that whereas the basal cortisol level was lower in CFS/ME patients than in healthy controls, responses to low levels of ACTH were exaggerated. When higher levels of ACTH were administered, the adrenal glands slowed production rather than responding with a greater output of cortisol. In other words, the adrenal glands over-reacted to a mild stimulus and under-reacted to a greater stimulus. Because these findings are incompatible with primary adrenal insufficiency, Dr. Demitrack's team concluded that CFS/ME patients demonstrate secondary adrenal insufficiency, probably originating in the hypothalamus.

These findings help explain why patients with CFS/ME respond poorly to stress. If the adrenal glands over-respond to minor stressors, the cumulative effects of daily stress can be as difficult to endure physiologically as a major stressful event. On the other hand, the blunted responses to ACTH indicate that with major stress, the body is unable to adjust accordingly. Both the constant state of arousal provoked by an oversensitive stress response and the underactive state of adrenal competency produce symptoms. In addition, it has been shown that cortisol, because it inhibits immune system function, may help reactivate latent viruses (e.g., EBV). Therefore, the person with CFS/ME can become significantly worse under stress, which makes reduction of stress such an integral part of the healing process.

## COPING WITH STRESS

As stress accumulates, so does the damage. A person who must endure the constant stress of a demanding job or social life while ill with CFS/ME may find it difficult to recover. This does not prevent people from "carrying on," or at least attempting to, even while quite ill. Letting go of obligations, responsibilities, and activities that have provided the framework for a productive life is a hard task, and one that many CFS/ME patients, particularly those with mild cases, would rather not face. Those who are severely ill have no choice. In either case, some adjustments are necessary because CFS/ME rarely accommodates the patient's former lifestyle.



Two important stress-reduction strategies involve *avoidance* and *reduction*. Very ill patients probably should concentrate on avoiding as much stress as possible; those who are moderately to mildly ill, and who cannot escape stress because of continuing work or family obligations, should concentrate on methods to reduce the effects of stress.

## AVOIDANCE OF STRESSORS

Dr. Cheney once compared his patients to a leaky boat. He would ask them, “How much can you throw overboard?” Throwing things overboard, as it turns out, is the key to avoiding stress. Avoidance strategies are appropriate for stress you can control, such as how much work you do and when. The goal is to avoid putting yourself in stressful situations in order to forestall a systemic stress response. Are you tempted to tell off your neighbor about her barking dog? *Don't*. The longer you avoid the cascade of stress hormone effects, the more time your body has to rest and repair itself.

- *Just say no.* You can refuse politely, if you wish, but when people call you on the telephone to participate in surveys, organize block parties, contribute to clothing drives, donate to worthy causes, subscribe to newspapers, or anything that contributes to your overall stress load, you need to let them know that you are not available. If it is something important, tell them you will participate when you feel better. If it is telemarketer calling, request that your name be removed from their calling list. (You may have to repeat yourself several times, but, by law, they must comply.) Although it may be difficult, it might also be wise to stop taking calls from annoying or demanding acquaintances. The same holds true for emails.
- *Set limits.* Make sure close friends and family members know when not to disturb you (nap or rest times). They should also be informed as to what you can and cannot do. Sometimes it is hard for people who used to depend on you to realize that you have limits now. Life will be easier for you, and for them, if you let them know that you cannot lift or carry, go out dancing, or anything else you formerly did, but cannot do now. Be clear; set some rules. You can set these rules without causing too much friction by inviting people to help you with your recovery. For example, by not calling after 8:00 PM (to allow your body to prepare for sleep), not asking you to do strenuous work, and so on, your friends can help you get necessary rest.
- *You don't have to finish what you start.* No doubt you were involved in a number of projects when you became ill. Let them go. Tell yourself that the world will just have to wait for you (it will, believe it or not). You can decide whether these projects merit finishing when you have recovered. Meanwhile, have somebody pack up your work and store it away.
- *Procrastinate.* Most tasks can be delayed for when you are better equipped to handle them. If you can't delay, then only do the most important task.
- *Ask for help.* For self-reliant individuals, asking for help feels like an admission of weakness. However, this is no time for false bravado. Ask your

friends and family to help you. Pass on as many chores to them as you can. Friends can make appointments for you and then drive you where you need to go, pay your bills (you just need to sign the checks, or better still, have them set up online payment), clean your house, make your bed, take care of your children, cook, fend off telemarketers, and perform the numerous daily chores that can be a constant drain on you. If friends are not available, many churches have volunteers whose mission is to help shut-ins.

- *Screen phone calls.* Answering machines were invented to record messages when you are out. For people with CFS/ME, they are most useful for recording messages when you are in. They are a wonderful aid for people who need a break from the demands of conversation during "down time" or who need to go to bed early or sleep late but do not want to miss an important call. It also helps to turn down the volume of your ringer. Telephone ring tones are designed (much like the cry of an infant) to elicit an immediate response. Simply hearing a telephone ring at full volume can be enough to jangle the nerves of someone who is ill.
- *Be selective about television programs.* Television can be either a detriment to your health or a godsend, depending on how you use it. Stressful news programs, specials on serial killers, tense thrillers, frenetic commercials, and the general rapid pace and constant light shifts can produce anxiety and tension in anyone who is ill. (Indeed, television can produce anxiety and tension even in those who aren't.) In general, it may be of greater benefit to watch DVDs: light comedies, mysteries, nature programs, old movies, and subjects that relax or inform (rather than arouse) will help distract your mind without taxing it.

## REDUCING THE EFFECTS OF STRESS

Many stressful situations cannot be avoided, such as the death of a family member, loss of a job or spouse, and accidents. But even comparatively minor stresses such as an unavoidable family visit or a medical appointment are guaranteed to produce symptoms in patients with CFS/ME. If avoiding the situation is simply not possible, learning how to deal with the cascade effects that a stress reaction produces will help to stabilize your system before long-term consequences set in.

- *If you are mildly ill, walk.* One of the best ways to rid the body of excess adrenaline is to walk. If you are severely ill and cannot walk, deep breathing will help calm the sympathetic nervous system.
- *Practice stress reduction exercises.* Stress reduction exercises are invaluable to reduce the amount of stress you feel, calm adrenal responses, gain perspective, and give yourself a break from pressures and demands. Meditation, hypnosis, biofeedback, deep breathing, relaxation tapes, and yoga are all excellent methods for reducing stress. Remember, the mind-body connection goes two ways. When the body begins to churn out anxiety-producing hormones, the mind can limit the extent of its arousal. Many

patients with CFS/ME have observed that even during severe illness and relapses, stress reduction techniques are invaluable for maintaining a sense of calm.

- *Take a break.* The first thing to remember when confronting any stressful situation is that the natural tendency is to overdo. Try not to give in entirely to the impulse and plan rest time. Lie down whenever you have a chance, and try to take your mind off situations that can easily become all-encompassing. Reducing stimulation also helps: turn off the television or radio, tell your children to play outside, switch off the lights, and unplug the phone. And breathe.
- *Develop a routine.* CFS/ME produces internal chaos; therefore, anything you can do to promote external order will be helpful. Following a routine can provide a sense of security and stability that can make stressful situations easier to handle. The routine can be simple. For people who are quite ill, a daily routine can simply consist of eating meals on a schedule. (Going to bed should always be on a schedule, whether you can sleep or not.) It is not particularly important when or how you perform your routine. The idea is to develop a regular and predictable pattern that helps structure your day and minimizes your body's need to adjust to change.
- *Find distractions.* Mental distraction is important and should be pursued when outside demands become overwhelming. Mystery or romance novels, soap operas, knitting, watching fish swim in a tank . . . in short, anything that takes your mind off your problems and puts the focus on something that requires no effort – and generates no anxiety – helps maintain tranquility.
- *Express yourself.* Another good way to deal with stressful situations is to share your thoughts and feelings with someone who understands. A sympathetic ear can help alleviate many of the helpless, trapped feelings that CFS/ME patients have when cornered by a stressful event and can eliminate some of the endless mental rehashing that accompanies decision-making under stress. If another person is not available, writing letters, keeping a journal, and drawing can be good forms of self-expression. Support groups and therapists experienced with CFS/ME can also provide a healthy outlet for stress-related emotions. Best of all is to find someone with CFS/ME who has shared your experience. If you are housebound and no one is close by, the internet can provide access to the world. Online CFS/ME Bulletin Boards and support groups can truly be lifesavers.
- *Herbs and supplements.* A number of herbs can help mitigate the effects of stress hormones. Valerian root, a plant that produces a mild sedative effect, is perhaps the best known. Skullcap is also calming and works well for the jitters and anxiety. Chamomile, hops, and passion flower are other calming herbs. Some of the essential oils, especially jasmine, clary sage, and lavender, can ease a stress reaction. Many people also find calcium and B vitamins soothing, but these are not generally useful in emergencies. Magnesium is a

potent down-regulator of nervous system excitability and should be taken on a daily basis by everyone with CFS/ME.

- *Acupuncture.* For those who respond to acupuncture (roughly 80% of the general population), it can work wonders to calm a hyperactive sympathetic nervous system. Setting up a weekly appointment during times of stress can help reduce the anxiety caused by excess norepinephrine, and, in turn, will make it easier to cope with both short- and long-term stressors.
- *Pharmaceuticals.* There are many anxiolytics available for people with anxiety and stress-related symptoms. The most commonly prescribed are benzodiazepines (minor tranquilizers). Dependency is always a problem with central nervous system depressants, so care should be taken to save these remedies for emergencies. In general, short-acting benzodiazepines, such as Xanax or Ativan, are the most addictive, while long-acting benzodiazepines, such as Klonopin, are the least.

SEE: Benzodiazepines; Herbs, Minerals, Vitamins; Acupuncture, Aroma Therapy, Biofeedback, Hypnosis, Meditation, Pacing, Visualization and Imagery, Yoga.

#### FURTHER READING

*Bruce Campbell discusses some good methods for handling stress.*

<http://www.recoveryfromcfs.org/chapter13.htm>

Chrousos, George P, and Gold, Philip W. "The Concepts of Stress and Stress System Disorders." *Journal of the American Medical Association* 267:1244-1252, 1992. *Somewhat technical but thorough review of the physiological and behavioral responses to stress.*

Friedberg, Fred. *Coping With Chronic Fatigue Syndrome: Nine Things You Can Do.* Oakland, Calif.: New Harbinger Publications, 1995.

*Dr. Friedberg discusses the effects of stress and offers relaxation exercises tailored to CFS/ME.*

Sapolsky, Robert. *Why Zebras Don't Get Ulcers: A Guide to Stress, Stress-Related Diseases, and Coping.* New York: W.H. Freeman and Co., 1994.

*Provides a good overview of how stress works.*

"Your brain and stress." <http://www.fi.edu/learn/brain/stress.html>

*Everything you ever wanted to know about how stress hormones affect the body.*

## CHAPTER 8: CLEANING UP: ELIMINATING TOXINS IN THE HOME

Sensitivity to chemicals is common in patients with CFS/ME. In a five-year study of 690 patients conducted by Dr. Dedra Buchwald, more than 50% of those with CFS/ME reported having chemical sensitivities. Research conducted by I. R. Bell in 1998 showed a similar percentage. A 2000 study by Jason et al found that roughly 40% of patients with CFS/ME also met the criteria for multiple chemical sensitivities (MCS). In fact, the percentage of CFS/ME patients with sensitivities to chemicals may be significantly higher.

Many clinicians have found that the majority of their CFS/ME patients develop sensitivities to common chemicals – petrochemicals in particular – even at very low concentrations. Car exhaust, diesel fumes, glues, dyes, inks, and perfumes are among those most frequently mentioned as producing headaches, dizziness, faintness, nausea, and malaise. Detergents, solvents, aerosol propellants, wood preservatives, and paints all contain petroleum derivatives, which, while generally regarded as safe unless used in large amounts, can provoke severe reactions in those with MCS, even in minute quantities.

Even those who do not experience the severe reactions typical of multiple chemical sensitivity should be careful to avoid exposure to synthetic chemicals. The metabolic disturbances that have been documented by CFS/ME researchers not only produce cellular fatigue, but also affect the body's ability to remove toxins. Alpha ketoglutarate and glutathione, two of the most powerful components of the body's detoxification system, have been found to be deficient in CFS/ME. To complicate the matter, many patients with CFS/ME have suboptimal liver function (the liver is the body's main detoxification organ). Because of these alterations in detoxification functions, CFS/ME can compromise the body's natural capacity to break down and eliminate toxins.

By far, the most important strategy for those with chemical sensitivities is avoidance. In a survey of multiple chemical sensitivity (MCS) treatments conducted by a DePaul University research team, all but one of the 304 respondents reported that "adopting a practice of avoiding exposures to chemicals which could cause MCS reactions" was helpful. The majority of the respondents reported that avoidance was of "enormous help" (*CFIDS Chronicle*, Winter 1996). Direct exposure to toxins can be significantly reduced by eliminating chemical offenders in the home, the environment that poses the greatest risk to individuals who are partially or completely housebound.

The following sections on cleaners, pesticides, and personal care products provide safe alternatives to the numerous harmful ingredients found in many commercial products.

### CLEANERS

Some of the most toxic chemicals we are routinely exposed to are found in the kitchen and bathroom. Many of us are unaware that household cleaners may contain substances that are carcinogenic (cause cancer), mutagenic (cause gene mutations), or teratogenic (cause birth defects). In addition, a number of the

chemicals added to general cleaners, spot removers, metal polishes, and other such products are listed by the Environmental Protection Agency (EPA) as "Priority" toxics. In other words, they are powerful poisons. The public is usually unaware of the hazards associated with these products because manufacturers are not legally required to state their ingredients of their products.

#### CHEMICALS COMMONLY FOUND IN HOUSEHOLD CLEANING PRODUCTS

The following chemicals commonly found in household cleaning products should be rigorously avoided:

- *Ammonia (irritant)*. Ammonia is an eye and respiratory tract irritant that can cause conjunctivitis, laryngitis, and burns. Because ammonia is toxic to the brain, breathing ammonia fumes is dangerous. The combination of ammonia with chlorine (found in bleach) produces a deadly gas. CFS/ME patients need to be particularly careful to avoid ammonia because the anaerobic cell metabolism characteristic of CFS/ME produces ammonia as a by-product. Products that contain ammonia include window cleaners, all-purpose cleaners, tub and tile cleaners, furniture and floor polish, and laundry detergents.
- *Benzene (carcinogen)*. Benzene attacks the central nervous system (CNS), blood, bone marrow, eyes, and respiratory tract. Benzene is found in spot removers and dishwashing detergents.
- *Chlorine (potential carcinogen)*. Chlorine causes erosion of mucous membranes, skin eruptions, severe respiratory tract irritation, and vomiting. Those with cystitis should be especially cautious to avoid chlorine because it can irritate the bladder. Chlorine is found in bleach, tub and tile cleaners, and spot removers.
- *Cresol (corrosive)*. Cresol affects the CNS, liver, kidneys, lungs, pancreas, spleen, and can be absorbed through skin and lungs. Disinfectants, air fresheners, and deodorizers can contain cresol.
- *Detergents*. Detergents can cause dermatitis, asthmatic episodes, flu-like symptoms, and severe eye damage. Tub and tile cleaners, bleach, dishwashing detergents, furniture and floor polish, oven cleaners, and rug and carpet cleaners contain detergents.
- *Ethanol*. Ethanol can cause CNS depression, nausea, and vomiting. Air fresheners, tub and tile cleaners, dishwashing detergents, glass and window cleaners, laundry detergents, metal polishers, and rug and carpet cleaners contain ethanol.
- *Formaldehyde (mutagen and likely carcinogen)*. Formaldehyde can cause respiratory problems, headaches, rashes, tiredness, and insomnia. Formaldehyde is found in air fresheners, disinfectants, mold and mildew cleaners, and water-resistant paper (such as paper towels, napkins, and toilet tissue).
- *Methylene chloride (carcinogen)*. Methylene chloride has been known to cause cardiac arrest. Shoe polish and paint strippers contain methylene chloride.

- *Naphthalene (carcinogen)*. Naphthalene can cause skin irritation, headache, and confusion. It attacks the kidneys, liver, red blood cells, and CNS. Air fresheners and deodorizers, glass and window cleaners, laundry detergents, rug and carpet cleaners, and spot removers contain naphthalene.
- *Petroleum distillates (carcinogens and poisons)*. Petroleum distillates can be found in drain cleaners, furniture and floor polish, glass and window cleaners, and metal polishes.
- *Phenols (carcinogens)*. Phenols cause skin eruptions, burning, numbness, gangrene, vomiting, and convulsions. Air fresheners and deodorizers, disinfectants, laundry detergents, and mold and mildew cleaners can contain phenols.
- *Toluene (carcinogen)*. Toluene causes nervous system damage, irritability, depression, and damage to the liver and kidneys. Toluene is found in spot removers.
- *Xylene(hazardous waste)*. Xylene causes nausea, cough, tinnitus, headache, mental confusion, and eye damage. Xylene can be found in air fresheners, spray paint, and shoe polish.

## SAFE NONTOXIC CLEANSERS

Fortunately, most cleansers commonly found in American homes have safe, easy-to-use substitutes.

The five nontoxic items needed to keep your home and belongings clean are salt, baking soda, soap, white vinegar, and borax. These can be found in any supermarket and are surprisingly effective, safe, and easy to use.

## AIR FRESHENERS AND ODORS

*Note: Commercial air fresheners do not "freshen," but merely mask odors.*

- Carpet odors — Sprinkle baking soda liberally (several pounds per room), and vacuum.
- Toilet bowls — Clean with borax to eliminate odors as well as disinfect.
- Garbage pails — Sprinkle the bottom with baking soda. Rinse with borax and water to disinfect.
- Urine — Dab or soak item with 50% solution of white vinegar and water.

**DISHWASHING SOAP.** Use liquid soap to wash, and vinegar to cut grease. For machines, buy biodegradable dishwasher soap.

**DISINFECTANTS.** Borax in water is a great disinfectant. In fact, hospitals that use it have discovered that borax disinfects as well as any commercial antiseptic product.

**DRAIN CLEANERS.** Pour a mixture of ½ cup salt and ½ cup baking soda, followed by a quart of boiling water into blocked drains. If that doesn't work, call a plumber.

**LAUNDRY DETERGENTS.** Presoak laundry with borax for one hour before washing. You can use laundry soap for cleaning, or a small amount of dye-free,

scent free detergent. (You will only need a quarter of the amount you normally use.) Seventh Generation makes an effective “green” detergent.

#### METAL POLISHERS

- Copper and brass — Rub with a mixture of salt and vinegar (or lemon juice).
- Chrome — Rub with lemon peel, rinse, and polish with a soft cloth.
- Aluminum — Soak in lemon juice or vinegar and boiling water.
- Gold — Wash in warm, soapy water, dry, and polish with a clean cloth.
- Silver — Soak in salted water in an aluminum pot (a nonaluminum pot with aluminum foil can be substituted). Or boil for 3 minutes in 1 quart of water with 1 tablespoon each of salt and baking soda.

**OVEN CLEANER.** Dissolve two tablespoons of liquid soap (not detergent) and two teaspoons of borax in enough warm water to fill a spray bottle. Spray the sides of the oven and leave for 20 minutes. Scrub with baking soda. Pumice can be used for hard, baked-on spills.

**RUG CLEANERS.** Mix two parts cornmeal and one part borax. Sprinkle liberally over carpet and let stand for one hour. Vacuum.

**SCOURING POWDER.** Baking soda is a mild abrasive and can be used for any cleaning job that requires scouring.

**SHOE POLISH.** Clean shoes with a damp cloth. Apply walnut oil and buff with a chamois cloth.

#### SPOT REMOVERS

- Blood — Soak cotton items in cold water. Blot spots on wool with hydrogen peroxide.
- Coffee — Mix egg yolk with water and rub on stain.
- Chewing gum — Rub with ice.
- Fruit and wine — Pour salt or hot water on the stain; soak in milk.
- Grease — Pour boiling water over stain and sprinkle baking soda on it.
- Ink — Soak in milk.
- Mildew — Pour soap and salt on spots and place in sunlight. Repeat if necessary.
- Rust — Saturate with lemon juice, rub with salt, then place in direct sunlight until dry.
- Scuff marks — Toothpaste will remove scuff marks left by shoes.

**TILE CLEANERS.** Use baking soda on a sponge as an abrasive. Use borax and water to disinfect. For mold, sponge on a mixture of vinegar and borax. (Acid kills mold.)

**WINDOW CLEANER.** Make a mixture of vinegar or cornstarch (about one tablespoon of either) and one quart of water and spray or wipe on windows with a clean sponge. Dry with newspaper. (Cloth leaves lint.)

**WOOD POLISH.** Mayonnaise makes a great furniture polish. For floor scratches, a dab of vegetable oil will hide the damage.

If you are unable to make your own mixtures, it may be more convenient to purchase nontoxic cleaners. Many brands are available from mail order suppliers and in supermarkets (in urban areas) or health food stores. (See Appendix D).



## PESTICIDES

Pesticides such as Raid and other vermin destroyers are often found in supermarkets in the same aisles as cleaning supplies. Their proximity to sponges and dishwashing liquid may lead the shopper to think they are no more toxic than soap. Yet household pesticides, because of the frequency with which they are used, combined with the fact that they are used indoors, where their fumes will be inhaled, are more a risk than the 1.1 billion pounds of pesticides U.S. farmers use on crops every year.

Exposure to household pesticides is not only dangerous, it is widespread. According to figures compiled by the EPA, some 78 million American households (approximately 75%), used pesticides in 2007. That means that nearly every man, woman, and child in this country has been exposed to pesticides in their homes.

What is so dangerous about pesticides? Most pesticides work by directly interfering with the insect's nervous system. Insecticides either prevent a key neurotransmitter from being broken down, producing a state of terminal excitement in the nervous system synapses, or they prevent the neurotransmitter from operating by binding to its receptor sites, so that the nervous system ceases to function. In the first instance, the insect dies of convulsions. In the second, the insect dies of paralysis. In both cases the principal mode of action is the disruption of the neurotransmitter acetylcholine.

Acetylcholine is also one of the most important neurotransmitters found in humans. One of its major functions is to chemically connect muscles to nerves, allowing nervous system control of movement. Acetylcholine also affects memory. (Patients with Alzheimer's disease demonstrate a deficit of this important neurotransmitter.) Human exposure to neurotoxins that disrupt acetylcholine function (such as the nerve gas poisoning in Gulf War veterans) produces myriad harmful effects, including loss of appetite, urinary frequency, sweating, excess salivation, diarrhea, jitteriness, emotional instability, combativeness, headache, and mental confusion.

Patients with CFS/ME should make a concerted effort to avoid pesticides. CFS/ME produces disruption of normal nervous system activity, which itself can affect the cholinergic (acetylcholine) pathways in the brain. At least one researcher, Dr. E. Snorrason of University Hospital in Reykjavik, Iceland, believes that upsets in the cholinergic system play a primary role in the development of CFS/ME symptoms. Further upsets in brain function, through exposure to neurotoxins in pesticides and other chemicals, will only worsen the condition.

