Traumatic Brain Injury, Panhypopituitarism and Hormonal Evaluations as a Standard of Care

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Las Vegas, Nevada
May, 4 2018

Objectives

- Epidemiology of Traumatic Brain Injuries
- What are the Signs and Symptoms and Long Term Consequences of Traumatic Brain Injuries
- Review the Diagnosis and “Traditional” Approaches to Treating TBI
- What is the Effect of TBI on Hormonal Homeostasis
- Hormonal Deficiencies as a Result of Traumatic Brain Injury.
- The Laboratory of TBI
- Treatment Strategies for TBI
- Case Studies

Epidemiology of Traumatic Brain Injuries

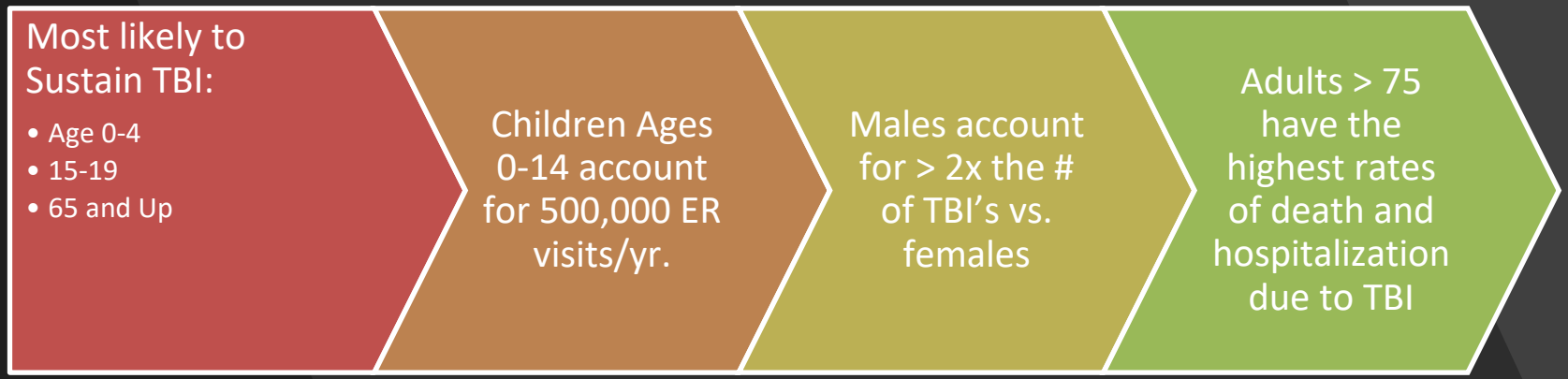
1.7 Million Sustai

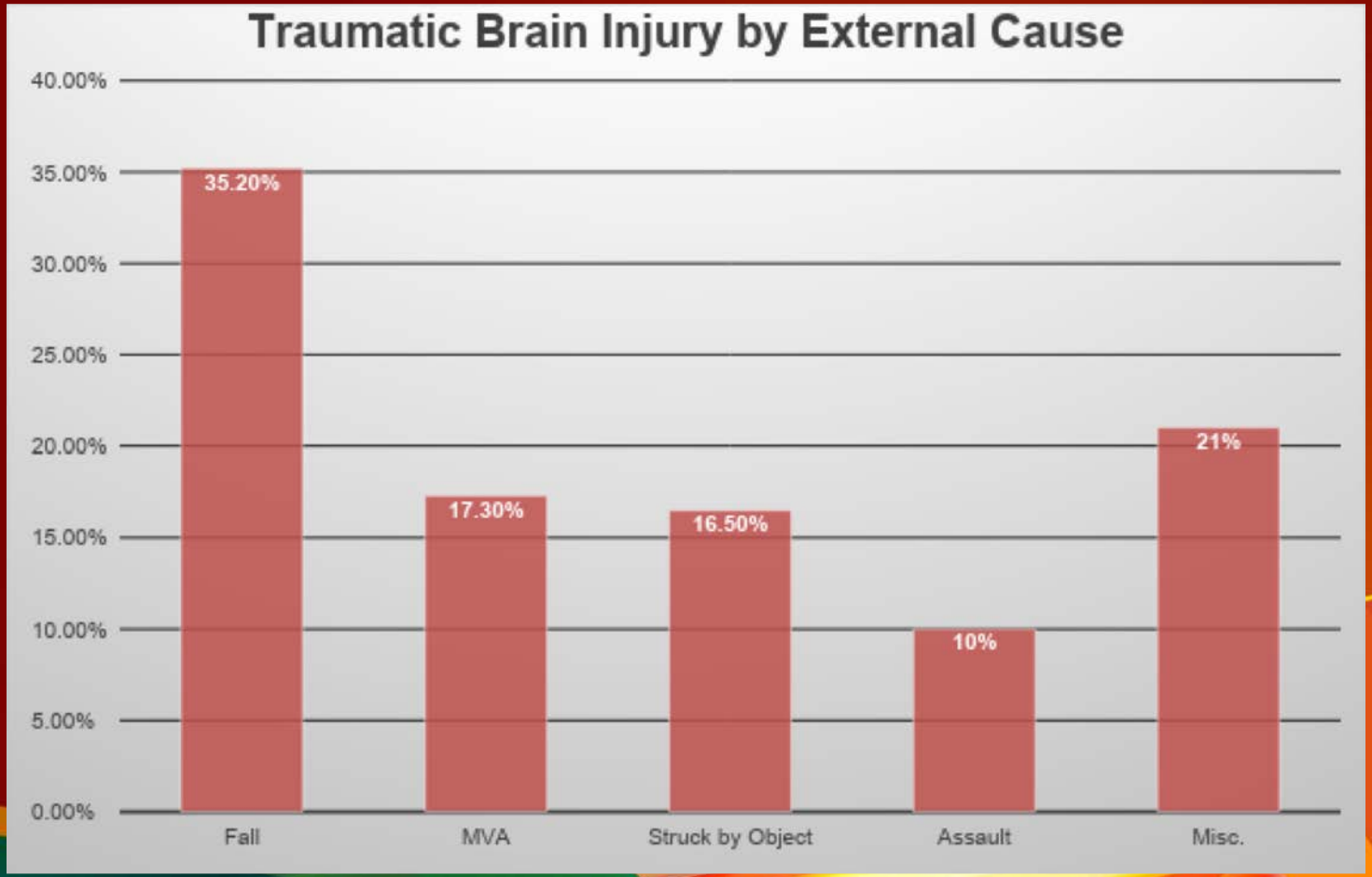
- 52,000 Die
- 275 K Hospitalizations
- 1.365 Million ER Visits
- 10 Million Undiagnosed or Underdiagnosed
- Symptoms Due to Head Trauma (CDC)

Epidemiology of Traumatic Brain Injuries

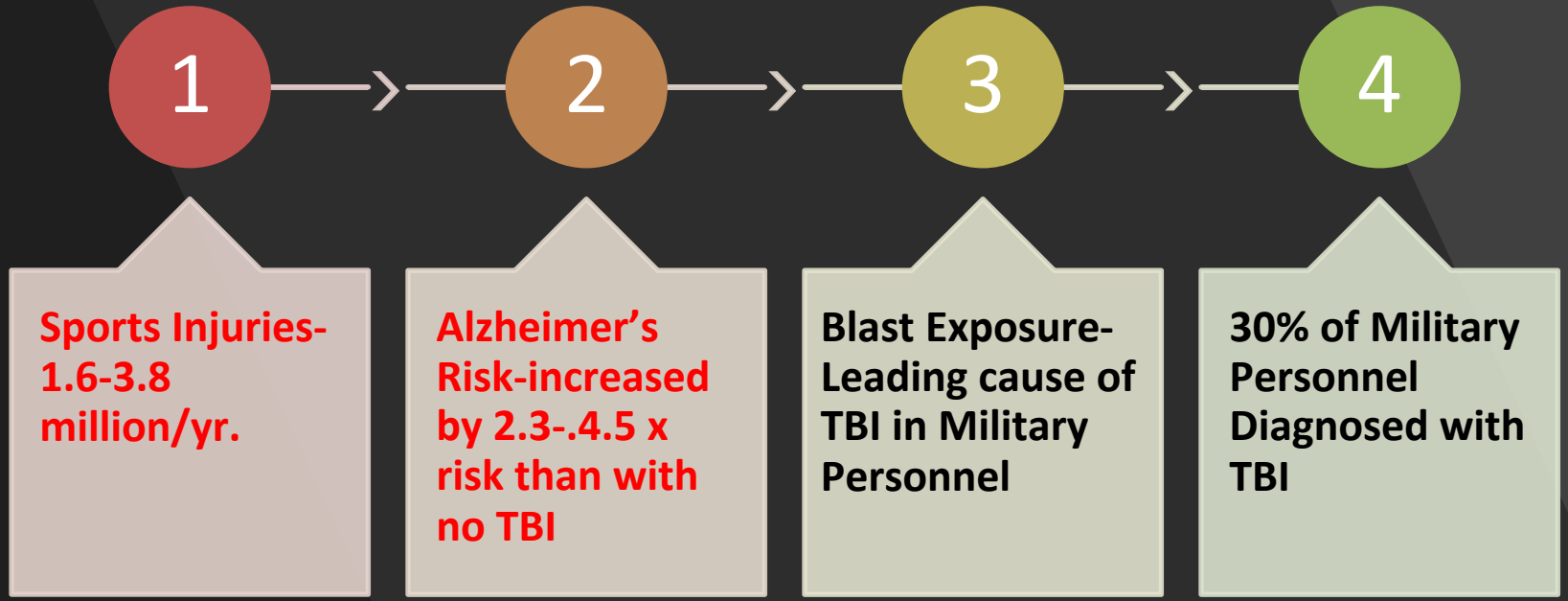
- 30% of injury related death is TBI
- 75% of TBI's are considered "mild"
- TBI results in $60 Billion/yr Lost Productivity

Epidemiology of Traumatic Brain Injuries




Traumatic Brain Injury by External Cause
40.00%
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
35.20%
17.30%
16.50%
10%
21%
Fall
MVA
Struck by Object
Assault
Misc.

TBI Demographics



Department of Defense

- 2000-2011
  - 339, 046 cases of mild TBI Diagnosed
  - Represents 4.2% of entire armed forces of the US

TBI Demographic Tidbits

- 2/3 TBI Survivors Live Normal Life Span
  - Recovery requires 5-10 years of therapy
- Pt. does not need of consciousness of strike head for diagnosis of TBI
- Severity of Injury Does Not Predict Severity of Sequelae
- TBI patient is 3x more likely to suffer a second TBI and 8x more likely to suffer a third episode

Olivia G.

CC: 17 y/o female w hx of concussion Hit in face w Volleyball No LOC. Was mumbling, disoriented in ER for 35 minutes then head "cleared."

% Headache, nausea, blurred vision,"feels slow"

PH

- **(L70.9) Acne, unspecified**
- **Menses painful. Regular**

PE: General: Normotensive, in no acute distress.

Eyes: PERRLA, EOMI full, conjunctiva clear, fundus WNL
Neuro: Physiological, no localizing findings.

Skin: Mild acne.

CT Scan in ER: WNL

Neurology: Analgesics. RTC if Neuro S/S Occur

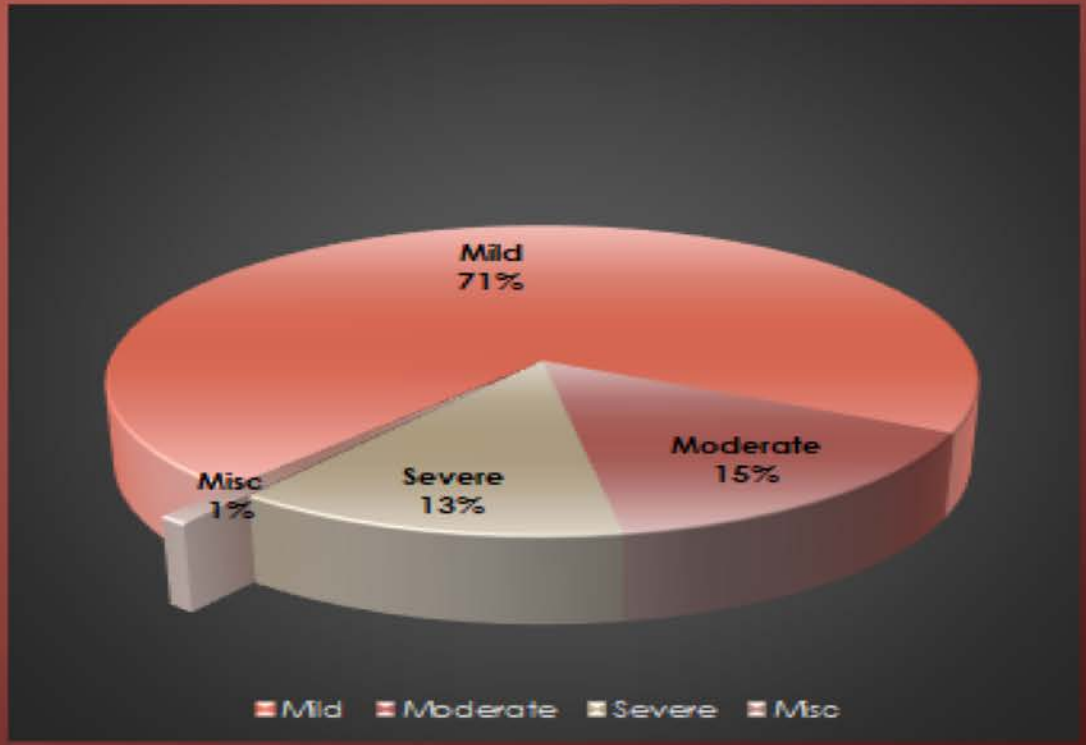
Severity of TBI

Concussions (36%)

Contusions (32%)

Skull Fractures (12%)

Brain hemorrhages (13%)



Repetitive Head Injury

- **NFL Study in 2006- Former players b ages 30-49 experience 19 times the incidence of Alzheimer's Dx., Dementia or other memory related issues Vs. same age general population**

Schwartz, A.; N.Y. Times, September 2009

- **20-33% of veterans returning from Middle East are diagnosed with PTSD (410,000 total in 2012 @ VA)**

Nation, April 2013

- **22 Deaths/Day from Suicide from 1999-2010**

Reuters, US Military Veteran Suicides Rise. One Dies Every 65 Minutes, 2/1/2013

Repetitive Head Injury

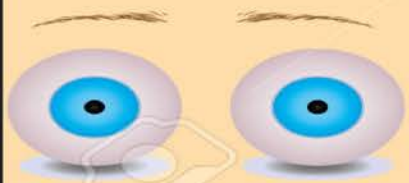
- 1 Million Returning Veterans Incarcerated

- 80-85% TBI Pts. Experience No Immediate Symptoms

Physical Diagnosis:

Glascow Coma Scale

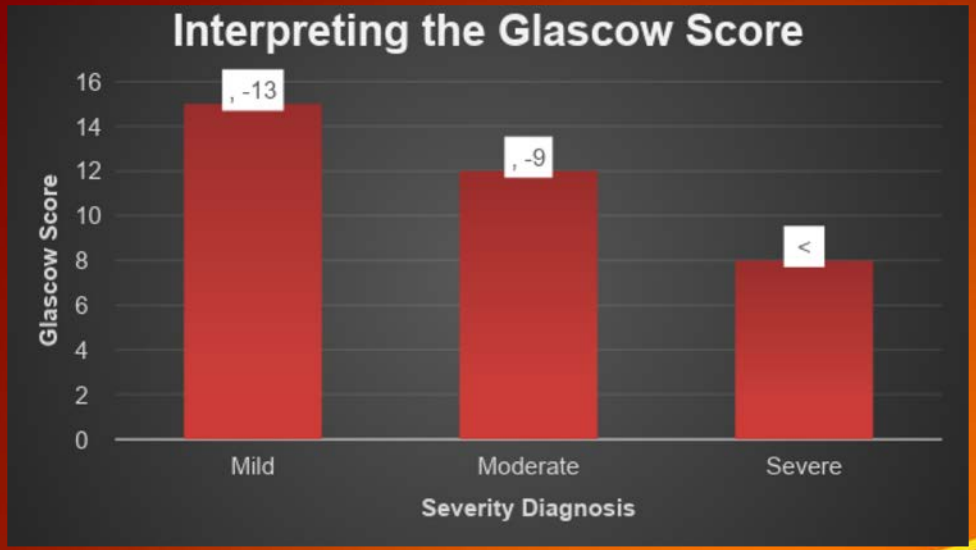
Glasgow Coma Scale

Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

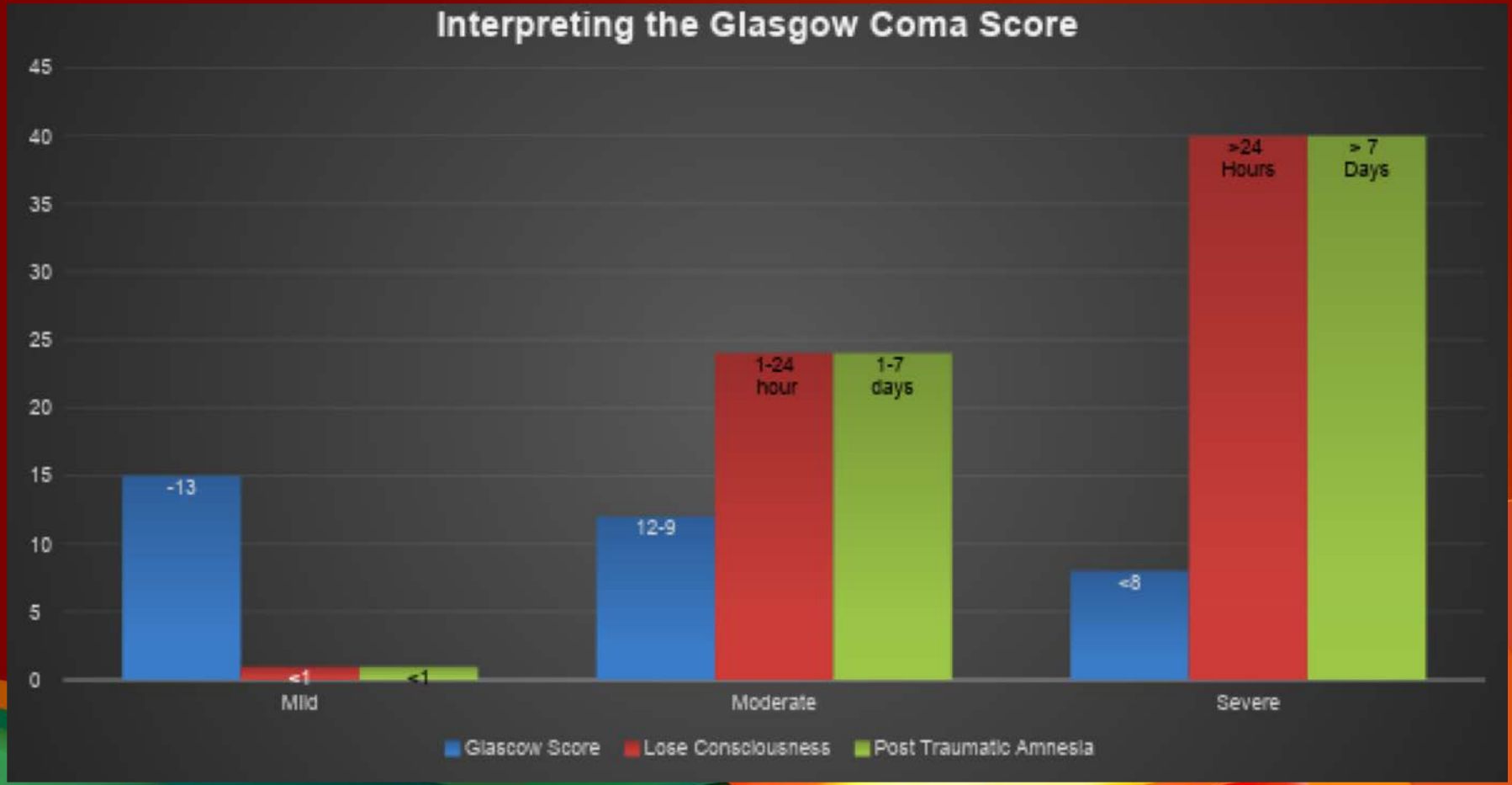
Total Score

Best score - 15
Comatosed - ⩽8
Unresponsive - 3

Interpreting the Glasgow Coma Score



- ***Many seemingly innocuous head injuries, do not manifest themselves weeks, months or even years after the fact.***


Interpreting the Glasgow Coma Score
45
40
35
30
25
20
15
10
5
0
-13
<1
<1
12-9
1-24 hour
1-7 days
<8
>24 Hours
> 7 Days
Mild
Moderate
Severe
Glascow Score
Lose Consciousness
Post Traumatic Amnesia

Olivia G.

17 y/o female w hx of concussion Hit in face w Volleyball

21 days post injury: % blurred vision, difficulty reading,

% fatigue but cannot sleep, is easily agitated, less active than normal and is irritable. (This is new behavior.)

Glascow Score: 14

PE: General: Normotensive, Clearly agitated. Appears not to comprehend questions immediately, then lashes out at mother when prompted to answer.

Exam: Normotensive, P 92, R 20, PO2 96

Visual Acuity LE 20/40, RE 20/50 Combine 20/40

Plan: Refused Benzos, Antidepressants-Hydroxyzine

Battlefield Acupuncture

Refer Back to Neuro, Refer to Ophthalmology

Symptoms of TBI

- Unconsciousness
- Inability To Remember The Cause of The Injury
- Confusion and Disorientation
- Difficulty Remembering New Information
- Headache and Dizziness
- Blurry Vision
- Nausea and Vomiting
- Ringing in the Ears
- Trouble Speaking Coherently
- Changes in Emotions or Sleep Patterns

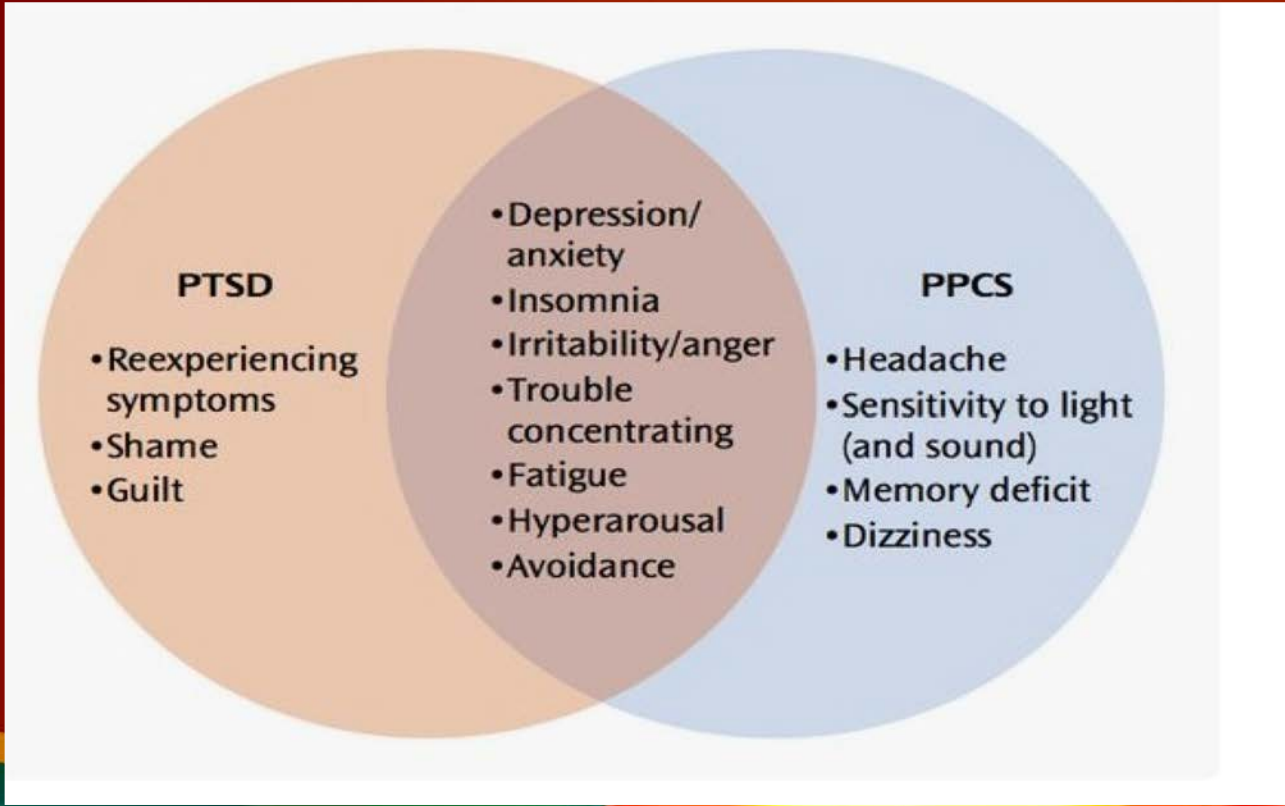
Symptoms of TBI

- Excessive sleepiness
- Inattention
- Difficulty concentrating
- Impaired memory
- An inability to learn new things
- Faulty judgment
- Slowed thinking
- Depression
- Irritability
- Emotional outbursts
- Disturbed sleep
- Diminished libido
- Difficulty switching between two tasks

TBI and PTSD
What's the Difference?