## SAFE PESTICIDES

- **ANTS.** Pour a thin line of talcum powder at the point of entry. Wipe the surrounding area with a wet sponge to erase the ant trail.
- **BEEETLES.** Place a bay leaf in flour containers. Keep food containers tightly closed.

- **COCKROACHES.** Mix sugar and boric acid and sprinkle on a piece of cardboard around garbage cans or wherever roaches gather. Boric acid causes gases to build up in the roaches' bodies. (Roaches cannot pass gas.)
- **FLIES.** Hang sticky paper made with honey on cardboard. Pierce and hang orange peels. (Flies do not like citric acid).
- **HEAD LICE.** Coconut oil contains dodecyl alcohol, which is lethal to lice. Wash hair with a bar soap or shampoo that contains coconut oil or coconut oil derivatives (cocamide, sodium lauryl sulfate). Leave shampoo in hair for 30 minutes. Rinse with a half-and-half mixture of white vinegar and water to loosen egg cases. Comb hair thoroughly, one section at a time, with a metal lice comb to remove nits (allow 2 hours for this process). Repeat in 10 days. A pre-rinse with a 50% solution of white vinegar and water followed by careful combing with a lice comb, can remove most of the eggs prior to shampooing.
- **MOTHS.** Hang sachets of rosemary and other strong-smelling herbs in closets or place cedar chips in drawers. The aromatic oils in cedar kill moth larvae. Avoid cedar if you have allergies.
- **TERMITES.** Remove rotting wood from around property. Kill termites with a heat lamp at 140° F.
- **TICKS AND FLEAS.** Wash and dry animal. Spray with rosemary tea to deter insects. Garlic and brewer's yeast added to pet food also help repel fleas.
- **GENERAL INSECT REPELLENT.** Pennyroyal tea sprayed on skin and clothes will deter most biting and stinging insects. The herb can be easily grown in a garden or pot.
- **GARDEN AND PLANT PESTS.** Numerous techniques can safely eliminate garden pests, including hosing down plants to prevent spider mites, planting chives around plants to discourage aphids, and purchasing beneficial predators such as ladybugs. Hot-pepper or soap spray will discourage most insects. For specific problems, consult an organic gardening manual (available in most libraries).

## PERSONAL CARE PRODUCTS

According to the Food and Drug Administration (FDA), a cosmetic includes anything that can be "rubbed, poured, sprinkled or sprayed on ... the human body ... for cleansing, beautifying, promoting attractiveness, or altering the body's appearance without affecting the body's structure or functions." Any cosmetic packaged after 1977 must include a list of ingredients on the label. However, there are some exceptions, notably deodorant soaps, hair dyes, fluoridated toothpastes, antiperspirants, sunscreens, and antidandruff shampoos.

In addition, a number of products contain ingredients that do not have to be specifically detailed (such as the 4000 ingredients that make up "fragrances"). Anyone with chemical sensitivities should be aware that the petrochemical components of cosmetics and personal health and hygiene products can provoke severe reactions because they are absorbed directly through the skin.

Some of the more noxious ingredients of cosmetic and health products include aerosol propellants (propane, methylene chloride), BHA/BHT (butylated hydroxyanisole/butylated hydroxytoluene), BNPD (reacts with amines on the skin to form carcinogenic nitrosamines), ammonia, coal tar colors, cresol, detergents, ethanol, formaldehyde, hexane, lead, mineral oil (blocks vitamin absorption), paraffin, phenol, plastics, quaternium 15 (releases formaldehyde), toluene, and xylene. Products that contain any of these, are scented, are applied by means of aerosols, or are artificially colored should be avoided by CFS/ME patients.

### SAFE AND NON-TOXIC PERSONAL CARE PRODUCTS

Many alternatives to commercial personal care products can be purchased from health food and vitamin stores, specialty shops, mail-order suppliers, and buyers' clubs. Following are suggestions for some commonly used personal care products.

- **DEODORANTS.** Commercial deodorants can contain triclosan, a liver toxin. Numerous nontoxic alternatives (such as crystals and plant-based products such as Weleda and Desert Essence) are available from health food stores.
- **HAIR DYES.** Commercial hair dyes are completely exempt from regulation and, as a result, contain numerous toxins. If you color your hair, use henna for red or walnut hull infusion for brown (available in health food stores).
- **LOTIONS AND HAND CREAMS.** Commercial lotions may contain ethanol, phenol, and mineral oil (which is more toxic when absorbed through the skin than when inhaled). Pure vegetable oils (olive, sesame, canola) or vegetable oil-based products such as those made by Nature's Gate can be substituted.
- **MOUTH WASH.** After brushing and flossing teeth, rinse mouth with baking soda and water to eliminate odor and reduce plaque. For those with gingivitis, an occasional rinse with hydrogen peroxide solution (10% peroxide, 90% water) will disinfect the mouth. Be careful not to overdo, because peroxide also destroys beneficial mouth flora. Rinsing with warm salt water will also kill bacteria.
- **SHAMPOO.** Many shampoos are relatively free of unnecessary additives (Dr. Bronner's, Raintree, and Kiss My Face, for example, all make gentle, fragrance-free shampoos). For dandruff, a vinegar rinse (50% solution) can work wonders. The vinegar not only removes soap buildup, it kills dandruff-causing yeasts that live on your scalp.
- **SHAVING CREAM.** Use petrochemical-free soap or shaving cream such as Tom's or The Body Shop.
- **SOAP.** Numerous soaps are made from vegetable oils, including Kiss My Face, The Body Shop, Conti Castile, Pears Transparent Soap, and The Soap Opera. Use scentless varieties.
- **TOOTHPASTE.** You can make toothpaste with a little salt, baking soda, and a drop of neem oil. Tom's, Desert Essence, or other pure toothpaste brands can also be purchased. Most commercial toothpastes contain saccharin, ethanol, mineral oil, or formaldehyde.

## OTHER HOUSEHOLD TOXINS

### AIR QUALITY

According to the Environmental Protection Agency (EPA), some 50% of all illnesses can be caused or aggravated by polluted indoor air. Viruses, mold, pollen, bacteria, dust mites, and other contaminants can build up in air conditioning and duct systems, creating health problems in otherwise healthy individuals. For CFS/ME patients air quality is of particular concern, especially for those with allergies. Recirculating dust and pollens can exacerbate allergic reactions, which in turn may lead to relapses. Even if you do not have allergies, it is important to make sure that the air you breathe is pure and free from common household contaminants such as carbon monoxide, dust, mold, and other irritants. Following are some steps to take to make sure your indoor air is pure.

- Have gas appliances and gas lines checked for leaks. In most cases your gas company will perform this service free of charge. Make sure gas appliances are properly vented. If you have the choice, opt for electrical appliances. They burn cleaner than gas and leave less residue in the air.
- If you suspect your duct system harbors molds, have it cleaned out. Many heating and air conditioning companies will clean and purify ducts, grills, blowers, and humidifiers for a fee.
- If you have allergies, purchase a high-efficiency particle air (HEPA) filter for your bedroom. Whole house units, such as those made by IQ Air, are more expensive, but may be worth it if your house is moldy.
- An ultraviolet light, which kills bacteria and viruses, can be installed in the cold air return. These can be purchased at some health food stores. Be sure to install the light where it cannot be seen because ultraviolet light damages the eyes.

The numerous neurotoxins, fumes, corrosives, carcinogens, and systemic irritants we are constantly exposed to are not good for anyone. People with illnesses, and in particular those with chemical sensitivities, should make every effort to avoid these ubiquitous poisons to diminish their harmful effects.

### WATER QUALITY

The quality of the water we drink has a profound effect on our well-being because water is needed for every metabolic process in the body. Our drinking water, however, much like the air we breathe, contains numerous contaminants that can have adverse effects on health. The EPA has identified more than 700 pollutants in drinking water, ranging from heavy metals that leech from old plumbing to chemical runoff from industry and agriculture. Many CFS/ME patients find that with the advent of the illness they become more sensitive to the pollutants and additives commonly found in drinking water, particularly to chlorine, which is added as a disinfectant to most municipal drinking water supplies. Fortunately, a number of affordable water purification systems are available to help alleviate this problem (see Appendix D).

**ACTIVATED-CARBON FILTERS.** These filters remove asbestos, bacteria, viruses, chlorine, heavy metals, and most organic compounds. The filter needs to be changed at least every six months to be effective. Many counter-top and under-the-sink models are available, as well as screw-on filters for shower heads. Manufacturers generally recommend using cold water from municipal sources for drinking water models. Granulated carbon is preferable to powdered carbon.

**REVERSE-OSMOSIS FILTERS.** Reverse osmosis purifies water by passing it through a fine membrane to remove asbestos, some bacteria and viruses, fluoride, heavy metals, minerals, nitrites, salts, and some organic compounds. Chlorine, however, is not removed. Reverse-osmosis filters are best used in conjunction with carbon filters. Filters should be changed every two years or as suggested by the manufacturer.

The best type of filter to use depends in part on the quality of the water. Before choosing a water purification system, it is wise to obtain a water analysis, which will indicate the hardness of the water, total dissolved solids, and pH level. If you cannot purchase a water filter, you can reduce contaminants in tap water by boiling water for ten minutes to kill bacteria and viruses and to remove most chlorine, chlorine by-products, and pesticides. The acid in a small amount of vitamin C, lemon juice or white vinegar also neutralizes the effects of chlorine. Don't bother buying bottled water. Most of it comes out of a tap.

**WATER DISTILLATION.** To distill water, the water is boiled and the steam is condensed to produce water free of most contaminants. Boiling effectively kills bacteria and viruses, and the evaporation process removes heavy metals and trace minerals that are too heavy to rise with the vapor. This method does not remove chlorine. While great for putting in your steam iron, distilled water not only tastes awful, it lacks all of the important minerals your body needs.

**SEE:** Allergies (chemical sensitivities) for further discussion of the role of chemical sensitivities in CFS/ME and for treatment suggestions. Appendix D contains a list of mail-order suppliers of nontoxic products.

## ORGANIZATIONS

American Academy of Environmental Medicine

6505 E. Central Avenue, #296

Wichita, KS 67206

Phone: (316) 684-5500

Fax: (316) 684-5709

Email: [administrator@aaemonline.org](mailto:administrator@aaemonline.org)

Website: <http://www.aaemonline.org/>

Chemical Injury Information Network

P.O. Box 301

White Sulphur Springs, MT 59645

Phone: (406) 547-2255  
Fax: (406)547-2455  
Email: [chemicalinjury@ciin.org](mailto:chemicalinjury@ciin.org).  
Website: <http://ciin.org/index.html>

National Environmental Health Association  
720 S. Colorado Blvd., Suite 1000-N  
Denver, CO 80246  
Phone: (866) 956-2258 (Toll free)  
(303) 756-9090 (Local)  
Fax: (303) 691-9490  
Email: [staff@neha.org](mailto:staff@neha.org)  
Website: <http://www.neha.org/index.shtml>

Chemical Sensitivity Foundation  
4 Wren Drive  
Topsham, ME 04086  
Phone: (207) 725-8570  
Email: [info@chemicalsensitivityfoundation.org](mailto:info@chemicalsensitivityfoundation.org)  
Website: <http://www.chemicalsensitivityfoundation.org/>

Environmental Health Network  
PO Box 1155  
Larkspur, CA 94977  
Phone: (415) 541-5075  
Website: <http://ehncea.org/>

Human Ecology Action League  
PO Box 509  
Stockbridge, GA 30281  
Phone: (770) 389-4519  
Fax: (770) 389-4520  
Email: [HEAL@aol.com](mailto:HEAL@aol.com)  
Website: <http://www.healnatl.org/index.html>

Multiple Chemical Sensitivities Referral and Resources

Website: <http://www.mcsrr.org/>

Pesticide Action Network

<http://www.panna.org/>

#### FURTHER READING

“Diagnosis: Multiple Chemical Sensitivity (MCS).” CFIDS Association of America.

<http://www.cfids.org/about-cfids/multiple-chemical-sensitivities.asp>

“EPA: Pesticides Industry Sales and Usage.” 2006 and 2007.

[http://www.epa.gov/opp00001/pestsales/07pestsales/market\\_estimates2007.pdf](http://www.epa.gov/opp00001/pestsales/07pestsales/market_estimates2007.pdf)

## BOOKS

Dadd, Debra Lynn. *Nontoxic and Natural*. Los Angeles: Jeremy P. Tarcher, 1984

*By now, this easy-to-use reference guide has become a classic. It contains alternatives for 1200 of the most commonly used household products; also includes a mail-order source list for nontoxic products.*

Dadd, Debra Lynn. *The Nontoxic Home*. Los Angeles: Jeremy P. Tarcher, 1986

*Offers an in-depth look at sources of toxins in the home and offers a broader range of solutions.*

May, Jeffrey C., and Connie L. May. *The Mold Survival Guide for Your Home and for Your Health*. Baltimore: Johns Hopkins University Press, 2004.

*This great little book contains everything you need to know about indoor mold contamination and remediation.*

Wittenburg, Janice Strubbe. *The Rebellious Body: Reclaim Your Life From Environmental Illness or Chronic Fatigue Syndrome*. New York: Insight Books, 1997

*A valuable reference guide providing medical explanations, diet recommendations, coping tips, and information on supplements.*

## RESEARCH

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Jason LA, Taylor RR, Kennedy CL. “Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms.” *Psychosom Med*. 2000 Sep-Oct;62(5):655-63.

<http://www.psychosomaticmedicine.org/content/62/5/655.full#R11-077059>

## CHAPTER 9: FOOD AND DIET

Diet is one of the most obvious places to begin making the necessary accommodations to the demands of a chronic illness. However, it is not always the easiest. For many people with CFS/ME, devising a workable diet poses numerous difficulties. About two-thirds of the CFS/ME population have recurring or chronic gastrointestinal symptoms such as heartburn, gas, nausea, diarrhea, constipation, and cramps. In most cases, these symptoms are caused by food sensitivities. Others may have concurrent problems such as interstitial cystitis or migraine headaches that require certain dietary constraints.

The remaining third of the CFS/ME population who do not have gastrointestinal symptoms, food sensitivities, or concurrent conditions that restrict diet still have the demands of a chronic illness to contend with. Although free from the necessity of maintaining strict dietary restrictions, these patients need to maintain as wholesome a diet as possible, if only to address the complicated problem of how best to help an ailing body to heal.

The disruptions in cell metabolism as well as immune and endocrine system function brought on by CFS/ME can lead to numerous nutritional deficiencies, including decreased concentrations of zinc, potassium, carnitine, and B and C vitamins. These deficiencies, in and of themselves, can decrease the degree to which the body can absorb and make use of nutrients.

Problems caused by disruptions in cell metabolism, malabsorption, and food sensitivities make it all the more important for CFS/ME patients to maintain an appropriate diet – that is, following a diet that will maximize the nutrients available to a healing body while minimizing any harmful effects that specific foods or food additives may produce.

### DEVISING A CFS/ME DIET

"What should I eat?" is a question asked by most CFS/ME patients, and, although the question makes a great deal of practical sense, it is not easily answered. Diet is an important consideration for anyone who is ill; in the case of CFS/ME, however, what constitutes an appropriate diet? Should we follow a special regimen (macrobiotic, vegetarian, wheat grass, raw, ash-free, fat-free, carbohydrate-free, yeast-free), or can we just throw caution to the wind and eat what we please since we feel so bad anyway?

These questions have no simple answers. CFS/ME patients react to foods with the same frustrating inconsistency as they do to medications. Whereas one person can maintain a vegetarian diet, another needs to eat meat at every meal. (Such was the case of one ardent vegetarian who found that after contracting CFS/ME she could not get through a day without eating several portions of red meat.) Some feel better after cutting back on carbohydrates and eliminating fruit. Because each person's digestive system reflects one's own unique case of CFS/ME – complicated by allergies, food sensitivities, bladder sensitivities, blood sugar problems – there can be no single "best diet."



That being said, CFS/ME patients need to watch their diet, but not necessarily severely restrict their food choices. Many people with CFS/ME have experienced setbacks, including severe weight loss, increased fatigue, and pain, from adopting highly restrictive diets, especially diets that eliminate several of the important food groups.

As not everyone needs the same foods, finding an appropriate diet may at first create some frustration. Finding a good diet, however, even in the most difficult circumstances, is not impossible. Most people proceed by trial and error, noting which foods make them feel better or worse. The following are some simple guidelines that may be helpful in devising your particular CFS/ME diet.

- *Listen to your body.* This is, perhaps, the most important rule for people with CFS/ME. If a particular food item makes you feel worse, don't eat it, even if it is supposed to be "good for you." Even "good" foods, such as salad, broccoli, nuts, fruit, and spinach can do harm if you cannot digest them. Your body will, in most cases, give you clear signs when it can't. Nausea, insomnia, headaches, anxiety, gas, diarrhea, and constipation are some of the side effects produced by the digestive system when it manufactures ammonia, indole, and greenhouse gases from food instead of usable vitamins, minerals, and proteins.
- *Eat sensibly.* Patients with CFS/ME need to consume a healthy, balanced supply of nutrients to provide the basic raw materials required to make them well. For those whose choices are not already restricted by food sensitivities, maintaining a broad, varied diet will provide the best basis for improvement.
- *Eat simply.* Try not to mix a lot of different ingredients in one dish. This will help with digestion and make it easier for you to identify food reactions. Use plain fresh vegetables, starches, and proteins.
- *Eat wholesome foods.* If possible, eat whole-grain foods for complex carbohydrates, vegetables for vitamins and minerals, and low-fat meat products for proteins. Avoid all processed foods, which contain artificial additives (even when advertised as "natural"). Be sure to check labels. Buy organic foods, whenever possible, to eliminate the extra burden of pesticides, hormones, and antibiotics abundant in most commercial produce and meats.

## FOODS TO AVOID

Some foods should be avoided because in most patients they will exacerbate symptoms. The following are the five foods most commonly recommended against by CFS/ME clinicians and patients.

1) **STIMULANTS** (coffee, tea, caffeinated sodas, cola, some herb teas, including ginseng, lomatium, mate, and ma huang). When energy levels are low, it is tempting to resort to "pick-me-ups" such as coffee, cola, or strong tea to boost energy. For most people, stimulants, such as coffee, provide a temporary boost, enabling them to get through a hard day or a crisis. However, because stimulants cause the adrenal glands to work harder, taking them will eventually result in a "crash." Often the long-term result of a short-term energy boost is simply not worth

it. Caffeine also worsens ongoing insomnia, leading to even greater exhaustion. Some nutritional supplements that provide good substitutes for stimulants are alpha ketoglutarate, ubiquinol, D-Ribose, vitamin B12, royal jelly, carnitine, and DHEA. (See Fatigue for further suggestions.)

2) ALCOHOL (wine, beer, hard liquor). Alcohol intolerance is one of the most common CFS/ME symptoms. Most people with CFS/ME find out rather early in the illness that even a small glass of beer or wine makes them quite ill. The reasons for alcohol intolerance are multifold: (1) alcohol acts on the central nervous system, which in CFS/ME patients can be hyper-reactive, (2) alcohol is toxic to the liver, (3) alcohol interferes with the methylation cycle, (4) alcohol is a vasodilator, which will exacerbate vascular symptoms (e.g., NHM and POTS). Because many CFS/ME patients have suboptimal liver function, ingestion of alcohol should be rigorously avoided. Those who are especially sensitive should also avoid herbal tinctures and alcohol-based mouthwashes.

3) SWEETENERS (sugar, corn syrup, sucrose, glucose, dextrose, brown sugar, fructose, aspartame, saccharin). Many people with CFS/ME crave sweets, especially when blood sugar levels fall in the late afternoon and before the onset of menstruation. Most researchers agree that this is due to faulty carbohydrate metabolism and subsequent low levels of ATP and blood glucose. Eating foods loaded with simple carbohydrates (sugars), however, only exacerbates the problem.

Blood sugar levels rise after the consumption of carbohydrates. This leads to an increased production of serotonin (the neurotransmitter responsible for inducing a state of relaxation). In CFS/ME patients, however, the release of serotonin can create unwanted effects. Serotonin inhibits the release of cortisol, the hormone responsible for reducing inflammation and releasing stored glycogen from the liver. Thus, when cortisol is inhibited, inflammation (a perennial problem in CFS/ME) increases. The problem becomes even more complicated when carbohydrate metabolism is disturbed and not enough glucose is formed from carbohydrates to maintain blood sugar levels. In that case, blood sugar levels plummet after the temporary elevation caused by the flood of sugar. The result is physical and mental exhaustion.

A young man with CFS/ME from New Jersey describes this problem succinctly: "I feel hung over when I've eaten a lot of sugar. I can't even get up the next day. I've been following a low-carb, no sugar, high-protein diet for a couple of years, and realize I must stay on it. For me, no sugar equals life. I'm much better on this [no sugar] diet."

If you have candidiasis or hypoglycemia, dried fruits (dates especially contain an enormous amount of sucrose) and starchy vegetables should also be avoided, particularly in the evening, because they may worsen insomnia. Avoid aspartame (Nutra-Sweet), which breaks down into wood alcohol in the bloodstream and can cause serious metabolic problems in people with CFS/ME.

4) ANIMAL FATS. Fat is the best source of energy, better than carbohydrates, sugars, or proteins. To serve as an energy source, fat must be metabolized, then transported into cells for use by the mitochondria. Patients with CFS/ME commonly

have deficits in fat metabolism. Liver and gallbladder function, which are vital for breaking down fats, are frequently impaired. Even more significant, CFS/ME patients have been shown to have deficiencies in the transport molecule acylcarnitine, which enables the body to use fats at the cellular level. Eat fats in moderation. Avoid rich foods and sauces. If you eat meat, use very lean cuts and remove the skin from chicken and other fowl. Of the fats, butter and light, pure vegetable oils such as canola or olive oil seem to be best for CFS/ME patients. It is worth the effort to experiment. Buy a high-quality brand; cheap oils become rancid quickly.

5) **ADDITIVES** (artificial colors, artificial flavors, preservatives, MSG). Sensitivities to petrochemicals and their by-products are common in CFS/ME patients. People may not realize that many food additives are derived from petrochemicals. Allergic reactions such as inflammation, itching, pain, insomnia, depression, hyperactivity, and headache caused by common food additives can be severe and can contribute to CFS/ME flares. Although all synthetic food additives should be avoided, the following are particularly problematic for patients with CFS/ME.