- **PTSD**
  - A Severe Anxiety Disorder that Develops Following Exposure to Extreme *Psychological* Trauma.
  - Exposure is to an **EXTERNAL** event in which there was a sense of helplessness.

PTSD is 100% Psychological
TBI has a Physical Component



Phases in TBI

- ***Phase I*-**Acute Phase-All traumas, mechanical, biochemical, radiation induced causing mechanical injury to brain

- ***Phase II*-**Secondary sequelae of inflammation causing progressive brain damage leading to psychological and cognitive impairment

An estimated 43.3% of Americans have residual disability 1 year after injury.

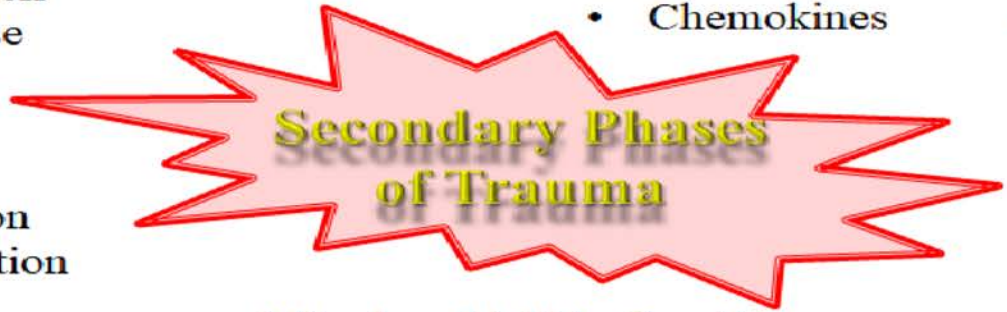
T

Phase II: Oxidative Stress

Oxidative Stress
- Reactive Oxygen
- Reactive Nitrogen
- Lipid Peroxidase

Inflammation
- TH1
- Cytokines
- Chemokines

Disruption of BBB
- Hypoxia
- Ischemia
- Cerebral Edema



Neurosteroids
- Deficiencies
- Enzyme Inhibition
- Retarded production

Mitochondrial Dysfunction
BAX ► AIF, CytoC.

Cell Death
- Necrosis
- Apoptosis
- Cavitation
- Loss of Brain

Excitotoxicity
- Glutamate
- Calcium

Disruption of Receptors
- NMDA, Sigma=1
- GABA-α and -β
- AMPA

Traumatic Brain Injury: Oxidative Stress and Neuroprotection. Antioxidants & Redox Signaling Vol. 00, N0. 00, 2013.
Carolin Cornelius, Vittorio Calabrese, et al

Focal Areas of Damage Extend Phase I into Phase II

- ***Thalamus:*** **(Damage=Coma)**
  - **Regulates Sleep, Wakefulness**
  - **Processes and relays sensory information to cerebral cortex**
  - **Regulates consciousness, arousal, awareness, activity**
- ***Hypothalmus*** **(Regulates Hormone Production)**
  - **Concerned w homeostasis,, autonomic nervous system**
    - **BP, Pulse, Respiratory Rate, Arousal**
  - **Regulates hunger, thirst, pain, pleasure, anger, aggression**
  - **Regulates Beta cell activity in Pancreas**

“Traditional Management of TBI”

- ***Antihypertensives*** - Prevent exacerbation of intracerebral hemorrhage in hypertensive encephalopathy. Eg. Nicardipine, labetolol; CCB help relieve vasospasm in SAH and decrease further damage
- ***Diuretics*** - Mannitol, CAI (Carbonic Anhydrase Inhibitors)
- ***Anticonvulsants***

“Traditional Management of TBI”

- ***Antipyretics***
- ***Antidotes***-

  Vit. K/FFP for warfarin overdose

  Protamine for heparin overdose

- ***Antacids***- prophylaxis for Cushing’s gastric ulcer
- ***Glucocorticoids***-reduces head and neck pain caused irritative effect of the subarachnoid blood.

"Traditional Management of TBI"

- ***Anti-Anxiety Agents*** may lessen feelings of uncertainty, nervousness, and fear.
- ***Anti-Coagulants*** may be used to prevent blood clots.
- ***Anti-Depressants*** may be used to treat symptoms of depression.
- ***Anti-Psychotics*** may be used to target psychotic symptoms of combativeness, hostility, hallucinations, and sleep disorders.

“Traditional Management of TBI”

- ***Muscle Relaxants*** may be used to reduce muscle spasms or spasticity.
- ***Sedative-Hypnotic Agents*** may be used to induce sleep or depress the central nervous system in areas of mental and physical response, awareness, sleep, and pain.
- ***Stimulants*** may be used to increase levels of alertness and attention.

What's Missing in "Traditional" Management of TBI

- The "Holy" Grail
- The Drug or Pharmaceutical Agent that will "Cure" the S/S of TBI
- Dozens and Dozens of protocols looking to show a minimal 10% improvement in clinical symptoms have all failed

Olivia G.-45 Days Post TBI

Symptoms consistent w Neuroinflammation Leading to Brain Hormone Disruption

Difficulty reading

Fatigue worsening

"Depressed"

Easily provoked, hypersensitive.

Cries easily.

Sent home from school for disruptive behavior.

Prisim lenses prescribed

"I hate them."

PE: General: Normotensive

Appears subdued.

Plan: Rx by Psychiatry, Rx: Mirtazapine 30 mg. 1 @ bedtime

What are Long Term Sequelae of TBI

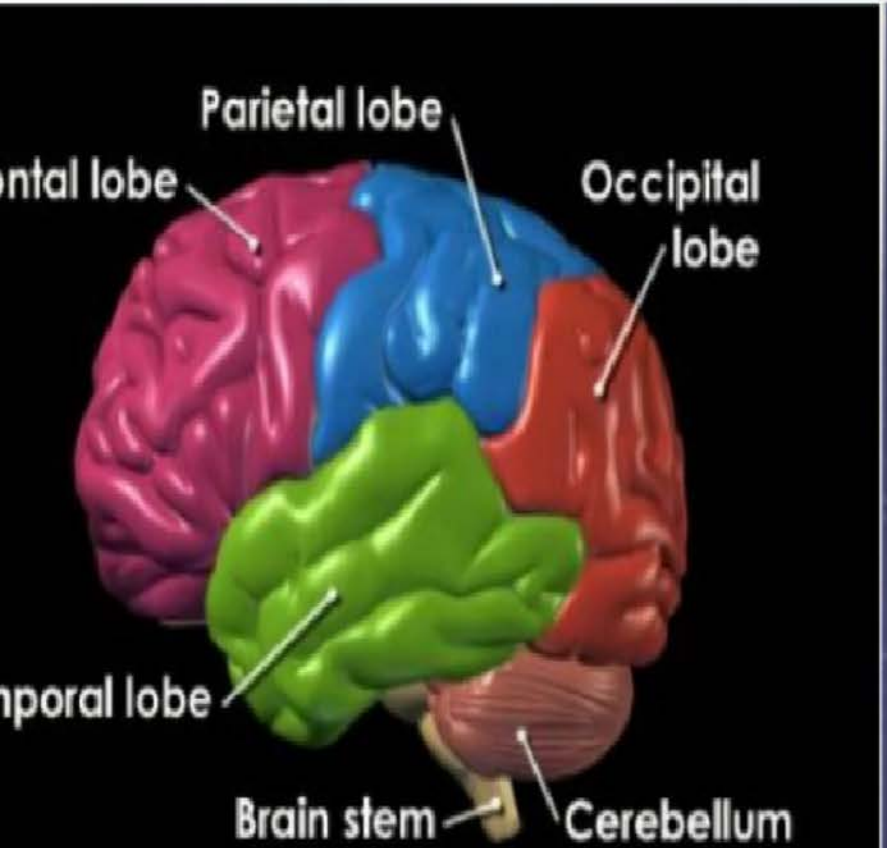
Axis I	48.3%
Major Depression	26.7%
Substance Abuse	11.7%
Phobias	8.3%
Panic Disorders	8.3%
Paranoia	8.3%

Koponen, S., et al.; Axis I and II Psychiatric Disorders After TBI:a 30 year follow up study; Journal of Psychiatry, 2002; 159(8)21

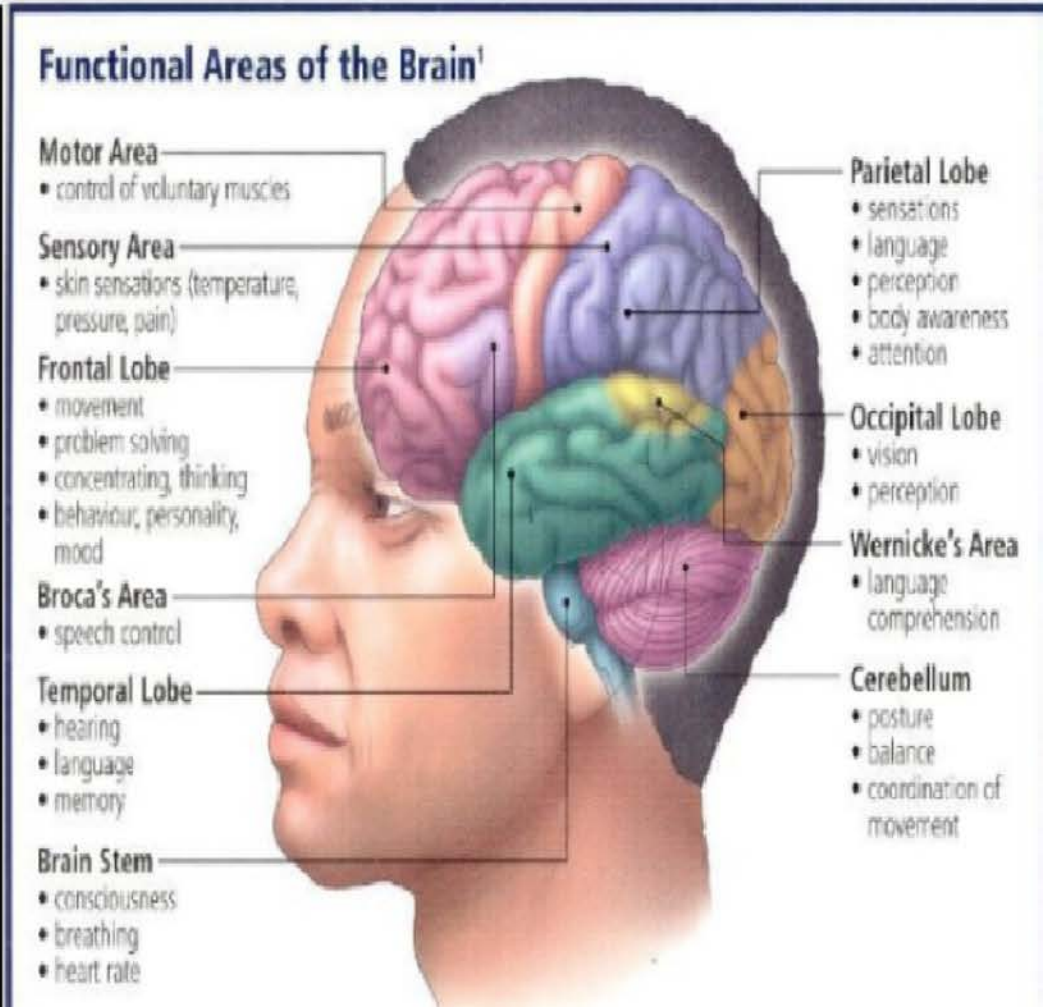
Axis II Psychopathology in TBI

Borderline Personality Disorder	34%
Obsessive-Compulsive Syndrome	27%
Paranoia	26%
Avoidance	26%
Antisocial Personality	21%

Hibbard, M., Bogdany, J.,Uysal, S., et. al.; Axis II Psychopathology in Individuals with TBI; BRAIN INJURY; 2000, Vol. 14, No. 1, Pages 45-61



Functional Areas of the Brain[1]



Functional Disorders in the Brain

- ***Frontal Lobe Symptoms***
  - **Mood Disruption**
  - **Personality Changes**
  - Paralysis
  - Sequencing
  - Perseveration
  - Inability to focus on a task
- ***Temporal Lobe***
  - **Short and long term memory Loss**
  - **Altered libido, sexual behavior**
  - **Increased aggression**
  - Persistent talking (Rt. Lobe injury)
  - Facial recognition
  - Wernicke's aphasia
  - Difficulty naming objects

Functional Disorders in the Brain

- **Parietal Lobe Symptoms**
  - ***Math, Reading Difficulty***
  - ***Unable to Focus VIsual Attention***
  - **Eye, Hand Coordination Difficulty**
  - **Unable to do 2 things at once**
  - Cannot name or draw objects
  - Agraphia
  - Lack of self awareness
  - **Can't distinguish rt. From left**
- **Occipital Lobe**
  - **Visual field cuts**
  - **Cannot locate objects**
  - Color difficulty
  - Hallucinations
  - Visual hallucinations
  - Inability to recognize words
  - Difficulty reading and writing

Functional Disorders in the Brain

- Cerebellum
  - *Tremors*
  - *Slurred Speech*
  - *Fine movement coordination*
  - *Walking ability*
  - Vertigo
  - Unable to reach out for objects
- Brain Stem
  - *Sleep*
  - *Balance and Movement*
  - *Swallowing*
  - *Vertigo*
  - Organization/perception
  - Balance and Movement
  - Insomnia
  - Decreased respiratory capacity

Limbic System

Structures

Cerebrum

Diencephalon

Midbrain,

Hippocampus

Amygdalae

Anterior thalamic nuclei

Septum, Limbic cortex

Fornix

Responsibility:

Long-term memories

Emotions

Motivation.

Cognition

Behavior

.

Limbic System

Limbic dysfunction and (HPA) axis dysregulation are key features of Affective Disorders.

Affective disorders are *mood disorders*. The main types of *affective disorders* are **depression, bipolar disorder, and anxiety disorder**

Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 1201 – 1213. James P. Herman, Michelle M. Ostrander, Nancy K. Mueller, Helmer Figueiredo . Dept of Psychiatry, Psychiatry North, ML 0506 2170 East Galbraith Road, University of Cincinnati College of Medicine, Cincinnati, OH, Dept of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine, Reading, OH

Olivia G.-Which Area of Brain is Affected?

90 days post injury:

Confessed to suicidal thoughts

% extreme fatigue, wakes up tired. Drinking Stimulants to stay awake

Grades deteriorating in school

c/o focusing issues when reading

Sent home from school for "poor hygiene"

Suspended for 3 days due to fighting

Gained twelve pounds.

School has written parents she is candidate for "special ed" status

Last 2 menstrual cycles irregular and late.

Went to P.P. with STD-Parents Unaware

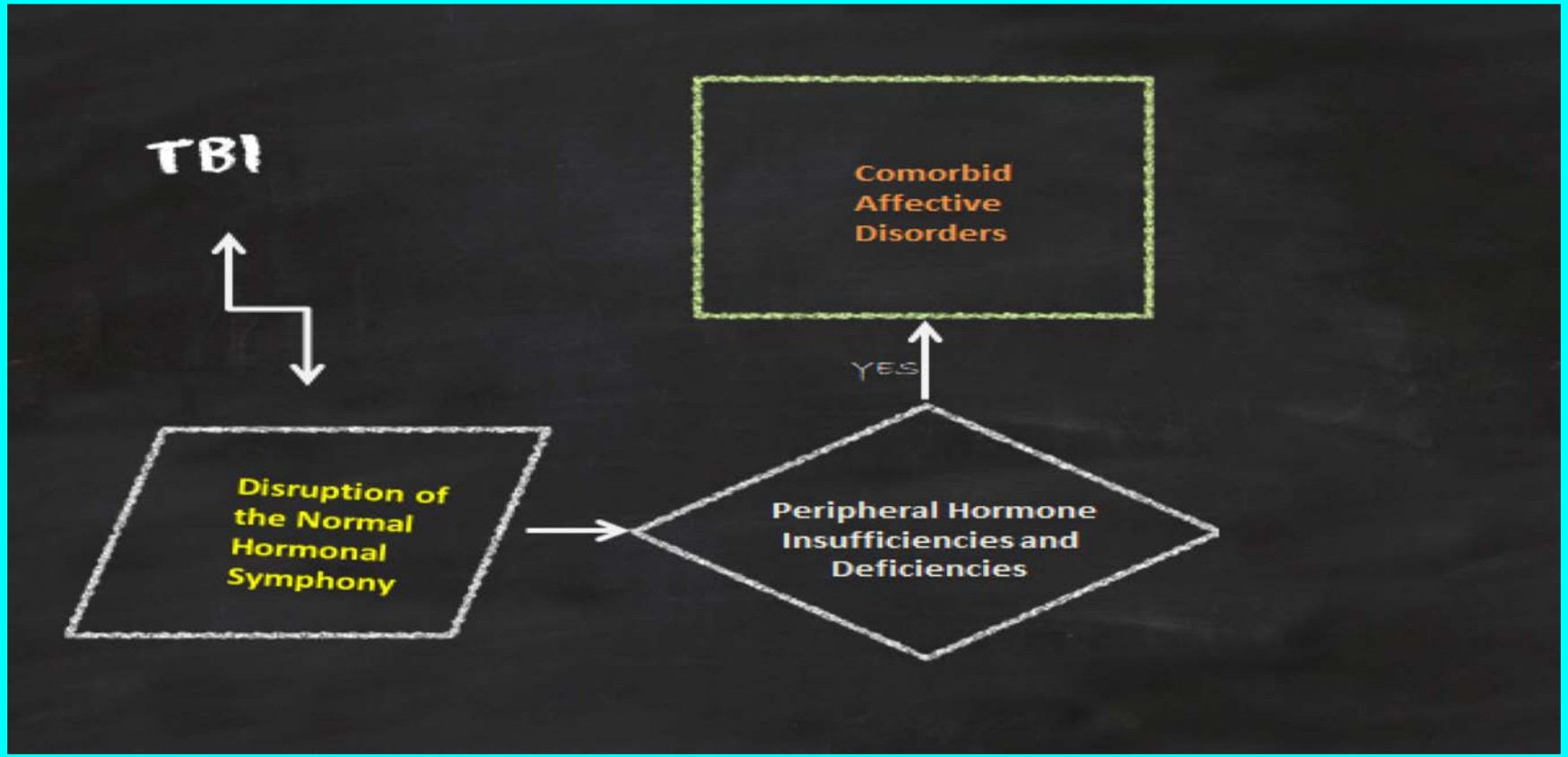
PE: Very depressed looking. Does not make eye contact. Slovenly dressed.

Plan: Rx by Psychiatry

Rx: Added Venlafaxine 75 mg to Mirtazapine 30 mg. 1 @ hs

Recommended inpatient hospitalization with parents.

The Missing Link?



The Breakthrough-Neurosteroids

Neuroactive Steroids-Traditional Concept of Hormones produced in Peripheral glands

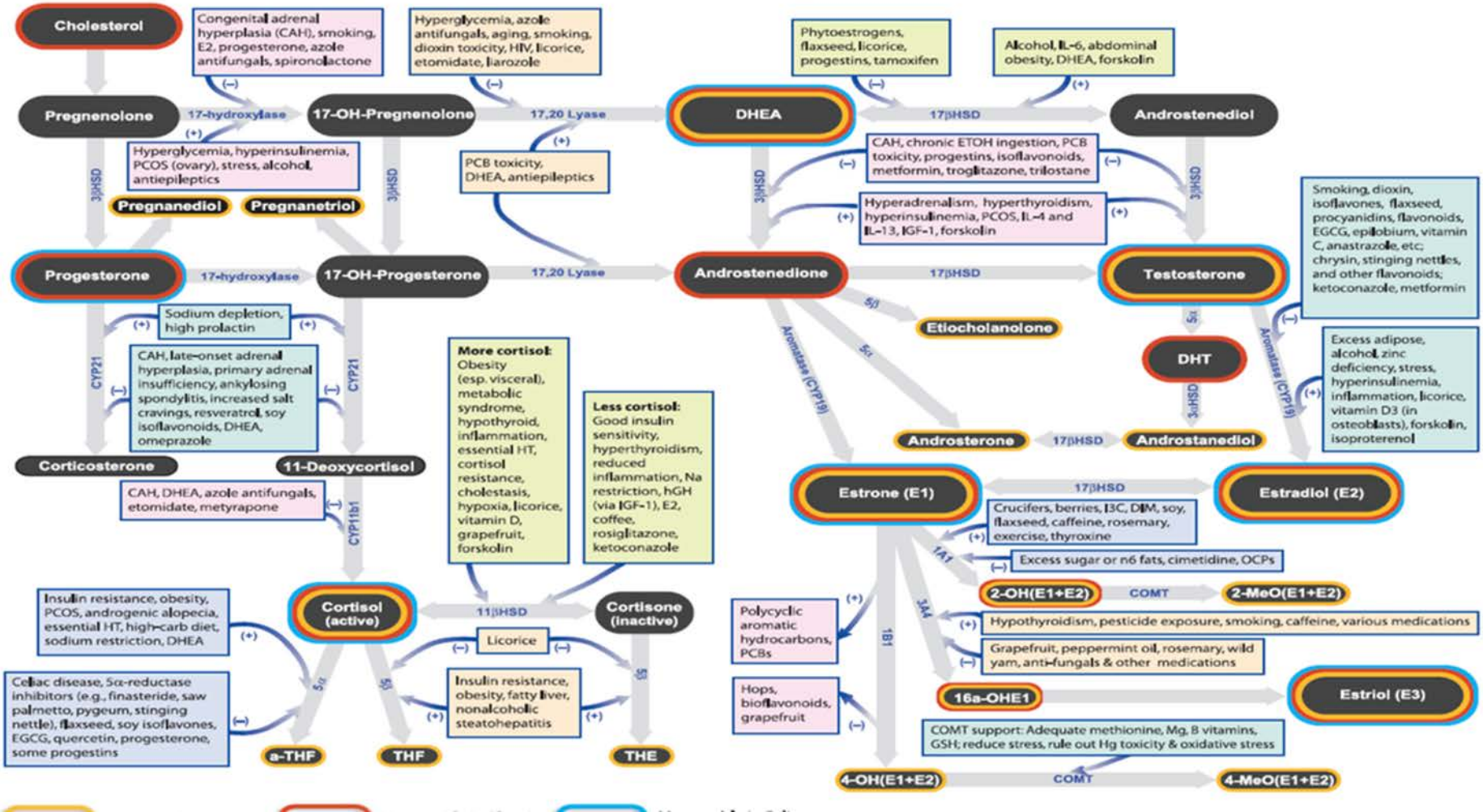
Neurosteroids-Hormones regionally in the manufactured in the brain.

Recently discovered phenomena accounts for the high degree of pathology associated with TBI

- **Follows same track as the *Steroidogenic Pathway.***
- ***Large role in Moods Disorder***

Baulieu, EE., Schumacher, R.," Neurosteroids: Beginning of the Story," Int. Review of Neurobiology, Paris, France; 2003;46:1

Steroidogenic Pathways



Intracranially Produced Hormones: Etiology of Hormone Deficiency in TBI

- **Progesterone, allo progesterone, and DHEA protect neurons in TBI and cerebrovascular events.**
  - **Protects nerves from oxidative stress**
  - **Promotes neuroregeneration**
  - **Regenerates myelin**
  - **Reduces inflammatory cytokines**
  - **Reduces interleukins**
- **Modulates neuronal and behavioral functions.**
- **Anxiolytic, antidepressant, anti-aggressive, anti-stress, anti-convulsant**

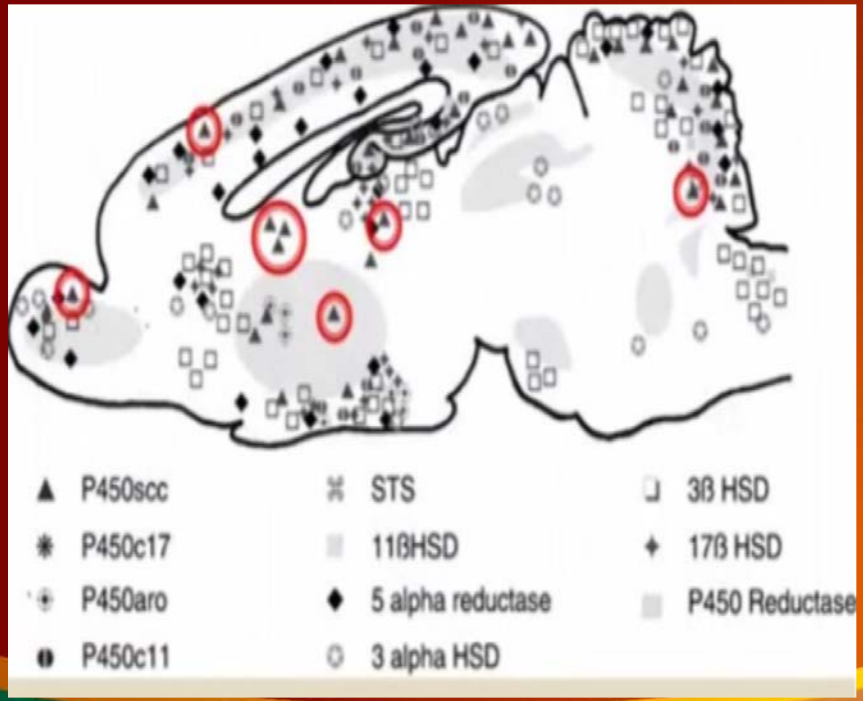
- **Alzheimer's and TBI Victims both exhibit a deficiency in allopregnanolone in their frontal lobes**

Neuro (Centrally Produced) Steroids

- Regulate Neurotransmitters
- Act as “Micro-Hormones” fine tuning the “Macro-Hormones” activity in brain
- Failure of Neurosteroid System=Erratic Brain Transmissions
- Expressed as depression, suicide, anxiety, panic attacks, phobia, psychosis

Baulieu, EE., Schumacher, R.,” Neurosteroids: Beginning of the Story,” Int. Review of Neurobiology, Paris, France; 2003;46:1

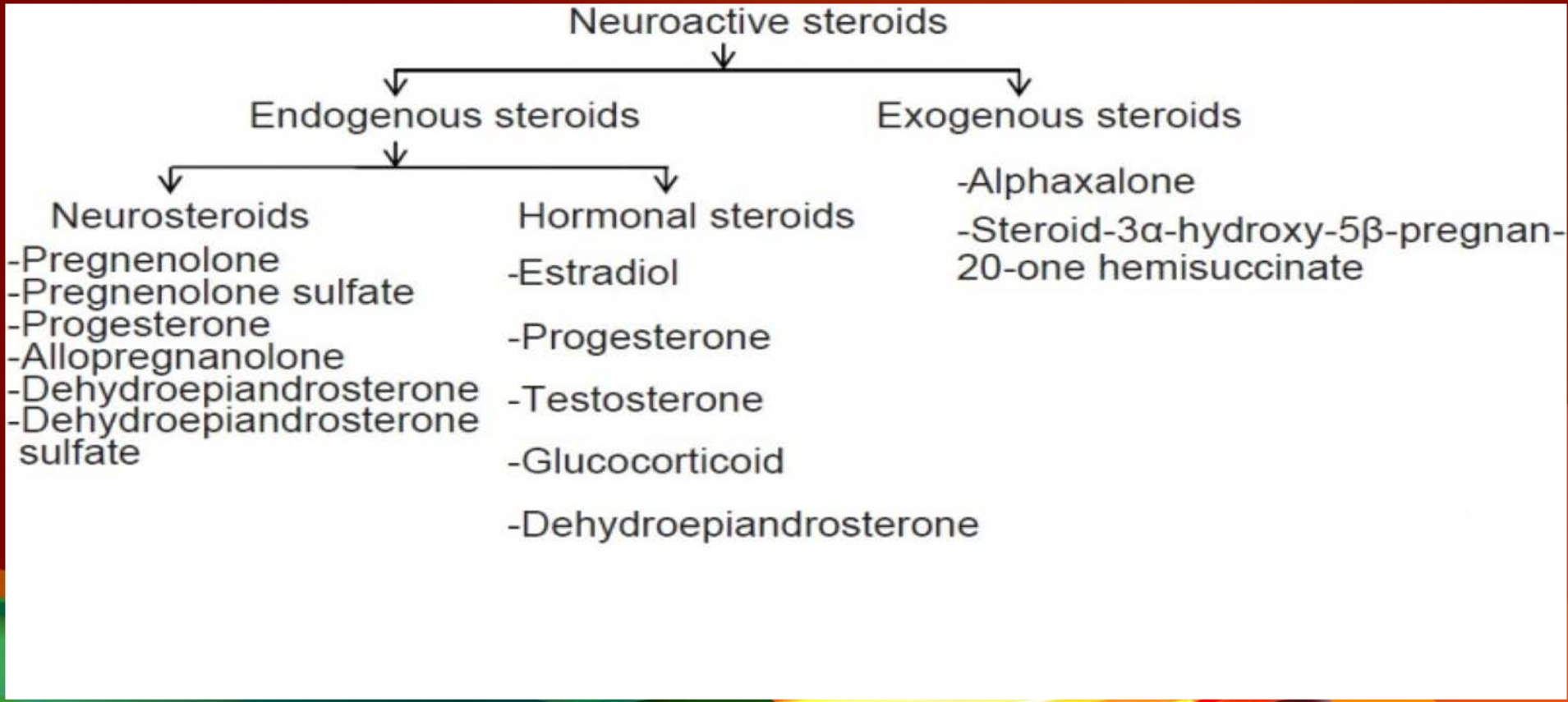
Enzymes Produced in the Frontal Lobe=Direct Match to Those in Periphery



Peripheral Enzymes

17 β -hydroxysteroid dehydrogenase	Aromatase	11β hydroxysteroid dehydrogenase 1&2	Cytochrome 3A4
Cytochrome P450 scc	18-hydroxy dehydrogenase	17α-hydroxylase	Cytochrome 1A1
18-hydroxylase	21-hydroxylase	11 β - hydroxylase	Cytochrome 1B1
17,20 lyase	3 β -hydroxysteroid	Catechol-O-Methyl-	Sulfatase (-SO4)

Centrally Generated Neuroactive Steroids



Psychopathology and Neuroactive Steroids in TBI

- **Post TBI depression, stress and memory processes are directly related to behavioral aspects of NAS hormones.**

- **Intact and /or disrupted neuroactive steroid production has a direct effect on behavior.**

Dubeovsky, B., Steroids, Neuroactive steroids, and Neurosteroids Psychopathology; Pro Neuropsychology Biol Psychiatry 2005 Feb; 29 (2): 169-192

Psychopathology and Neuroactive Steroids in TBI

- *High doses of antianxiety agents and antidepressants suppress hormone production in the brain.*
- LH, FSH, GH most commonly affected
- Basic minerals are similarly overproduced
  - Zinc/Copper ratio becomes unbalanced with an associated accumulation of aluminum in the brain.
    - i.e. Inc. Aluminum=Dec. zinc
    - Most Alzheimer's, Cancers, and Chronic Infections result in a zinc deficiency
    - Zinc deficiency preference the production of Beta amyloid deposits in the brain
  - RX Zinc 30-60 mg. 1-2/d
    - Natural Estrogen Blocker (Blocks conversion of T to E2

Longone, et. al., Neurosteroids as neuromodulators in the treatment of anxiety disorders. Front. Endocrinol. 2011

Psychopathology and Neuroactive Steroids in TBI

- **Balancing GH, Thyroid Hormone and LH/FSH Axis Hormones in the immediate post trauma (within 48 hours) time frame decreased mortality by 50%.**

- Mortality rates evened out with placebo within 30 days.

Wright, D.W., Randomized Clinical Trial of Progesterone for Acute Brain Injury.; Annals of Emergency Medicine; 2006 07; 932

Olivia G.

Diagnosis: Treatment Resistant Depression

- 180 days post injury:
- Suspended from school. Got into fight with two “former friends.” Olivia had locker lock in hand and punch “friend” fracturing her jaw.
- During suspension failed suicide. Tried to cut her wrists. 30 day involuntary admission to psych hospital.
- Now on 4 Antidepressants, antipsychotic drugs.
- Mirtazapine, Venlafaxine, Haloperidol, and Aripiprazole.
- Has gained 18 Pounds,no menses in last 3 cycles
- Nightly fevers, muscle pain, heart racing, headaches

Parents at “wits end.” Discussed w psychiatry. “Standard of care is to increase # and amount of each drug to maximum dose or side effect tolerance.

TBI vs. Hypopituitarism

TBI

Fatigue (100%)

Depression w Anxiety/Panic (50-77%)

Difficulty Concentrating

Memory impairment

Decreased Libido; Sexual Dysfunction

Insomnia

Faulty Judgement, Slow Thinking

Irritability w emotional outburst

Substance Abuse

http://www.bcftbi.org/about-tbi/behavior.asp

Hypopituitarism

Fatigue, Lethargy

Depression w Panic

Difficulty Concentrating

Memory Impairment

Decreased Libido, Sexual Dysfunction

Insomnia

Faulty Judgement

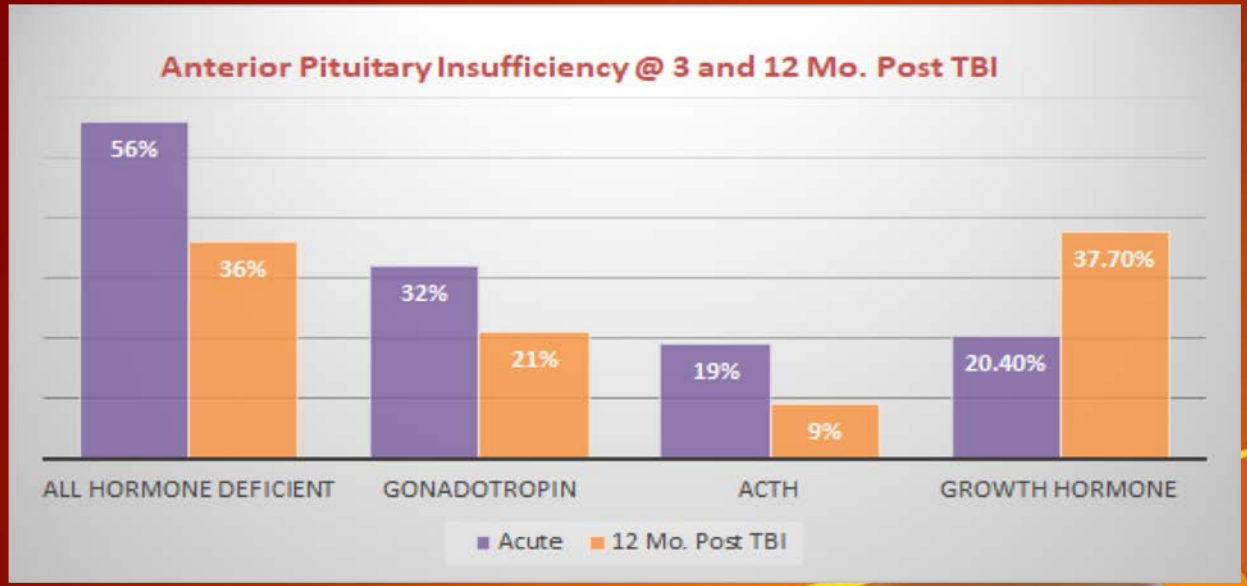
Emotional Outbursts

Substance Abuse

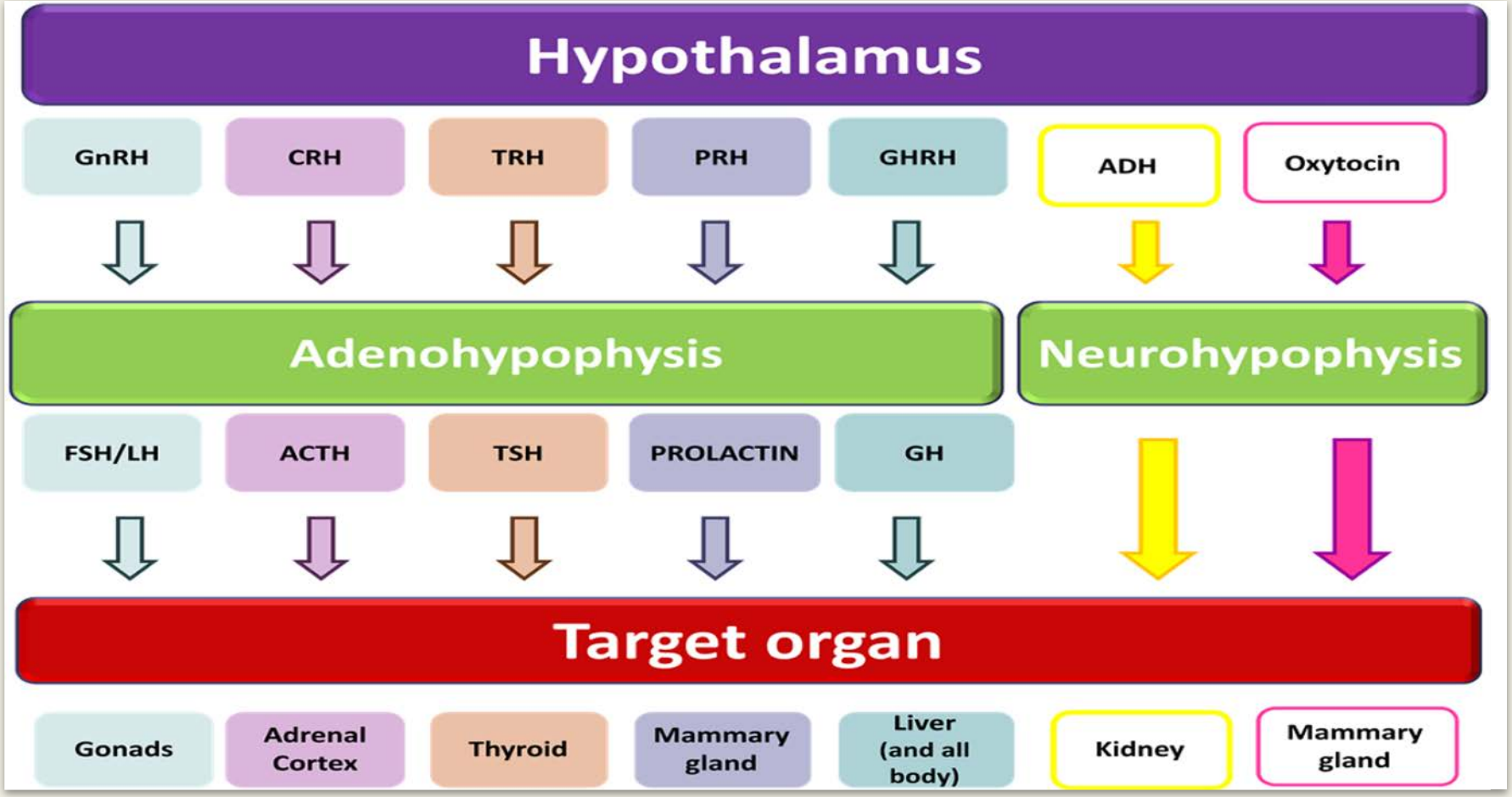
https://www.pituitaryinjuryfoundation.org/about/

⅓ CVA Patients Experience Long Term Hypopituitarism

Bondanelli M1, Ambrosio MR, Carli A, Bergonzoni A, Bertocchi A, Zatelli MC, Ceruti S, Valle D, Basaglia N, degli Uberti EC., **Predictors of pituitary dysfunction in patients surviving ischemic stroke.** J Clin Endocrinol Metab. 2010 Oct;95(10):4660-8. doi: 10.1210/jc.2010-0611. Epub 2010 Jul 21.



Schneider HJ1, Schneider M, Saller B, Petersenn S, Uhr M, Husemann B, von Rosen F, Stalla GK.; **Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury.** Eur J Endocrinol. 2006 Feb;154(2):259-65.


Hypothalamus
GnRH
CRH
TRH
PRH
GHRH
ADH
Oxytocin
Adenohypophysis
Neurohypophysis
FSH/LH
ACTH
TSH
PROLACTIN
GH
Target organ
Gonads
Adrenal Cortex
Thyroid
Mammary gland
Liver (and all body)
Kidney
Mammary gland

Let's Drill Down

• Growth Hormone Deficiency (GHD)

- ***First and most common deficiency***
- **Acute Injury Incidence rate: 20%.**
- **12 month follow up rate increases to 35-40% of survivors.**

1. Aimaretti, G; et al., Hypopituitarism and Growth Hormone Deficiency after TBI. Growth Hormone IGF Res 2004 June 14 Suppl A:S114-7
2. Agha A. Phillips J. Thompson C.J. Hypopituitarism following traumatic brain injury (TBI) Br. J. Neurosurg. 2007;21:210–216.
3. Kelly DF, McArthur DL, Levin H, et al. Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. *J Neurotrauma.* 2006 Jun;23(6):928-42.
4. Leon-Carrion J, Leal-Cerro A, Cabezas FM, et al. Cognitive deterioration due to GH deficiency in patients with traumatic brain injury: a preliminary report. *Brain Inj.* 2007 Jul;21(8):871-5.

Growth Hormone

- TBI with GHD
  - Rapid weight gain
  - Excessive anxiety
  - Depression along
  - Deficits in:
    - Attention
    - Executive Functioning
    - Memory
    - Emotion
    - Cognition
    - Mood Anxiety/Depression
  - Poor overall physical health and quality of life

- GH Replacement
  - Improvements in:
    - Cardiovascular Risk
      - Reduces IL-6, Il-1, cRP, Homocysteine
    - Concentration
    - Memory
    - Depression
    - Anxiety
    - Fatigue
    - Lean body mass
    - Lumbar vertebral bone density
    - 14.4 % decrease in adipose-tissue mass
    - Skin thickness

Growth Hormone Post TBI

GH Deficiency Associated w Cognitive Dysfunction and "Atypical Depression"

Correction of GHD :

- **Tempers:**
  - Intensity of Outbursts
  - Hostility
  - Paranoid Ideation
  - Anxiety, Phobia
  - Somatization
  - Obsessive Compulsive S/S
- **Improves:**
  - Verbal and Non-Verbal Memory
  - Cognition
  - Mental Alertness
  - Work Capacity

GHD Patients = 9 fold ↑ incidence of cardiovascular mortality

Cook, D. Yuen, K, et. al., Medical Guidelines for Clinical Practice for Growth Hormone Use in GHD Adults and Transition Patients. American Academy of Clinical Endocrinologists, 2009

GH Lab Values and Rx.

Lab Values: GH 5.0 ng/ml
IGF-1 200 ng/ml
IGFBP-3 4000 ng/ml

RX:

Injectables: *HGH* 0.8-1.2 IU/day SQ5-7 IU day/wk.
Semorelean w or W/O GNRH 2 or 6 (2 causes nausea, 6 hunger)
Peptide CJC 1295 with DAC 0.5-2.0 mg q. week (Can cause hot flash for 5-15 minutes)

Oral Spray:
HGH Spray (Homeopathic)
Secretropin, Dynotropin

Olivia G.