- *Artificial colorings* (lake colors, tartrazine, AZO dyes, FD&C, or "coal tar colors"). These are derived from petroleum, and although described as "food" colors, are primarily used to dye cloth. The toxic compounds in FD&C colorings have been linked to cancer, bladder polyps, adrenal damage, impairment of thyroid function, and kidney lesions. Artificial colorings also block the enzyme phenolsulphotransferase-P (PST-P). PST-P deficiency has been noted in hyperactive children and in patients with migraine headaches.
- *MSG and MSG-containing substances* (monosodium glutamate, monopotassium glutamate, hydrolyzed vegetable protein [HVP], hydrolyzed plant protein, sodium caseinate, calcium caseinate, and Flavorings). Glutamic acid, from which MSG is derived, is an amino acid found in most plant and animal proteins. (Glutamate is the salt form of glutamic acid.) When the glutamic acid is separated from the proteins that would normally inhibit or slow its absorption, the bloodstream is flooded. Since glutamate acts as an excitatory neurotransmitter, a number of neurological and allergy-like symptoms can result, including sneezing, itching, hives, rashes, headache, asthma attacks, acid stomach, excessive thirst, bloating, restlessness, balance problems, chest pain, joint pain, and severe depression. CFS/ME patients have reported all of these symptoms, and others. Read product labels for MSG before buying. In restaurants, ask the chef to prepare your food without MSG.

It is a good idea, in general, to read labels before you buy. Many foods labeled "natural" contain numerous additives that can cause reactions in people with sensitivities. Prepared foods are notorious in this regard, so try to stick to simple foods with ingredients you can pronounce.

## FOOD SENSITIVITIES

Sensitivities and allergies to various foods are common enough in CFS/ME to merit special mention. Food sensitivities, while not as dangerous as allergies, can produce such a wide array of symptoms, including restlessness, anxiety, panic attacks, migraine, joint pain, insomnia, nightmares, rashes, and malaise, that they might not be recognized as such in a person with the usual broad spectrum of CFS/ME symptoms. To complicate matters, food sensitivities are rarely detected on standard allergy tests. For that reason, many patients may be unaware that some of the worst symptoms they experience may be due to the food they are eating, especially since sensitivities tend to fluctuate over time (true food allergies tend to be lifelong).

Since awareness that diet may be leading to symptoms may come as a surprise to a person who has not had any previous experience with food intolerance or allergies, the initial search to find well-tolerated foods may, at first, seem daunting. For a subset of patients, reactions may be so severe that food intake is drastically restricted. One person described herself as "living on Cheerios" for the first few months of her illness. People with extreme sensitivities may have to resort to heroic measures such as intravenous feeding to get some nutrition into their bodies. If you are among the very sensitive, food supplementation will be a necessity.

For most CFS/ME patients with sensitivities, however, food intake need not be so restricted. A number of CFS/ME physicians have noted that eliminating a few offending foods from the diet can improve symptoms dramatically.

Dr. Robert H. Loblay and Dr. Anne R. Swain, two clinicians working on CFS/ME research in Australia, discovered that about one-third of their patients considered themselves "much better" after eliminating offending foods from their diets. These patients reported significant improvement in specific symptoms such as headache, muscle pain, malaise, depression, and irritability after adopting a modified diet. Treatment surveys conducted by a DePaul University research team and by Dr. Fred Friedberg also confirm that about one-third of patients who adopt anti-allergy diets experience moderate to major improvement in CFS/ME symptoms.

The task of identifying offending foods is made easier by the fact that most food sensitivities tend to fall into groups that, among CFS/ME patients, can be fairly predictable. The following list, compiled with the help of numerous individuals with CFS/ME, may help you to identify the most common symptom-producing foods.

*NIGHTSHADE FAMILY* (eggplant, pepper, tomato, potato). All members of the nightshade group contain atropine, an alkaloid that is an anticholinergic (inhibits acetylcholine) and produces inflammation. A number of people with CFS/ME report alleviation of joint pain after eliminating these foods from their diets. Some patients report they while they can't eat baked potatoes, they can eat them boiled (with the liquid discarded).

*MILK PRODUCTS.* Dr. David Bell reports that most of his patients have sensitivities to milk products. Many people, even in the general population, develop a deficiency in lactase, the enzyme that breaks down lactose. Lactose intolerance can produce bloating, gas, and discomfort. In addition, milk thickens mucus, which can worsen symptoms for patients with allergies. Some people who cannot consume whole milk (or cheese) find they can drink skim milk. Others find they can substitute nonfat yogurt or cheeses that are not aged (cream cheese, cottage cheese, farmer's cheese) for full-fat or aged dairy products.

*FRUITS.* Fruits contain large amounts of fructose. People with severe problems from defective carbohydrate metabolism experience less fatigue and general malaise with a fruit-free diet. Those with fewer problems sometimes find they can eat fruit after a meal rather than on an empty stomach. Patients also report that some fruits (citrus, for example) are harder to digest than others.

*GAS-PRODUCING FOOD* (onions, cabbage, Brussels sprouts, broccoli). People with gastrointestinal problems should avoid gas-producing foods. Sometimes negative effects are mitigated by cooking these foods thoroughly.

*SPICY FOODS* (black pepper, curry, garlic). Many people with food sensitivities seem to do best with a bland diet, especially in the acute phase. Avoid spicy foods if you have gastrointestinal problems.

*RAW FOODS.* Even though salads provide necessary fiber, many CFS/ME patients experience discomfort after eating raw vegetables. Eating well-cooked vegetables and grains usually mitigates digestive disturbances.

*YEAST-CONTAINING FOODS* (brewer's yeast, fermented products, mushrooms, aged cheese, B vitamins). Patients with yeast overgrowth (Candida) should avoid yeast products, not because yeast products cause Candida to grow, as is commonly believed, but because people with Candida overgrowth tend to become sensitive to yeasts and molds. Even if you do not have a Candida overgrowth, molds, in general, seem to produce strong reactions in people with CFS/ME.

*ACID FOODS* (fruits, tomatoes, vinegar). Patients with interstitial cystitis or recurrent gastritis should avoid acidic foods, which usually exacerbate symptoms (see Urinary Tract Problems).

*NUTS.* Nuts contain large amounts of arginine, the amino acid needed for herpesviruses to replicate. For this reason, they should be avoided. They also tend to produce allergic reactions in those who are sensitive.

*SOY PRODUCTS.* Soy products sometimes provoke reactions such as headache or gastrointestinal pain in sensitive individuals.

## FOOD ROTATION

People with numerous food allergies and sensitivities may want to rotate their foods. The rationale behind food rotation is that when your body takes a rest from the chemical components of the food you are eating, it will not mount an immune attack on later exposure. Supposedly, the body will "forget" its first exposure to a food after four days. Thus a rotation diet calls for a four-day delay before eating a suspected food a second time. Some very sensitive people may want to wait a week before repeating foods. Foods that produce strong reactions (diarrhea, acid stomach, nausea, headache, hives, itching, any other allergic response) should be strictly avoided. If your diet is very restricted, a four-day interval may not be possible. In that case, allow as much time as you can between foods.

Addressing underlying digestive problems that may be causing allergies and sensitivities, such as small intestinal bacterial overgrowth (SIBO) and leaky gut syndrome is absolutely crucial. (See Digestive Disturbances.) In all cases of digestive disturbances it is important to supplement your diet, if you can, with an easily absorbed all-round vitamin and mineral supplement (soluble powders are best) to avoid nutritional deficiencies.

## PREPARATION TIPS

Anything you can do to lessen work in the kitchen will help you improve your diet because you will have more energy to plan and eat meals. If you are acutely ill or bedbound, make it a priority to get some help in the kitchen. People who feel too tired or sick to cook may not eat, which creates problems above and beyond those caused by CFS/ME. If friends offer to help, ask them to prepare meals. If you are alone, try some of the following suggestions to cut down on your work load.

- *Prepare meals in advance.* Cook during periods of higher energy or ask someone to prepare food and freeze it in individual portions.
- *Buy frozen food.* Frozen organic and natural foods are available from health food stores as well as many supermarkets in urban areas. Cascadian Farms markets its own frozen organic corn, potatoes, carrots, and other vegetables as does Whole Foods. You can also purchase frozen organic meats and main dishes that do not contain artificial additives.
- *Order food by phone.* Many grocery stores will deliver for a small fee. Call to see which will take orders by phone.
- *Contact volunteer services.* Many churches and local organizations have volunteers to help you shop and cook meals.

## A FINAL WORD ON FOOD AND DIET

Experiment with your diet to find one that works best for you, but remember to use common sense. Many nutritionists, chiropractors, naturopaths, and countless authors of best-selling diet books have special regimens they claim will produce immediate health gains. Often the pressure to adopt one of these diets can be

intense, especially if your friends or acquaintances have heard rumors of cases in which people with cancer, diabetes, heart disease, or other conditions have been cured simply by following a particular diet.

Special diets can certainly help people with CFS/ME, but we have yet to see a case of anyone who has been cured by adopting any of the diets that have been popularized over the past decade. Quite the contrary; a number of CFS/ME patients have experienced setbacks as a result of rigorous dieting. Some report rapid weight loss with diets that severely restrict carbohydrates. Others have reported exacerbation of weakness from diets that eliminate proteins. Make diet changes slowly, proceed with caution (much as you would with any new treatment), and keep in mind that you are the best judge of what is good for you.

SEE: Allergies (food), Candida, Digestive Disturbances, Headaches, Hypoglycemia, Urinary Tract Problems for diet suggestions and treatments pertaining to specific symptoms.

#### ORGANIZATIONS

Food Allergy Network  
11781 Lee Jackson Hwy., Suite 160  
Fairfax, VA 22033-3309  
Phone: (800) 929-4040  
Fax: (703) 691-2713  
<http://www.foodallergy.org/>

Kids With Food Allergies, Inc.  
Mailing Address:  
73 Old Dublin Pike, Ste 10, #163  
Doylestown, PA 18901  
Phone: (215) 230-5394  
Fax:(215) 340-7674  
<http://www.kidswithfoodallergies.org/>

#### FURTHER READING

Brostoff, Jonathan and Linda Gamlin. *The Complete Guide to Food Allergy and Intolerance*. New York: Crown Publishers, 1989  
*This is the most complete guide to symptoms, causes, and management of food sensitivities.*

Dumke, Nicolette M. *Allergy Cooking With Ease*. Lancaster, PA: Starburst Publishers, 1992  
*A compilation of recipes accommodating every type of allergy.*

## CHAPTER 10: SPECIAL NEEDS OF CHILDREN AND ADOLESCENTS WITH CFS/ME

Maya's story . . .

*In the spring just before her eighth birthday, Maya began complaining of stomach aches and headaches. Her mother had become ill with CFS the previous fall, but because Maya's parents had been assured that children could not contract CFS, they attributed Maya's symptoms to flu. Maya's stomach aches and headaches did not go away, however, and friends began suggesting that Maya was imitating her mother to get attention. That summer her symptoms seemed to clear up, and Maya went to spend a month with her grandparents. During this time Maya started sleeping excessively. Her grandmother was accustomed to letting children sleep until they awakened naturally, but when Maya was asleep all night and half the day, she realized something was wrong.*

*In the week before the start of the school year, Maya began complaining again of stomach aches and headaches. Now she also had diarrhea. The doctor thought she might have worms and gave her medication, but her symptoms worsened. Sore throat and low-grade fever developed. Maya was reexamined by the family physician, who noted that the lymph nodes under her jaw were enlarged, and prescribed an antibiotic.*

*Maya's condition did not improve with the medication and soon other problems developed. In contrast to her long hours in bed during the summer, she now had insomnia and often stayed awake the whole night. She said that even when she did sleep it felt as though she hadn't. Sometimes before going to bed she would hold her chest and say she "couldn't breathe." When she did finally sleep, her rest was interrupted by horrible nightmares, and she would awaken terrified and crying. Her ankles hurt her so much in the morning she could barely walk, and she lost interest in school. She said math gave her a headache, and she did not do her assignments. Her teachers became frustrated when she said she could not remember spelling and other material she had previously learned and labeled her a "problem."*

*To confound matters, Maya had become extremely volatile and seemed to be either perpetually angry or weeping. Maya herself was confused by her outbursts and, when asked what was wrong, would cry out, "I don't know!" Her appetite disappeared, and she complained that food tasted bad. Maya lost weight. When her friends came to call, she told them to play without her.*

*Within a season, Maya had been completely transformed from a lively little girl to a thin, pale recluse. Her last words at night before she went to bed were always, "I can't believe how bad I feel."*

*At that point her mother was almost certain that Maya also had CFS. She consulted with a CFS specialist and with the family physician, who was already familiar with her mother's case. Both were of the opinion that Maya indeed had CFS. The news was devastating.*

*Maya's parents took her out of school, and tutored her at home. There were days when Maya did not get out of bed, but her parents stuck to the treatment plan*



*advised by their nutritionist and physician (primarily supplements), and slowly Maya's health began to improve.*

*Fifteen months after Maya left school, she returned. The school day always left her tired, but she was able to keep up with her work, and within two months she had caught up with her class, despite severe anxiety about taking tests. Her mother wrote a note to the gym teacher requesting that Maya be excused from running and all other aerobic activities. A tutor came once a week to help Maya with spelling, handwriting, and math—three areas that caused her particular problems.*

*After-school activities were still curtailed, but Maya's cheer and zest for life had returned, and she was eager to get on with her life. Her mother steered her toward quieter activities that did not tax her strength but helped boost her self-confidence, such as crafts, languages, music, and art lessons. Although she was clearly less energetic than other children and experienced a flare-up of symptoms when she overexerted herself or caught a cold (a frequent occurrence), she was still able to participate fully in most activities and events.*

That was Maya's story as I wrote it fifteen years ago. Maya is now 27. She finished college, and is now in grad school preparing to become a family therapist. Although she recovered from CFS/ME, the illness left a permanent mark on her. In her teens she developed Hashimoto's disease, an autoimmune disease that attacks and eventually destroys the thyroid. She also developed PCOS (polycystic ovarian syndrome) and migraines. Her monthly medication bills are staggering, and she struggles to maintain stability amidst the chaos of her endocrine system.

Maya's later health problems may not be typical of most cases of pediatric CFS/ME, but the fact is that because children with CFS/ME are not tracked there is no way of knowing how CFS/ME may affect their future health. There are no statistics, few follow-up studies, and very little longitudinal data, so we may never know the long-term effects of CFS/ME on children. And while there has been sufficient interest in pediatric CFS/ME to generate a set of special pediatric criteria, there is still not enough attention paid to the population most at risk from the health and social consequences of this illness.

## INCIDENCE

Contrary to the long-held myth that CFS/ME rarely attacks children, it does, and in significant numbers. In early community-wide outbreaks of CFS/ME, children were among the most frequently affected. In the Lyndonville, New York, outbreak, Dr. David Bell noted that children younger than 18 years represented 30% of the total number of individuals affected.

In contrast to the adult population with CFS/ME, in which women predominate, the illness seems to affect boys as often as girls. Dr. Bell has reported a nearly equal gender distribution in his practice. He also has reported that 45% of his pediatric patients have a family member ill with CFS/ME.

While, in most regards, CFS/ME in children is indistinguishable from CFS/ME in adults, there are some important differences. According to Dr. Bell, the

pattern of onset seems to be more age related in children. In children between the age of eight years and the onset of puberty, CFS/ME usually develops gradually. After puberty, CFS/ME generally begins with acute onset of symptoms, usually resembling the flu or mononucleosis. In children younger than eight years old, CFS/ME is nearly impossible to diagnose because of the diffuse, transient nature of the symptoms and the difficulty most young children have in giving a detailed description of symptoms. This is not to say that younger children do not contract CFS/ME. Parents of children four, five, and six years of age have reported CFS/ME-like symptoms in their children. However, most clinicians will not venture to make a diagnosis for a very young child.

Children with CFS/ME tend to experience more gastrointestinal problems (manifested as stomach aches) and flu symptoms (sore throat and swollen glands). Children also tend to experience all symptoms with equal severity. Dr. Bell has noted that, whereas adults generally report certain symptoms as consistently more severe than others, children can experience severe headaches and stomach aches one day, severe leg pains and insomnia on the next, and severe joint pains on the third.

In 2009, Margaret May, Alan Emond and Esther Crawley, three associates at the Centre for Child and Adolescent Health in Bristol, U.K., undertook to identify possible subtypes of pediatric CFS/ME. After assessing 333 cases of pediatric CFS/ME, the authors found that they tended to group themselves into three subtypes:

1. Musculoskeletal - those with muscle and joint pain and hypersensitivity to touch. This subtype was associated with worse fatigue, physical function, and pain;
2. Migraine - noise and light hypersensitivity, headaches, nausea, anxiety, abdominal pain and dizziness. This subtype was the most strongly associated with physical function and pain;
3. Sore throat – associated with sore throat and tender lymph nodes but not associated with fatigue or pain.

Obviously, these subtypes are not inclusive. For example, they don't take into account cognitive difficulties or sleep disturbance, two of the most frequently reported symptoms in pediatric CFS/ME. However, it is important to note that the subtypes, while associated with severity, were not linked to the patient's age or to the length of the illness. This suggests that pediatric CFS/ME may follow a somewhat different course from CFS/ME in adults, in whom symptoms often undergo considerable change over time.

Recently, the International Association of Chronic Fatigue Syndrome Working Group has devised a specific pediatric case definition for CFS/ME that encompasses the unique characteristics of children with this illness. (See Jason Criteria at the end of this chapter for the complete criteria.) The primary differences between the adult case definition of CFS/ME and the pediatric definition are:

- The pediatric definition only requires three months of ongoing symptoms.

- Physical symptoms, such as dizziness, pain and flu-like symptoms predominate.
- Sudden onset is not included (up to 25% of children have insidious onset).
- Cognitive impairment is emphasized.

In addition, children will have all the adult manifestations of the illness: headaches, GI symptoms, sleep disturbance, light sensitivity, and pain. It should be stressed that in children with CFS/ME most of these symptoms will occur in clusters and will be difficult to distinguish from what doctors routinely refer to as “just a virus.”

## DIAGNOSIS

Most pediatricians cannot make the diagnosis of CFS/ME unless they have had experience with the illness. Given the plethora of symptoms it is more likely that a pediatrician unfamiliar with the illness will make a diagnosis of childhood migraine, atypical epilepsy, school phobia, attention deficit disorder, rheumatoid arthritis, asthma, or irritable bowel syndrome (among others). For this reason alone, it might take so long to get a diagnosis that your child may well have recovered by then. The continuing widespread misconception that children don't contract CFS/ME also makes securing a diagnosis difficult. If symptoms are severe and prolonged, the doctor will probably look for other causes. However, routine test results tend to be normal for most children with CFS/ME, although low sedimentation rate, slightly elevated white blood cell count, and low titers of antinuclear antibodies are common.

Because most doctors order only routine tests for children who come to their offices with flu-like symptoms, a family physician will rarely make the diagnosis of CFS/ME, even if the child is seen in the office every few weeks. As in the case of adults with CFS/ME, more complex immune system tests (natural killer cells, T and B cells) may reveal abnormalities. Tests for viral involvement (Epstein-Barr virus or human herpesvirus 6) are unpredictable, but, like immune system testing, are rarely performed. At this point, the child may receive a diagnosis of "school phobia" from the physician. In this case, the child needs extra support from family members – and most likely will need a new pediatrician as well.

The persisting attitude on the part of doctors and teachers that the child is "faking" symptoms for psychological reasons causes profound damage to children with CFS/ME. Misdiagnosing CFS/ME as school phobia, depression, or separation anxiety, or chalking it up to family problems places the blame squarely on the shoulders of the child. When adults experience this kind of skepticism, they usually are able to defend themselves against the mistaken ideas of others. Children are unable to do so; they depend on adults for information, explanations, sympathy, and advice. To throw disbelief in the face of a child who not only has all the physical symptoms of CFS/ME, but is terribly frightened and in profound need of reassurance is not only cruel, it is detrimental to the child's future emotional growth.

Parents of a child with CFS/ME should keep in mind that even though school officials and doctors may attribute their child's complaints to psychological causes, they seldom can back up their opinions. School phobia, for example, is a manifestation of separation anxiety. Children with separation anxiety display symptoms when anticipating separation, but which resolve when separation does not occur. In CFS/ME, symptoms are present not only during school hours, but after school and on weekends as well. Also, symptoms such as fever, lymph node pain, night sweats, and muscle and joint pain are not features of school phobia. Those who are apt to diagnose depression run into the same inconsistencies; lymph node pain and fever are not typical of depression. Children with CFS/ME can become depressed, but usually do so because no one believes they are ill. No study to date has revealed primary depression among children with CFS/ME.

Another difficulty parents may encounter is that some doctors insist that withholding the diagnosis of CFS/ME is better for the child. They argue that making the diagnosis will encourage self-identification as a "sick person." This is a fallacious argument. A sick child certainly is aware of that fact. Denying reality will only produce more emotional and psychological distress.

#### PROGNOSIS

The prognosis for the majority of children with CFS/ME is good. In Dr. Bell's 13-year follow-up of children with CFS/ME, 80% had recovered, which is good news. Most recover within three years, which, while for a child is a very long time, is relatively short compared to most adult cases. In some children, however, severe cases can last for many years. These are marked by neurological symptoms such as seizures, myoclonus, and paresthesias. Children with severe or long-term neurological symptoms need to be under the continuing care of a neurologist as well as a CFS/ME specialist.

#### TREATMENT TIPS

Treatments for children with CFS/ME are more restricted than for adults and, as a consequence, clinicians tend to be somewhat more cautious in their approach. Dr. Bell, for example, does not recommend giving children many of the drugs commonly prescribed for adults, particularly antidepressants (personal communication, 1993). The justification for a more conservative approach is that the child's normal neurological growth might be affected. Nor do most doctors recommend experimental CFS/ME treatments in children who have not finished growing.

Many alternative treatments and supportive therapies, however, can be beneficial for children. In fact, some of these gentler therapies (herbs and vitamins, especially) have been more successful in children than in adults. Dr. Charles Lapp recommends valerian root (500 to 750 mg nightly) to help with insomnia. He also uses a mild antihistamine such as Benadryl (25 to 50 mg; a clear liquid is available for those with sensitivities to dyes), Tylenol PM, or Excedrin PM to help children sleep. Children also respond well to supportive therapies such as hydrotherapy, massage, and acupuncture (for pain).

Cognitive problems in childhood are particularly troubling because these are crucial years for intellectual development. Children with CFS/ME often experience particular difficulties in maintaining attention (attention deficit disorder), retaining information (memory formation), and focus (concentration). Often they lose confidence in their ability to learn. Dr. Linda Iger, a psychologist who has worked extensively on neurocognitive aspects of CFS/ME, has outlined the following useful strategies to help children with CFS/ME cope with school tasks.