Diagnosis: Treatment Resistant Depression

Growth Hormone

(Morning Lab Draw)

	Olivia	Median
Growth Hormone	0.6 ng/ml	5 ng/ml
IGF-1	78 ng/ml	> 200 ng/ml
IGFBP3	2950 ng/ml	> 4000 ng/ml

IGF-1 as proxy

IGFBP 3 logarithmic relation to GH Pulse

Estrogen and Quercetin can stimulate IGf BP 3

Psychological Sequelae of TBI

- ***Behavioral Alterations are a primary factor leading to long term disability including:***
  - Employment, Maintaining Social Relationships, and Social Roles
- ***Cognitive sequelae are overshadowed by psychiatric issues including:***
  - Depression, **Suicide Ideation,** Anxiety, Agitation, Anger, Paranoia, Sexual Issues and Drug/Etoh Abuse

Fork,M., Bartels C., Ebert, AD, et.al. Neuropsychological Sequelae of Diffuse Traumatic Brain Injury; Brain Injury, 2005 Feb;19(2):101-8

Psychological Sequelae of TBI

- **Depression, Depression, Depression**
- **Fatigue, Fatigue, Fatigue**

- 50-77% of TBI Patients Experience Depression within 1 year
  - 20% of general population diagnosed w depression
- 44 % suffer from comorbidities
- ***10-30 % Experience Treatment Resistant Depression***

Classic Major Depression Symptoms (Need 5 of 9)

1. Sadness or depressed mood most of day or almost every day
2. Loss of enjoyment of previously pleasurable activity
3. Major weight change (5% in 1 month)
4. Insomnia or excessive sleepiness almost every day
5. Noticeable physical restlessness or feeling rundown
6. Fatigue or energy loss every day
7. Feeling of hopelessness or excessive guilt
8. Concentration and decision making problems
9. Recurring thoughts of death/suicide/suicide plan or attempt

Treatment Resistant Depression

Treatment Resistant Depression=Failed Monotherapy

- Uncontrolled Depression on 1-4 agents
- >3 antidepressants carries a 90% failure rate
- Patients accumulate side effects then are treated with other drugs to counteract
  - I.E. Adderall for concentration and Somnolence

Khalid Saad Al-Harbi; Treatment-resistant depression: therapeutic trends, challenges, and future directions; Patient Prefer Adherence. 2012; 6: 369–388. Published online 2012 May 1. doi: 10.2147/PPA.S29716

CME 1.0

Part 2- Challenges in Managing Treatment-Resistant Depression

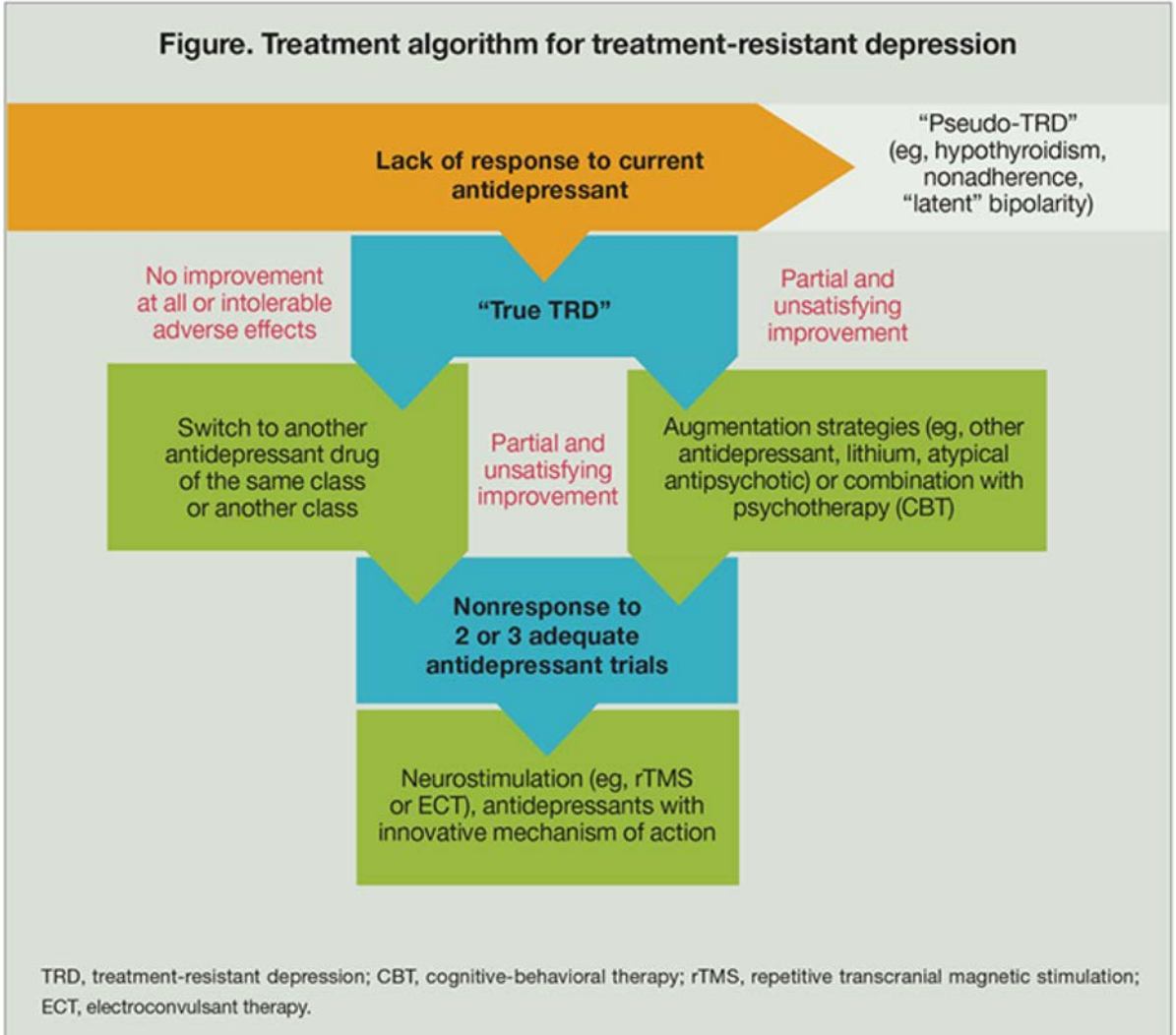
Speakers: Charles B. Nemeroff, MD, PhD and Michael E. Thase, MD

Duration: Approximately 60 minutes

Availability: Friday, June 23, 2017, 9:00 AM
to Saturday, June 23, 2018, 8:59 PM

Treatment Resistant Depression=Failed Monotherapy

https://neuroserieslive.platformqhealth.com/ces/workflow



? Hormonal Deficits

Treatment Resistant Depression:

Deficient in HGH

Thyroid

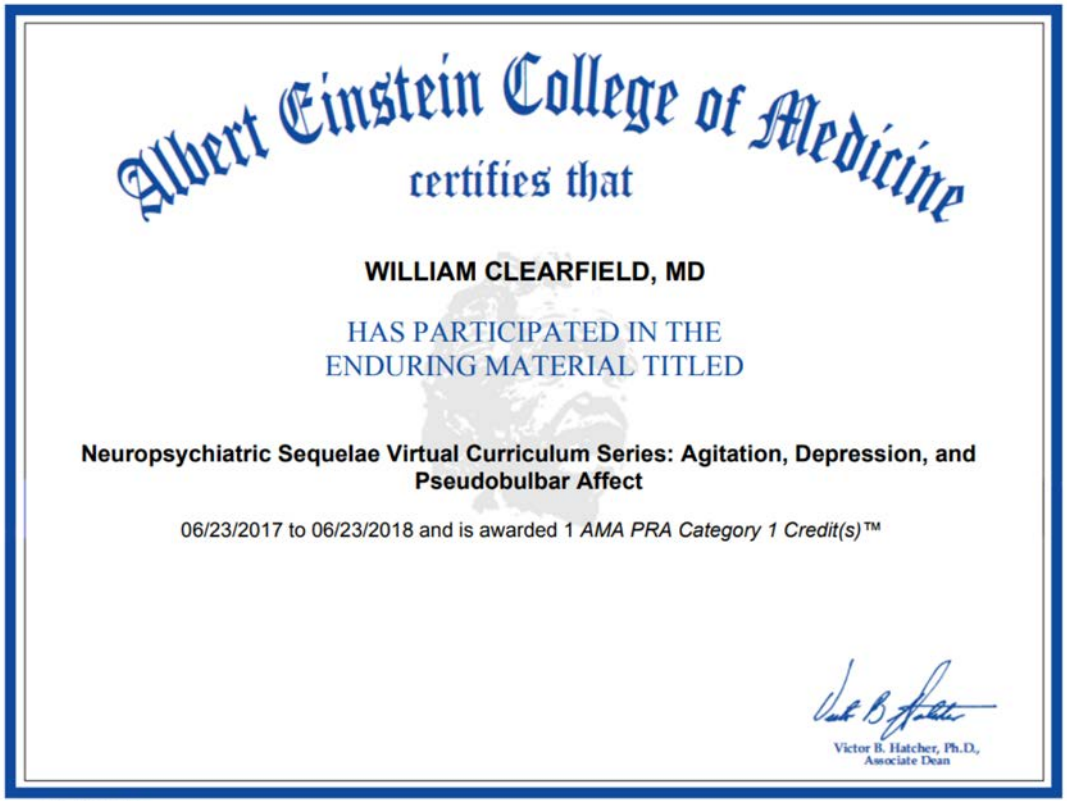
Testosterone

Elevated Cortisol

Treatment Resistant Anxiety

Traditional Rx. of Treatment Resistant Anxiety

1. 2 SSRI's + 1 SNRI + CBT → if no relief
2. Psychiatric Referral → if no relief
3. Evaluate for Comorbidities → if no relief
4. Add Tricyclic Antidepressant + Atypical Antidepressants →
5. Add atypical antipsychotics
    a. Pregabalin
    b. Gabapentin



Albert Einstein College of Medicine

certifies that

WILLIAM CLEARFIELD, MD

HAS PARTICIPATED IN THE
ENDURING MATERIAL TITLED

Neuropsychiatric Sequelae Virtual Curriculum Series: Agitation, Depression, and Pseudobulbar Affect

06/23/2017 to 06/23/2018 and is awarded 1 *AMA PRA Category 1 Credit(s)*™

Victor B. Hatcher, Ph.D.,
Associate Dean

www.mecme.org

Olivia G.

Diagnosis: Treatment Resistant Depression

Etio: Closed Head Injury

S/S: Visual Disturbance

- **Poor Reading Comprehension**
- **Menstrual Irregularities**
- **Hyperarousal**
- **Fatigue**
- **Major Depression**
- **Antisocial Behavior**
- **Suicide Attempt**

Major Depressive Disorder is Most Prevalent Post TBI

- **Growth Hormone Deficiency**

- **Testosterone Deficiency is a Major Cause of Depression**
  - **Anxiety, aggression, Mood Disorder, Arousal, Sexual Dysfunction, Suicidal Ideation**

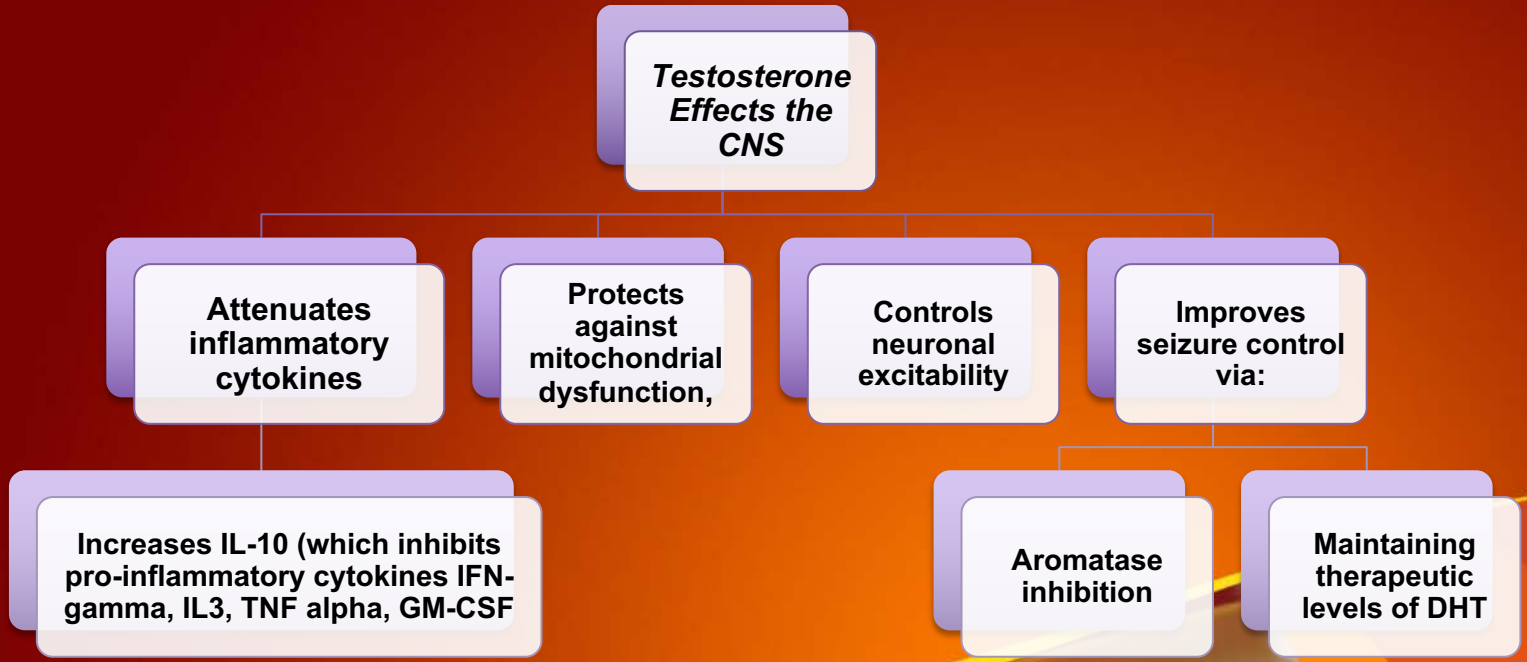
- **Androgen Receptors are Present Throughout the Brain**
  - **Androgens have ongoing effects in mature brain**
  - **Androgens impact cognitive function.**

Craft, S; et. al. Androgen Effects on Cognitive Function, William Brenner Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, Washington, 2007

What Does the Literature Say?

Hormones and Depression	Google Scholar "Hits" 2000-2012	Google Scholar "Hits" 2000-2016	Google Scholar "Hits" 1/2/2017-2/15/2018
Testosterone and Depression	70,400	128,000	8780
Estrogen and Depression	51,000	59,700	11,100
Progesterone and Depression	26,000	29,000	6110
Thyroid and Depression	77,600	123,000	15,500
DHEA and Depression	12,800	16,000	1510
GH and Depression	111,000	153,000	16,800 1/1/18-2/15/18=2310

Testosterone and Depression Post TBI



Reddy DS. Testosterone modulation of seizure susceptibility is =mediated by neurosteroids 3 alpha androstanediol and 17 beta estradiol. Neuroscience.: 2004

Testosterone and Depression Post TBI

Testosterone Effects the CNS

- **Free testosterone in lowest quartile=highest incidence of depression**

Male

- **At Risk: *295* ng/dL Free T *6.0* ng/ml (Median 12-14 ng/ml)**
- **Depression: *147.5* ng/dL Free T *3.0* pg/ml**

Female

- **At Risk: *22* ng/dL (median 44 ng/dL) ; Free T *1.0* ng/dL (median 2-4 ng/dL)**
- **Depression: *11* ng/dL ; Free *0.5* ng/dL**

Olivia G.

Diagnosis: Treatment Resistant Depression

	Olivia	Median
Total Testosterone	12.72 ng/ml	44 ng/ml
Free Testosterone	0.08 ng/ml	2-4 ng/ml
DHEA-S	49.2 ug/dL	235 ug/dL
DHT	4 ng/dL	<30 ng/dL

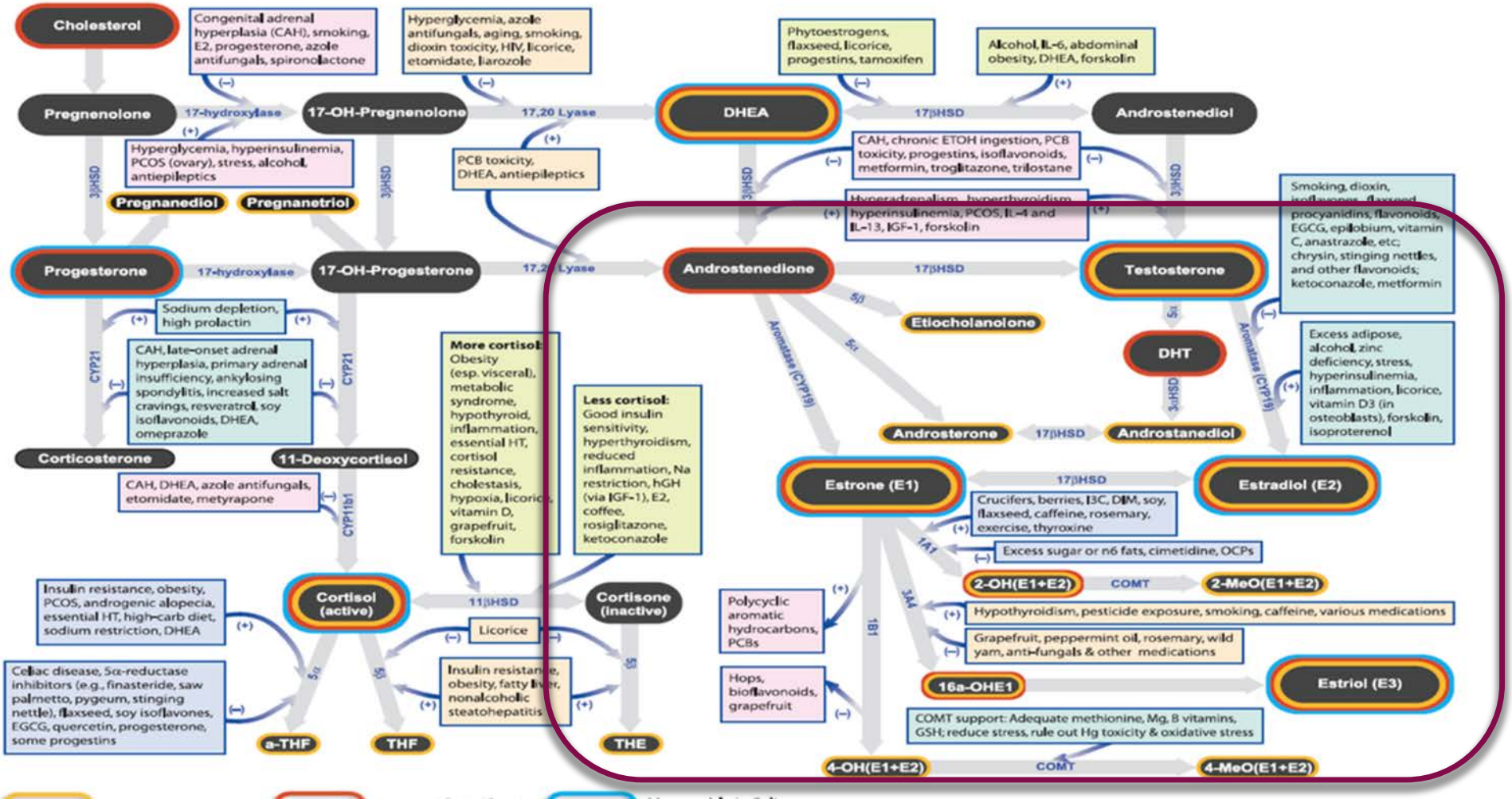
Testosterone and Depression Post TBI

Testosterone decreases pain, anxiety and improves cognitive function by converting to DHT

Modulates Anorexia Nervosa

Testosterone Levels Inversely Proportional to Degree of Depression

Steroidogenic Pathways



The Word on 5 Alpha Reductase is "Goldilocks"

DHT makes androgens (testosterone) more potent •

Activity:

- Metabolizes progesterone into a-Pregnanediol
- Metabolizes cortisol into a-THF (b-metabolites of both through 5β activity)

Upregulated leads to high androgen symptoms:

- Men (thinning hair, prostate issues)
- Women (PCOS, thinning hair, acne, facial hair growth)

Increased enzyme activity:

- High insulin and obesity

Edinger, KL; Frye, CA, *Testosterone's analgesic, anxiolytic and cognitive-enhancing effect may be due in part to actions of its' 5 alpha-reduced metabolites in the hippocampus;* Behav Neurosci; 2004 Dec;118(6):1352-64.
Albany, NY

5 Alpha Reductase Inhibitors

Gordon, M.; Traumatic Brain Injury; 2016 Millennium Health Centers Inc.. p.258

Decreased enzyme activity=

- ***Impotence, depression, cognitive impairment, CV Disease***

Preferred 5 AR (peripheral not central inducers)

- **Saw palmetto, Nettles, EGCG, progesterone, zinc, Pygeum, Pumpkin Seed Extract**

Testosterone and DHT Elevation

- **Finasteride and Dutasteride block conversion centrally**
  - **Cross BBB resulting in depression, fatigue, and sexual dysfunction**
  - **Recommend Saw Palmetto, Pygeum, Pumpkin Seeds, Pomegranate Juice to control conversion of T to DHT**
  - Edinger KI: Testosterone's Analgesic, Anxiolytic and Cognitive Enhancing Effects May Be Due to action of 5 Alpha reductase metabolites in Hippocampus. Behavioral Science 2004 Dec:118(6):1352-64

Testosterone Metabolizes into Estradiol

- S/S Estrogen Excess in Men
    - Breast Enlargement
    - Prostate Enlargement
    - Difficulty Urinating
    - Increased Emotional Lability
    - Tearfulness

Estrogen in Men

Estrogen levels increase as men age due to:

- **Increases in aromatase activity**
- **Obesity**
- **Alcohol excess**
- **Environmental estrogens**
- **Estrogen containing food**
- **Zinc deficiency**
- **Liver dysfunction**
- **Supraphysiologic Testosterone Therapy**
- **Calcium deficiency**
- **Diabetes**

Optimal Levels 20-30 pg/ml

Avoid Estrogen Excess w Physiologic T Doses

- Use Physiologic Dose
  - Age 25-35 (M)Mean T Production=4.1-11 mg/d
    - » (F) Mean T Production=1.42-2.85 mg/d
  - Males: 40-80 mg IM weekly or 40 mg q.o.d.
    - Pellets: 500-1200 mg/Rx. (Lasts 4-6 mo.)
  - Females 10-20 mg/wk.
    - Pellets: 80-150 mg/Rx.

Supraphysiologic Testosterone Doses

↑ Estrogen/DHT

↓ Central Neurosteroids

(Allopregnenolone,Pregnenolone, Deoxycorticosterone)

↓ GABA (inhibitory neurotransmitter- i.e . (-) x (-) = (+)

↑ IL-1, IL-2, IL-6, TNF-a, and IFN-gamma ↑ E-2 =

Agitation, Aggression, Irritability

– E Blocker+Loss of E Brain Production, ↓ Blood Flow,

• ↓ E Stimulation of HGH

Testosterone Production Rates In Normal Adults. Journal of Clinical Investigation Vol. 42, No. 11, ***1963***, Stanley G. Korenman, Hildegard Wilson, Mortimer Lipsett, Endocrinology Branch, National Cancer Institute, Bethesda, MD.

Avoid Estrogen Excess w Physiologic T Doses

Neuroprotective

- Maintains cerebral blood flow, lactate production
- Lowers risk of PTSD after trauma.
- Modulates pain.
- Strongest predictor of acute mortality and poor long-term outcome.
- Decreases risk, onset and progression of neurological deterioration
    - Alzheimer's Disease, schizophrenia
    - Aids in recovering from stroke and TBI.

Avoid Estrogen Excess and Use of E Blocker

RX

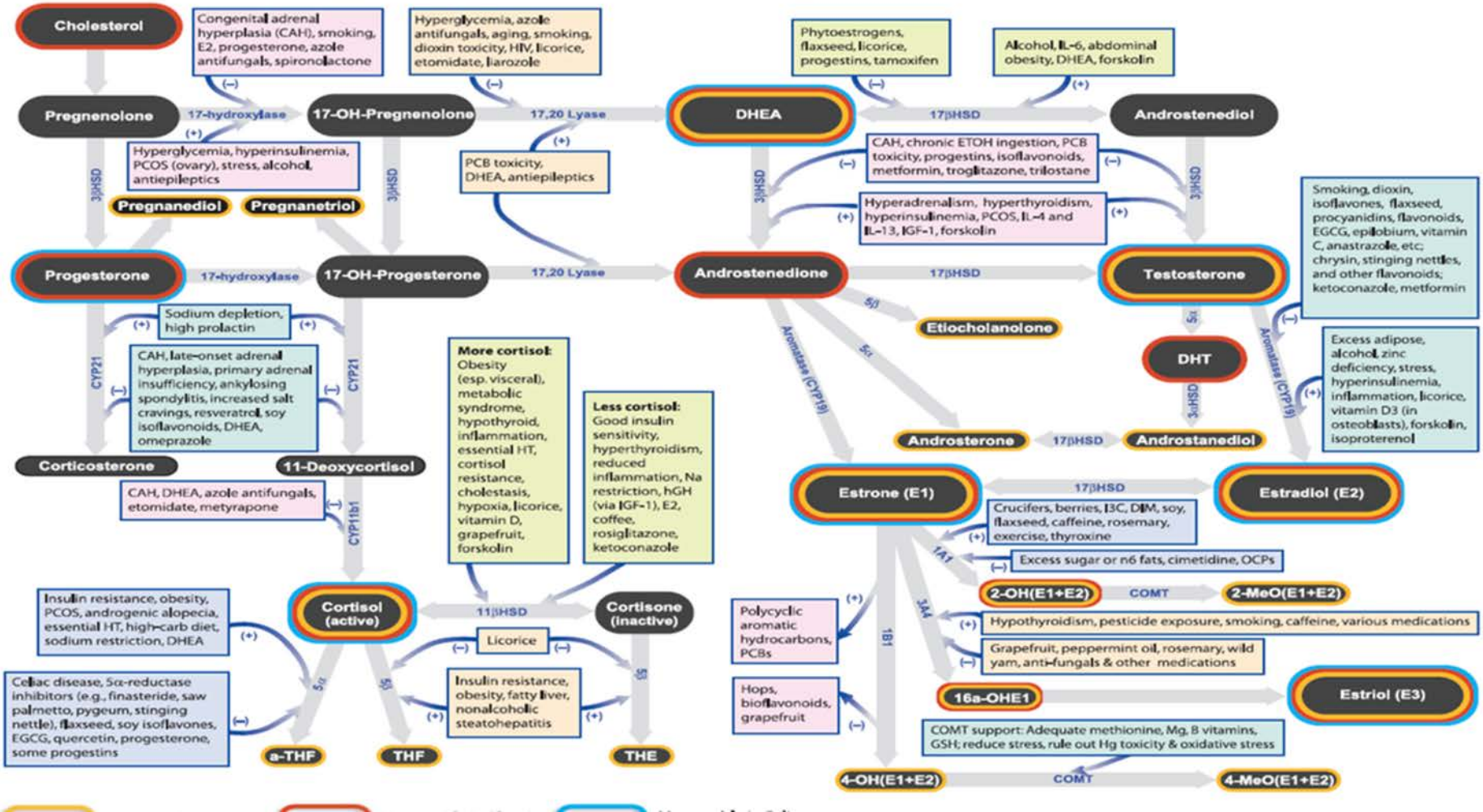
- Zinc Citrate (30-90 mg/d)
- Quercetin (250 -500 mg/d)
- Glycyrrhiza – licorice
- Grape seed extracts composed mainly of proanthocyanidins
- Resveratrol
- DIM (1-3 gm/d p.o.}
- Chrysin (250 mg bid p.o., topical 50 mg/d)
- Progesterone Cream 2-5%, Caps 10-15 mg/d
- Myomin
- Berberine
- Vitamin K
- Anastrozole (0.5-1.0 mg 1-3x/wk)

Testosterone, Estrogen and Depression Post TBI

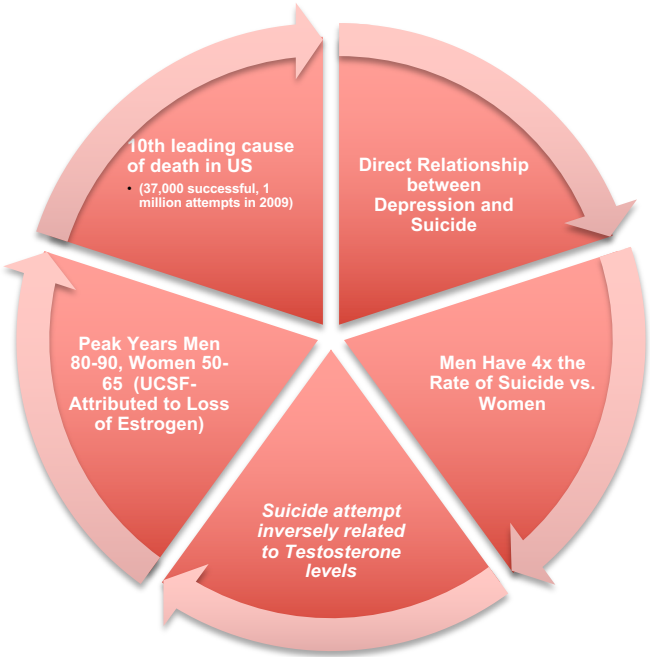
Protocol includes adding in upstream hormones shut down by T:

- **Pregnenolone-stimulate progesterone production=neuroprotective**
- **DHEA-improves myelin sheath**

Steroidogenic Pathways



TBI ➡ Low T ➡ Depression ➡ Suicide



Testosterone and Anxiety

Testosterone reduces anxiety, enhances cognitive performance.