- *Limit periods of concentration.* The average adult can concentrate for only 50 minutes at a stretch. Children with CFS/ME generally lose their ability to concentrate after about 20 minutes (or less, depending on the severity of the illness). Dr. Iger recommends that children time themselves to discover their concentration "ceiling," or limit of concentration. Whatever that amount of time—whether it's 5 minutes or 30—is as much time as should be devoted to a single topic. When concentration wanes, Dr. Iger recommends taking a break for about 10 minutes. Children should get a glass of water, look out the window, or close their eyes and "kick back." In other words, they need to give the brain a break. This work-rest pattern should be repeated twice, then take a long break.
- *Use passive learning.* Often, focusing on a topic makes it harder to absorb. Children with CFS/ME may find the task of learning new information easier if they don't concentrate directly on it. For example, a random list of geographic features may be impossible to memorize if tackled directly. The same information is much easier to process if encountered in the form of a story or video. Your local library may have entertaining materials (PBS video series are particularly helpful) that might help the child absorb information indirectly.
- *Limit information.* It is difficult for most people to remember long strings of facts or numbers. For people with CFS/ME the task is nearly impossible. Most children (and adults) with CFS/ME simply find themselves "going blank" after too much input. Try to limit information input to small increments. For example, a string of numbers such as 4358962 may be difficult to retain. When this set of numbers is broken up into two sets, for example, 435-8962, it is like a phone number. Sets of three and four numbers are much easier to retain than sets of seven digits. Try to use this strategy when faced with memorizing numbers or facts.
- *Eliminate distractions.* Studying with music or television in the background is not a good idea for children with CFS/ME. The additional stimulus of music or talking makes it difficult to concentrate. Find a quiet, nondistracting study place for them.
- *Reduce anxiety.* Anxiety can have disastrous effects on attention span, focus, and retention. For this reason, many children with CFS/ME find themselves unable to take tests. Children who feel themselves becoming anxious (for example, during a test) should practice deep-breathing and stress-reduction

exercises. Self-hypnosis and meditation techniques can also be quite helpful (see Hypnosis, Meditation; and Stress Reduction and Elimination).

Unfortunately, it is still quite difficult to find pediatricians knowledgeable about CFS/ME. Many doctors are unaware that children can contract CFS/ME, even when they know it occurs in adults. If you suspect your child has CFS/ME, it might be well worth the trip to consult with a specialist, in order to both confirm a diagnosis and devise a treatment plan best suited to your child's symptoms and age. A pediatrician who is open-minded will follow the specialist's recommendations. Having a supportive physician can make a world of difference to both the child with CFS/ME and his or her parents.

Of equal importance to medical support is giving careful attention to managing the illness at home. Children with CFS/ME spend the majority of their time at home with their families, which means that proper home management of CFS/ME is vital for recovery. The following management tips can help provide a basis for dealing with CFS/ME in a child and can help make the experience considerably easier for all involved.

### *MANAGING CFS/ME AT HOME*

**PROVIDE SUPPORT AND UNDERSTANDING.** Support and understanding are the most important aspects of helping a child with CFS/ME. Suspicions of malingering will invariably cause self-esteem problems in children. It is important to show children that you believe them, that what they are feeling can be explained, and that you will do everything in your power to help them. Make sure your doctor demonstrates the same attitude.

**MAINTAIN SOCIAL INVOLVEMENT.** It is crucial for children with CFS/ME to maintain relationships with friends, even if they are out of school. Brief play times for younger children or visits for older children are essential to keep up flagging spirits. To avert depression, don't let your child become too isolated.

**REQUEST FREQUENT DIAGNOSTIC REEVALUATION.** Though CFS/ME rarely leads to other diseases, some symptoms are similar enough to those of anemia, heart, and lung disease to warrant reappraisal. There is one published case of a child in whom juvenile diabetes developed after the onset of CFS/ME. New or worsening symptoms should always be investigated.

**INSIST ON ADEQUATE REST.** Children are more active than adults, and the amount of activity a child with CFS/ME can sustain is normally greater than in an adult. Children should be encouraged to be active, but not beyond their limits. An observant parent can judge a child's limits by early warning signs such as paleness, darkness around the eyes, hyperactivity, talkativeness, restlessness, lethargy, crying and irritability, loss of appetite, and sensitivity to light and noise—all signs that the child must rest immediately.

**PROVIDE SCHOLASTIC SUPPORT.** Home tutors are useful, whether the child is being taught at home or in school. According to federal law all children who are ill for more than a few weeks are eligible for tutoring by teachers from the public school district. (Public Law 94-142, the Education of All Handicapped Children Act of 1975, part of the Individuals with Disabilities Act.) The most recent amendments to the Individuals with Disabilities Education Act (IDEA) were passed by Congress in December 2004, with final regulations published in August 2006. A form must be filled out by your doctor to verify that the child is chronically ill. A teacher is then assigned to come to your house, usually three times a week. If the school district balks at sending a teacher (they often have numerous excuses, none of them legal), cite the law and threaten legal action, if necessary. If tutoring through the public schools does not work out, many cities have volunteer tutoring programs for children who cannot attend school. Tutoring can be done by a teenager (if the child is younger), college students in education programs, or retired teachers. The child who is still attending school needs to rest during gym and study hall. It helps to have a note from your doctor.

**KEEP A REGULAR NONSTRESSFUL SCHEDULE.** Stressors of any kind can worsen CFS/ME in children, as they do in adults. To avoid as much physical stress as possible, make sure your child follows a fairly fixed schedule for eating, sleeping, and activities. Adjust his or her schedule accordingly during remissions, but remember that even if the child appears well, late bedtimes and overactivity will only cause a relapse. This is not a good time to burden children with too many expectations or insist on competitive activities, however normal they may be for others in their age group.

Parents must walk that fine line between allowing normal activities, which are essential for a child's growth and happiness, and excesses, which court relapse. Learning to pace a child with CFS/ME is one of the most difficult tasks a parent can master, but it is well worth it in the long run. Eventually the child learns to pace him or herself. Let your child have fun, but keep an eye on his or her limits.

As you care for your child with CFS/ME, don't forget to take care of yourself as well. Nothing is more heartbreaking than watching a child suffer. Seek out support groups, friends, and family members for moral support and take advantage of the resources available for children with long-term or disabling illnesses. Remember that, for your child, you are the most important person in the world. Take good care of yourself.

## ADOLESCENTS

Of all those who contract CFS/ME, adolescents are hit the hardest. Unlike adults, who have achieved independence, or children, who are still very much dependent on their families, CFS/ME forces teens into a "Twilight Zone" in which they can never achieve the independence that they strive for. Nor can they completely rely on their families, because adolescence is a time in which social

groups have more importance than at any other time in life. Teens establish their identities in terms of what their peers think of them. Adolescence is also a time in which young adults look ahead to college, training for a career, the fulfillment of dreams. It is nothing short of tragic when their future is taken away.

Because they are more self-aware, teens can describe what the illness feels like, which is a boon to both parents and doctors. However, because the teen years are also noted for emotional swings, hormonal surges, and general insecurities, it is more likely that adolescents with CFS/ME will be relegated to therapists than their younger counterparts. Unfortunately, being sent to a therapist merely reinforces the sense that their suffering is being dismissed as “not real,” and adds the stigma of mental illness to an already unbearable isolation.

Naida Edgar Brotherston, a Canadian social worker who has researched how CFS/ME affects adolescents, compiled a series of in-depth interviews with four young women who contracted CFS/ME in their teens. These touching interviews capture the true impact of what it is like for young people with CFS/ME. It is a horrific experience, filled with endless frustration and hopelessness. One young woman, Val, describes her inability to attend college as “another loss, another grief.” After giving up on school, she says, “I spent several months just at a loss because never before in my life had I nothing to look forward to, nothing to aim for, nothing to go for.”

The alienation that teens with CFS/ME feel is further exacerbated by their awareness of how their illness affects their families. Even the strongest parents cannot help but show their own sorrow and frustration when their children become ill. Young people are well aware of how their parents feel, and of how other siblings are affected, and very likely will blame themselves. Shame vies with anger in these young people, causing frequent outbursts, and profound emotional lability.

## DIAGNOSIS

The 2006 case definition proposed by Jason et al is meant to apply equally to children and adolescents. However, there are some important differences between the two age groups. Unlike children, in whom symptoms may be noticed only gradually, most teens can pinpoint exactly when they became ill. Typically, teenagers contract CFS/ME after a viral infection, commonly mononucleosis.

Teens, especially girls, also suffer from a higher rate of postural tachycardia syndrome (POTS), a form of orthostatic intolerance, than do adults. Dr. Julian Stewart, professor of pediatrics at the New York Medical College, has observed that the symptoms of patients with chronic POTS are quite similar to those of CFS/ME. In fact, the correlation may be as high as 90%.

In 1999 Dr. Stewart tested 26 adolescents with CFS/ME (11-19 years of age) with an upright tilt test to determine blood pressure levels when standing. Out of the 26 CFS/ME patients, 25 experienced severe symptoms, including fainting, pooling of blood in the extremities, and rapid heart rate. None of the healthy controls exhibited these symptoms. Given these striking findings, your physician may recommend a tilt table test (HUTT) to confirm orthostatic intolerance, especially if symptoms increase upon standing.



## TREATMENTS

Most doctors adopt a conservative approach when treating both children and adolescents, because their bodies are still developing. For example, drugs such as antidepressants, which are often prescribed for adults, are not recommended for teens. Neither are narcotics for pain, or any of the stronger psychotropic medications.

Many of the nutritional supplements used by adults with CFS/ME can be extremely helpful for this age group, particularly antioxidants. A 2010 study performed in the U.K. by Kennedy et al showed that children (up to 18 years) with CFS/ME showed evidence of oxidative stress. In addition, their plasma levels of vitamin E and vitamin C, two important antioxidants, were significantly reduced.

Treating orthostatic intolerance is recommended. Although not enough research has been done on effective treatments for OI in teens, adequate intake of liquids to maintain blood volume, as well as other management strategies for OI are important. (Please see Cardiac and Cardiovascular Symptoms.)

## MANAGEMENT TIPS

Parents walk a fine line when it comes to caring for a teen with CFS/ME. Under normal circumstances, teens oscillate between “Leave me alone! I can do this myself!” and “Help me!” but in CFS/ME these shifts can be startlingly swift. For the most part, it is up to the parents to judge when to leave an ill teen to his or her own devices, and when to step in.

There are some situations, however, in which parents must always step in. Teens are not in a position to fend for themselves when it comes to dealing with adults in authority: doctors, school officials, counselors, and state bureaucrats. In all of these situations, just as with younger children, the parent must act as an advocate.

Parents should also intervene when it becomes clear that the teen is overexerting him or herself. Exercise intolerance is the hallmark symptom of CFS/ME, both for adults and for teens. The “push-crash” pattern commonly seen in adults who do too much on “good” days, and then must spend several days in bed recuperating, is universal among teens. Unlike younger children, who simply lie down when they've had enough, adolescents will attempt to keep up. For teens with CFS/ME, this is a recipe for disaster.

The following tips will help you develop effective strategies for coping with your teen's CFS/ME:

- *Believe your child.* First and foremost, you must believe your child when she says she is ill. CFS/ME is typified by waxing and waning symptoms, a characteristic that is increased in young people. If your daughter is able to get up and go to school one day, but not the next, she is not faking it. If you discount your child's symptoms, you will only make them worse. In addition, you will lose your child's trust. In a teen, this can lead to depression.
- *Help your teen maintain social ties.* Nothing is more devastating for teens than the loss of friends. You may have to bend a little on family policy, but

making friendships a priority (rather than household chores, or even doing homework) is essential for your teen's well-being.

- *Limit physical activity.* A 2010 study by Huang et al at the Children's Memorial Hospital in Chicago found that adolescents with CFS/ME who pushed themselves in an attempt to maintain similar activity levels as their peers paid for it in terms of fatigue severity and an increased need for sleep (particularly during the day). Pushing the envelope will only make the process of recovery longer and harder.
- *Be flexible.* Some days your son may be able to get up and help around the house, other days he won't. Don't saddle your child with a schedule. When he is able to help out, he will.
- *Stay calm.* It may be difficult, especially during emotional outbursts, to stay calm and collected. But, this is what you must do. Remind yourself that your child is ill. Getting upset or angry yourself will only make matters worse.
- *Abandon expectations.* The latter part of adolescence is fraught with anxiety. "Will I be able to get into college?" "How will I support myself?" "What will I do for the rest of my life?" Even in normal circumstances, adolescents have a lot to worry about. These are the years parents tend to pressure their teens to keep up with homework, get good grades, and fulfill responsibilities for the sake of their future success. However, a sick adolescent has even more anxieties than someone who is well. "Will I be able to finish high school?", "Will I have any friends?", "Will I have a life?" This is not the time to put pressure on your teen. If your son is falling behind, or if he simply cannot face the challenges of coursework, it can wait. When he is healed, there will be time to pick up where he left off.

## SPECIAL CASES

One of the worst things that can happen to a child, especially an ill one, is to be taken away from his or her parents and placed, without recourse, in an institution or foster home. It is hard to imagine that in this day and age, such a thing can happen. Unfortunately, in a country in which even criminals are allowed due process, children do not have any such right. All it takes is an "opinion" from one doctor or even a school administrator to set the wheels in motion. Often these opinions come in the form of psychiatric "diagnoses."

Munchausen-by-Proxy, or Factitious Disorder by Proxy, is a rare psychiatric disorder in which a parent will make a child sick either to gain attention, or simply to exert a form of control. Since this disorder did not exist as a diagnosis until the 1970s, there is very little consensus as to what the syndrome actually comprises.

According to the DSM IV, the essential feature of Factitious Disorder by Proxy is "the deliberate production or feigning of physical or psychological signs or symptoms in another person who is under the individual's care. The most common induced and simulated conditions include persistent vomiting or diarrhea, respiratory arrest, asthma, central nervous system dysfunction (e.g., seizures, uncoordination, loss of consciousness), fever, infection, bleeding, failure to thrive,

hypoglycemia, electrolyte disturbances, and rash.” According to the DSM IV, cases are often characterized by an atypical clinical course and inconsistent laboratory test results that are at variance with the seeming health of the victim.

Warning signs of Factitious Disorder by Proxy include: patient has multiple allergies, the illness is multisystemic, prolonged or unusual, parent has medical knowledge or background, patient has poor tolerance of treatments, parent encourages staff to perform numerous tests and studies, the general health of the patient is inconsistent with results of laboratory tests, and parent is overly attached to patient.

It doesn't require a great leap of the imagination to see that CFS/ME fits quite well into the current description of this disorder. Children with CFS/ME rarely show abnormal test results, yet they are ill. Their symptoms are multisystemic, allergies predominate, and there is poor tolerance of medication. Their parents, because they must self-educate, are familiar with medical terms. And, because children with CFS/ME are so ill, parents are “overly attached.”

In the hands of a physician or a school counselor who does not believe that CFS/ME is a real disease, or who does not understand it, or who simply believes the child or parents are “faking it” (this attitude is unfortunately quite prevalent in schools), the diagnosis of Factitious Disorder by Proxy can become a powerful weapon.

In 1986 Ean Proctor, a 12-year-old boy living on the Isle of Man, fell ill with CFS/ME. He obtained a diagnosis of ME (myalgic encephalomyelitis) from a neurologist. Ean's case was quite severe. By 1988 he was confined to a wheelchair and could no longer speak. Nonetheless, Ean was removed from his home after a psychiatrist (Dr. Simon Wessely), decided that Ean was mentally ill. He was taken to a psychiatric ward in a hospital, where the staff informed him that his parents were letting him die. Because they did not believe he was actually unable to get out of his wheelchair, they let him soil himself rather than take him to the bathroom. They also pushed him into a swimming pool, in the belief that he was faking his paralysis. Ean promptly sank to the bottom. After five months of legal battles, the Proctors finally got their son back, but not until they had nearly bankrupted themselves with legal costs.

Nearly two decades later, this horrific incident was repeated with tragic results. Sophia Mirza, a young woman who had fallen ill in 1999, became the first person in Great Britain to officially die of CFS/ME. Her death was hastened by the enforced removal of Sophie from the care of her mother in 2003. As her mother describes it, one day a policeman forced her door open and a psychiatrist and social worker forcibly moved Sophia to a psychiatric ward. There she was left on her own, much as Ean Proctor had been. Unable to care for herself, Sophia rapidly declined. After 13 days she was returned to her mother. However, she never recovered from her ordeal, and in 2005 she finally succumbed. After the autopsy revealed inflammation in 80% of the dorsal root ganglia of her spine, Sophia Mirza's death was officially attributed to CFS/ME.

Lest anyone think that this sort of travesty is limited to overseas, the forcible removal of children ill with CFS/ME occurs in the United States as well. In 2009 Ryan Baldwin, a severely ill 16-year-old who had contracted CFS/ME at the age of 11, was taken from his home by the Buncombe County Department of Social Services in North Carolina and placed in foster care. The allegation was Factitious Disorder by Proxy. For the next nine months Ryan was moved from one foster home to another, often hours away from his home. His foster families believed he was faking his illness, and he was forced into physical therapy, which only made him worse. In 2010 Ryan was at long last returned to his family. When Ryan was finally allowed to testify in court he spoke movingly. "I cannot express in words how much of a living hell that last eight months of my life have been," he said. "I can't stress how pointless, unnecessary and painful this whole thing is and has been."

Parents of children with CFS/ME need to be aware that having a child with CFS/ME entails more than simply helping their child get well. While that is the ultimate goal, any parent who has gone through the experience can tell you that there are many other battles to be fought along the way. The fact that so many of us have fought these battles, and have won, is in itself proof that we can rise to the challenge.

### *ORGANIZATIONS*

Tymes Trust

PO Box 4347

Stock

Ingatestone

CM4 9TE

U.K.

Tel: 0845 003 9002

Advice Line hours : 11am-1pm and 5pm-7pm Weekdays.

*Outside these hours you may leave a message and they will call you back.*

Website: <http://www.tymestrust.org/>

*Tymes Trust is the longest established national U.K. service for children and young people with ME and their families.*

National Information Center for Children and Youth With Disabilities

PO Box 1492, Washington, DC 20013

Website: <http://nichcy.org/>

*This site provides information on national disability laws for children, including information on 504 plans, and IEPs. Also includes state resources.*

### *MORE INFORMATION*

Resources for Children and Youth with CFIDS/ME.

Website: <http://www.masscfids.org/children-a-youth>

*The Massachusetts CFIDS/ME Association has compiled an invaluable list of resources for parents of children with CFIDS/ME. Sections on diagnosis,*

*pediatric case definition, impact of CFIDS/ME on child and family, coping in school, educational right, as well as resources for kids. If you have a child with CFS, this page will be a lifesaver.*

CFIDS Association of America: NMH and OI in Children and Adolescents.

Website: <http://www.cfids.org/youth/articles/medical/nmh.asp>

*This page contains links to research articles concerning orthostatic intolerance, POTS and NMH in children and adolescents.*

New York Medical College: <http://www.nymc.edu/fhp/centers/syncope/POTS.htm>

*Excellent list of doctors who treat OI, by state and international:*

<http://www.ndrf.org/physicia.htm>

*Resource page for OI and chronic illnesses. Includes research, list of doctors, articles, and much more. <http://www.chronic-illness.org/blog/postural-tachycardia-syndrome-pots>*

*Back to School: Resources for Youth with CFS/ME:*

<http://www.cfids.org/cfidslink/2005/back2school.asp>

#### FURTHER READING

*Ryan Baldwin's story:* <http://www.mountainx.com/article/27112/Home-for-good>

*The story of Ean Proctor:* <http://www.cfscentral.com/2010/06/hard-cell.html>

*Josie O'Connor's story:* <http://www.cfids-cab.org/MESA/peds2.html>

*Sophia Mirza:* <http://www.sophiaandme.org.uk/>

*Phoenix Rising thread on Sophia Mirza:*

<http://forums.phoenixrising.me/archive/index.php/t-2705.html>

“What is CFIDS in Youth?” <http://www.cfids.org/youth/youth.asp>

*This is an older publication of the CFIDS Association of America, but it still contains a great deal of relevant information.*

*Journal of Chronic Fatigue Syndrome* (Volume 2, Number 2, 1997)

*This issue focuses on research and issues involving children with CFS/ME.*

“Migraines in Children.” <http://emedicine.medscape.com/article/1179268-overview>

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#### DEFINITION OF ME/CFS FOR CHILDREN\* (Jason et al)

- I. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue over the past 3 months that:
- A. Is not the result of ongoing exertion
  - B. Is not substantially alleviated by rest
  - C. Results in substantial reduction in previous levels of educational, social and personal activities
  - D. Must persist or reoccur for at least three months
- II. The concurrent occurrence of the following classic ME/CFS symptoms, which must have persisted or recurred during the past three months of illness (symptoms may predate the reported onset of fatigue).
- A. Post-exertional malaise and/or post-exertional fatigue.  
With activity (it need not be strenuous and may include walking up a flight of stairs, using a computer, or reading a book), there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient’s cluster of symptoms to worsen. The recovery is slow, often taking 24 hours or longer.
  - B. Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance.  
May include prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening), and/or day/night reversal.
  - C. Pain (or discomfort) that is often widespread and migratory in nature. At least one symptom from any of the following:

- Myofascial and/or joint pain (Myofascial pain can include deep pain, muscle twitches, or achy and sore muscles. Pain, stiffness, or tenderness may occur in any joint but must be present in more than one joint and lacking edema or other signs of inflammation.)
- Abdominal and/or head pain (May experience eye pain/sensitivity to bright light, stomach pain, nausea, vomiting, or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines.)

Two or more neurocognitive manifestations:

- Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis)
- Difficulty focusing (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli in a classroom, or to focus on reading, computer/work activity, or television programs)
- Difficulty finding the right word
- Frequently forget what wanted to say
- Absent mindedness
- Slowness of thought
- Difficulty recalling information
- Need to focus on one thing at a time
- Trouble expressing thought
- Difficulty comprehending information
- Frequently lose train of thought
- New trouble with math or other educational subjects

E. At least one symptom from two of the following three categories:

- Autonomic manifestations: Neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on the feet—disturbed balance, shortness of breath.
- Neuroendocrine manifestations: Recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change—loss of appetite or abnormal appetite, worsening of symptoms with stress.
- Immune manifestations: Recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation—generally minimal swelling noted, new sensitivities to food, odors, or chemicals.

III. Exclusionary conditions:

A. Any active medical condition that may explain the presence of chronic fatigue, such as:

1. Untreated hypothyroidism
2. Sleep apnea
3. Narcolepsy



4. Malignancies
5. Leukemia
6. Unresolved hepatitis
7. Multiple Sclerosis
8. Juvenile rheumatoid arthritis
9. Lupus erythematosus
10. HIV/AIDS
11. Severe obesity (BMI greater than 40)
12. Celiac disease
13. Lyme disease

B. Some active psychiatric conditions that may explain the presence of chronic fatigue, such as:

1. Childhood schizophrenia or psychotic disorders
2. Bipolar disorder
3. Active alcohol or substance abuse—except as below:
  - a) Alcohol or substance abuse that has been successfully treated and resolved should not be considered exclusionary.
4. Active anorexia nervosa or bulimia nervosa—except as below:
  - a) Eating disorders that have been treated and resolved should not be considered exclusionary.
5. Depressive disorders

IV. May have presence of concomitant disorders that do not adequately explain fatigue, and are, therefore, not necessarily exclusionary.

1. Psychiatric diagnoses such as:
  - a) School phobia
  - b) Separation anxiety
  - c) Anxiety disorders
  - d) Somatoform disorders
  - e) Depressive disorders
2. Other conditions defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, such as:
  - a) Multiple food and/or chemical sensitivity
  - b) Fibromyalgia
3. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented.
4. Any condition that was treated with definitive therapy before development of chronic symptomatic sequelae.
5. Any isolated and unexplained physical examination, laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition.

## APPENDIX A: RESOURCES – WEBSITES, BLOGS, FORUMS, BOOKS, VIDEOS

*The Internet is the greatest invention since the printing press as far as the dissemination of information is concerned – which has been both a blessing and a curse. Too much information can be overwhelming, especially for people with CFS/ME. We've tried to narrow the field for you with the following selection. For those who like to cuddle up with something more cozy than a computer screen, there is a book section toward the end.*

## GENERAL WEBSITES

*MEDICAL RESEARCH*

## Medline/Pubmed

Website: <http://www.ncbi.nlm.nih.gov/pubmed/>

*With over 21 million articles, Pubmed is the largest medical research database in the world. You can search by topic, by author, or by title. Also includes clinical trials, journals, and medical subheadings database.*

## The Cochrane Collaboration

Website: <http://www.cochrane.org/>

*The Cochrane Collaboration provides meta-analyses and impartial reviews of supplements, pharmaceuticals, and healthcare topics.*

## ME Research U.K.

Website: <http://www.mereseach.org.uk/information/researchdbase/index.html>

*If you are looking for medical research specifically concerning CFS/ME, this site has the largest collection on the web (over 3000 articles).*

*FREE OR LOW-COST PRESCRIPTIONS*

## Partnership for Prescription Assistance

Phone: (888) 477-2669

Website: <http://www.pparx.org/>

*From the website:* “The Partnership for Prescription Assistance has assisted nearly seven million people in the medicines they need for free or nearly free.”

## Rx Assist's List of Patient Assistance Programs

Website: <http://www.rxassist.org/pap-info/default.cfm>

*From the website:* “RxAssist is a nationally recognized, web based medication assistance resource center. Established in 1999 with funding from The Robert Wood Johnson Foundation, RxAssist gives providers, advocates, consumer and caregivers comprehensive, up-to-date information in an easy to use format.”

## Free Medicine Program

Website: <http://freemedicineprogram.org/>

*From the website:* “Our mission at the Free Medicine Program is helping patients in obtaining prescription drugs and medications absolutely free of charge.”

### BenefitsCheckUp

Website: <http://www.benefitscheckup.org/>

*BenefitsCheckUp is free service of the National Council on Aging to help adults over 55 find help with prescriptions and other basic necessities. From the website: "There are over 2,000 federal, state and private benefits programs available to help adults over 55. But many people don't know these programs exist or how they can apply."*

### Rx Hope

Website: <https://www.rxhope.com/>

*Rx Hope specializes in helping small, emerging pharmaceutical companies manage their Patient Assistance Programs. From the website: "As an integral part of the Triplefin group of companies, we are a highly professional team of caring and concerned people dedicated to making the patient assistance process as easy and comfortable as possible for the patient, the healthcare provider and the pharmaceutical company."*

### The Medicine Program

Website: <http://www.themedicineprogram.com/>

*The Medicine Program is a patient advocate organization. It is a free service. Their goal is to "assist you and your family find, apply and qualify for the right Patient Assistance Program(s). By working closely with you, your doctor and the drug manufacturers we help cut through the red tape and assist you in receiving your medicine free-of-charge."*

### Needy Meds

Website: <http://www.needymeds.org/>

*The mission of NeedyMeds is to make information about assistance programs available to low-income patients and their advocates at no cost. Databases such as Patient Assistance Programs, Disease-Based Assistance, Free and Low-Clinics, government programs and other types of assistance programs are the crux of the free information offered online.*

### DATABASES

*Extensive list of CFS/ME treatments of every kind. This site has everything.*

Website: <http://lassesen.com/cfids/contents.htm>

*ImmuneSupport provides an excellent database of treatments as well as protocols.*

Website: <http://www.immunesupport.com/chronic-fatigue-syndrome-treatment.htm>

*http://www.askapatient.com/ This is the best source of patient experiences with pharmaceuticals. (Not restricted to CFS/ME)*

### FM/CFS/ME Resources

Website: <http://www.fmcfsmc.com/>

*Databases for doctors (worldwide), drugs, disability attorneys, and support groups.*

### NEWS AND INFORMATION

## Phoenix Rising

Website: <http://phoenixrising.me/>

*Phoenix Rising is Cort Johnson's brain-child, and it is one of the best overall information sites out there. This website has literally everything: research, advocacy, treatments, personal accounts and the best boards you will ever find.*

## Dr. Sarah Myhill

Website: <http://drmyhill.co.uk/>

*Dr. Myhill runs a great website, with all her views and treatments available for the reading. She covers every topic thoroughly, with excellent, clear explanations of what causes symptoms and how to treat them. This site is essential reading for patients with CFS/ME as well as doctors and clinicians.*

## Dr. David Bell

Website: <http://www.davidsbell.com/>

*Dr. Bell, although now retired, has continued to be active in the CFS/ME community. This website contains issues of his informative newsletter, the Lyndonville News, as well as Dr. Bell's free ebook, The Faces of CFIDS. Dr. Bell writes in a clear straightforward style, making his literature and research reviews accessible to any audience.*

## Dr. Jacob Teitelbaum

Website: <http://www.endfatigue.com/>

*Dr. Teitelbaum's informative articles can all be found here.*

## Co-Cure

Website: <http://www.co-cure.org/>

*Co-Cure is a long-standing organization with a proven track-record of providing excellent, reliable information to the CFS/ME community. They keep a "good doctor" list, research, and hundreds of articles going back to 1996.*

## The CFS Report

Website: <http://www.cfidsreport.com/>

*The CFS Report has a lot of everything: news reports, links, research, advocacy, and a video of Dr. Montoya speaking at Stanford University about CFS/ME.*

## ME-CFS Knowledge Center

Website: <http://cfsknowledgecenter.com/index.php>

*This site truly is a knowledge center. It provides general information, links to organizations, lists of support groups, and a video library.*

## National Alliance for Myalgic Encephalomyelitis (NAME)

Website: <http://www.name-us.org/index.html>

*NAME provides access to a large body of CFS research, organized by year and by topic.*

## Fibromyalgia

Website:

[http://fmaware.org/PageServer3818.html?pagename=community\\_supportGroupDirectory](http://fmaware.org/PageServer3818.html?pagename=community_supportGroupDirectory)

*This page contains a list of every FM support group in the U.S. as well many located abroad.*

## Fibromyalgia

Website: <http://fmscommunity.org/sptgrp.htm>

*FMS support groups located in the U.S.*

## Partnership for Research in CFS and ME

Website: <http://www.prime-cfs.org/>

*Huge, searchable database of patient experiences with ME.*

## ME Support

Website: <http://www.mesupport.co.uk/>

*This is a resource site with links to every ME/CFS organization in the world with extensive local links in the U.K.*

## The Medical Insider

Website: <http://www.medicalinsider.com/index.html>

*This informative and well-organized website covers all bases: research, treatment, analysis, and links to practitioners in the U.K.. Great explanations of the mechanisms of CFS/ME (with pictures!). If you don't understand Pall's NO/ONOO<sup>-</sup> hypothesis, or Cheney's theories on diastolic dysfunction, the Medical Insider will enlighten you. Also lists many European and U.K. online suppliers for supplements.*

## CFS/ME and Fibromyalgia Self Help

Website: <http://cfidselfhelp.org/>

*A website created by Bruce Campbell, who before becoming ill, was a consultant to self-help programs for chronic illness at the Stanford University Medical School. The site contains some good articles on coping techniques.*

## ME Society of America

Website: <http://www.cfids-cab.org/MESA/>

*The ME Society of America was created by Maryann Spurgin, a long-time veteran of CFS/ME. The site has not been updated since 2009, but it still contains many useful links, research articles, videos, and personal stories, all beautifully organized for easy access.*

*BLOGS*

## Beyond-the-headlines reporting on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Website: <http://www.cfscentral.com/>

*Mindy Kitei is an established journalist with a pithy style and a nose for news that will appeal to any reader. A must-see for anyone who wants to keep up on the latest in CFS/ME events.*

## CFS Patient Advocate

Website: <http://cfspatientadvocate.blogspot.com/>

*“Consuegra” is the father of a young woman who fell ill with CFS/ME several years ago and has been housebound ever since. This blog is an excellent source of information. Videos of the 2011 Mt. Sinai conference are posted here*

*(archives: Dec, Nov 2011), including Dr. Kenny De Meirleir's enlightening presentation on GcMAF.*

#### Nice Guidelines Blog

Website: <http://niceguidelines.blogspot.com/>

*“Dr. Speedy” is a medical doctor and an ME patient. This blog is packed with Dr. Speedy's insightful and delightfully irreverent critiques of the latest medical and research articles. You could spend all day here.*

#### Osler's Web Blog

Website: <http://www.oslersweb.com/blog.htm>

*Hillary Johnson's pithy, irreverent, and always cogent comments on the latest doings in the world of CFS/ME news.*

#### Biomedical ME/CFIDS

Website: <http://biomedicalmecfs.blogspot.com/>

*A blog that says what we are all thinking.*

#### Life as We Know It

Website: <http://cfs-facts.blogspot.com/>

*The newest research about living with Chronic Fatigue Syndrome (CFS)/XMRV/HGRAD/fibromyalgia, with personal observations by a long-time CFS/ME veteran.*

#### One Agent for Change

Website: <http://agentforchange.blogspot.com/>

*Marly Silverman, founder of PANDORA, started this blog “to serve as a catalyst for change that is much needed on the issues affecting millions of individuals stricken with neuroendocrine-immune disorders worldwide.”*

#### Living With Chronic Fatigue Syndrome

Website: <http://livingwithchronicfatiguesyndrome.wordpress.com/>

*This blog was started by a young Australian who came down with ME/CFS in his teens. Fortunately for us, he has kept a careful log of his symptoms as well as every treatment he has tried. This kind of information is immensely helpful for other people who either have or are considering trying these treatments.*

#### CFS/ME

Website: <http://pochoams.blogspot.com/>

*This is an interesting European blog written by Carlitos. The author has been treated by Dr. De Meirleir and has posted his experience.*

#### Hope for FM and CFIDS Sufferers

Website: <http://cfidsresearch.blogspot.com/>

*This blog is maintained by molecular biologist, Dr. Timothy Lockett. It contains the best explanations I have read not only of XMRV, but of recent research on CFS/ME.*

#### Slightly Alive

Website: <http://slightlyalive.blogspot.com/>

*Mary Schweitzer's blog.*

## FORUMS

*Do you want to know how other people cope with CFS/ME, how they recovered, what treatments they've tried, what doctors they've seen? This is where you get all that, and more.*

#### Phoenix Rising Forums

Website: <http://forums.phoenixrising.me/>

*This is our personal favorite. Lots of great information by people who know what they're talking about.*

#### Not Crazy

Website: <http://forum.notcrazy.net/>

*This is an Australian forum with an Aussie sense of humor and very nice section on recovery. The name of the forum comes from the Matchbox 20 song, "I'm not crazy I'm just a little unwell."*

#### ME/CFS Forums

Website: <http://www.mecfsforums.com/>

*This is a very broad-based info center – 123,975 posts on 10,442 topics by 1550 members.*

#### Pro-Health Forums

Website: <http://www.prohealth.com/me-cfs/blog/boardhome.cfm>

*ProHealth calls itself "commerce with compassion." Their boards are open to just about any topic.*

### PERSONAL WEBSITES

#### ME/CFS Fibromyalgia – The Invisible Disease

Website: <http://www.cfs-info.com>

*Jayne Barnard, a long-time CFS/ME veteran, has assembled this informative: news, research, humor, information for professionals and a forum.*

#### Fighting Fatigue

Website: <http://www.fightingfatigue.org/>

*Sandy Robinson has written scores of articles about CFS, FM and interstitial cystitis. They are all on this site.*

#### Living with CFS/ME

Website: <http://www.fikus.net/?cfs>

*Maija Haavisto, a Finnish journalist and medical writer with CFS/ME, has kept careful track of every treatment she has tried, and there have been many. Haavisto's knack for organization is apparent on this website, which contains not only detailed information about CFS/ME treatments, but a clear description of relevant symptoms, book reviews, articles and useful links. A free ebook containing descriptions of hundreds of CFS/ME medications, Reviving the Broken Marionette: Treatments for CFS/ME and Fibromyalgia (abridged version) is available on her website.*

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS): Helpful Hints for Daily Living and Information on Services and Resources.

Website: <http://mecfshints.com/>

*This is an informative website run by Priscilla Ling, an occupational therapist with ME.*

Dr. Teitelbaum's website.

Website: <http://www.endfatigue.com/>

Hillary Johnson on twitter: <http://twitter.com/oslersweb>

## SOCIAL NETWORKING

HealKick

Website: <http://www.healkick.com/>

*For young adults with neuroimmune illnesses.*

The ME-CFS Community

Website: <http://www.me-cfscommunity.com/>

*This is a worldwide community for individuals who wish to learn from, and directly communicate with those who are afflicted with ME/CFS.*

CF Alliance discussion group.

Website: <http://health.groups.yahoo.com/group/CFAlliance/>

*From the website: "All info and opinions posted are ONLY about CFS/ME/FM and their related illnesses such as Brainfog, IBS, RLS, TMJ, Lupus, Sjögren's, Candida, Raynaud's, Celiac, Sinusitis, Lyme, Arthritis, Chronic Pain, GWS and MCS. ONLY helpful health and disability info, caring support and mutual respect are posted here."*

## FREE ONLINE PUBLICATIONS

*Diagnosing and Treating Chronic Fatigue Syndrome*, by Dr. Sarah Myhill

<http://drmyhill.co.uk/wiki/CFS> - CFS Book published by Dr Sarah Myhill

*Faces of CFS*, by Dr. David Bell. <http://www.davidbell.com/DSBFaces.htm>

## BOOKS

Bell, David S. *The Doctor's Guide to Chronic Fatigue Syndrome*. New York: Addison-Wesley Publishing Co., 1994.

*Dr. Bell's guide, although ostensibly pitched to doctors, is not technical. The material is presented in a clear format, is easy to read, and is well organized. The strongest parts of the book are the overview and description sections. Dr. Bell's book is very useful for the new reader.*

Bell, David S. *Cellular Hypoxia and Neuro-Immune Fatigue*. WingSpan Press, 2007.

*In this book, Dr. Bell theorizes that there is a spectrum of neuro-immune illnesses which produce cellular hypoxia (cellular starvation). These illnesses can be triggered by a variety of factors--viral, bacterial, environmental, or CNS trauma. No matter what the trigger, they all lead to a condition in which the body continues to produce inflammatory chemicals, notably nitric oxide. The end result is a hyper-aroused immune response that interferes with the cellular production of ATP, the body's source of energy. There is a lot of research to*



*support this theory (which has been explored more deeply at the molecular level by Dr. Pall). Dr. Bell, as always, writes in a clear style that is accessible to any reader.*

Berne, Katrina H. *Running on Empty: Chronic Fatigue Immune Dysfunction Syndrome (CFIDS)*. Alameda, Calif.: Hunter House, 1995.

*This is one of the classics in the CFS/ME literature. It contains information on testing, symptoms, resources, and a history of the illness, which together comprise the essential information every person with CFS/ME must know.*

Bested, Alison, Russell Howe and Alan Logan. *Hope and Help for Chronic Fatigue Syndrome and Fibromyalgia*. Cumberland House (subsidiary of Sourcebooks, Inc.): 2008.

*Hope and Help is a little book with a lot of practical advice. It contains information on the current theories concerning the cause of the illness, diagnosis, coping techniques, and treatment protocols.*

Goldstein, Jay A. *Betrayal by the Brain*. Binghamton, N.Y.: Haworth Medical Press, 1996.

*and*

Courmel, Katie. *A Companion Volume to Dr. Jay A. Goldstein's Betrayal by the Brain*. Binghamton, N.Y.: Haworth Medical Press, 1996.

*Dr. Goldstein's book gives insights into the limbic system dysfunction that characterizes CFS/ME. Because it is geared to physicians, it is very technical. The companion guide by Katie Courmel provides the layperson with an easy-to-read interpretation of Dr. Goldstein's work.*

Hyde, Byron M, ed. *The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*. Ottawa, Ontario: Nightingale Research Foundation, 1992.

*The Cambridge Easter Symposium on ME/CFS held in Cambridge, England, in April 1990 forms the bulk of this book. Despite the fact that the 75 papers included in this volume represent research that is several years old, the information contained in them, and in the review chapters, is not outdated. Chapter topics include historical reviews of ME/CFS epidemics, ME/CFS in children, diagnosis, infectious origins of ME/CFS (viral research), skeletal muscle and heart involvement, neurological injury, neuropsychological changes, food sensitivities, immunology, blood cell changes, and treatment. For anyone who wishes to explore the more technical aspects of ME/CFS, this book is a gold mine of information.*

Johnson, Hillary. *Osler's Web, Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic*. New York: Crown Publishers, 1996.

*In her thoroughly researched book, Johnson tells the inside story of the recent medical and political events surrounding the CFS/ME outbreaks of the 1980s.*

Ostrom, Neenyah. *50 Things You Should Know About the Chronic Fatigue Syndrome Epidemic*. New York: TNM, Inc, 1992

*In spite of the fact that this book was written in 1991, Ostrom's points are surprisingly and, in the case of government funding, sadly relevant today.*

*Research over the last ten years has shed light on many of the questions marks that pepper this little book, but ,on the whole, the 50 things you needed to know back then are still among the 50 things you need to know today.*

Pall, Martin. *Explaining “Unexplained Illnesses”:* Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others. New York: Harrington Park Press, trade division of Haworth Press, Inc, 2007.

*This book lays out Martin Pall's NO/ONOO<sup>-</sup> (“No! Oh, no!”) hypothesis in detail. The book is quite technical, which makes it tough going for the layperson. However, Pall has come up with a remarkable new paradigm for understanding multisystem diseases, which makes this book a valuable addition to any CFS/ME library. His section on treatments, and why they work for multisystem illnesses is important for everyone to read.*

Richardson, John. Enteroviral and Toxin Mediated Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Other Organ Pathologies. NY: Haworth Press, 2001.

*Dr. Richardson, a family physician in the U.K., treated more than 7000 patients (over a period of four decades) who had contracted enteroviral illnesses. Out of these, 1780 never fully recovered. Dr. Richardson kept careful notes on each and every one of these chronic cases, documenting the course of their illness, subsequent organ pathologies, and charting when and where the bulk of these cases originated (the late 1980s). His detailed case studies provide invaluable material for anyone hoping to understand the persistence and widespread effects of enteroviral infections.*

Rosenbaum, Michael, and Susser, Murray. *Solving the Puzzle of Chronic Fatigue Syndrome.* Tacoma, Wash.: Life Sciences Press, 1992.

*The authors offer a wide range of theories and ideas regarding CFS/ME. Dr. Susser and Dr. Rosenbaum view CFS/ME as a complex disorder, and in light of the fact that a single agent or pathogen has yet to be discovered, they suggest treating CFS/ME as a mixed-infection syndrome. The authors test their patients for parasites, yeast, bacteria, and viruses and investigate possible underlying medical conditions that may mimic or worsen CFS/ME (such as hypothyroidism, adrenal insufficiency, environmental illness, heavy metal poisoning, and allergies).*

Shomon, Mary. *Living Well With Chronic Fatigue Syndrome and Fibromyalgia: What Your Doctor Doesn't Tell You . . . That You Need to Know.* New York: HarperCollins, 2004.

*This is a good, basic introduction to CFS/ME that covers a lot of ground without losing coherence. Written in an accessible style and well organized. Shomon's book is probably the best place to start if you haven't already done a lot of reading on the subject.*

Thorson, Kristin, ed. *Fibromyalgia Syndrome and Chronic Fatigue Syndrome in Young People: A Guide for Parents.* Tucson, Ariz.: Health Network, 1994.

*This book offers essential information on the care and management of children with CFS/ME. It also provides appendices that detail the laws and services applicable to students in the United States. The guides in the back of the book are quite useful for teachers.*

Vanderzalm, Lynn. *Finding Strength in Weakness*. Grand Rapids, Mich.: Zondervan, 1995.

*Ms. Vanderzalm interviewed 70 people with CFS/ME, and drew on her own experience as a mother of children with CFS/ME (and ill herself) to write this book about the impact of CFS/ME on a family. Her avowedly Christian perspective may put some people off. However, since it is one of the few books concerning this topic, the information it contains should be useful to all who read it. The foreword is written by David Bell, M.D.*

Wilkinson, Steve. *Chronic Fatigue Syndrome: A Natural Healing Guide*. New York: Sterling Publishing Co., 1990.

*This is one of the more detailed books on alternative treatments for CFS/ME. Wilkinson worked as an alternative health care practitioner in Great Britain and treated a number of patients for ME before he contracted the illness himself. The sections describing the benefits of acupuncture, aroma therapy, hypnosis, meditation, and dietary supplements, while brief, offer a good sampling of some of the alternative treatments considered useful for many CFS/ME symptoms.*

### PERSONAL ACCOUNTS

Fisher, Gregg Charles. *Chronic Fatigue Syndrome: A Victim's Guide to Understanding, Treating and Coping With This Debilitating Illness*. New York: Warner Books, 1987.

*This book is both a personal account of Gregg Fisher and his wife's illness and a CFS/ME guide, including all that was known about the illness in 1987. He also has many helpful suggestions for dealing with the Social Security Administration, coping with the subjective fallout of having a major illness (emotional upset), and maintaining relationships with incredulous friends and acquaintances.*

Kenny, Timothy. *Living With Chronic Fatigue Syndrome: A Personal Story of the Struggle for Recovery*. New York: Thunder's Mouth Press, 1994.