Analgesic, anxiolytic, and cognitive effects are due to action on 5 alpha reductase metabolites in hippocampus effect

Edinger, KL; Frye, CA, *Testosterone's analgesic, anxiolytic and cognitive-enhancing effect may be due in part to actions of its' 5 alpha-reduced metabolites in the hippocampus;* Behav Neuroscie; 2004 Dec;118(6):1352-64. Albany, NY

The presence of a LOW Prolactin level can be a tip-off in a patient with treatment resistant anxiety. Having a high dopamine (Prolactin inhibiting factor) will suppress the production of Prolactin from the Anterior Pituitary.

Hormones Used to Treat Depression

- **Testosterone**
- **Growth Hormone**
- **Thyroid Augmentation**
- **Estrogen as adjunct (not effective as stand alone)**
- **DHEA-antidepressant, mood regulator, energy, confidence, improved sense of wellbeing**

Howland, MD, J., "*Use of Endocrine Hormones for Treating Depression.*" Psychosocial Nursing and Mental Health Services Psychopharmacology, Dec 2010, Vol 10, 123-161

Laboratory Evaluation in TBI

"The Optimal Physiological Level"

Major National Lab

Total Testosterone Range (264-916)=1180/2 = 590 Median

(Prior to July 17, 2017 Range (348-1197)= 772.5 Median

Range lowered due to obesity crisis showing improvement w low testosterone levels

Diagnostic Imaging in TBI

- **CT Scan-Plain No Contrast**
  - **Most Useful Study**
- MRI w Neuroquant
- Functional MRI (functional assessment)
- DTI
- PET Scan (Functional assessment)

Laboratory Evaluation in TBI

- Hormone ranges are based upon pooled data.

- Usually a two standard deviations a randomized mean defines the range.
- Ranges may be narrow; i.e.
  - Post-menopausal Progesterone (0.1-0.8 ng/ml)
- Ranges may be broad; Total Testosterone: 264 to 916 ng/ml. **(New)**

Laboratory Evaluation in TBI

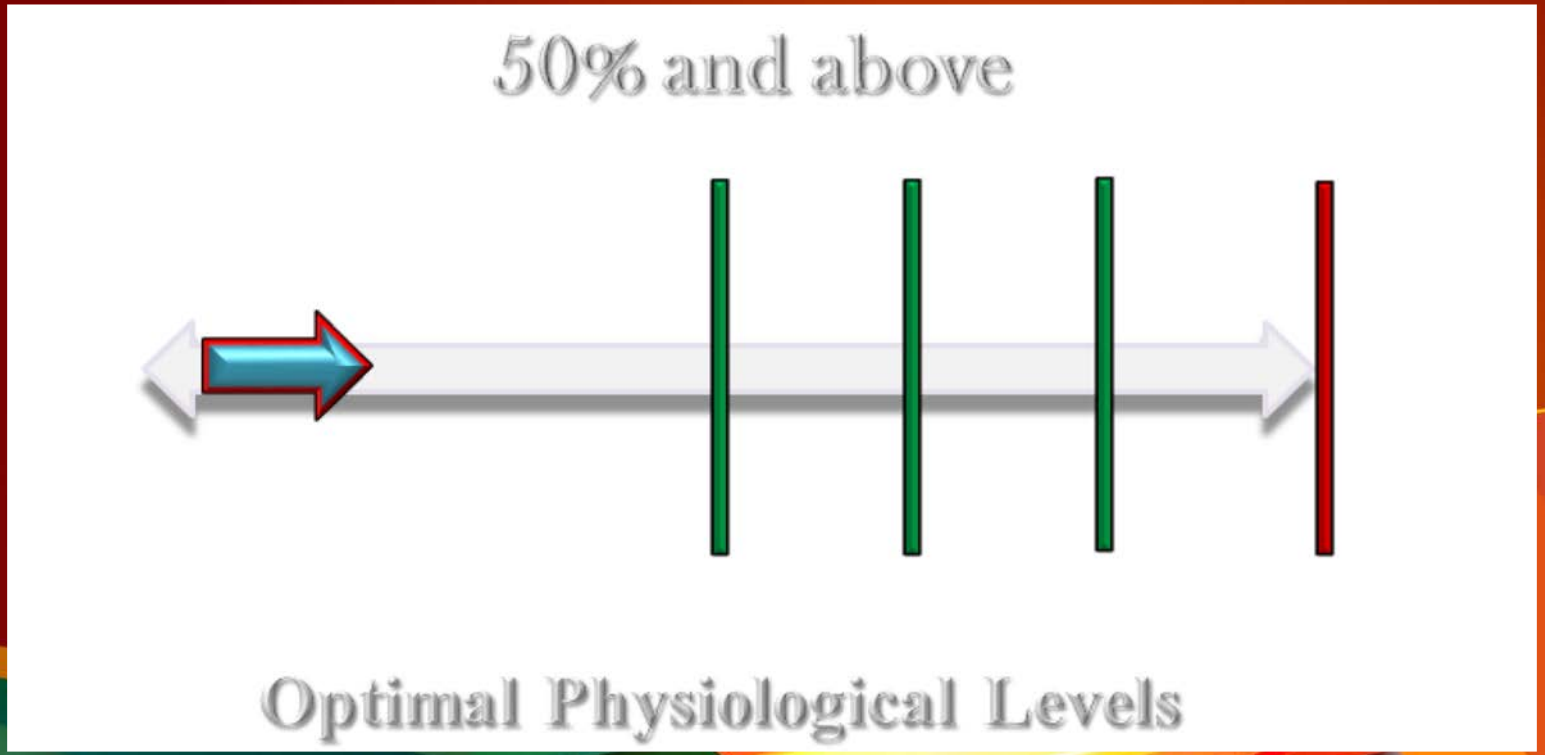
“ The Optimal Physiological Level”

Hormone levels should be centered around the median level of its acceptable range.

The ideal net effect is that the levels are close to the median of the range

"The Optimal Physiological Level"

Goal is in Upper ½ to ¾ of Median



Lab Studies

Central	*Peripheral*
TSH	free T3, free T4, reverse T3, TPO, anti thyroglobulin
GH	IGF-1, IGFBP3
LH/FSH	Testosterone, (free, total) DHEA-S; Male-DHT, Estradiol Female (Estrone, Estradiol, Progesterone)
ACTH	Cortisol A.M. and P.M. or 4 Point Cortisol Saliva Test
Others	CBC, Chem Profile, Lipid Profile, cRP, Homocysteine, Insulin, 25-OH Vit D, Pregnenolone, PSA (Total and fractionated), Zinc, Prolactin

Laboratory Target Ranges

(Labcorp., Access Medical Care Values)

Hormone	Median Male	Median Female	Range
DHEA-S	200 ug/dL	277 ug/dL	M (88-487) F (30-260)
Total Testosterone	690 ng/ml	44 ng/ml	M (280-1100) F (15-70)
Free Testosterone	14 ng/ml	2-4 ng/ml	M (1.9-27) F (0.2-2.6)
DHT	<52 ng/dL	<15 ng/dL	M (11.2-95) F (<30)
SHBG	45 pg/ml	<75 ng/dL	M (10-80) F (20-130)

Laboratory Target Ranges

Hormone	Median Male	Median Female	Range
Estrone	<30 pg/mL	<100 pg/mL	M (<60) F (<100)
Estradiol	<25 pg/ml	90 pg/ml	M (7.6-42.6) F (<54) Postmenopausal
Progesterone	0.8ng/ml	5-7 ng/m	M (0.2-1.4) F (0.1-0.8) postmeno.
Pregnenolone	<194 ng/dL	<205 ng/dL	M (38-350) F (250-500)
Vitamin D 3	>60 ng/ml	>60 ng/dL	M (30-100) F (30-100)

Laboratory Target Ranges

Hormone	Median Male	Median Female	Range
LH	5.1 mIU/mL	6.2 mIU/ml (Day 21 or postmenopausal)	M (1.7-8.6) F (Phase Dependent)
FSH	6.95 mIU/ml	8.6 mIU/ml	M (1.5-12.4 mIU/ml) F (Phase dependent)
Prolactin	11.25 ng/ml	13.75 ng/ml	M (2.5-19) F (2.5-19)
Pregnenolone	210 ng/dL	210 ng/dL	M (38-350) F (250-500)
Insulin	<5 uIU/ml	<5 uIU/ml	M (2.6-24.9) F (2.6-24.9)

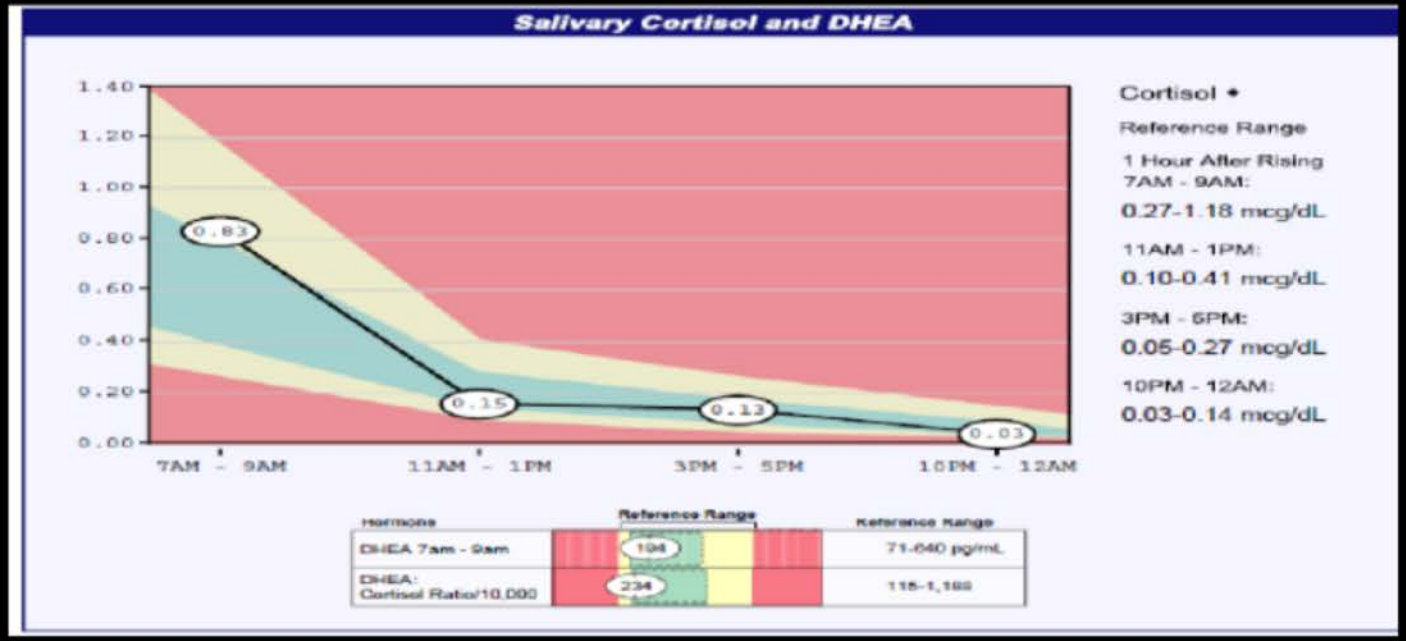
Hormone	Median Male	Median Female	Range
Growth Hormone (Morning Draw)	5 ng/ml	5 ng/ml	M (5) F (5)
IGF-1	>200 ng/ml	>200 ng/ml	M (60-220) F (60-220)
IGFBP-3	4000 ng/ml	4000 ng/m	M (2314-5700) F (2838-4954)
ACTH	<35 pg/dL	<35 pg/dL	M (7.2-63.3) F (7.2-63.3)
Cortisol (AM)	12.8 pg/ml	12.8 ng/dL	M (6.2-19.4) F (6.2-19.4)
Cortisol (PM)	7.4 ug/dL	7.4 ug/dl	M (2.3-12.3) F (2.3-12.3)

Laboratory Target Ranges

Hormone	Median Male	Median Female	Range
TSH	2.5 mIU/ml	2.5 mIU/ml	M (0-4.2) F (0-4.2)
free T4	1.5 ng/dL	1.5 ng/dL	M (0.9-1.7) F (0.9-1.7)
free T3	3.2 pg/ml	3.2 pg/ml	M (2.0-4.3) F (2.0-4.3)
Reverse T3	<15 ng/dL	<15 ng/dL	M (9.0-27) F (9.0-27)
TPO	<34 IU/ml	<34 IU/ml	M (<34) F (<34)
antithyroglobulin	<1.0 IU/ml	<1.0 IU/ml	M (<1) F (<1)

Normal Saliva Cortisol Pattern

n

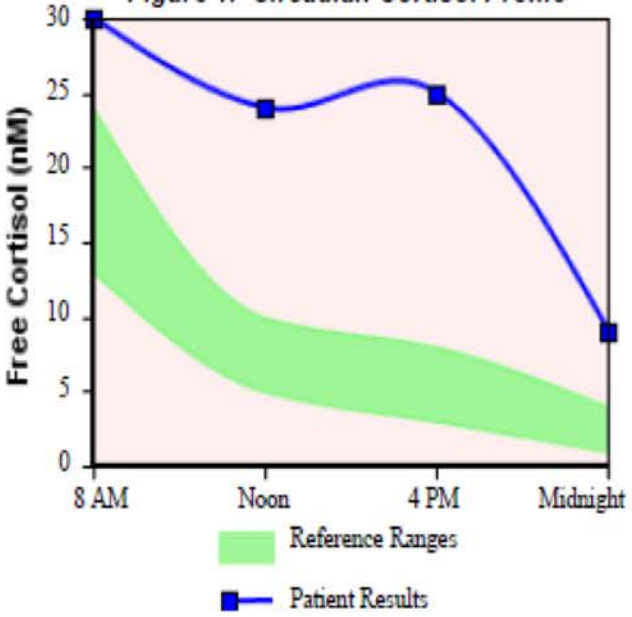


Cortisol Excess

Test	Description	Result		Ref Values
ASI	**Adrenal Stress Index (Original) - Saliva**			
TAP	**Free Cortisol Rhythm - Saliva**			**Adults (M/F):**
	06:00 - 08:00 AM	39	Elevated	13-24 nM
	11:00 - 1:00 PM	24	Elevated	5-10 nM
	04:00 - 05:00 PM	25	Elevated	3-8 nM
	10:00 - Midnight	9	Elevated	1-4 nM
	Total Cortisol Output:	97		***22 - 46 nM***

The Total Cortisol Output is the sum of the four cortisol values. Elevated values may indicate hypercortisolism or exogenous exposure, and low values suggest adrenal hypofunction.

Figure 1. Circadian Cortisol Profile

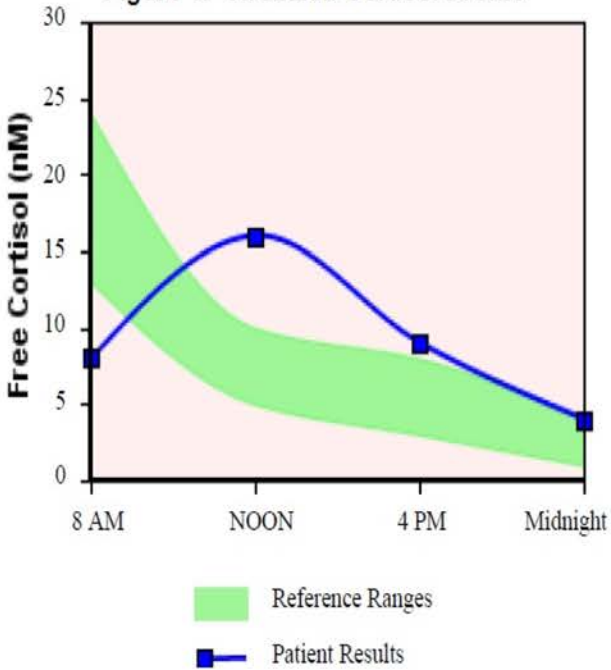


Cortisol Excess-6 Months Later

Test	Description	Result		Ref Values
TAP	**Cortisol rhythm (saliva)**			
TAP	**Cortisol rhythm (saliva)**			**Adults (M/F):**
	06:00 - 08:00 AM	8	Depressed	13-24 nM
	11:00 - 1:00 PM	16	Elevated	5-10 nM
	04:00 - 05:00 PM	9	Elevated	3-8 nM
	10:00 - Midnight	4	Normal	1-4 nM
	Total Cortisol Output:	37		***22 - 46 nM***

The Total Cortisol Output is the sum of the four cortisol values. Elevated values may indicate hypercortisolism or exogenous exposure, and low values suggest adrenal hypofunction.

Figure 1. Circadian Cortisol Profile

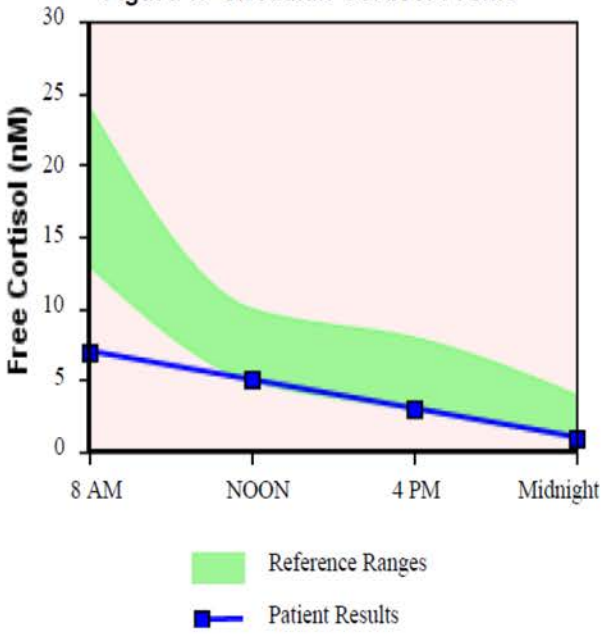


Cortisol Deficiency

Test	Description	Result		Ref Values
TAP	**Free Cortisol Rhythm - Saliva**			
TAP	**Free Cortisol Rhythm - Saliva**			**Adults (M/F):**
	06:00 - 08:00 AM	7	Depressed	13-24 nM
	11:00 - 1:00 PM	5	Normal	5-10 nM
	04:00 - 05:00 PM	3	Normal	3-8 nM
	10:00 - Midnight	1	Normal	1-4 nM
	Total Cortisol Output:	16		***22 - 46 nM***

The Total Cortisol Output is the sum of the four cortisol values. Elevated values may indicate hypercortisolism or exogenous exposure, and low values suggest adrenal hypofunction.

Figure 1. Circadian Cortisol Profile



Calculations

1. *free T3/Reverse T3*
    a. “Normal” = 1.06
    b. “Neuro Permissive Environment” > 2.0

Elevated rT3 due to:

Elevated Cortisol

B12 deficiency

Low Ferritin

Low Iron

Diabetes

2. TSH Index=TSH + 0.1345 (free T4)

a. Range = 1.3 – 4.1
b. <1.3 = Central (Brain) Issue
c. >4.1=peripheral issue
    i. (Cortisol▲
    ii. Selenium ▼, Iodine▼

TSH	**0.875 N**	<2.5 mcu/ml*
T3, Free	**2.1 LN**	> 2.5 pg/ml
T4, Free	**0.90 LN**	> 1.5 ng/ml
rT3	**217 HN**	80-250 pg/ml
T3/rT3 Ratio	**0.96 L**	>1.06
TPO	**13.0 N**	<35

Ex: **Low T3 Syndrome**

TSH <1.0;

T4 and T3 < median

Elevated rT3

High Cortisol

T3/rT3 Ratio below 1.06.