*This book documents Tim Kenny's struggle with severe CFS/ME. Kenny, a journalist, wanted to share his own battle with CFS/ME to inspire others to keep up the fight. His essay on fatigue is particularly cogent.*

### JOURNALS

The CFIDS Chronicle

Website: <http://www.cfids.org/archives/chronicle-issues.asp>

*The CFIDS Chronicle was the quarterly journal of the Chronic Fatigue and Immune Dysfunction Association of America. At the time it was published (1991-2008) it was the best, in terms of variety and depth of coverage, of all the*

*publications offered by independent CFS/ME organizations. It is well worth reading back issues.*

CFIDS Chronicle, Fall 2005/Winter 2006

Website: <http://www.cfids.org/special/pharma.pdf>

*Special CFIDS Chronicle issue on treatment. Still very timely.*

Research 1<sup>st</sup> News

Website: <http://www.cfids.org/>

*This is the online newsletter distributed by the CFIDS Association of America. Free.*

Journal of Chronic Fatigue Syndrome

Website: <http://www.cfs-news.org/jcfs.htm>

*This is a quarterly medical journal edited by Dr. Nancy Klimas and Dr. Roberto Patarca. The basic mission of the journal is to blend basic scientific, clinical, and epidemiological research in a peer-review format. Subscription required.*

Quest Newsletter

Website: <http://www.mefmaction.com/index.php>

[option=com\\_content&view=article&id=157&Itemid=208](http://www.mefmaction.com/index.php?option=com_content&view=article&id=157&Itemid=208)

*The National ME/FM Action Network publishes a quarterly newsletter, which is included in their membership fee. "Quest" keeps members up-to-date on medical, legal and advocacy issues.*

## VIDEOS

*Living Hell: The Real World of Chronic Fatigue Syndrome* (1 hour)

Website: <http://vimeo.com/9714250> (*The video is not titled*)

*Produced in 1993 by Authentic Pictures and directed by Lennie Copeland, this video accurately and thoroughly represents CFS/ME from the perspective of those who have the illness, as well as those who have treated it. In spite of its age, Living Hell remains the best documentary produced on CFS/ME.*

Youtube

*Type in "Chronic Fatigue Syndrome" for dozens of videos. Interviews with Dr. Lapp, Dr. Klimas, Dr. Teitelbaum and many more.*

*Videos of 2011 Mt. Sinai Conference with Dr. Kenny De Meirleir, Dr. Derek Enlander, and Dr. Eric Schadt.*

Website: <http://blip.tv/mecfscenter>

## APPENDIX B: NATIONAL AND INTERNATIONAL ORGANIZATIONS WEBSITES WITH LISTS OF USEFUL ORGANIZATIONS

CFS Knowledge Center: *comprehensive international links:*

<http://cfsknowledgecenter.com/worldwide-links.php>

The CFS Report: *links page:* <http://www.cfidsreport.com/Links.htm>

Alliance for Myalgic Encephalomyelitis: *links page:* <http://www.name-us.org/Links.htm>

Fibromyalgia Network: *links page:* <http://www.fmnetnews.com/coping-resources/links>

### *INTERNATIONAL AND TRANSNATIONAL*

The International Association for CFS/ME (IACFS/ME)

27 N. Wacker Drive Suite 416

Chicago, IL 60606

Phone: (847) 258-7248

Fax: (847) 579-0975

Email : [Admin@iacfsme.org](mailto:Admin@iacfsme.org)

Website: <http://www.iacfsme.org/>

The IACFS/ME is a non-profit international organization geared towards the professional community. The mission of the IACFS/ME is to promote, stimulate and coordinate the exchange of ideas related to CFS, ME and fibromyalgia (FM) research, patient care and treatment. The annual fee for Regular Professional Membership is \$100 with a two year membership fee of \$150. The fee for a Lifetime Professional Membership is \$1,000. Associate Membership is for students, patients and their families, and other interested individuals. The annual fee for Associate Membership is \$40 with a two-year membership fee of \$60.

The IACFS/ME publishes a peer review online journal, the *Bulletin of the IACFS/ME*, which accepts original research papers, case reports, short notes, reviews of the literature, and book reviews. Letters to the Editor are also welcome. Abstracts are available without charge online.

The IACFS/ME holds a yearly conference.

The Worldwide Patient Alliance

Website: <http://mcwpa.org/>

*From the website:* The grassroots ME/CFS Worldwide Patient Alliance formed in 2010 because of an increasing demand for sufferers to be empowered and have greater influence. For too long, the public and patients have been left out of the ME/CFS debates, yet they are the main ones impacted. One of the primary aims of the MCWPA is to enable sufferers of myalgic encephalomyelitis/chronic fatigue syndrome to make public statements concerning inadequacies in government agencies, lack of research cooperation and ignorance of their illness.”

### *EUROPE*

European ME Alliance

Website: <http://www.euro-me.org/> <http://www.euro-me.org/>

The European ME Alliance is a collaboration of ME support charities and organizations in Europe which intend to provide a common view and the scientific facts regarding the neurological illness myalgic encephalomyelitis (ME/CFS). Member countries include: Belgium, Denmark, Germany, Holland, Ireland, Italy, Norway, Spain, Sweden, Switzerland and the U.K.

#### *UNITED STATES - NATIONAL*

The CFIDS Association of America

PO Box 220398

Charlotte, NC 28222-0398

Telephone: 704-365-2343

Website: <http://www.cfids.org/>

Email: [cfids@cfids.org](mailto:cfids@cfids.org)

*From their website:* The CFIDS Association of America is the largest charitable organization dedicated to chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome (CFIDS). Since 1987, the Association has invested more than \$29.5 million in initiatives to bring an end to the pain, disability and suffering caused by CFS.

The CFIDS Association offers information and resources to patients, family members, caregivers, support groups, media professionals the general public and health care professionals. The Association focuses its resources on research, policy and communications that will advance understanding, diagnosis, treatment and prevention of CFS.

*SolveCFS* is the Association's newest print publication, replacing the *CFIDS Chronicle* in 2009. The Association's e-newsletter, *CFIDSLink*, is delivered to subscribers at the beginning of every month. It contains treatment articles, coping tips, public policy and media reports, personal stories and a wealth of information vital to people living with CFS. *CFIDSLink* is free. Archived issues are available.

The National CFIDS Foundation

103 Aletha Road

Needham, MA 02492

Phone: (781) 449-3535

Fax: (781) 449-8606

E-mail: [info@ncf-net.org](mailto:info@ncf-net.org)

Website: <http://www.ncf-net.org/>

The National CFIDS Foundation is a national non-profit organization founded in 1997. The Foundation's objective is to fund research to find a cause, expedite treatments and eventually a cure, as well as providing information, education, and support to people who have CFIDS (chronic fatigue and immune dysfunction syndrome also known as chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME) and many other names).

The National CFIDS Foundation's dues are \$30/year. (Waivers are available upon request.) The Foundation publishes a quarterly newsletter, *The National*

*Forum.* Selected articles from back issues and research updates are available on their website.

#### PANDORA

(Patient Alliance for Neuroendocrine-immune Disorders  
Organization for Research & Advocacy)  
255 Alhambra Circle, Suite 715  
Coral Gables, Florida 33134

HELPLINE: (954) 783-6771

Website: <http://www.p-a-n-d-o-r-a.org/>

PANDORA is a grassroots advocacy organization that promotes awareness of ME/CFS, Fibromyalgia, Gulf War illnesses (GWI), multiple chemical sensitivities (MCS) and chronic Lyme disease. PANDORA cooperates with other patient organizations to advocate for physician education, increased government-funded research and government policies that make advancement in improving patients' quality of life.

#### *UNITED STATES – RESEARCH*

Whittemore Peterson Institute  
University of Nevada, Reno MS 0552  
1664 N. Virginia St.  
Reno, NV 89557-0552  
Phone: (775) 682-8250  
Fax: (775) 682-8258  
Email: [info@wpinstitute.org](mailto:info@wpinstitute.org)  
Website: <http://www.wpinstitute.org/>

“The Whittemore Peterson Institute for Neuro-Immune Disease exists to bring discovery, knowledge, and effective treatments to patients with illnesses that are caused by acquired dysregulation of both the immune system and the nervous system, often resulting in life long disease and disability.”

#### *UNITED STATES – SUPPORT FOR CFS CAREGIVERS*

Well Spouse Foundation  
PO Box 801  
New York, NY 10023  
212-644-1241 (local telephone)  
800-838-0879 (toll-free telephone)  
Website: <http://www.wellspouse.org/>

The Well Spouse Association advocates for and addresses the needs of individuals caring for a chronically ill and/or disabled spouse/partner. The Association offers peer to peer support and educates health care professionals and the general public about the special challenges "well" spouses face every day. The Association coordinates a national network of support groups (please see their

website for an extensive list), publishes a newsletter (*Mainstay*), advocates on behalf of caregivers, and helps families cope with the emotional and financial stresses associated with chronic illness.

### *UNITED STATES - CHILDREN*

National Information Center for Children and Youth With Disabilities

1825 Connecticut Ave NW, Suite 700

Washington, DC 20009

Phone: (800) 695-0285 (Toll-free, Voice/TTY)

Phone: (202) 884-8200 (Voice/TTY)

Fax: (202) 884-8441

Email: [nichcy@fhi360.org](mailto:nichcy@fhi360.org)

Website: <http://nichcy.org/>

The National Information Center for Children and Youth With Disabilities provides free information to assist parents, teachers, caregivers, and others in helping children and youth with disabilities. The website includes a comprehensive section on disability and education law regarding children.

CFS in Youth

Website: <http://cfids.org/youth.asp>

CFS in Youth was a sister organization of the CFIDS Association of America. It is no longer active, nonetheless, their website contains useful research articles on pediatric CFS/ME, medical information, and websites.

### *UNITED STATES – REGIONAL*

*Note: Most regional organizations and support groups provide information packets, referral services, hotlines, and up-to-date state and local information.*

#### NORTHEAST

The Connecticut CFIDS & FM Association, Inc.

P.O. Box 3010 Milford, CT 06460

InfoLine: (800) 952-2037

Website: <http://www.ct-cfids-fm.org/>

Massachusetts CFIDS/ME & FM Association

Mailing address:

P.O. Box 690305

Quincy, MA 02269-0305, USA

Phone: (617) 471-5559

Website: <http://www.masscfids.org/>

NJCFSA (New Jersey)

PO Box 477

Florham Park, NJ 07932

NJCFSA Helpline: 888-835-3677 (during business hours)

Website: <http://www.njcfsa.org/>



Vermont CFIDS Association  
PO Box 3162  
Burlington, VT 05408  
Phone: (800) 2961445  
Website: <http://www.vtcfids.org/>

### *MIDWEST*

Chronic Fatigue Syndrome, Fibromyalgia, & Chemical Sensitivity Coalition of Chicago (CFCCC)

PO Box 277  
Wilmette, IL 60091  
Phone: (773) 650-1332  
Website: [www.cfccc.net](http://www.cfccc.net)

The CFCCC was organized for the purposes of support, education, and advocacy for people with chronic fatigue syndrome, fibromyalgia, and chemical sensitivity. Their website provides contact information for support groups for patients, families, and caregivers; phone buddies; information/presentations for school nurses, social workers, and other professions; information and referrals to resources; newsletter, *The Canary Times*; a resource directory; and lending library. While most resources are located in the Chicago area, the website also provides a number of national resources as well.

Wisconsin ME/CFS Association  
747 Lois Drive  
Sun Prairie, WI 53590  
Phone: (608) 834-1001  
EMail: [wicfsme@yahoo.com](mailto:wicfsme@yahoo.com) or [bp.fero@charter.net](mailto:bp.fero@charter.net)  
Website: <http://www.wicfs-me.org/>

### SOUTH

The Northern Virginia Chronic Fatigue Syndrome / M. E., Fibromyalgia, and Orthostatic Intolerance Support Group.

Website: <http://www.cfsnova.com/index.html>

CFS/FM Organization of Georgia  
Website: <http://www.cfog.us/>

### WEST

Portland Fibromyalgia – ME/CFS Group  
Tamara Staples, Group Leader  
Email: [tamara@portlandfibrocfs.com](mailto:tamara@portlandfibrocfs.com)  
Phone: (503) 476-9520

*and*

Tami Stackelhouse, Co-Leader  
Email: [tami@myrestoredhealth.com](mailto:tami@myrestoredhealth.com)  
Phone: (971) 832-9322  
Website: <http://portlandfibrocfs.com/>

The Rocky Mountain CFS/ME & FM Association  
7020 E Girard Ave, Suite 207  
Denver, CO 80224  
Phone: (303) 423-7367  
Website: <http://www.rmcfca.org/index.html>

California Capital CFIDS Association (CCCA)  
PO Box 660362  
Sacramento, CA 95866  
Phone: (916)484-3788  
Email: [CalCapitalCFIDS@bigfoot.com](mailto:CalCapitalCFIDS@bigfoot.com)  
Website: <http://www.ottem.org/ccca/>

OFFER (Utah)  
1002 E. South Temple, Suite 408  
Salt Lake City, UT 84102  
Phone: (801) 328-8080  
Fax: (866) 555-1112  
Email: [support@offerutah.org](mailto:support@offerutah.org)  
Website: <http://www.offerutah.org/>

CFS and FM Support Group of Dallas/Ft Worth  
CFS/FM Support Group  
513 Janann St  
Euless, TX 76039  
Website: <http://www.dfwcfids.org/index.shtml>

Portland Fibromyalgia – ME/CFS Group  
Tamara Staples, Group Leader  
[tamara@portlandfibrocfs.com](mailto:tamara@portlandfibrocfs.com)  
*and*  
Tami Stackelhouse, Co-Leader  
[tami@myrestoredhealth.com](mailto:tami@myrestoredhealth.com)  
Website: <http://portlandfibrocfs.com/>

*ABROAD*

ARGENTINA

Asociacion Civil Fibroamerica

Website: <http://fibroamerica.blogspot.com/>

Enfermedades Cronicas Socialmente Invisible

Website: <http://www.arbitrio.com.ar/>

AUSTRALIA – NATIONAL AND REGIONAL

The Alison Hunter Memorial Foundation

PO Box 6132

North Sydney NSW 2059

Australia

Telephone/Fax +61 2 9958 6285

Website: <http://www.ahmf.org/aboutus.html>

Alison Hunter was the founding president of ME Young Adults (MEYA), established in 1992 at Royal North Shore Hospital, Sydney. The Foundation is primarily concerned with advocacy and research. The website contains a very large data base with abstracts of all research conducted on ME/CFS between 1956 and the present.

NATIONAL - ME/CFS Australia Ltd.

Postal Address: PO Box 7100, DANDENONG VIC 3175

Office Address: Suite 5, 106 Foster Street, DANDENONG VIC 3175

Phone: (03) 9793 4500

Website: <http://www.mecfs.org.au/home>

Western Australia

ME/CFS Society WA

The Centre for Neurological Support

The Niche, 11 Aberdare Road

Nedlands, Perth. Western Australia 6009

Tel: 08 9346 7477

Fax: 08 9346 7534

Website: <http://www.mecfswa.org.au/>

New South Wales

ME Chronic Fatigue Syndrome Society of NSW Incorporated

Postal Address:

PO Box 5403,

Chatswood NSW 1515

Office Address:

Suite305A, 425 Victoria Ave

Chatswood NSW 2067

Phone: (02) 9904 8433

ABN: 28 688 072 304

Website: <http://www.me-cfs.org.au/>

Northern Territory ME/CFS Society

Office Address:

Suite 5, 106 Foster Street

Dandenong VIC 3175

Postal Address:

PO Box 7100

Dandenong VIC 3175

Phone:

Support Line: (03) 9791 2199 (9am - 5pm, Monday - Friday; please leave a message if line is not attended)

Administration: (03) 9791 3100 (9am - 5pm, Monday - Friday)

Email: [admin@mecfs-vic.org.au](mailto:admin@mecfs-vic.org.au)

Website: <http://www.mecfs-vic.org.au/welcome-mecfs-australia-northern-territory>

South Australia ME/CFS Society

Mailing address:

GPO Box 383,

Adelaide,

South Australia 5001

Office:

[266 Port Road,](#)

Hindmarsh,

South Australia 5007

Ph: (08) 8346 3237 ('834 MECFS') Office Hours: Wednesdays, 10am-3pm

Support Line: (Mondays and Thursdays, 10am-3pm) Ph: (08)8346 3237

SA country callers: Ph: 1300 128 339 (local call)

Website: <http://sacfs.asn.au/>

QUEENSLAND

ME/CFS/FM Support Association Qld Inc.

27 Scott Street,

Toowoomba Qld 4350, Australia

Phone: (07) 4632 8173 or (07) 4659 5239

Fax: (07) 4632 8173

Email: [mefmtba@bigpond.com](mailto:mefmtba@bigpond.com)

Website: <http://www.mecfsfmq.org.au/>

Canberra

ACT ME/CFS Society

Address:

Building 1 (first on the left)

Pearce Community Centre

Collett Place (opposite Pearce shops on Hodgson Crescent)

Pearce

Office hours are: 9.30am to 4.30pm Monday to Friday

Phone: 02 6290 1984

Fax: 02 6290 4475

Website: <http://www.mecfscanberra.org.au/>

ME/CFS Society Victoria

Office Address:

Suite 5, 106 Foster Street

Dandenong VIC 3175

Postal Address:

PO Box 7100

Dandenong VIC 3175

Phone: Support Line: (03) 9791 2199 (9am - 5pm, Monday - Friday; please leave a message if line is not attended)

Administration: (03) 9791 3100 (9am - 5pm, Monday – Friday)

Email: [admin@mecfs-vic.org.au](mailto:admin@mecfs-vic.org.au)

<http://www.mecfs-vic.org.au/>

Tasmania (contact Victoria office)

<http://www.mecfs-vic.org.au/welcome-mecfs-australia-tasmania>

BELGIUM

ME Society - Belgium

<http://www.meab.be/>

CANADA

FM-CFS Canada

99 Fifth Avenue

Suite 412

Ottawa ON

Canada K1S 5P5

Website: <http://fm-cfs.ca/>

National ME/FM Action Network

512, 33 Banner Road

Nepean, ON K2H 8V7

Phone: 613-829-6667

Fax: 613-829-8518

Email: [mefmaction@ncf.ca](mailto:mefmaction@ncf.ca) (Subject lines of all emails must begin with “May 12”)

Website: <http://www.mefmaction.com/>

Nightingale Research Foundation

Dr. Byron Hyde, Chairman

121 Iona Street  
Ottawa Ontario  
K1Y 3M1  
Canada  
Fax: (613) 523-1958  
Email: [info@nightingale.ca](mailto:info@nightingale.ca)  
Website: <http://www.nightingale.ca/>

## DENMARK

ME/CFS Foreningen (ME/CFS Association)  
RÅDHUSTORVET 1, 1. SAL  
3520 FARUM  
TEL: 44 95 97 00  
Email: [MAIL@ME-CFS.DK](mailto:MAIL@ME-CFS.DK)  
Website: <http://www.me-cfs.dk/>

Foreningen for myalgisk encefalomyelitis (ME Association)  
Telefonisk træffetid på tlf. 29 37 05 59:  
Website: <http://www.dmef.dk/>

## FRANCE

Association Française du Syndrome de Fatigue Chronique et de Fibromyalgie.  
Maison des Associations  
72 rue Royale - 59000 Lille  
Email: [jv.sfcf@numericable.fr](mailto:jv.sfcf@numericable.fr)  
Website: <http://asso.nordnet.fr/cfs-spid/index.html>

## GERMANY

Fatigatio e.V.: Bundesverband Chronisches Erschöpfungssyndrom  
(CFS/CFS/ME/ME)  
Albrechtstr.15  
D-10117 Berlin  
Tel: 030 – 310 18 89 -0  
Fax: 030 - 310 18 89-20  
Website: <http://www.fatigatio.de/>

## ME/CFS Actuell

Website: <http://www.cfs-aktuell.de/>

## GREAT BRITAIN

The ME Association  
7 Apollo Office Court  
Radcliffe Road

Gawcott  
Bucks MK18 4DF  
Tel: 01280 818964 (between 9.30am and 4.30pm)  
Website: <http://www.meassociation.org.uk/>

Action for M.E.  
PO Box 2778  
Bristol BS1 9DJ  
Tel: 0845 123 2380 (lo-call) or 0117 927 9551  
Fax: 0117 927 9552  
Opening hours 9am - 5pm Monday - Friday (closed Bank Holidays)  
Tel: 0845 123 2314  
Website: <http://www.actionforme.org.uk/>

Association for Young People With ME  
AYME  
10 Vermont Place  
Tongwell  
Milton Keynes  
MK15 8JA  
Telephone: 08451 23 23 89  
Email: [info@ayme.org.uk](mailto:info@ayme.org.uk)  
<http://www.ayme.org.uk/>

Blue Ribbon for the Awareness of ME (BRAME)  
30 Winner Avenue  
Winterton-on-Sea  
Great Yarmouth  
Norfolk  
NR29 4BA  
U.K.  
Tel/Fax: 01493 393717  
Email: [info@brame.org](mailto:info@brame.org)  
Website: <http://www.brame.org/>

Invest in ME  
PO Box 561  
Eastleigh  
Hampshire SO50 0GQ  
U.K.  
FAX: 02380 000040  
Email: [info@investinme.org](mailto:info@investinme.org)  
Website: <http://www.investinme.org/index.htm>

ME Research U.K.  
The Gateway, North Methven Street  
Perth PH1 5PP, U.K.  
Telephone: 01738 451234  
Email: meruk@pkavs.org.uk  
Website: <http://www.mereseach.org.uk/>  
Partnership for Research in CFS and ME  
Website: <http://www.prime-cfs.org/>

25% ME GROUP (Representing the severely ill)  
21 Church Street  
Troon  
Ayrshire  
KA10 6HT  
Phone Main Office: 01292 318611 - Office Hours 9.30 to 5pm - Monday to Friday  
Website: <http://www.25megroup.org/home.html>

Tymes Trust (Representing young people)  
PO Box 4347  
Stock  
Ingatestone  
CM4 9TE  
Phone: 0845 003 9002  
Advice Line hours : 11am-1pm and 5pm-7pm Weekdays.  
Outside these hours you may leave a message and we will call you back.  
Website: <http://www.tymestrust.org/>

Young Action Online (in partnership with Tymes Trust)  
Website: <http://www.youngactiononline.com/>

## IRELAND

Irish ME Trust  
Carmichael House  
North Brunswick Street  
Dublin 7  
Telephone: Lo-call 1890 200 912  
Int. tel: 00 353 1 401 3629  
Int. fax: 00 353 1 401 3736  
Website: [http://www.imet.ie/imet\\_website/links/links.html](http://www.imet.ie/imet_website/links/links.html)

Irish ME/CFS Association  
PO Box 3075  
Dublin 2



Tel: 01-2350965  
Email: [info@irishmecfs.org](mailto:info@irishmecfs.org)  
Website: <http://irishmecfs.org/contact.html>

Northern Ireland ME Association  
28 Bedford Street  
Belfast  
BT2 7FE  
Tel/Fax: 028 9043 9831  
Email: [jo@nimea.org](mailto:jo@nimea.org)  
Website: <http://www.nimea.org/index.html>

## SCOTLAND

The ME Association/Scotland  
Website: <http://www.meassociation.org.uk/?p=1054>

## WALES

Welsh Association of ME/CFS Support (WAMES)  
Email: [enquiries@wames.org.uk](mailto:enquiries@wames.org.uk)  
Website: <http://www.wames.org.uk/ffram.htm>

## HOLLAND

ME/CVS Verniging (ME/CFS Association)  
Website: <http://www.me-cvsvereniging.nl/>

ME/CFS Foundation  
Nordic Grove 16  
1211 BG Hilversum

The Netherlands  
Tel: 035-6211290 (werkdagen van 10:00-12.30)  
Fax 035-6211219  
Email: [info@me-cvs-stichting.nl](mailto:info@me-cvs-stichting.nl)  
Website: <http://www.me-cvs-stichting.nl/>

Start Pagina (Comprehensive Dutch resources)  
Website: <http://me.startpagina.nl/>

ITALY  
CFS Italia  
Website: <http://www.cfsitalia.it/>

## JAPAN

CFS Network Japan

Website: <http://www.bekkoame.ne.jp/~sage-m/cfs-E/index.htm>

## MALTA

M.E Sufferers Malta

P.O. Box 25

Pieta PTA 1310

Malta

Website: <http://www.mesufferersmalta.org/>

## NEW ZEALAND

Associated New Zealand ME Society (ANZMES)

ANZMES Inc.

P.O. Box 36-307

Northcote, Auckland, New Zealand

Phone: (09) 269 6374

Email: [info@anzmes.org.nz](mailto:info@anzmes.org.nz)Website: <http://www.anzmes.org.nz/>

## NORWAY

[Norges Myalgisk Encefalopati Forening](#)

Kontoradresse

Kr. Augustsgt. 19

0164 Oslo

Telefon: 22 20 34 24

Kontortid: tir - ons – tor

Telefontid kl. 11.30 - 15.30

Email: [post@me-foreningen.no](mailto:post@me-foreningen.no)Website: <http://www.me-foreningen.no/>

## PORTUGAL

National Association Against FM/CFS

Av Santos Dumont, 67, 1,

1050-203 Lisboa

Hours: 2nd, 4th and 6th Friday from 14h to 18h

Phone: 217973294 (only during office hours)

Email: [sede@myos.pt](mailto:sede@myos.pt)Website: <http://www.myos.pt/>

## SOUTH AFRICA

The ME Association of Southern Africa

P.O.Box 1802

Umhlanga Rocks

4320  
South Africa  
Email: [arl@telkomsa.net](mailto:arl@telkomsa.net)  
Website: <http://www.me.org.za/>

## SPAIN

Fundación para la Fibromialgia y el Síndrome de Fatiga Crónica  
Passeig Manuel Girona  
3 33- BARCELONA (Spain)  
Tel: +34-93- 280 46 26/605 85 25 91  
Email: [info@fundacionfatiga.org](mailto:info@fundacionfatiga.org)  
Website: <http://www.fundacionfatiga.org/>

Associació Catalana d'Afectats per la Síndrome de Fatiga Crónica / Encefalomièlitis  
Miàlgica  
Plaça Comas  
13-14 baixos  
08028 Barcelona  
Telèfon: 933.214.654.  
Atenció els dilluns i dimecres de 17:00 a 19:00 i dijous de 11:00 a 13:00  
Website: <http://www.acsfcem.org/>

## SWEDEN

RME - Riksföreningen för ME-patienter (RME - the National Association for ME patients)  
Box 11037  
404 21 Göteborg  
E-post: [info@rme.nu](mailto:info@rme.nu)  
Telephone: 031-15 58 99  
Website: <http://www.rme.nu/>  
Association of ME  
Email: [kasper.ezelius@me-foreningen.se](mailto:kasper.ezelius@me-foreningen.se)  
Website: <http://me-foreningen.se/>

## SWITZERLAND

Verein CFS Schweiz  
CH-8000  
Zürich Schweiz  
Phone: +41 78 616 96 80  
Website: <http://www.verein-cfs.ch/>

## FIBROMYALGIA

American Fibromyalgia Syndrome Association  
6380 E. Tanque Verde, Suite D  
Tucson, AZ 85715  
Phone: (520) 733-1570  
Website: <http://www.afsafund.org/>

Advocates for FM Funding, Treatment, Education and Research (AFFTER)  
P. O. Box 768  
Libertyville, IL 60048-0768  
Phone: (847) 362-7807  
Email: [info@affter.org](mailto:info@affter.org)  
Website: <http://www.affter.org/>

Fibromyalgia Network  
PO Box 31750  
Tucson, AZ 85751-1750  
Phone: (800) 953-2929 (weekdays 9:00 a.m. to 5:00 p.m. MST)  
Local: 520-290-5508  
Email: [inquiry@fmnetnews.com](mailto:inquiry@fmnetnews.com)  
Website: <http://www.fmnetnews.com/>

National Fibromyalgia and Chronic Pain Association  
Website: <http://www.fmcpaware.org/>  
National Fibromyalgia Association  
Website: <http://fmaware.org/>

## ORGANIZATIONS FOR RELATED CONDITIONS

A  
merican Academy of Allergy, Asthma & Immunology  
555 East Wells Street  
Suite 1100  
Milwaukee, WI 53202-3823  
Phone: (414) 272-6071  
Website: <http://www.aaaai.org/home.aspx>

American Chronic Pain Association  
PO Box 850  
Rocklin, CA 95677  
Phone: 1-800-533-3231  
Fax (916)632-3208  
Email: [acpa@pacbell.net](mailto:acpa@pacbell.net)

Website: <http://www.theacpa.org/default.aspx>

American Sleep Association

Website: <http://www.sleepassociation.org/>

Arthritis Foundation

P.O. Box 7669

Atlanta, GA 30357-0669

Phone: (800) 283-7800

Website: <http://www.arthritis.org/>

Asthma and Allergy Foundation of America

8201 Corporate Drive

Suite 1000

Landover, MD 20785

Phone: (800) 727- 8462

Website: <http://www.aafa.org/display.cfm?id=10&sub=29>

Chemical Injury Information Network

PO Box 301

White Sulphur Springs, MT 59645

Phone: (406) 547-2255

Fax: (406) 547- 2455

Website: <http://ciin.org/>

Chemical Sensitivity Foundation

4 Wren Drive

Topsham, ME 04086

Phone: (207) 725-8570

Email [info@chemicalsensitivityfoundation.org](mailto:info@chemicalsensitivityfoundation.org)

Website: <http://www.chemicalsensitivityfoundation.org/>

Environmental Health Network

PO Box 1155

Larkspur, CA 94977

Phone: 415-541-5075

Website: <http://ehnca.org/>

Food Allergy Network

11781 Lee Jackson Hwy., Suite 160

Fairfax, VA 22033-3309

Phone: (800) 929-4040

Fax: (703) 691-2713

Website: <http://www.foodallergy.org/>

Human Ecology Action League (HEAL)  
P.O. Box 509  
Stockbridge, Georgia 30281  
Phone: (770) 389-4519 – Fax : (770) 389-4520  
Email: HEALNatnl@aol.com or [HEAL3@aol.com](mailto:HEAL3@aol.com) (Membership)  
Website: <http://www.healnatl.org/>

Lupus Foundation of America  
2000 L Street, N.W., Suite 410  
Washington, DC 20036  
Main Phone: (202) 349-1155 (8:30 a.m. - 5 p.m. ET, Monday - Friday)  
Information request line: English / Para información en español 1-800-558-0121  
Fax: 202-349-1156  
Website: <http://www.lupus.org/newsite/index.html>

National Gulf War Resource Center, Inc.  
2611 SW 17th Street  
Topeka, KS 66604  
Phone: Toll free (866) 531-7183  
Fax:(785) 235-6531  
Email: [jim@ngwrc.org](mailto:jim@ngwrc.org)  
Website: <http://www.ngwrc.org/>

National Organization for Rare Disorders  
55 Kenosia Avenue  
PO Box 1968  
Danbury, CT 06813-1968  
Phone: (203) 744-0100  
Fax: (203) 798-2291  
*Washington Office:*  
1779 Massachusetts Avenue  
Suite 500  
Washington, DC 20036  
Phone: (202) 588-5700  
Fax: (202) 588-5701  
Website: <http://www.rarediseases.org/>

National Organization for Seasonal Affective Disorder  
Website: <http://www.nosad.org/>

Sjögren's Syndrome Foundation  
6707 Democracy Boulevard  
Suite 325  
Bethesda, MD 20817

Toll Free Phone: (800) 475-6473  
Local call: (301) 530-4420  
Fax: (301) 530-4415  
Website: <http://www.sjogrens.org/>

Society for Mitral Valve Prolapse Syndrome/Dysautonomia  
PO Box 431  
Itasca, IL 60143-0431  
Website: <http://www.mitralvalveprolapse.com/>

## OTHER USEFUL ORGANIZATIONS

Clearinghouse on Disability Information  
550 12th Street, S.W., Room 5133  
Washington, DC 20202-2550  
Website: <http://healthfinder.gov/orgs/HR0035.htm>  
(202) 245-7307 (Voice)  
(202) 205-5637 (TTD)  
(202) 245-7636 (FAX)

*From the website:* The Clearinghouse provides information to people with disabilities, or anyone requesting information, by doing research and providing documents in response to inquiries. Information provided includes areas of federal funding for disability-related programs. Clearinghouse staff is trained to refer requests to other sources of disability-related information, if necessary.

U.S. Social Security Administration  
1-800-772-1213

Website: <http://www.ssa.gov/>

The Social Security Administration pays disability benefits under two programs: the Social Security Disability Insurance Program and the Supplemental Security Income (SSI) Program. Medical requirements for both programs are the same. Eligibility for Social Security is based on prior work history and SSI benefits are based on financial need. Most people with CFS/ME who apply for Social Security are denied once or twice and must go through an appeals process.

Social Security Disability Insurance

Phone: 1-800-772-1213

Website: <http://www.ssa.gov/dibplan/index.htm>

National Organization of Social Security Claimants Representatives (a lawyer referral service)

560 Sylvan Ave, Suite 2200

Englewood Cliffs, NJ 07632

Phone: 201-567-4228 | Fax: 201-567-1542

Lawyer Referral Service: 800-431-2804

Website: <http://www.nosscr.org/contact.html>

Most people have greater success with experienced lawyers than with filing their own appeals. Lawyers who process Social Security appeals usually charge a percentage of back payments owed you by the government (if your appeal is successful).

Centers for Medicare & Medicaid Services

7500 Security Boulevard

Baltimore MD 21244-1850

Website: <http://www.medicare.gov/default.aspx>

Social Security and Disability Resource Center

Website: <http://www.ssdrc.com/>

*From the website:* The SSDRC is published, edited, and maintained by Tim Moore, a former disability claims examiner for the social security administration's disability determination services (DDS), as well as a former caseworker with a background in many assistance programs, including medicaid for disabled adults. The goal of this site is to provide information about how the federal government's disability programs work, the idea being that qualified information may lead to better choices as to how to initiate and pursue claims and appeals, and potentially avoid time-consuming and costly mistakes.



## APPENDIX C: CFS/ME CLINICS, CLINICIANS, RESEARCH INSTITUTES, AND LABORATORIES

*The following is a list of clinics, clinicians, and researchers who have made contributions in the area of CFS/ME treatment. It is by no means a complete list. (For example, it does not include doctors outside the United States and Canada.) If you are seeking a clinician, either to diagnose or treat CFS/ME, we strongly recommend you consult the databases below. Since most specialists require that you have a local primary health care physician to monitor treatments, it is well worth the effort to find a cooperative physician before you seek the services of a specialist.*

### DATABASES FOR LOCATING CFS/ME PHYSICIANS

*Searchable database of CFS/ME doctors by country and state.*

<http://www.chronicfatiguetreatments.com/wordpress/treatments/chronic-fatigue-doctors/>

*Co-Cure's "Good Doctor" list. Organized by country and state:* <http://www.co-cure.org/Good-Doc.htm>

*Devin Starlanyl's list of CFS/ME doctors:*

<http://homepages.sovnet.net/~devstar/provider.htm>

*List of well-known CFS/ME doctors, general information and links to their websites.*

<http://aboutmecfs.org.violet.arvix.com/Trt/TrtDocProts.aspx>

*List of CFS/ME doctors in Europe and U.S:* <http://esme-eu.com/list-of-me-cfs-doctors-in-europe-and-usa/list-of-me-cfs-doctors-in-europe-and-usa-article152-169.html>

*Database for FM specialists in the U.S. and abroad:*

<http://fmscommunity.org/findingadoctor.htm>

*FM/ME/CFS database of doctors in 79 countries:*

[http://fmcfsmc.com/doctor\\_database.php](http://fmcfsmc.com/doctor_database.php)

*Long list of doctors in Australia:*

<http://forums.phoenixrising.me/showthread.php?5938-CFS-ME-Good-Doctor-List>

### INTERNATIONAL RESEARCH COLLABORATIONS

Simarron Research Foundation for Chronic Fatigue Syndrome

948 Incline Way

Incline Village, NV 89452

Website: <http://simmaronresearch.org/>

*This is an international research collaboration between Dr. Peterson, Bond University (Australia), Stanford University, and Wisconsin Viral Research Group. Their primary goal is to identify the cause and develop a treatment for CFS/ME.*

Mt Sinai ME/CFS Center

c/o Derek Enlander MD

860 Fifth Avenue  
New York NY 10065

Website: <http://www.enlander.com/>

*The Mt. Sinai group is a research collaboration initiated by Dr. Derek Enlander which includes virologist Illa Singh, geneticist Eric Schadt, immunologist Dr. Miriam Merad, Dr. Kenny De Meirleir and Dr. David Bell. Videos of the 2011 Mt. Sinai conference are posted here: <http://blip.tv/mecfscenter>*

#### ARIZONA

*Scott Rigden, MD*

2410 W. Ray Road, Suite 4

Chandler, AZ 85224

Phone: 480-820-4297

Fax: 480-838-4953

Website: <http://www.drscottrigden.com/>

*Only accepts patients from Arizona.*

*Neil Singer, M.D.*

3700 W State Route 89a Ste A

Sedona, AZ 86336

Tel: (928) 204-4901

More Information:

[http://www.vitals.com/doctors/Dr\\_Neil\\_Singer.html#ixzz1cTCen1qH](http://www.vitals.com/doctors/Dr_Neil_Singer.html#ixzz1cTCen1qH)

*Murray Susser, M.D.*

9328 Raintree Drive

Scottsdale, AZ 85260

Tel: (480) 240-2600

[sussermd@gmail.com](mailto:sussermd@gmail.com)

Website: <http://www.murraysussermd.com/>

#### CALIFORNIA

*Sheila Bastien, Ph.D.* (neuropsychologist)

2126 Los Angeles Avenue, Berkeley, CA 94707-2618

Tel: (510) 526-7391

*John Chia, MD*

23560 Crenshaw Blvd, Torrance, CA 90505

Tel: (310) 784-5880

*Dr. Chia is both a respected researcher and a clinician. Patients report that it is "worth the wait."*

*Michael J. Goldberg, M.D., F.A.A.P.*

5620 Wilbur Ave., Suite 318, Tarzana, CA 91356

Tel: (818) 343-1010

*Holtorf Medical Group. Kent Holtorf, M.D.*

23456 Hawthorne Blvd, Suite 160, Torrance, CA 90505.  
Tel: (310) 375-2705.

*and*

48 N. El Molino Ave., Suite 101, Pasadena, CA 91101.  
Tel: (626) 796-7500.

*and*

1065 East Hillside Blvd., Suite 108, Foster City, CA 94404.  
Tel: (650) 638-1141

*and*

491 Allendale Rd., Suite 222, King of Prussia, PA 19406.  
Tel: (610) 265-0500

Website: <http://www.holtorfmed.com/>

*Dr. Garth Nicolson*

The Institute for Molecular Medicine

31677 Virginia Way

P.O. Box 9355

South Laguna Beach, CA 92652

Telephone: (949) 715-5978

*and*

*Department of Immunology*

16371 Gothard Street H

Huntington Beach, California 92647-3652

USA

Telephone: (714) 596-7821

Fax: (714) 596-3791

Office Hours: 8:00 am - 5:00 pm

Email: [mail@inmed.org](mailto:mail@inmed.org)

Website: <http://www.immed.org/>

*From the website:* "The mission of the Institute for Molecular Medicine is to contribute to the understanding of and the prevention and cure of catastrophic human chronic diseases, such as autoimmune diseases, fatigue illnesses, rheumatic diseases, cancer, AIDS, and infectious and genetic diseases."

*Dr. Jose Montoya*

Chronic Fatigue Clinic

Stanford School of Medicine

300 Pasteur Dr A175 MC 5309

Stanford, CA 94305

Tel: (650) 723-6961 Fax: (650) 725-8418

Website: <http://chronicfatigue.stanford.edu/>

*Primarily research oriented. Long waiting list.*

*Michael J. Powell, D.O.*

Fibromyalgia Treatment & Learning Center  
650 University Avenue, Suite 200  
Sacramento, CA 95825  
Tel: (916) 922-8400

*Patient comment:* "I highly recommend him for not just CFS or ME, but also for other hard to diagnose illness."

*Michael Rosenbaum, MD*

Preventive Medical Center of Marin  
25 Mitchell Blvd., Suite 8  
San Rafael, CA 94903  
Tel: 415-927-9450  
Tel: 415-507-9450  
Fax: 415-472-7636

Email: [info@drmichaelrosenbaum.com](mailto:info@drmichaelrosenbaum.com)

Website: <http://www.drmichaelrosenbaum.com/index.html>

*Nutritional, integrative and alternative healthcare.*

*Murray Susser, M.D.*

2211 Corinth Avenue  
Suite 204  
Los Angeles, CA 90064  
Tel: (310) 479-8909

*and*

9328 Raintree Drive  
Scottsdale, AZ 85260  
Tel: (480) 240-2600

Email: [sussermd@gmail.com](mailto:sussermd@gmail.com)

Website: <http://www.murraysussermd.com/>

## CONNECTICUT

*Fred Friedberg*

PO Box 456

Kent, CT 06757

Telephone: 516-702-4213 Fax: 860-619-8069

Email: [info@lifebalance7.com](mailto:info@lifebalance7.com)

Website: [http://www.lifebalance7.com/index.php?page\\_id=1](http://www.lifebalance7.com/index.php?page_id=1)

*Psychologist. President of the International Association for Chronic Fatigue Syndrome/ME.*

## FLORIDA

*Nancy G. Klimas, M.D*

Chronic Fatigue & Immune Disorders Research and Treatment Center  
 8720 N. Kendall Drive (also known as SW 88th Street)  
 Suite 108  
 Miami, FL 33176  
 Email: [info@cfsclinic.com](mailto:info@cfsclinic.com)  
 Phone: (305) 595-4300  
 Fax: (305) 598-4155  
 Website: <http://www.cfsclinic.com/>

*This is the first of a nationwide network of CFS clinics. "These clinics would follow the methodologies created by Dr. Klimas in her current clinic, using solid, evidenced- based medicine to treat this unique population."*

More Information *Very informative review by a satisfied Klimas patient.*

<http://forums.phoenixrising.me/showthread.php?10696-My-experience-with-Klimas>

## MARYLAND

*Richard E. Layton, M.D.*

901 Dulaney Valley Road  
 Dulaney Center II, Suite 101  
 Towson, MD 21204

Telephone: 1-888-337-2707 (In Maryland, call 410-337-2707)

Website: [www.allergyconnection.com](http://www.allergyconnection.com)

*Clinical ecologist and allergist. Uses provocation/neutralization method and sublingual drops.*

*Peter Rowe, M.D.*

Professor of Pediatrics

Johns Hopkins University School of Medicine  
 Division of General Pediatrics and Adolescent Medicine  
 David Rubenstein Child Health Building  
 200 N. Wolfe St. / Room 2077  
 Baltimore, MD 21287

Phone: 410-955-9229

Fax: 410-614-1178

Email: [prowe@jhmi.edu](mailto:prowe@jhmi.edu)

Website: <http://www.hopkinschildrens.org/staffDetail.aspx?id=3226>

*Dr. Rowe only treats adolescents.*

*Dr. Grace Ziem, Occupational & Environmental Medicine*

16926 Eyler's Valley Road  
 Emmitsburg, MD 21727

Phone: 301-241-4346

Website: [www.chemicalinjury.net](http://www.chemicalinjury.net)

*Treats patients with chemical sensitivities.*

## MASSACHUSETTS

*Don Goldenberg, M.D.*

Newton-Wellesley Hospital  
2000 Washington Street, Suite 304, Newton, MA 02462  
Tel: (617) 243-5440 Fax:(617) 243-6453

*CFS/ME, FMS and other hard-to-diagnose illnesses.*

*Dr. Barry Elson*

Northampton Wellness Associates  
395 Pleasant Street  
Northampton, MA 01060  
Phone: 413-584-7787  
Fax: 413-584-7778

Website: <http://www.northamptonwellness.com/>

*The center treats a wide variety of hard-to-treat illnesses, including CFS/ME, fibromyalgia, IBS, MCS and many more. The integrative approach uses conventional treatment as well as nutritional support, IV treatment, dietary counseling, stress management and chelation.*

## MICHIGAN

Fatigue Clinic of Michigan

*Edward Conley, M.D., Director*

G3494 Beecher Road Flint, MI 48522

Tel: (810) 230-8677

Website: <http://cfids.com/>

*Focuses on mitochondrial dysfunction, gut dysbiosis, adrenal support, immune dysfunction, food allergies, yeast overgrowth, hormone balancing, and nutritional deficiencies.*

*A. Martin Lerner, M.D., M.A.C.P*

32804 Pierce Road

Beverly Hills, MI 48025

Telephone: (248) 540-9866

Fax: (248) 540-0139

Website: <http://www.treatmentcenterforcfs.com/>

*Dr. Lerner is a highly respected member of the CFS/ME medical community.*

*His particular area of interest is virology. Treatments include antivirals.*

*Ruth Walkotten DO, NP*

2947 Russell Rd

Muskegon, MI 49445

Tel: (231) 733-1989

*"She has excellent people skills and is a close listener ... very easy to trust."*

## NEVADA

*Daniel Peterson, M.D.*

Sierra Internal Medicine

926 Incline Way

Incline Village NV 89452  
Mailing address:  
P.O. Box 7870  
Incline Village, NV 89452  
Tel: (775) 832-0989 Fax: (775) 832-3046

NEW JERSEY

*Richard Podell, M.D.*  
Medical Arts Center, 11 Overlook Rd., Suite 140  
Summit, NJ 07901  
Tel: (908) 273-7770

*and*

53 Kossuth St.  
Somerset, NJ 08873  
Tel: (732) 565-9224

Website: <http://www.drpodell.org/>

*Holistic doctor specializing in alternative medical treatments for CFS/ME.*

*Dr. Majid Ali*

Institute of Integrative Medicine  
140 West End Avenue, Suite 1H  
New York, NY 10023  
(212) 873-2444

*and*

95 East Main Street  
Denville, NJ 07834  
(973) 586-4111

Website: <http://www.majidali.com/new.htm>

*Does not accept insurance.*

NEW YORK

*Dr. Steven Bock, M.D. and Dr. Kenneth Bock*

Center for Progressive Medicine  
1662 Central Ave.  
Albany, NY 12205  
Tel: (518) 218-0082  
Fax: (518) 218-0081

*and*

Rhinebeck Health Center  
108 Montgomery Street  
Rhinebeck, NY 12572  
Tel: (845) 876-7082  
Fax: (845) 876-4615

Website: <http://www.rhinebeckhealth.com/rhc/>

*Dr. Derek Enlander*

860 5th Avenue, Suite 1C  
New York, NY 10065  
Phone: (212) 794-2000  
Phone: (212) 794-9588  
Fax: (212) 327-2125  
Website: <http://www.enlander.com/>

*Patricia Fennell, MSW*

Albany Health Management Associates, Inc.  
582 New Loudon Rd.  
Latham, NY 12110  
Phone: (518) 482-0422 Fax: (518) 783-4793  
Website: <http://www.albanyhealthmanagement.com/index.shtml>