Low T3 etio. is Pituitary Trauma

3. Insulin Resistance (FBS x Fasting Insulin/405)

a. <2.9 =normal
b. <1.9 = optimal

I.R. is Independent of HbA1C

Ex: FBS = 97 (Normal 65-99)
Insulin=17 (2.6-24.9)
I.R. = 4.07

Ex. FBS = 101
Insulin = 4.8
I.R. = 1.197

4. Estrogen/Progesterone Ratio

- Optimal time to perform lab testing is days 19-21

E1+E2/Prog.=E/P Ratio

Goal <250

E1= 37 **Median=<200 pg/ml**

E2= 21
= 58 pg/ml

Prog= 1.1
= 5-7 ng/ml

P/E= 52.2

Estrogen Dominant

E1= 86

E2= 112

Prog=0.04

P/E = 2886

Estrogen/Progesterone Ratio (Gordon, M. TBI, San Diego, 2015)

Symptoms	*<250*	*250-1000*	*1000-5000*	*>5000*
Headaches	Intermittent	Mild	Moderate	Severe
Sleep Issues	Intermittent	Mild	Moderate	Severe
Sleep Deprivation	NP	Intermittent	Mild	Moderate
Bloating	NP	NP	Mild	Moderate
Mood Swings	NP	Mild	Moderate	Severe
Anxiety	NP	Intermittent	Mild	Severe
Depression	NP	Intermittent	Mild	Severe
Panic Attacks	NP	Intermittent	Mild	Severe
Mastalgia	Intermittent	Mild	Severe	Severe

5. Progesterone/Estrogen Ratio (Estrone Not Available)

- Optimal time to perform lab testing is days 19-21
- Menopausal=Any day

Normal

E2 = 62 **Median=90 pg/ml**

Prog.= 7.6 **=0.45**

P x 1000/ E2 **=122.58**

Prog. x 1000/Estradiol

< 100=Estrogen Dominant

100-500=Normal

> 500=Prog. Excess

Estrogen Dominant

E2=38 **Median=90 pg/ml**

Prog.= 0.8 **= 0.45**

P x1000/E2 **=21.05**

6. Total Testosterone/SHBG

	Test	Normal	T Deficient
Male	Serum tot. testo/SHBG (free testo index in mmol)	20 90-100	<17 <80
Female	Serum tot. testo/SHBG (free testo index in mmol)	8 8	<6 <6

Male Hormone Testing	Results	Range
Growth Hormone		**5ng/ml***
Somatomedin C (IGF-1)		**> 200 ng/ml**
IGFBP-3		**>4000 ng/ml**
DHEA-S		**245 ug/dl***
Estrone (E1)		**< 60 pg/ml***
Estradiol (E2)		**<25 pg/ml***
Progesterone		**0.8 ng/ml***
Pregnenolone		**110 ng/dl***
EP Ratio		**< 250**

DHT		< 55 ng/Dl
SHBG		< 75 pg/ml
FSH		7 mIU/ml*
LH		5.1mIU/ml
Prolactin		14 ng/ml*
Zinc		95mcg/dL
Insulin		<30mIU/L
Vitamin D3		>60 ng/dl*
ACTH		35 pg/ml *
Cortisol		< 15 ug/dl

MALE LABS

Testosterone Free		12-14 pg/ml*
Testosterone Total		690 ng/ml*

TSH		**<2.5 mcu/ml***
T3, Free		**> 2.5 pg/ml**
T4, Free		**> 1.5 ng/ml**
rT3		**80-250 pg/ml**
T3/rT3 Ratio		**>1.06**
TPO		**<35**

Female Labs

Female Hormone Testing	Results	Range
Growth Hormone		5ng/ml*
Somatomedin C (IGF-1)		> 200 ng/ml
IGFBP-3		>4000 ng/ml
DHEA-S		195 ug/dl*
Estrone (E1)		< 200 pg/ml*
Estradiol (E2)		90 pg/ml*
Progesterone		5-7 ng/ml*
Pregnenolone		100 ng/dl*
EP Ratio		< 250

DHT		*< 30ng/Dl*
SHBG		*< 75 pg/ml*
FSH		*7 mIU/ml**
LH		*5.1mIU/ml*
Prolactin		*14 ng/ml**
Zinc		*95mcg/dL*
Insulin		*<30mIU/L*
Vitamin D3		*>60 ng/dl**
ACTH		*35 pg/ml **
Cortisol		*< 15 ug/dl*

Testosterone Free		2-4 pg/ml*
Testosterone Total		<44 ng/ml*

TSH		<2.5 mcu/ml*
T3, Free		> 2.5 pg/ml
T4, Free		> 1.5 ng/ml
rT3		80-250 pg/ml
T3/rT3 Ratio		>1.06
TPO		<35

Female Hormone Testing	Result	Range
Growth Hormone	0.6	5ng/ml*
Somatomedin C (IGF-1)	78	> 200 ng/ml
IGFBP-3	2950	>4000 ng/ml
DHEA-S	49.2	195 ug/dl*
Estrone (E1)	274	< 200 pg/ml*
Estradiol (E2)	191	90 pg/ml*
Progesterone	.06	5-7 ng/ml*
Pregnenolone	131	100 ng/dl*
EP Ratio	3457	< 250

DHT	*23*	*< 30ng/Dl*
SHBG	*88*	*< 75 pg/ml*
FSH	*6.8*	*7 mIU/ml**
LH	*5.0*	*5.1mIU/ml*
Prolactin	*7.2*	*14 ng/ml**
Zinc	*89*	*95mcg/dL*
Insulin	*8*	*<30mIU/L*
Vitamin D3	*17*	*>60 ng/dl**
ACTH	*16*	*35 pg/ml**
Cortisol	*3.41*	*< 15 ug/dl*

OLIVIA G.

Testosterone Free	0.8	2-4 pg/ml*
Testosterone Total	12.7	<44 ng/ml*

TSH	0.98	<2.5 mcu/ml*
T3, Free	3.6	> 2.5 pg/ml
T4, Free	1.8	> 1.5 ng/ml
rT3	168	80-250 pg/ml
T3/rT3 Ratio	2.14	>1.06
TPO	19	<35

Psychiatric Issues in TBI

OCD in TBI

- **Post-traumatic OCD has a relatively specific pattern of symptoms even in patients with mild TBI and is associated with a variety of other psychiatric disorders, particularly non-OCD anxiety.**

- **The patterns of cognitive deficits and MRI findings suggest *dysfunction of frontal-subcortical circuits*.**
    - Mood changes (Emotionally Labile).
    - Changes in social behavior.
    - Changes in personality.
    - Diminished Executive Functions.

Obsessive-Compulsive Disorder and Traumatic Brain Injury: Behavioral, Cognitive, and Neuroimaging Findings. Marcelo L. Berthier, M.D., Jaime Kulisevsky, M.D., Alexandre Gironell, M.D., and Oscar L. López, M.D. Dept of Medicine and Dermatology, University of Malaga, Malaga, Spain; Dept of Neurology, Sant Pau Hospital, Autonomous University of Barcelona, Barcelona, Spain; and Dept of Neurology and Alzheimer's Disease Research Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Agitation

Agitated behavior (hurting oneself) is present along a continuum with varying levels of behavioral disturbance:

Inattention

Disinhibition

Emotional Lability

Impulsivity

Motor Restlessness → **Agitation**

Patterns of agitated behaviour during acute brain injury rehabilitation. Brain Injury, September 2010; 24(10): 1214–1221. Melissa T. Nott et al., Brain Injury Rehabilitation Service, Westmead Hospital, Wentworthville, NSW, AU, Faculty of Health Sciences, The University of Sydney, Sydney, NSW, AU, and Dept of Rehabilitation

Aggression (Hurting Others)

- Aggression after TBI is common but not well defined. Hurting others.

- The prevalence of aggression was found to be **28.4%** and to be predominantly verbal aggression.
- *Post-TBI aggression associated with:*
  - New-onset major depression
  - Poorer social functioning
  - Poorer function of activities of daily living

Aggression after Traumatic Brain Injury: Prevalence and Correlates. Rao, Vani., Et al. *J Neuropsychiatry Clin Neurosci.* (2009) ; 21(4): 420–429. Division of Geriatric Psychiatry and Neuropsychiatry, Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD.

Aggression

- ***Testosterone*** **down-regulates the production of Allopregnanolone which is associated with irritability, impulsive aggression, and signs of major depression.**

- ***Allopregnenolone*** **is a metabolite of pregnenolone which is affected in neurodegeneration secondary to *neuroinflammation.***

- ***High T converts to DHT in the CNS. Can precipitate Panic and Anxiety.***
  - **Mechanism is the decrease in ALLO-P. (T ↓ Allo P up to 50%)**
  - **(Allo-P is Calming)**
  - **↓ Allo- P = Major depression, anxiety, PMDD, and Alzheimer's disease.**

Changes in brain testosterone and Allopregnanolone biosynthesis elicit aggressive behavior. PNAS, Feb 8, 2005, Vol. 102 No. 6 2135–2140. Graziano Pinna*, Erminio Costa, and Alessandro Guidotti Psychiatric Institute, Dept of Psychiatry, College of Medicine, University of Illinois, Chicago, IL 60612

Testosterone Downregulates Allopregnenolone

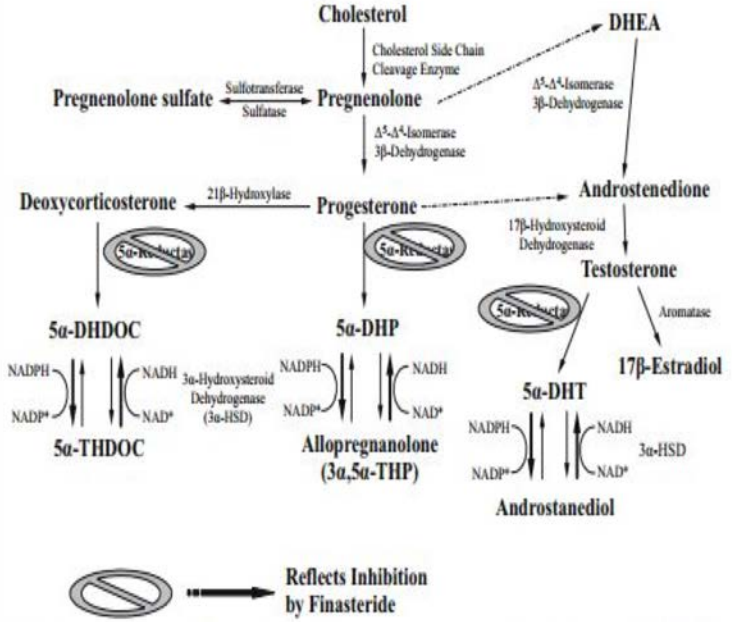


Fig. 1. Biosynthesis of the GABAergic neuroactive steroids 3α,5α-THP, 5α-THDOC and androstanediol and the point in the pathway where finasteride exerts its inhibitory effect. The broken lines indicate that 17-OH pregnenolone and 17-OH progesterone are omitted from the diagram in the formation of DHEA from pregnenolone and formation of androstenedione from progesterone, respectively. DHEA, dehydroepiandrosterone.

Psychosis
(Thyroid Components)

Influences:

- **Dopaminergic**
  Myelination
- **Serotonergic**
  Inflammatory Processes
- **Glutamatergic systems**
- **GABAergic**

Thyroid acts a "fine-tuning mechanism" in functioning of neural networks

Revisiting Thyroid Hormones in Schizophrenia. Journal of Thyroid Research Volume 2012, Article ID 569147. N. Santos, et., at. Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Campus de Gualtar, Braga, Portugal, Dept of Pathology, Leiden University Medical Center, Leiden, The Netherlands Institute of Medical Psychology, Faculty of Medicine, U. of Coimbra, Coimbra, Portugal

Dementia

Restored Hormone Levels to Physiologic Mean=

Improved Energy, Decreased Tremor and Gait Stabilization in 1-6 weeks.

- **Elderly women +/- AD > 80 yrs. significantly lower E2 and Testosterone in AD**
- **Women age 60-79 No difference in normal vs. AD**
- **Low progesterone levels in frontal lobe in PD**

Brain levels of sex steroid hormones in normal aging and Alzheimer's Disease Rosario, E., Chang, E., *Neurobiology of Aging* 32 (2011) 604-613

- **Males-Normal and AD=decreased androgens; estrogens remain steady at all ages.**
- **Males low testosterone and frontal lobe dysfunction is "Double Whammy" in PD**

Plasma testosterone levels in Alzheimer's and Parkinson Diseases Neurology. 2004; (62(3):411-3 Okun, MS;, Delong, MR, Hanfelt, J. et al. Gainesville, Fl.

Arousal and Attention

- **Elderly males: Low E2, High T=better performance on cognitive testing.**
- **“Optimal” levels necessary for cognitive functioning**

Endogenous Sex Hormones and Cognitive Function in Older Men J. Clin Endocrinol Metabol 84:3681-3685, 1999 BArrett-Conner, E., Goodman-Gruen, D, and Patay, B., La Jolla, Calif and Phoenix, Az.

Head Trauma and Sexual Dysfunction

- **Changes in sexual interest/desire are cited as the most common sexual problem**
- **Deceleration injuries damage:**
  - ***Frontal lobes***
  - ***Pituitary***
  - ***Limbic system injury ↑ the chance that a sexual problem will arise after head injury.***

- **Patients with a *Basal Frontal Lobe* injury exhibited sexual disinhibition and increased sexual drive manifested as exhibitionism**

Head injury and sexual dysfunction. Brain Injury, 1996, VOL. 10, NO. 10, 703-717. Mark L. Elliott, Laurel S. Biever. Ohio State University, Columbus, OH, USA

Cognition-Think Thyroid

- Among those with MCI, **Total T3 levels are inversely associated with cognitive performance across all domains.**

- Those with relatively high T-T3 levels showed little impairment in memory as well as in visuospatial and executive functions.

- Those with TT3 levels at or below the lower boundary of the normal range performed comparably to healthy controls.

Thyroid Hormones Are Associated with Poorer Cognition in Mild Cognitive Impairment (MCI). Dementia and Geriatric Cognitive Disorders 2010;30:205–211 a Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Mölndal , Sweden; b Depts of Neurology and Medicine, State University of New York, Downstate Medical Center, Brooklyn, N.Y. , USA

Cognition

Pregnenolone sulfate regulates neurotransmission in the hippocampus- ➡

Learning and memory.

Neurosteroids in the Hippocampus: Neuronal Plasticity and Memory Schumacher M. Stress **1997** Oct;2(1):65-78

Pregnenolone correlates with cognitive performance ➡ improved with replacement

Pregnenolone increases Acetylcholine in:

Amygdala, cerebral cortex and hippocampus

Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations. Horm Behav **2001** Sep;40(2):215-7 Mayo W; INSERM U259, Institut Francois Magendie, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France.

Cognition

- Beneficial changes in cognition occur in hypogonadal men using T replacement levels and DHT treatment
- Changes in cognition can be reliably measured during a relative steady-state dose level.
- Testostosterone, estradiol and IGF-1 have independent and selective effects on cognition

Cognitive changes associated with supplementation of testosterone or DHT in mildly hypogonadal men: a preliminary report. J Androl 2003 Jul-Aug;24(4):568-76. Cherrier MM; Craft S; Matsumoto AH Department of Psychiatry and Behavioral Sciences, University of Washington Medical School, Seattle, Washington 98108, USA.

Cognition

- **17-alpha-estradiol is found to be neuroprotective, after an ischemic stroke and oxidative stress, and in Alzheimer's disease; and influences spatial memory and Hippocampal-dependent synaptic plasticity.**

17-alpha-estradiol: a brain-active estrogen? Endocrinology 2005 Sep;146(9):3843-50. Toran-Allerand CD; et al. Department of Anatomy and Cell Biology, Columbia University College of Physicians and Surgeons, 650 West 168th Street, Black Building, Room 1615, New York, New York 10032, USA

Hormones for Cognition Improvement

1. ***Pregnenolone***
2. ***Thyroid***
3. ***Testosterone***
4. ***Estradiol***

Fatigue

- Prevalence of fatigue does not appear to change over time, in a study of individuals with TBI living in the community
- 68% reported fatigue at 2 years post-injury
- At 5 years post-injury 73%, reported problems with fatigue.

Fatigue after TBI: Association with neuroendocrine abnormalities. Brain Injury, June 2007; 21(6): 559–566. Tamara Bushnik, Jeffrey Englander, & Laurence Katznelson. Rehabilitation Research Center, PM&R, Santa Clara Valley Medical Center, San Jose, CA, USA, and Pituitary Center, Depts. of Neurosurgery and Medicine, Stanford University Medical Center, Stanford, CA, USA.

Narcolepsy

- **Chronic, daytime sleepiness** is a major, disabling symptom in patients with traumatic brain injury (TBI).
- Loss of the hypothalamic neurons that produce the wake-promoting neuropeptide **hypocretin (orexin)** causes the severe sleepiness of **narcolepsy**,
- The partial loss of these cells may contribute to the sleepiness of Parkinson's disease and other disorders.
- ***This study found that the number of hypocretin neurons is significantly reduced in patients with severe TBI.***
- **Constant fatigue is the #1 symptom across TBI.**

Loss of hypocretin (orexin) neurons with traumatic brain injury. Ann Neurol . 2009 October ; 66(4): 555–559. Christian R. Baumann1, Claudio L. Bassetti L., Philipp O. Valko, Johannes Haybaeck, Morten Keller, Erika Clark, Reto Stocker4, Markus Tolnay, and Thomas E. Scammell. Dept. of Neurology, Dept. of Neuropathology, Dept. of Forensic Medicine, and Dept. of Surgical Intensive Care, University Hospital, Zurich, Switzerland. Dept. of Neurology, Beth Israel Deaconess Medical Center, Boston, USA

Thyroid and TBI

- 10-30 % of TBI Patients Develop Hypothyroidism
- Thyroid Function in Depression
  - T4 (Total and free) = → or ↑ **(25%) above reference range)**
  - T3 (Total and free) = ↓
  - Reverse T3 ↑
    - Total T3/rT3>1.06 provides for adequate T3 function
  - Cortisol ↑
- RX w T3/T4 combination
  - improved weight loss
  - overall sense of well being
  - cognition
  - functionality

Vitamin D and TBI

s Anti-Inflammatory Functions in the Brain (Activates TNF, IL 1, IL 6, NF B, p65 cytokines)

- Milos, C, et al. Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats; Neurobiology of Aging 32 (2011) 864-874

Protects against-Depression, Alzheimer's Dx., Dementia

Serum 25 OH Vit. D goal: 50-80 ng/dL

x: Typically 5000-10,000 IU/d

- Every 1000 IU supplement increases Vit. D3 by 8 ng/dL

Estradiol and TBI

Nauert PhD, R. (2017). Estrogen Levels Influence Susceptibility to PTSD. *Psych Central*. Retrieved on June 26, 2017, from https://psychcentral.com/news/2017/01/20/estrogen-levels-influence-susceptibility-to-ptsd/115390.html Dr. Seeman, Clarke Psychopathology in Women and Men: Focus on Female Hormones Am J Psychiatry, Toronto, Canada **1997**; 154:1641–1647

"Pre-existing" low estrogen levels leave women susceptible to the development PTSD.

Conversely, high estrogen levels may be protective.

Estrogen:

- Lowers risk of PTSD after trauma. Is Neuroprotective.
- Modulates pain.
- Strongest predictor of acute mortality and poor long-term outcome.
- CSF estradiol is lower after TBI

Estradiol and TBI

- **Estrogen:**
  - Maintains cerebral blood flow, lactate production
  - Prevents apoptosis (cell death), and acts like a growth factor.
  - Increases under stressful conditions such as critical illness and trauma.
  - Decreases risk, onset and progression of neurological deterioration
    - Alzheimer's Disease, schizophrenia
    - Aids in recovering from stroke and TBI.
  - Prevents neuronal loss in CNS
  - *Estradiol exhibits many properties of anti-anxiety, antiphychotic agents*

- Nauert PhD, R. (2017). Estrogen Levels Influence Susceptibility to PTSD. *Psych Central*. Retrieved on June 26, 2017, from https://psychcentral.com/news/2017/01/20/estrogen-levels-influence-susceptibility-to-ptsd/115390.html

Dr. Seeman, Clarke Psychopathology in Women and Men: Focus on Female Hormones Am J Psychiatry, Toronto, Canada 1997; 154:1641–1647.

Progesterone and TBI

Prevents neuronal loss in CNS

Reduces age related myelin loss in peripheral nerves

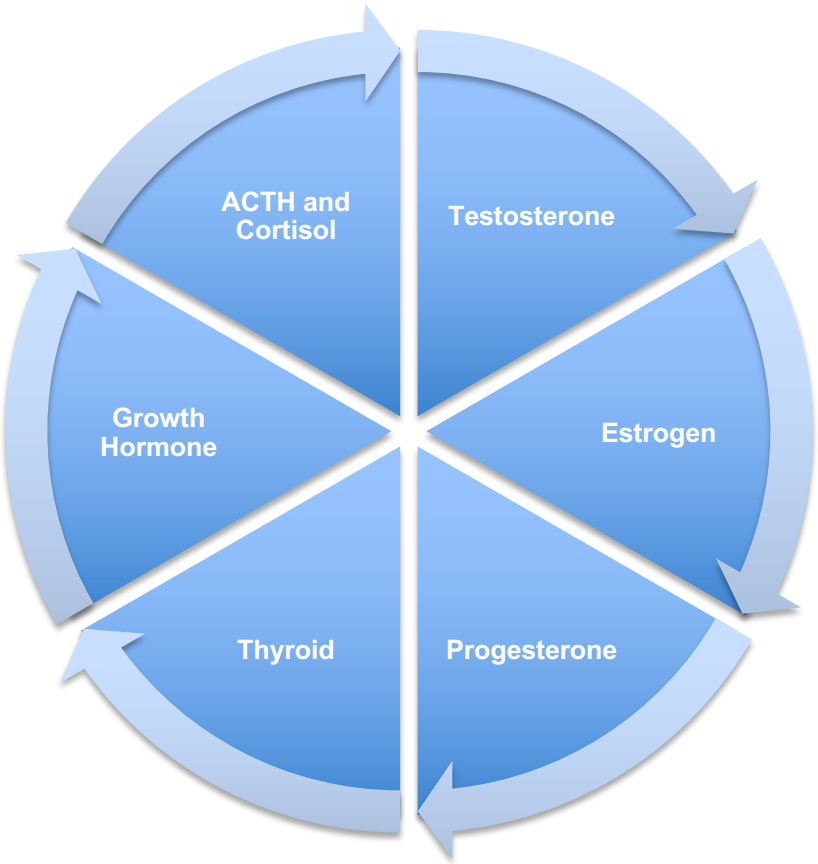
- Takes 6 mo. to see improvement

Attenuates IL-1B and TNF-alpha, cerebral inflammatory cytokines

- TBI releases IL-1B and TNF-alpha release in bloodstream
  - results in cerebral edema
  - Permanent neuron loss

Treatment

- 1. **Primary Hormones**
- **2. Secondary Hormones**
- **3. Supplements**
- **4. Oxidative Stress Relief**



Primary Hormones

Testosterone Vehicles

Product	Dose	Lab Level	Comments
Clomid**	50mg 3-5x a week	2-3 months	Less than 40 years of age and prophylaxis.
AndroGel 1%	1-4 pumps/day	T(T)>350-750ng/dL	Apply to shoulder and upper arms only.
AndroGel 1.62%	1 x day	T(T)>350-750ng/dL	High DHT levels and Estradiol.
Testim 1% Gel	5-10g/day	T(T) 300-1000ng/dL	High DHT levels and Estradiol.
TestoCream 10%	½ - 1 gram/day	F(T)> 10-14ng/dL	Apply to flank if not in contact with other people.
Testosterone Cypionate IM	40-100mg/week-Male 10-30mg/week - Female	F(T)> 10-14ng/dL T(T)>300-1000ng/dL	Once weekly subcutaneous or IM injection.
Testosterone Pellets	Based upon weight.	F(T)> 10-14ng/dL T(T)>300-1000ng/dL	Initially high levels dropping over 4-6 months. Once implanted cannot remove.
Testosterone Lozenge (Troche)	Males: 25-50mg BID3x/wk Female:12.5-25mg.BID3x/wk	F(T)> 10-14ng/dL T(T)>300-1000ng/dL	Short half-life needing frequent dosing.
Testosome®	Males: 1cc Oral AM, Daily Females: 1cc Oral, TIW	Male: F(T)> 10-14ng/dL Female: F(T)> 2-4ng/dL	Short half-life with excellent absorption. CNS benefits include improved focus, concentration, decrease anxiety, improved depression, rise in libido and mental energy.¥
	¥- Based upon 3 months of testing with 10mg dose sampling.		

Clomiphene Citrate

- Three year study (2014-2016) on the use of Clomid in two groups: Less than 40 and greater than 40.
- 2016 study: Less than 40 with a Free T of 5-10 get one tablet every 3rd day. Blood work in 12 weeks.
- Older than 40 get UL-Testosterone protocol (20mg) every 3rd day with 25/50mg tablet of Clomid or no clomid. Blood work in 8-12 weeks.

Clomiphene Citrate

Telephone conversation

I reviewed test results.

Pituitary MRI is normal. Thyroid ultrasound is consistent with Hashimoto's thyroiditis without nodules.

We discussed treatment options for testosterone. I indicated that the clomiphene that he has used and has had success with it is not FDA approved for this purpose and we do not know the long-term effects. However it is available to him and maybe the most convenient thing to use. Also will likely preserve his fertility if that is currently intact. Exogenous testosterone will suppress his testosterone and spermatogenesis which doesn't mean it cannot recover in the future and be stimulated by hCG. These are all unknowns. Also is not a good idea for a young man his age to go without testosterone. Feels chronic fatigue and complete loss of libido.

I offered to get him another opinion with another endocrinologist or at another Medical Center. I also offered to send him to a urologist for subcutaneous testosterone implants and also consultation. He will consider his options and let me know.

Outcomes of Clomiphene Citrate Treatment in Young Hypogonadal Men.