*The center provides counseling for people with chronic illnesses.*

*Dr. Leo Galland, M.D.*

156 Fifth Avenue  
Suite 519  
New York, NY 10010  
Tel: (212) 989-6733  
Website: <http://www.mdheal.org/>

*Dr. Henry Lasky*

3141 U.S. Route 9w Ste 600  
New Windsor, NY 12553  
Tel: (845) 561-3407

*Rheumatologist. Treats fibromyalgia.*

*Susan Levine, M.D.*

115 E 72nd St.  
New York, NY 10021  
Tel: (212) 472-4816

*Dr. Roger Mazlen*

30 Middle Neck Road  
Roslyn, NY 11576  
Tel toll-free: (866) 237-7807  
Telephone: (516) 869-0717  
Fax: (516) 869-0718  
Email: [rgm1@aol.com](mailto:rgm1@aol.com)

Website: <http://www.drmazlen.com/>

*Dr. Mazlen has treated over 1000 cases of CFS/ME. Integrative medicine.*

*Accepts insurance.*

*Dr. Benjamin Natelson*

Phillips Ambulatory Care Center, Suite 4K  
Beth Israel Medical Center



10 Union Square East  
New York, NY 10003-3314  
Tel: (212) 844-6768  
Website: [http://www.painandfatigue.com/clinical\\_care.html](http://www.painandfatigue.com/clinical_care.html)  
*Accepts Medicare.*

#### NORTH CAROLINA

*Paul Cheney, M.D., Ph.D.*

One Vanderbilt Park Dr., #230

Asheville, NC 28803

Tel: (828) 274-6665

Website: <http://www.cheneyclinic.com/about>

*Dr. Cheney is one of the world's foremost specialists in CFS/ME. Most of his patients are severely ill. It takes several months to get an appointment. Staff is very unhelpful.*

Hunter-Hopkins Center

*Dr. Charles Lapp*

7421 Carmel Executive Park Dr.

Charlotte, North Carolina 28226

Telephone: (704) 543-9692

Facsimile: (704) 543-8547

Email: [drlapp@drlapp.net](mailto:drlapp@drlapp.net)

Website: <http://drlapp.com/>

*Dr. Lapp is one of the best known doctors in the CFS/ME medical community. He was the Director of the Cheney Clinic from 1992-1995. Does not accept insurance.*

*Dr. Jorge Flechas, M.D.*

Flechas Family Practice

80 Doctors Drive, Suite 3, Hendersonville, NC 28792

Telephone: (828) 3233

*Myra Preston, PhD*

7820 Ballantyne Commons Pkwy

Charlotte, NC 28277

Phone: (704) 543-0427

Website: <http://www.siberimaging.com/about.html>

*Biofeedback.*

*Alan Spanos M.D., M.A.*

Blue Ridge Clinical Associates

1829 East Franklin Street

Franklin Square Building 200-A

Chapel Hill, NC 27514

Telephone: (919) 967-2927 Fax: (919) 967-1705

Website: <http://www.alanspanosmd.com/>

*Pain Specialist and well-versed in CFS/ME. Must have a Primary Care*

*Physician who will collaborate as your first line doctor. Does not take Medicare.*

## OREGON

*The Frida Center for Fibromyalgia*

6400 SW Canyon Court, Suite 100

Portland, OR 97221

Phone: (503) 477-9616

Fax: (503) 477-9808

Website: <http://www.fridacenter.com/>

*The Center aims to be a resource for the treatment, research, and education of fibromyalgia. The Frida Center is staffed by Dr. Ginevra Liptan and sleep expert, Dr. Keith Ironside, as well as Cheryl Hryciw, MS, FNP.*

*From the website: "The Frida Center is a relaxing place, where we focus on getting to know the whole picture of our patients' health. Visits with our providers are calm, comfortable, and not hurried."*

## PENNSYLVANIA

*Holtorf Medical Group*

491 Allendale Rd., Suite 222,

King of Prussia, PA 19406.

Tel: (610) 265-0500

Website: <http://www.holtorfmed.com/>*Clymer Healing Center*

5916 Clymer Rd

Quakertown, PA 18951

Tel: (800) 300 5168, (215) 536-8001

Fax: (215) 536-9099

Website: <http://www.healing.org/>

*A holistic healing center.*

## TEXAS

*Dr. William Rea*

Environmental Health Center

8345 Walnut Hill Lane, Suite 220

Dallas, TX 75231

Telephone: (214) 368-4132

Website: [www.ehcd.com](http://www.ehcd.com)

*For patients with MCS.*

*Dr. Patricia Salvato, M.D.*

Diversified Medical Practices PA

6300 Richmond Ave Ste 202

Houston, TX 77057

Telephone: (713) 961-7100

*Dr. Salvato gets consistently good ratings from patients. However, her staff are reported to be rude and incompetent.*

Read more:

[http://www.vitals.com/doctors/Dr\\_Patricia\\_Salvato.html#ixzz1buP9t9ez](http://www.vitals.com/doctors/Dr_Patricia_Salvato.html#ixzz1buP9t9ez)

*Dr. Larry Sharp*

8509 Western Hills Blvd, Suite 300

Fort Worth, Texas 76108

Tel: (817)246-7676

Website: <http://www.drlarrysharp.com/contact.asp>

*I. Jon Russell, M.D., Ph.D.*

7703 Floyd Curl Dr

San Antonio, TX 78229

Phone: (210) 257-1400

*Nationally recognized FM researcher and rheumatologist .*

UTAH

*Dr. Lucinda Bateman*

Fatigue Consultation Clinic.

1002 E. South Temple, Suite 408

Salt Lake City, UT 84102

Tel: (801) 359-7400 Fax: (801) 359-7404

Email: [FCClinic@Xmission.com](mailto:FCClinic@Xmission.com)

Website: <http://www.fcclinic.com/Dr.Bateman.htm>

WASHINGTON

*Dr. Dedra Buchwald, M.D., Director*

Chronic Fatigue Clinic

Harborview Medical Center

325 Ninth Avenue

7<sup>th</sup> Floor, Maleng Building

Seattle, WA 98104

Telephone: (877) 744-9700

*“The Chronic Fatigue Clinic offers comprehensive care and services for patients who experience persistent fatigue, as well as widespread pain, throughout their bodies, fibromyalgia and other conditions.”*

UNITED STATES, NATIONAL

Jacob Teitelbaum, M.D.

Medical Director of the Fibromyalgia and Fatigue Centers (FFC's)

For a local FFC Center please see the link below.

Website: <http://www.fibroandfatigue.com/treatment-center-locations-and-contact-information.html>

## CANADA

*Dr. Alison Bested*, Director  
 Complex Chronic Disease Clinic  
 BC Women's Hospital & Health Centre  
 4500 Oak Street  
 Vancouver, BC  
 V6H 3N1  
 Tel: (604) 875-2424  
 Toll free in BC only: (888) 300-3088

*Dr. Bested is reported to see patients on Wednesdays.*

*Dr. John Cline*  
 Cline Medical Clinic  
 233 Prideaux Street  
 Nanaimo B.C. V9R 2M9  
 Tel: (250) 753-3030  
 Toll Free: 1-877-333-3030  
 Email for general information: [info@clinemedical.com](mailto:info@clinemedical.com)  
 Website: [clinemedical.com](http://clinemedical.com)

*Integrative medicine, chelation, biofeedback, allergies.*

*Nova Scotia Environmental Health Centre*  
 3064 Highway 2, PO Box 2130  
 Fall River, Nova Scotia  
 B2T 1K6 Canada  
 Phone: (902) 860-0057 Fax: (902) 860-2046  
 Email: [nsehc@cdha.nshealth.ca](mailto:nsehc@cdha.nshealth.ca)  
 Website: <http://www.cdha.nshealth.ca/environmental-health-centre>

*Holistic medicine. Treats MCS, FMS, CFS/ME.*

Nightingale Research Foundation  
*Dr. Byron Hyde, Chairman*  
 121 Iona Street  
 Ottawa, Ontario  
 K1Y 3M1  
 Tel: (613) 523-1958  
 Email: [info@nightingale.ca](mailto:info@nightingale.ca)  
 Website: <http://www.nightingale.ca/>  
*Accepts 10-20 patients a year.*

## RESEARCH INSTITUTES

Whittemore Peterson Institute  
 University of Nevada, Reno MS 0552  
 1664 N. Virginia St.  
 Reno, NV 89557-0552

Phone: (775) 682-8250

Fax: (775) 682-8258

Email: [info@wpinsitute.org](mailto:info@wpinsitute.org)

Website: <http://www.wpinsitute.org/>

*The WPI is a research institute for neuro-immune diseases such as ME/CFS, fibromyalgia, atypical MS, and autism.*

CFS Foundation of Dr. Martin Lerner

32804 Pierce Road

Beverly Hills, MI 48025

Telephone: (248) 540-9866

Fax: (248) 540-0139

Website: [http://www.treatmentcenterforcfs.com/CFS\\_Foundation/index.html](http://www.treatmentcenterforcfs.com/CFS_Foundation/index.html)

*Dr. Lerner is a widely published CFS/ME researcher and clinician. His primary focus is on antiviral treatments. The CFS Foundation was established to advance research, treatment and further the understanding of CFS/ME. From the website: "The foundation hopes to establish a molecular biology laboratory to develop specific diagnostic testing for subsets of CFS and a training center dedicated to the training of medical professionals in the treatment of those suffering from CFS."*

The Enterovirus Foundation

268 Bush Street, #4044

San Francisco, CA 94104

Telephone: (415) 393-9558p

Fax: (415) 358-4222

Website: <http://www.enterovirusfoundation.org/index.shtml>

*The Enterovirus Foundation was co-founded by Lisa Ross Faust, a businesswoman who, along with her daughter, fell ill with an enteroviral infection that led to CFS/ME. The Board of Directors includes Dr. John Chia, a noted researcher whose work on the role of enteroviral infections in CFS/ME has been exemplary.*

HHV-6 Foundation

1253 Coast Village Road, Suite #105

Santa Barbara, CA 93108

Phone: (805) 969-1174

Fax: (800) 645-6950

Website: <http://www.hhv-6foundation.org/>

*The Scientific Director of the HHV-6 Foundation is Dharam Ablashi, co-discoverer of the HHV-6 virus and a 22-year veteran of the National Cancer Institute. Ablashi is also the co-founder of the EBV Association and the IACFS/ME. The Foundation encourages scientific exchange between investigators by holding conferences for virologists and clinical researchers. From the website: "The Foundation also seeks to raise awareness among*

physicians of the many conditions that have recently been associated with HHV-6 infection and encourage the discovery of antiviral compounds appropriate for HHV-6.”

Solve CFS BioBank

SolveCFS

The CFIDS Association of America

PO Box 220398

Charlotte, NC 28222-0398

Phone: (704) 365-2343

Fax: (704) 365-9755

Website: <http://www.solvecfs.org/SOLVECFSBIOBANK/tabid/99/Default.aspx>

*The Solve CFS Biobank is part of the research arm of the CFIDS Association of America. The BioBank is a repository for blood and tissue samples and clinical information to advance the discovery of a biomarker.*

Center for Clinical & Epidemiological Research, University of Washington

Box 359780

1730 Minor Avenue, Suite 1760

Seattle, WA 98101

Phone: 206-543-3717, 888-223-0868

Fax: 206-543-3830

*Dr. Dedra Buchwald, long-time CFS/ME researcher and clinician, is the director of the CCER. The chronic fatigue and pain research program at the UW CCER evolved out of Dr. Buchwald's Chronic Fatigue Clinic at Harborview Medical Center in Seattle, Washington. From the website: “The research program that has grown out of this clinical effort has focused on illuminating the "5 P's" model of chronically fatiguing conditions: predisposition, precipitants, perpetuators, predictors of chronicity, and perceptual factors involved in the illness.”*

CFS Initiative

Website: <http://cfinitiative.org/>

*From the website: “Chronic Fatigue Initiative is a nonprofit organization fostering and supporting collaboration among the world’s leading medical research, treatment and public health organizations in understanding the causes, therapies and epidemiology of Chronic Fatigue Syndrome (CFS). Headquartered in New York City and funded by the Hutchins Family Foundation, CFI seeks to accelerate the medical community’s knowledge of CFS through research grants and collaborative processes across institutions.”*

## LABORATORIES

Metametrix Clinical Lab

3425 Corporate Way

Duluth, GA 30096

Phone: (770) 446-5483 (Office hours 8:30 AM - 6:00 PM EST)

Toll-free: (800) 221-4640

Fax: (770) 441-2237

Email: [inquiries@metamatrix.com](mailto:inquiries@metamatrix.com)

Website: <http://www.metamatrix.com/>

*Metamatrix is recognized internationally as a pioneer and leader in the development of metabolic, toxicant, and nutritional testing. The mission of Metamatrix is to improve health worldwide by providing clinical laboratory tests that identify nutritional imbalances and toxicities underlying chronic diseases.*

Genova Diagnostics  
63 Zillicoa Street  
Asheville, NC 28801

USA

Telephone: (800) 522-4762

Fax: (828) 252-9303

Website: <http://www.gdx.net/>

*Europe:*

Genova Diagnostics  
Parkgate House  
356 West Barnes Lane  
New Malden  
Surrey  
KT3 6NB  
U.K.

Phone: +44 (0)20 8336 7750

Fax: +44 (0)20 8336 7751

*Genova Diagnostics provides more than 125 specialized diagnostic assessments, covering a wide range of physiological areas including digestive, immunology, metabolic function and endocrinology. For CFS/ME, recommended tests include Candida panels, intestinal permeability, heavy metal toxicity, adrenal and thyroid function, CMV and EBV titers, oxidative stress, nutritional profile, allergies, and a comprehensive stool analysis for digestive function.*

R.E.D. Laboratories N.V./S.A.

Z.1 Researchpark 100

B-1731 Zellik

BELGIUM

Phone: +32-(0)2-481-5310

Fax: +32-(0)2-481-5311

Client relation hours: 9 a.m. to 4 p.m.

Website: <http://www.redlabs.be/>

*Testing for immune system markers: CD4CD8 ratio; ANA; activated immune complexes – IgG sub-fractions including IgG1 and IgG3, circulating immune complexes IL2 & IL4; Th1 –Th2 response to mitogen stimulation, flow cytometry for activated/elevated lymphocytes; antilamin antibodies; humoral autoimmunity for polypeptides of the nuclear envelope (NE); antibodies in neuronal cells MAP2 (kinase regulators); 37kDa 25A RNase L immunoassay.*

UNEVX (Lab of the Whittemore-Peterson Institute)

P.O.Box 8849

1664 No Virginia Street

Reno, NV 89507

*Corporate Office:*

UNEVX - Bldg 160/MS0554

University of Nevada Reno

1664 No Virginia Street

Reno, NV 89557

Phone: (775) 682-8280

Fax: (775) 682-8290

Email: [info@unevx.com](mailto:info@unevx.com)

*Immune system testing (see R.E.D. Labs list), XMRV.*

Health Diagnostics and Research Institute (formerly Vitamin Diagnostics, Inc.)

South Amboy Medical Center

540 Bordentown Ave.

Suite 2300

South Amboy, New Jersey 08879

Telephone: (732) 721-1234

Fax: (732) 525-3288

*Testing for nagalase, methylation panel.*

Wisconsin Viral Research Group

10437 Innovation Dr.

Suite 321

Milwaukee, WI 53226

Phone: 414-774-8612 (9AM to 4PM Central)

Email: [info@wisconsinlab.com](mailto:info@wisconsinlab.com)

*Specializes in viral testing.*



## APPENDIX D: MAIL-ORDER SUPPLIERS GENERAL RESOURCES FOR CFS SUPPLIES

*CFS Support of Northern Virginia (NOVA) keeps an extensive list of shopping resources.*

Website: <http://www.cfsnova.com/resources-shopping.html#vitamin>

### ALLERGY SUPPLIES

National Allergy Supply. <http://www.natlallergy.com/>

Allergy Store. <http://www.allergystore.com/>

Achoo Allergy. <http://www.achooallergy.com/iqairpurifiers.asp>

Allergy Buyer's Club. <http://www.allergybuyersclub.com/>

AllAllergy Net. <http://www.allallergy.net>

### NUTRITIONAL SUPPLEMENTS

PureFormulas

Phone: (800) 383-6008

Website: <http://pureformulas.com/>

*This is a great supplier – high quality supplements at very affordable prices. Free shipping! Very fast delivery. They include a 10% discount card with each delivery.*

Vitacost.com

130 Lexington Parkway

Lexington, NC 27295

Toll Free: 1-800-381-0759

U.S. Direct Dial: 1-336-956-0800

Website: <http://www.vitacost.com/>

*Vitacost has a huge selection of standard supplements (the ones you find in health food stores). Nobody can beat their prices.*

Bronson Laboratories

350 South 400 West #102

Lindon, Utah 84042-1931

USA

Toll-free phone: (800) 235-320

Fax: (800) 596-4242

Website: <http://www.bronsonvitamins.com/>

*Reasonably priced vitamins, amino acids, herbs, personal care products, digestive aids, minerals, and antioxidants obtained directly from the manufacturer.*

Iherb

17825 Indian Street

Moreno Valley, CA 9255

Phone: (951.616.3600)

Fax: 951.616.3601

Website: <http://www.iherb.com/>

ProHealth, Inc.

2040 Alameda Padre Serra

Santa Barbara, CA 93103

Toll Free: (800) 366-6056

U.S.: (805) 564-3064 or Internationally at 001.805.564.3064

Fax: (805) 965-0042 or Internationally at 001.805.965.0042

Monday through Friday 7am to 5pm (PT)

*ProHealth (formerly The CFIDS and Fibromyalgia Health Resource) offers a broad selection of supplements frequently recommended for people with CFS/ME. Their website contains a Research section that includes over 1,000 articles about CFS/ME.*

## NEEDS

3160 Erie Boulevard East

DeWitt, NY 13214

Phone: (800) 634-1380

Website: <http://www.needs.com/>

*NEEDS (Nutritional Ecological Environmental Delivery System) is virtually an institution among mail-order resources. NEEDS maintains a huge selection of brand-name vitamins, supplements, herbs, Bach remedies, and glandular preparations at a discount.*

## Integrative Therapeutics

Customer Service Department

825 Challenger Drive

Green Bay, WI 54311

Phone: (800) 931-1709.

Website: <http://www.integrativeinc.com/>

*High quality supplements for GI support.*

## TransPacific Herbal Products

8499 S. Tamiami Trail #274

Sarasota, FL 34238

Phone Orders: (800) 336-9636

Questions: (941) 966-9886

Website: <http://www.transpacificherbalproducts.com/>

*Chinese herbs for sinus infections, allergies, yeast control, blood sugar, PMS, arthritis, flu and colds, alertness, eyes, circulation, herpes, headaches, immune system, hair loss, liver function, and more.*

## Wellness Health & Pharmaceuticals

3401 Independence Drive

Suite 231

Birmingham, AL 35209

Toll Free: 800) 227-2627

Website: <http://wellnesshealth.com/>

*Compounding pharmacy: glutathione, Armour thyroid, bioidentical hormones. Also OTC National brands, including Allergy Research Group, Kal, Montana Naturals, Nature's Way, Natrol, Schiff, Twinlab, Kyolic, Cardiovascular Research Ltd., and Rainbow Light, at a discount.*

Willner Chemists

100 Park Avenue

New York, NY 10017

Toll free phone: (800) 633-1106

Local phone: (212) 682-2817

Website: <http://www.willner.com/>

*Wide selection of specialty supplements, personal care products, herbs, and naturopathic remedies.*

## NONTOXIC HOME AND HEALTH PRODUCTS

AFM Safecoat

Monday - Friday 9:00-5:00 Pacific Time

Phone: Administration: (619) 239-0321 x110

Technical Support: (619) 239-0321 x102

Toll Free Voice Mail: (800) 239-0321

Website: <http://www.afmsafecoat.com/index.php>

*Nontoxic paints, stains, waxes, enamels, adhesives, caulking, carpet guards, mildew control, and other products especially formulated for people with chemical sensitivities.*

Auro Organic Paints – U.K.

AURO U.K.

Cheltenham Road

Bisley

Stroud

Gloucestershire

GL6 7BX

Phone: 01452 772020

Fax: 01452 772024

Email: [sales@auroorganic.co.uk](mailto:sales@auroorganic.co.uk)

Website: <http://www.auro.co.uk/>

*Manufactures paints, varnishes, waxes, glues, cleansers, and polishes made from beeswax, natural oils, chalk, plants, and other natural ingredients.*

The Body Shop

Phone: 1-800-263-9746

Website: <http://www.thebodyshop-usa.com/>

*Cosmetics, lotions, shampoos, soaps, body brushes, and other personal care products. Website includes store locator in U.S. and abroad.*

Earthsake

815 Gilman Street

Berkeley, CA 94710

Toll-free Phone: (877) 268-1026

Local Phone: (510) 868-1797

Fax: (510) 848.5051

Website: <http://www.earthsake.com/natural.html>

*All natural bedding, sleep accessories, bedroom furniture, natural spectrum lighting – everything you need to make your bedroom a safe, comfortable environment.*

Janice's

Phone Orders: 1-800-526-4237

Website: <http://janices.com/>

*Organic bedding, sheets, pillows, quilts, blankets, comforters, clothing. Personal care and cleaning products.*

Livos Plant Chemistry

Email: [info@livos.us](mailto:info@livos.us)

Website: <http://www.livos.us/>

*Manufactures paints, oil finishes, shellacs, stains, varnishes, adhesives, thinners, waxes, and polishes made from natural ingredients.*

NEEDS

3160 Erie Boulevard East

DeWitt, NY 13214

Phone: (800) 634-1380

Website: <http://www.needs.com/>

*Large selection of cosmetics, household products, paints, air purifiers, water filters, and other products for people with chemical sensitivities. No order is too small.*

The Old Fashioned Milk Paint Company

436 Main Street

Groton, MA 01450-0222

Phone: (978) 448-6336

Fax: (978) 448-2754

Website: <http://www.milkpaint.com/>

*Manufacturing milk paint from milk protein, lime clay, and earth pigments since 1974. Products contain no lead, chemical preservatives, fungicides, or petrochemicals (available in 20 colors).*

Seventh Generation

60 Lake Street

Burlington, VT 05401

Toll free: 1-800-456-1191

Local: 1-802-658-3773

Website: <http://www.seventhgeneration.com/>

*Biodegradable soaps, natural shoe polishes, water filters, natural shampoos, and personal care products.*

NEW AGE

Sounds True

413 S. Arthur Avenue

Louisville, CO 80027

Toll-free telephone, U.S. only: 800-333-9185

Local telephone: 303-665-3151

Website: <http://www.soundstrue.com/shop/Welcome.do>

*Self-help, psychology, meditation, inspirational, alternative health, and music with Deepak Chopra, Thich Nhat Hanh, Desmond Tutu, Ram Dass, Sogyal Rinpoche, and other spiritual luminaries. Over 500 CDs and instructional DVDs.*

## BIBLIOGRAPHY

*Due to the ephemeral nature of online sources, only print publications are included in this bibliography. Online sources are posted at the end of individual entries. Books on CFS/ME can be found in Appendix A: Resources.*

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