Long-term follow-up of CC treatment for HG shows that it is a effective and safe alternative to testosterone supplementation in men wishing to preserve their fertility.

Katz DJ1, Nebulsi O, Tal R, Mulhall JP.

BJU Int. 2012 Aug;110(4):573-8. doi: 10.1111/j.1464-410X.2011.10702.x. Epub 2011 Nov 1.

Treatment Considerations

- **Human Chorionic Gonadotropin (HCG)**
- Produced in Human Placenta
- Stimulates testes to produce testosterone
- Does not affect sperm count or testicular volume
- Preferred if patient is under 40

Treatment Considerations

- **Human Chorionic Gonadotropin (HCG)**
- Dose to Preserve Size or Semen Volume:
- 250 IU SQ days 6 and 7 of weekly IM injection
- 250 IU SQ every 3rd day for Transdermal Gel
- Dose as Stand Alone Therapy:
  - 3000 IU SQ q 2 wks (increases free T by 25%)
    - Or
  - 1000 IU SQ 2x/wk

Can develop antibody

- RX should be 2 months on, 1 month off.

Estrogens

- Estradiol leads to decrease production of:
  - Testosterone
  - DHEA
  - Progesterone
  - Pregnenolone

- E2 supplementation leads to transient increase in Cholesterol

Estrogen/Progesterone Ratio

- Optimal time to perform lab testing is days 19-21

- Measuring both Estrone (E1) and Estradiol (E2) with progesterone (PROG) will allow for the calculation of the EP Ratio.

E1+E2/P=E/P Ratio

- Estrogen Dominance as a comorbid factor to TBI can cause greater disturbance in neurochemistry especially with GABA.

- **If E1 is elevated, control w 7 Keto-DHEA**

Estrogen/Progesterone Ratio (Gordon, M. TBI, San Diego, 2015)

Symptoms	*<250*	*250-1000*	*1000-5000*	*>5000*
Headaches	Intermittent	Mild	Moderate	Severe
Sleep Issues	Intermittent	Mild	Moderate	Severe
Sleep Deprivation	NP	Intermittent	Mild	Moderate
Bloating	NP	NP	Mild	Moderate
Mood Swings	NP	Mild	Moderate	Severe
Anxiety	NP	Intermittent	Mild	Severe
Depression	NP	Intermittent	Mild	Severe
Panic Attacks	NP	Intermittent	Mild	Severe
Mastalgia	Intermittent	Mild	Severe	Severe

Progesterone/Estradiol Ratio

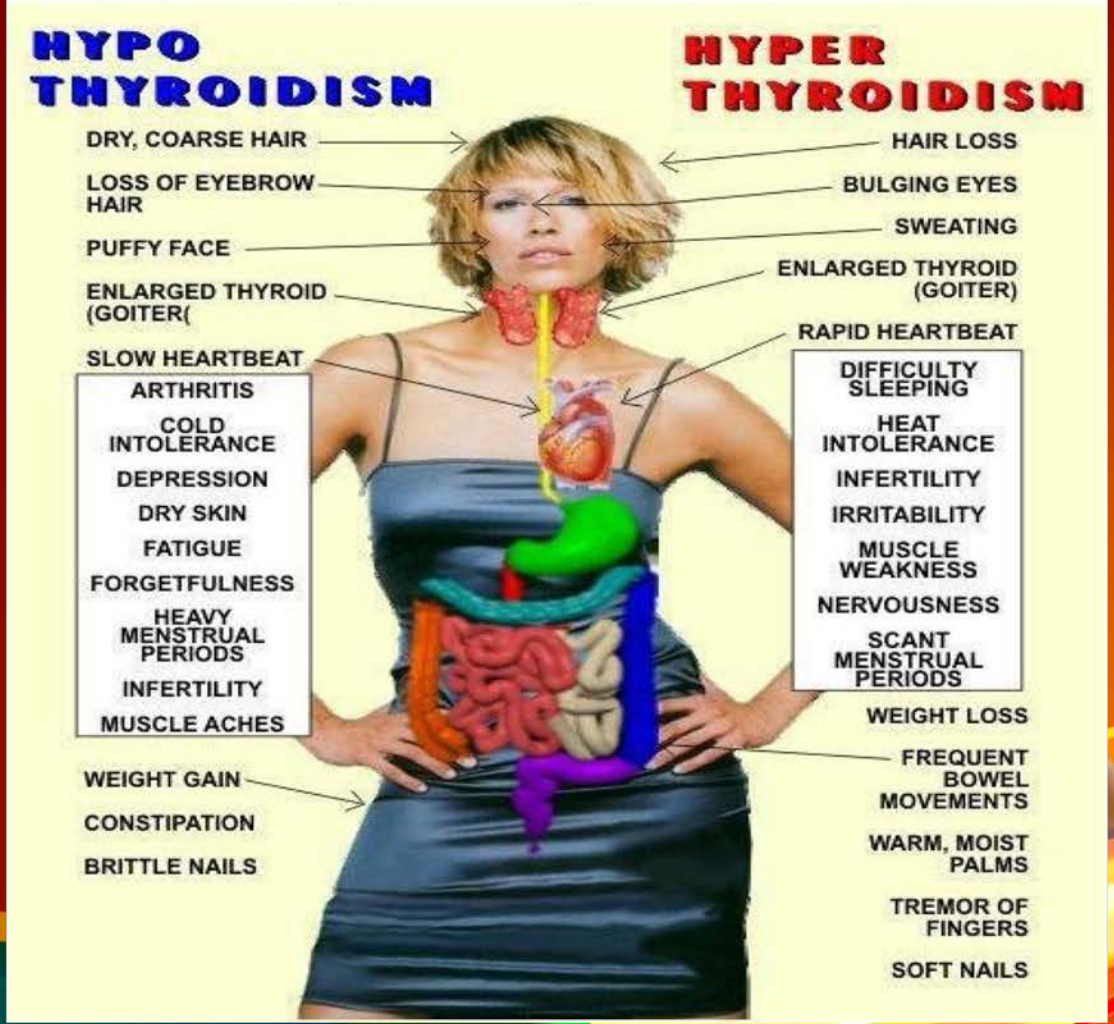
- **Alternative Measurement**
  - ***Serum: Pg x 1000/E_2=P/E_2 Ratio***
  - ***Saliva: Pg/E_2=Pg/E_2 Ratio***
- **Results**

<100	=	Estrogen Dominant
100-500	=	Normal Ratio
>500	=	Progesterone Dominant

Female Hormone Treatment (Gordon, M. TBI, San Diego, 2015)

	Estradiol	Estriol	Progesterone	Testosterone	Application
Starter	0.2mg	2.0 mg	100 mg	1 mg	Vaginal
Breast Tender	0.1 mg	2.0 mg	100 mg.	1 mg	Vaginal
Fatigue	0.2 mg	2.0 mg	50 mg.	1 mg	Vaginal
Libido	0.2 mg	2.0 mg	100 mg.	2 mg	Transdermal
Basic	0.2 mg	2.0 mg	100 mg.	No	Transdermal
Breast	0.1 mg	2.0 mg	100 mg.	No	Vaginal
Cancer	none	2.0 mg	100 mg.	1-2 mg.	Vaginal

Thyroid Dysfunction



Treatment

- **Thyroid**

- The notable benefits of T3 and T4 on brain recovery and neurobehavior are clear.

- Controversy still exists between monotherapy with T4 and combination therapy with T3.

- If adequate levels of fT3 are obtained without the surreptitious presence of rT3, then neuroregeneration is possible.

Treatment

Serum TSH: Cut-off points within ref. range abovewhich there is ↑ risks of disease			
mU/L	↑ Risks of disease		Reference
>3.6			
> 3.3 (higher quartile)	↑ severe form of depression		Berlin I 1999 Nyrnes A 2006
3-3.6	↑ body mass index over 7 years		Nyrnes A 2006
	↑ waist circumfer., BMI, glucose, TG, systolic BP		Waterhouse DF 2007
> 3	↑ cardiac abnormalities (pat. + auto-immune thyroiditis)		Zoncu S 2005
	↑ post-partum hypothyroidism		Azizi F 2004
> 2.1	↑ Stenoses, multi-vessel disease (angina patients)		Yun KH 2007
> 2	↑ homocysteine & CRP (patients + L-thyroxine)		Gursoy A 2006
≥ 2	↑ Familial predisposition to hypertension		Gumieniak O
≥ 2	↑ Hypercholesterolemia	(patients + auto-immune thyroid antibodies)	Michalopoulou G 1998
1-1.99	↑ Overt hypothyroidism		Geul KW 1993
> 1.98	↑ aggravation of coronary heart disease		Auer J 2003
≥ 1.9	↑ systolic & diastolic blood pressures (men)		Iqbal A 2006
> 1.9	↑ auto-immune thyroid ATPO+ (pregnant women)		Sieiro Netto L 2004
≥ 1.8	↑ systolic & diastolic blood pressures (women)		Iqbal A 2006

The Case (for Adding T3)

Remyelination and Recovery.

- **Myelin repair-**T3 regulates the cell cycle of oligodendrocytes by either stopping their maturation from OLPC to terminal OL or by enhancing maturation for additional myelin production.

- **Inflammation-**
  - inhibits D1 synthesis (converts T4 to T3)
  - increases D3 which converts **T4 to rT3**.

LOW T3 IS STRONGEST INDEPENDENT PREDICTOR OF CARDIAC DEATH

- Low T3 < 3.1 Free T3
- Low-T3 syndrome is a strong predictor of death in cardiac patients and might be directly implicated in poor prognosis of cardiac patients.
- Strongest independent predictor of death

  > lipids or EF

- Lervasi, G et al. Low-T3 Syndrome, A Strong Prognostic Predictor of Death in Patients With Heart Disease *Circulation.* 2003;107:708

Doctor's Solution

T4 Only

- Levothyroxine, Levoxyl, Synthroid

American Association of Clinical Endocrinologists and American Thyroid Association emphatically declared, in 2012, "Standard treatment is replacement with Levothyroxine. "

Garber, J.,Cobin, R., Gharib, H., et al., Clinical Practice Guidelines For Hypothyroidism In Adults, Endocr Prac. 2012; 18(No.6) 989. Hollowell JG et al. J Clin Endocrinl Metab 2002 87(2)489-499

Any Treatment Other Than Desiccated T4 Is Outside Realm Of Medicine

Guarva, S., Hypothyroidism, *"Scinece Based Medicine"*"https://www.sciencebasedmedicine.org/hypothyroidism--facts--controversies-and--pseudoscience/

T4 Only

Diet

Bone Broth-Helps restore gut barrier (i.e. heals the “leaky gut”)

Fermented Vegetables and Beverages (i.e. sauerkraut, kimchi, beet kvass, coconut water kefir, etc.). High in Probiotics

Fish and Shellfish-High in omega-3 fats. Eat at least one pound of cold-water, fatty fish per week EPA and DHA needs.

Organ Meats-Loaded micronutrients that promote healthy immune function.

Diet

- Goitrogens-Limit to 3-6 servings/week raw. Steaming/boiling reduces goitrogenic effect.
- Eggs (both whites and yolks)
- Nightshades (potatoes, tomatoes, sweet and hot peppers, eggplant, tomatillos, pepinos, pimentos, paprika and cayenne pepper)
- Nuts-30-day elimination if nut sensitive. Common allergen.

Limit Goitrogens (3-6 Servings/Week)

Cruciferous Vegetables

- Bok Choy
- Broccoli
- Brussel Sprouts
- Cabbage
- Canola
- Cauliflower
- Chinese Cabbage
- Collard Greens
- Horseradish
- Kale
- Kohirabi
- Mustard Greens
- Radishes
- Rutabaga
- Turnips

Others

- Soy
- Pine Nuts, Peanuts
- Millet
- Strawberries
- Pears, Peaches
- Bamboo Shoots
- Spinach
- Sweet Potatoes

Immune Modulators

- Low Dose Naltrexone
- Plant Sterolins

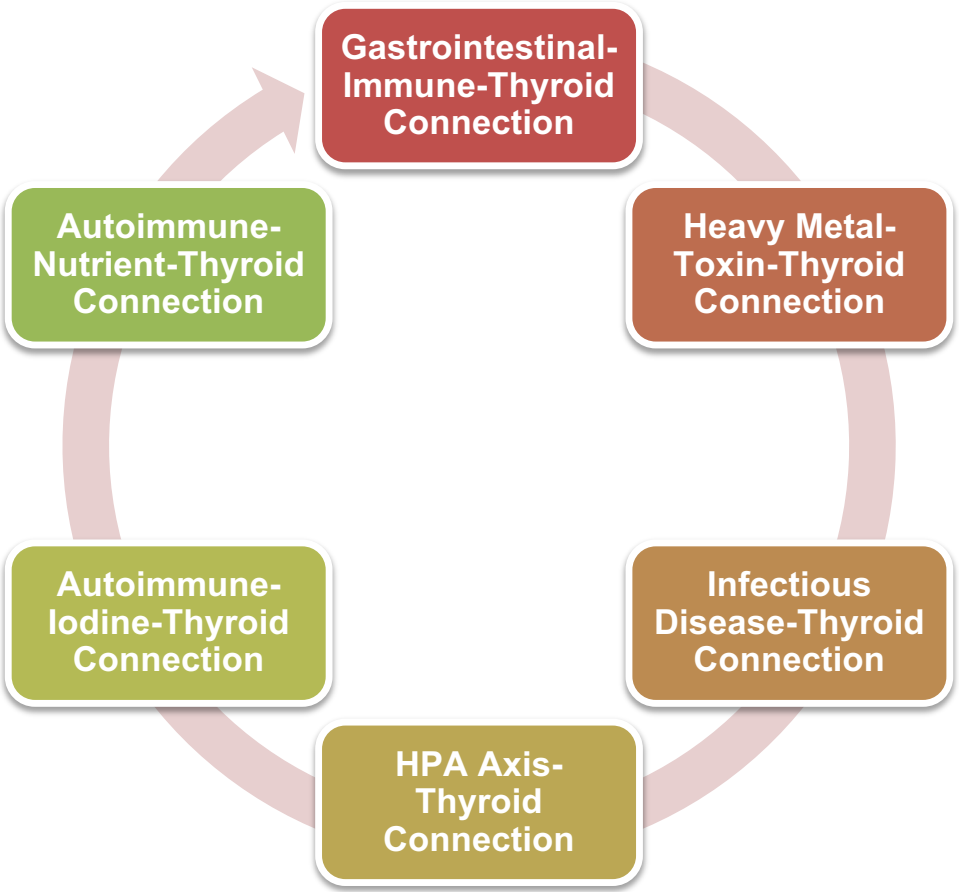
Promote a balanced immune system
- Protects against negative stress responses
- Limits cortisol activity

Modulates the autoimmune response in Hashimoto's Thyroiditis.
- Can decrease antibodies by 90%

Improves balance of T-helper 1 to T-helper 2 cells
Down Regulates overactive immune responses.*

- Bouic PJ1, Lamprecht JH., Plant sterols and sterolins: a review of their immune-modulating properties.Altern Med Rev. 1999 Jun;4(3):170-7.
- Yamada H, Yoshino M, Matsumoto T, et al. Effects of phytosterols on anti-complementary activity. Chem Pharm Bull 1987;35:4851-4855

Shameless Plug to Invite Me Back for "The Thyroid Show"



Growth Hormone Algorithm

+Lab Evaluation

Secretagogue (SRx) →

Retest 3 Mo. →

Increased → Continue 6 mo. then discontinue. Retest in 6 mo.

No Change or Decrease → Increase Dose; Retest 6 mo.

No Change or Decrease → Glucagon Stimulation Test or Insulin Stimulation Test

If + Consider HGH

Secretagogue #1

- *Active Ingredients:* Pyroglutamine,L-Glutamine, L-Arginine, L-Lysine, L-Valine,L-Tyrosine Alpha-ketoglutarate, L-Ornithine, L-alphaglycerlphosphoryl-choline, Gamma Amino Butyric Acid(GABA), and Mucina pruriens.

- *Other Ingredients:* Deionized water, Lecithin, Phospholipids, Sodium citrate, Citric acid, Maltodextrin, Potassium sorbate, Artificial color and Flavor.

Secretagogue #2

Arnica Montana 6X, Deer Antler Velvet 8X, Hepar Bovinum 6X, HGH 24X, 30X, IGF 1 8X, Pituitary Bovinum 5C, 7C, 9C, Thuja Occidentalis 6X

Semorelean w GNRH 2 or 6

CJC 1295 w DAC

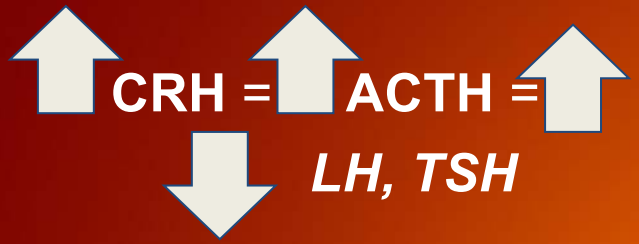
L-Dopa Raises Growth Hormone

- *Oral doses (0.5 g) caused a significant rise in plasma GH.*
- *The rise in plasma GH persisted for 120 minutes after the administration of the drug.*
- *The data suggest that a dopaminergic mechanism in the median eminence or a norepinephrine-sensitive site in the hypothalamus or limbic system may be involved in the regulation of growth-hormone secretion.*
- *Parkinson's disease patients, on L-dopa therapy, enjoy an elevated plasma GH for a substantial part of the day*

Stimulation of Human-Growth-Hormone Secretion by L-Dopa. N Engl J Med 1970; 283:1425-1429 Dec. 24, 1970. A. E. Boyd, III, M.D., Harold E. Lebovitz, M.D., and John B. Pfeiffer, M.D. From the divisions of Endocrinology and Neurology, Department of Medicine, Duke University Medical Center

ACTH and Cortisol

- TBI =
  - ***Acute increase*** in the *Corticotropin Releasing Hormone (CRH)* from the Hypothalamus.



- ↑ Cortisol = ↑ production of rT3 from T4 with a corresponding
  - ↓ free T3

- Not until Cortisol is corrected can there be an improvement in the production of T3.

ACTH and Cortisol

- 15% of Moderate to Severe TBI develop 1° or 2° Adrenal failure within 7-60 days.

- High Cortisol/DHEA Ratio=Active Depression
- Low Cortisol/DHEA Ratio=Depression Lessens

ACTH and Cortisol

Two peripheral systems for the regulation of Cortisol:

1. **Traditional**: CRH from the hypothalamus, inducing ACTH released from the pituitary causing an increase in adrenal cortical production and release of Cortisol.

2. **Non-Traditional**: Catecholamines stored in the splanchnic nerves can induce Cortisol production by release of dopamine, epinephrine, and norepinephrine and a wide variety of neuropeptides. (exercise and body trauma)

- **Due to the non-ACTH regulation of the adrenal cortex, you can have low levels of ACTH with high levels of Cortisol.**

Treatment

- Secondary Hormones
  - Pregnenolone
  - DHEA
  - Prolactin

Pregnenolone

A comparison of the pre- and postsynaptic effects of PS demonstrated that it was 100-fold more potent in inhibiting presynaptic GABAergic synaptic mechanisms than $GABA_A$ receptors.

The net effect is a reduction in neurotransmission with potential clinical impact on anxiety, panic attacks, agitation, aggression, and insomnia.

- **Social Phobias**

A Presynaptic Action of the Neurosteroid Pregnenolone Sulfate on GABAergic Synaptic Transmission. *Mol Pharmacol* 64:857–864, 2003 Zakaria MT, CHEDLISH, VI, and Jaideep: Kapur, Department of Neurology, University of Virginia Health Sciences Center, Charlottesville, Virginia

Pregnenolone Steal Syndrome

- S/S Chronic fatigue and adrenal insufficiency.

- Pregnenolone is “stolen” from the Steroidogenic Cascade as the substrate for cortisol instead of your other hormones.

- Pregnenolone is normal or elevated; DHEA is low to low-normal or;
  - *Pregnenolone and DHEA are low to low normal.*

- If stressed, the body uses Pregnenolone (and DHEA) to make Cortisol.

- W deficiency in Pregnenolone, Progesterone, or even 11 DOC, and DHEA will be reduced in production in favor of the adaptogenic Cortisol.

Pregnenolone Steal Syndrome

Pregnenolone levels can drop by:

- Statins
- Pregnenolone Steal Syndrome
- Rapid conversion to Cortisol (under stressors)

Benefits: Direct modulation of neurotransmission with stabilization of NMDA, $GABA_A$ and Sigma-1 Receptors.

Dose: Lab <100 Rx 30mg

>100 RX 60mg

Pregnenolone Steal Syndrome

Pregnenolone Steal	*Result*	*Median*
Pregnenolone	*131* ng/dL	110 ng/dL
Progesterone	*2.1* ng/ml	0.8 ng/ml
ACTH	35.8 pg/ml	35 pg/ml
Cortisol	*3.41* ug/dL	15 ug/dL
DHEA	106.2 ug/dL	245 ug/dL
free Testosterone	*8.76* ng/ml	14 ng/ml

DHEA and DHEA-S

- Stimulates oligodendrocytes to make myelin.
- Reduces Glia production of the inflammatory Cytokine IL-6.
- Protects the heart from Ischemic Heart Disease.
- Decreases cholesterol
- Decreases formation of fatty deposits
- Prevents blood clots
- Increases bone growth

DHEA and DHEA-S

- Promotes weight loss
- Increases brain function
- Increases lean body mass
- Increases sense of well-being
- Helps one deal with stress
- Supports the immune system
- Helps the body repair itself and maintain tissues
- Decreases allergic reactions
- Lowers triglycerides

DHEA and DHEA-S

- Raises HGH production during the night.
- Has an antidepressant effects (1952).
- Improves wound healing.

Measure DHEA-S Female 200-250 ug/dl

Male 500-600 ug/Dl

Rx: (F) 10-25 mg/d (M) 25-100 mg/d

Deficiency and Excess S/S are similar to Testosterone

DHEA Post TBI

- Double Blind Crossover study =
- 67% men and 84% women experience increased strength, energy and psychological well being after 3 months .
- 50% reduction in depressive symptoms.
- Increases Pregnenolone (Negative Feedback)
  - ⬆ Cortisol=
    - Mood elevation.

- Recommended Dose DHEA 25 mg with Pregnenolone 25 mg

Yen, SS Morales, AJ, et. al.; Replacement of DHEA in aging men and women. Ann NY Academy of Science 1995;774:128-142

Cortisol Treatment

1. Adaptogenic Herbs (See Supplements)
    - Rhodiola,
    - Ginseng,
    - Cordyceps
2. DHEA
3. Pregnenolone
4. Adrenal Glandulars

or

1. Adaptogenic Herbs
2. Adrenal Glandulars
3. Cortef (Low Dose) 7.5 mg am, 5 mg noon, 2.5 mg 4 pm

Cortisol and TBI

- Cortisol levels and symptom severity is due to the augmenting effects of cortisol on dopamine activity.
- Elevation of Dopamine can increase symptoms of Anxiety and Panic Attacks.
- Elevated dopamine levels decrease Prolactin Production
  - (Tip Off to Rx. Resistant Anxiety)

- Cognitive Functioning, Cortisol Release, and Symptom Severity in Patients with Schizophrenia. BIOL PSYCHIATRY 2000;48:1121–1132. Deborah J. Walder, Elaine F. Walker, and Richard J. Lewine. Departments of Psychology and Psychiatry, Emory University, Atlanta, Georgia.

Prolactin

<25% of range (2.5-19 ng/ml)= (<5.375 ng/ml) =

Elevated Dopamine or GABA.

S/S =anxiety, panic attacks, restlessness, and fidgetiness.

(Treatment Resistant Anxiety Look for Low Prolactin)

> 75% = HP axis damage **(16.125 ng/ml)**

Increase Prolactin = ⇩ LH = ⇩ Testosterone

Loss of Dopamine or GABA=

Pituitary Adenoma or Prolactinoma.

Biological Psychiatry. Vol. 32, No.11, Dec. 1992, Pages 1004–1011

Prolactin

Elevation in Prolactin:

- Diminishes LH production and release
- Lowers testosterone
- Causes of elevation:
  - Hypothalamic dysregulation of pituitary
  - Adenoma

Decreases of Prolactin:

- Caused by elevation in Dopamine
  - Edginess
  - Agitation
  - Aggressiveness
  - Anxiety
  - Panic

Prescriptions

Amantadine-Facilitates dopamine release, blocks MAO-A, NMDA receptors

Reduces Parkinson's s/s, extrapyramidal syndromes, akathisia

Improves apathy, mental clarity

Dose 100mg/d x 28 d then 2x/d

Statins- *Dose: Atorvastatin 10 mg within 24 hours of TBI*

Cerebral Blood Flow *:*

Decrease: Thrombosis, Platelet activity, Inflammatory cytokines

Cerebral edema, microglial activity, oxidative stress, Apoptosis

Increases: Neurogenesis, Angiogenesis

Prescriptions

Bromocriptine- *(Hyperprolactinemia)*

Down regulates prolactin (Stimulates prolactin inhibiting factor)

Dopaminergic effect-

Improves cognition

Dose: 2.5 mg 2-3 x/d

Selegiline- *(Apathy, Cognition)* *Dose: 5 mg 2x/d*

MAO-B inhibitor

Immune booster

Anti-neurodegenerative effect; Protects against DNA damage

Increases: Growth Hormone, nitric oxide and anti-inflammatory interleukins

Release SOD-free radical production inhibitor

Prevents/reverses iron induced memory loss

Supplements

Vitamin D3

MVI
Methylated B6, B12, Folate
Phosphatidylserine
L Threonine
DL-Phenylalanine
Zinc Citrate

Omega 3 FA

Ribose

Glutathione
Tocopherols
Ascorbic Acid
Carnosine
Melatonin
Lipoic Acid
PQQ
Coenzyme Q 10
Quercetin

Supplements

Vitamin D3

(Measure 25 OH Vitamin D-Normal 30-100 ng/ml, goal 50-80 ng/ml)

↑ nerve growth in the brain

Planning, processing information, formation of new memories.

↓ vitamin D levels = poor brain function

Sun Exposure for 20 minutes adds 20,000 IU/d.

Supplementation: for every 1000 IU ↑ blood level by 8 ng/ml

Use at bedtime

Supplements

Methylated B6, B12, Folate-Synthesizes neurotransmitters.

Malfunction of the methylation cycle is due to diet deficient in B6, B12, Folate

- Lab: ↑ **homocysteine (Goal <10)**

Normal Homocysteine ensures proper metabolism of neurotransmitters

Balances mood

Cognition

Maintains Brain Volume

Mental fogginess and Memory Retention

Slows Brain Atrophy in Elderly

Peripheral Neuropathy

Supplements

Phosphatidylserine

- Major component of cell membranes
- Releases neurotransmitters and has role in synaptic activity
- Supports brain function
- Mental concentration, memory retention

- Dose: 100 mg 3x/d or 300 mg @ bedtime

L-Theanine

- Reduces anxiety
- Blocks excitatory stimuli at glutamate receptors in the brain
- Stimulates inhibitory, GABA.
- Relieves stress without drowsiness or impairing motor behavior.
- Improves alertness and attention.
- Supporting cognitive function and preventing cognitive loss
- Stroke prevention
- Schizophrenia s/s reduction
- **Dose: 250-400 mg @ bedtime**

Supplements

DL-Phenylalanine

- Essential amino acid DLP is a precursor to as dopamine, norepinephrine, epinephrine, and serotonin.
- Increases mental alertness, controls addictive substance abuse, promotes sexual arousal, and releases Ghrelin, an appetite curbing hormone.
- Breaks down opiate-like substances enkephalins in the brain.
- Modulates chronic pain.
- Supports emotional well being, memory and learning. Promotes endorphin release. Calms stressed joints and muscles.
- ***Think cravings, substance withdrawal***

Supplements

Supplements

Zinc Citrate

- Deficiency associated with decreased Testosterone, increased Estradiol.
- Synthesizes and secretes LH and FSH
- Essential role in gonadal differentiation, testicular growth and development of seminiferous tubules, spermatogenesis, testicular steroidogenesis, androgen metabolism and interaction with steroid receptors.
- Zinc supplementation results in an increase in serum testosterone.
- Acts as Aromatase (Estradiol Synthetase Enzyme)
- **Dose: Zinc CItrate**
  - Zinc less than 50 mcg/dL; RX 30mg Zinc Citrate BID to TID
  - Zinc greater than 50 mcg/dL; 30 mg/Day.

Supplements

Diindolylmethane (DIM)

A metabolite of indole–3–carbinol (I3C) found in cruciferous vegetables such as; broccoli, kale and Brussels sprouts.

Anti-carcinogenic, anti-oxidant, anti atherogenic effects

3,3'-Diindolylmethane Inhibits Lipopolysaccharide-Induced **Microglial Hyperactivation** and Attenuates Brain Inflammation

Reduces TNF-alpha, IL-6, IL-Beta, NF-*KB, PGE2*

Think “Non Hormonal Relief of estrogen Deficiency Symptoms”

Dose: 100 mg 2-3 x/d

Supplements

Omega 3, Omega 6 Fatty Acids (Dose: 1000-4000 mg/d)

- Major constituent of the cell membrane
- Reduces irregular phospholipid metabolism during neuronal damage.
- Omega-3 FAs available:
  - Alpha Linolenic Acid (**ALA**), Eicosapentaenoic acid (**EPA**), and Docosahexaenoic acid (**DHA**).
- Arachidonic Acid, the primary N-6FA in the brain →
  - Cyclooxygenase (COX) and lipoxygenase (LOX) enzyme metabolism →
    - Pro-inflammatory O6/O9 that →
      - **increases cerebral edema, ischemia,**
      - **infiltration of leukocytes,**
      - **production of pro-inflammatory cytokines.**

Supplements

Ribose (Dose: 5 grams 3x/d)

- Phosphorylated to become ATP, in fact the backbone of all energy molecules. (Energy)
- Core of RNA, mRNA, tRNA and DNA.
- Transports inorganic phosphate into Oxidative Phosphorylation. (Energy - R-5-P)
- Poly (ADP-ribose) polymerase-1 (PARP-1), the DNA repair enzyme.

- "Think" Energy
- Approximately 66% of patients experienced significant improvement while on D-ribose, 45 % increase in energy.
- Average improvement in overall well-being of 30% ($p < 0.0001$).

The use of D-ribose in Chronic Fatigue Syndrome and Fibromyalgia: a pilot study. Journal of alternative and complementary medicine. Volume 12 number 9. pages 857-862. 2006.

Supplements

Glutathione

- Tripeptide (glu-cys-gly); most abundant non-protein thiol found in the brain.
- Glutathione acts as an antioxidant
  - Serves as a substrate for the enzyme glutathione peroxidase.
  - Mainly found in astrocytes.
- Functional impairment associated with glutathione deficiency

Dose: 50-100 mg 1-2 times/day in liposomal base or
600-1000 mg IV push (diluted in 3 cc NSS) over 5 minutes.

Note: Do not mix with Vitamin C

Supplements

N-Acetyl Cysteine (NAC)

Glutathione Precursor

Anti-oxidant, free radical capabilities against Superoxides, H2O2and hydroxyl radicals.

Neurovascular-protective effects after TBI.

Early post-injury treatment with NAC reversed behavioral deficits associated with mTBI.

NAC + Vitamin E ⇩ Nf KappaB

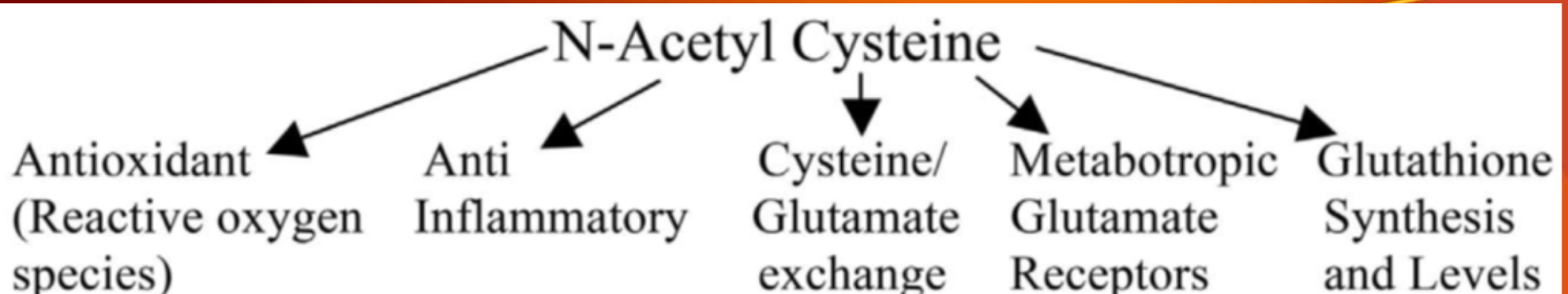
Efficacy of N-Acetylcysteine in Traumatic Brain Injury. PLOS ONE,April **2014**,Vol 9,4 , Katherine Eakin L., Renana Baratz-Goldstein, Chiam G. Pick, Ofra Zindel, Carey D. Balaban, Michael E. Hoffer, Megan Lockwood1, Jonathan Miller , Barry J. Hoffer , Dept of Neurosurgery, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA, Dept of Anatomy and Anthropology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel, Dept of ENT, Neurobiology, Communication Sciences and Disorders, and Bioengineering, U of P, PA, USA, Dept of ENT, Spatial Orientation Center, Naval Medical Center San Diego, San Diego, Ca, USA, Graduate Program in Neurodegeneration, Taipei Medical University, Taipei City, Taiwan

Supplements

N-Acetyl Cysteine (NAC)

A 4 gram loading dose was given followed by 2 grams twice a day, then reduced to 1.5grams BID after 4 days.

Early treatment with NAC resulted in a seven day symptom resolution rate of 86% as compared to 11% in those receiving placebo and began therapy between 24–72 hours after blast exposure.



Tocopherols and Tocotrienols

- Vitamin E compounds
  - Tocopherols (alpha-, beta-, gamma-, and delta-)
  - Tocotrienols (alpha-, beta-, gamma-, and delta-).

- Vitamin E is a potent, lipid-soluble, antioxidant with neuroprotective benefits.

- Pre-traumatic supplementation with alpha-tocopherol reduces TBI-induced lipid peroxidation, oxidative injury, and impairment in spatial memory.

- Gamma-tocopherol most effective scavenging free radicals and reducing nitrogen oxygen species causing inflammation (RNS).

- Promotes nerve regeneration

Dose: Mixed Tocopherols (Gamma 500 mg/ Alpha 400 mg) 1-3 times /day

Supplements

Ascorbic Acid

- Vitamin C is distributed throughout the brain
- Concentration in CSF is about tenfold higher than in plasma.
- Serves as a strong reducing agent
- Donates electrons directly neutralizing ROS
- Recycles the Tocopherol radical to its active reduced form.
- Dose: Ascorbyl palmitate form:500-1000 mg 2x/d
  - IV 15-25 gm Vitamin C in 500 cc NSS over 1-2 hours 1/wk
    - (Do not use if G6PD deficient)

Supplements

L-Carnosine

- Dipeptide found in glial and neuronal cells throughout the brain.
- Acts as a chelator for divalent cations like Cu2+ and Zn2+
- Suppresses amyloid-beta peptide toxicity
- Inhibits production of oxygen free-radicals, scavenge hydroxyl radicals and reactive aldehydes,
- Suppresses protein glycation.
- Carbonic acid activator (CA is decreased in Alzheimer's)
- Stimulates proteolysis, dissipates cross linkages, reduces inflammation

Dose: Stand alone-1000 mg/d

In combo w pregnenolone, quercetin, DHEA use 250 mg.

Supplements

Melatonin

- Produced in the pineal gland
  - Crosses the blood brain barrier; Enters neurons and glial cells.
  - Potent scavenger of peroxyl and hydroxyl radicals
  - Prevents initiation and propagation of lipid peroxidation
  - Stimulates brain glutathione peroxidase.

- Acts as an antioxidant in both lipophilic and hydrophilic environments
- Inhibits nitric oxide synthase (NOS)
  - Prevents the toxic effect obtained after its interaction with superoxide radicals.

Dose: 0.5 mg/night 2 hours before bedtime. Every 7 nights increase 0.5 mg nightly until "hungover in am." Then decrease by 0.5 mg until no longer foggy in am

ER form used for those unable to stay asleep

Supplements

Alpha Lipoic Acid-

Lipid peroxyl radical (LOO•) scavenger.

Neuroprotective

Regenerates other endogenous electron-donating antioxidants:

- Vitamin E
- Glutathione
- Vitamin C.

Dose; 400-800 mg 1/d

Supplements

Curcumin

- Immune modulator, antioxidant, anti inflammatory
- Reduces chemokines
- Reduces free radicals and improves cell viability in oxidative stress environment
  - Useful in Alzheimer's
- Anti-inflammatory, anti-carcinogenic, anti-infertility, anti-bacterial, anti-diabetic, anti-venom, anti-fibrotic, hypotensive activity.

Dose: 400-600 mg 2-3 times/d

Supplements

CoEnzyme Q 10

- Potent free radical scavenger in lipid and mitochondrial membranes.
- Increases cerebral cortex concentrations
  - » increase in cerebral cortex mitochondrial concentrations of CoQ10.
- Exerts neuroprotective effects in neurodegenerative diseases associated with TBI.
- Preserves respiratory and cardiac mitochondrial function.

Dose: 100 mg./d + 100mg for every “risk” factor (Cardiac, respiratory, disease, statin therapy, neurologic compromise)

Use w/ PQQ

Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc. Natl. Acad. Sci. USA Vol. 95, pp.8892–8897, July 1998 Medical Sciences Coenzyme. Russell T Matthews, L. Yang, S. Browne, M. Baik, F. Beal., Neurochemistry Laboratory, Neurology Service, Mass. General and Harvard Medical School, Boston, MA 02114

Supplements

PQQ

- Antioxidant, influences nerves
- Maintains mitochondrial hemostasis
- Promotes nerve growth factor
- Supports intracellular neuronal response
- Maintains NMDA receptor activity
- Promotes learning and memory

- Dose: Use with CoEnzyme Q 10 20 mg PQQ and 100 mg Co Q 10

Supplements

***Quercetin* = Energy and Allergies**

Similarity to resveratrol in generating mitochondrial biogenesis.

- Increases mRNA expression of: PGC-1α, SIRT1, mtDNA, and cytochrome c concentrations.
-
- Increases production of ATP.
- Increases Glutathione Levels
- Effective (when combined w stinging nettle) in allergy relief.
- Protects **neuronal cells from oxidative stress-induced neurotoxicity**.

Protective Effect of Quercetin in Primary Neurons Against Aβ (1-42): Relevance to Alzheimer's Disease. Mubeen Ahmad Ansari, Hafiz Mohammad Abdul, Gururaj Joshi, Wycliffe O. Opii, and D. Allan Butterfield, Dept of Chemistry, Center of Membrane Sciences, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536, USA

Supplements

Quercetin

- Cerebral metabolism has important consequences on motivation, mood, fatigue, anxiety, depression, and central motor drive from the cortex; **ATP dependent.**

- Within 7 days of introduction of Quercetin, mitochondrial biogenesis with increased oxidative phosphorylation by facilitating transcription, translation, and replication are recorded. = Energy

    - Dose: 500 mg 2x/d

Quercetin increases Brain and Muscle Mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol 296: R1071–R1077, 2009. J. Mark Davis, E. Angela Murphy, Martin D. Carmichael, and Ben Davis. Div. of Applied Physiology, Dept of Exercise Science and Dept of Com. Science and Disorders, Arnold School of Public Health, U. of South Carolina, Columbia, South Carolina. USA.

OLIVIA G.

Female Hormone Testing	Result	Range
Growth Hormone	0.6	5ng/ml*
Somatomedin C (IGF-1)	78	> 200 ng/ml
IGFBP-3	2950	>4000 ng/ml
DHEA-S	49.2	195 ug/dl*
Estrone (E1)	274	< 200 pg/ml*
Estradiol (E2)	191	90 pg/ml*
Progesterone	.06	5-7 ng/ml*
Pregnenolone	131	100 ng/dl*
EP Ratio	3457	< 250

DHT	*23*	*< 30ng/Dl*
SHBG	*88*	*< 75 pg/ml*
FSH	*6.8*	*7 mIU/ml**
LH	*5.0*	*5.1mIU/ml*
Prolactin	*7.2*	*14 ng/ml**
Zinc	*89*	*95mcg/dL*
Insulin	*8*	*<30mIU/L*
Vitamin D3	*17*	*>60 ng/dl**
ACTH	*35.6*	*35 pg/ml**
Cortisol	*3.41*	*< 15 ug/dl*

Testosterone Free	0.8	2-4 pg/ml*
Testosterone Total	12.7	<44 ng/ml*

TSH	0.98	<2.5 mcu/ml*
T3, Free	3.6	> 2.5 pg/ml
T4, Free	1.8	> 1.5 ng/ml
rT3	168	80-250 pg/ml
T3/rT3 Ratio	2.14	>1.06
TPO	19	<35

FIXING OLIVIA G.

1. GH Deficiency
2. Estrogen Dominance
3. Hypoprolactinemia
4. Low Vitamin D3
5. Low Testosterone
6. Pregnenolone Steal

1. **Secretagogue 2-3 Sprays at hs.**
2. **Progesterone**
   a. **1 gm @ hs 5% Cream nites 14-25 or 100 mg po**
3. **GABA/5 HTP**
4. **Vit. D3 q 1000 IU inc level 8 ng/dL**
5. **Zinc CItrate 50 mg**
6. **Pregnenolone 30 mg/DHEA 25 mg**

Male Testing	Result	Range
Growth Hormone	4.7	5ng/ml*
Somatomedin C (IGF-1)	232	> 200 ng/ml
IGFBP-3	4182	>4000 ng/ml
DHEA-S	88	245 ug/dl*
Estrone (E1)	<5	< 60 pg/ml*
Estradiol (E2)	68	<25 pg/ml*
Progesterone	0.96	0.8 ng/ml*
Pregnenolone	121	110 ng/dl*
EP Ratio		< 250

DHT	33	< 55 ng/Dl
SHBG	58	< 75 pg/ml
FSH	5.8	7 mIU/ml*
LH	8.9	5.1mIU/ml
Prolactin	13	14 ng/ml*
Zinc	68	95mcg/dL
Insulin	19	<30mIU/L
Vitamin D3	99	>60 ng/dl*
ACTH	42	35 pg/ml *
Cortisol	22	< 15 ug/dl

Joel P.

Testosterone Free	2.8	12-14 pg/ml*
Testosterone Total	262	690 ng/ml*

TSH	0.99	<2.5 mcu/ml*
T3, Free	3.1	> 2.5 pg/ml
T4, Free	1.8	> 1.5 ng/ml
rT3	32.6	80-250 pg/ml
T3/rT3 Ratio	0.95	>1.06
TPO	199	<35

Fixing Joel P.

Diagnosis

1. Hypogonadism/Excess Estrogen
2. Adrenal Excess
3. Hashimoto's Thyroiditis
4. Hyperinsulinemia (Mild)

Treatment

1. Testosterone 60 mg IM weekly or 1000 mg Pellets
2. Zinc Citrate 30 mg bid
3. DHEA/Pregnenolone 50mg/50 mg
4. Adaptogenic Herbs or Cortef 5 mg/d
5. Plant Sterolins/LDN (TPO)
6. Cinnamon/Chromium/Berberine
7. 4 Point Cortisol Saliva Test

3 Year Study-Millennium WAF Project

200 Vets and Active Military

- **History of TBI**
- **PTSD**
- **Blast Trauma,**
- **Treatment Resistant Depression**

3 Year Study-Millennium WAF Project

- Laboratory Evaluation as Noted Above
- Treatment
  - Supplements
    - N-Acetylcysteine
    - Tocopherols
    - EPA/DHA
    - Alpha Lipoic Acid
    - PQQ
    - Quercetin

3 Year Study-Millennium WAF Project

- **Hormone Restoration**
  - **Clomid**
  - **Thyroid**
  - **Testosterone Cypionate/Propionate**
  - **Estrogen/Progesterone (when indicated)**

3 Year Study-Millennium WAF Project

No. #	Mean Age	Program Time	History of Suicide	Medication Status (%off)	Median Improvement
57m/1f	39.8	415 Days	2 attempts	90%	73%
Ranges	23-77 YRS	125-1069 Days	1- 6x	4-16 meds	10% - 100%

No.	Clomid (CPC)	Testosterone (TPC)	Combination (CPC+TPC)
57/1	**47**	**11**	3

91% had a 50% improvement in 90 days.

58 military individuals, 57 males and 1 female, a variety of traumas(TBI), with and without PTS, all on multiple medications, multiple suicide attempts, and disrupted socialization. Average of treatment time 415 days (13.5mos), 90% off medication with a 73% improvement in overall condition.

Data: % Improvement & Ages

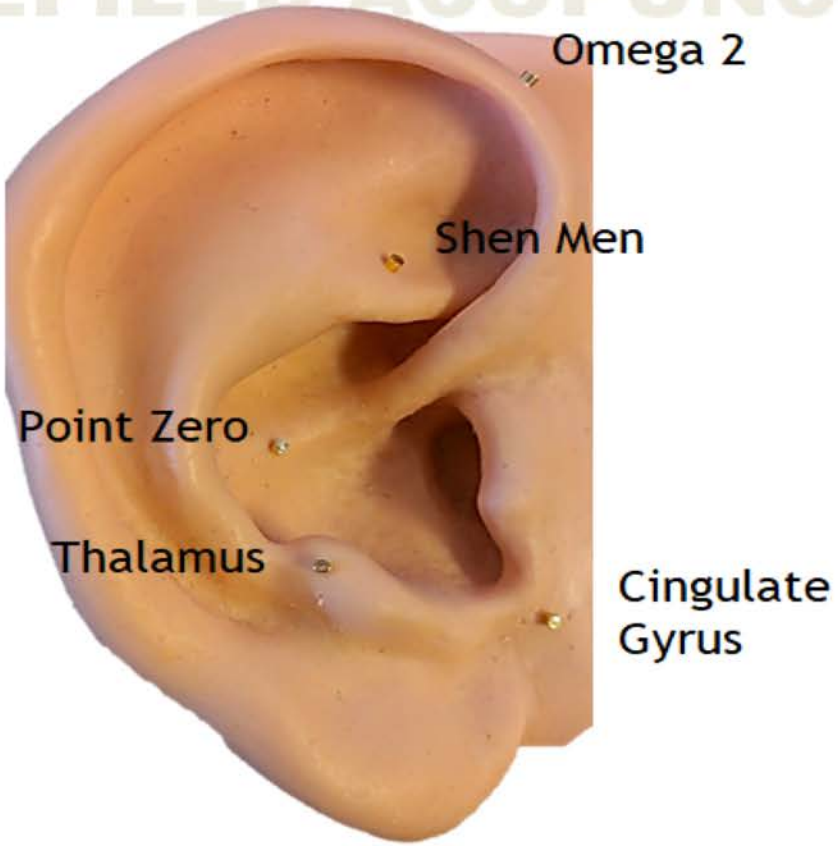
91% with a 50% or greater response.

Population by Age					
20s	30s	40s	50s	60s	70s
6	29	13	5	3	2

Distribution - Percent Improvement									
10%	20	30	40	50	60	70	80	90	100%
4	1	0	0	6	7	13	8	9	9

Age Group to Percent Improvement						
Age	20-29	30-39	40-49	50-59	60-69	70-79
%	77.5	73.8	69.2	67.0	80.0	57.5

BATTLEFIELD ACUPUNCTURE (BFA)



Conclusion

- **80% of TBI Injuries are mild without LOC**
- **Acute hormone deficiencies occur in 56% of Head Injuries**
- **36% continue on to Chronic Hormone Deficiency**
- **Psychotropic Meds Mask Symptoms**
  - **Psychotropic meds do not address underlying cause**
- **Plan: Replace Deficient Hormones to Physiologic Levels**