The Endocrinology of Traumatic Brain Injury

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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 Sustain

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

https://www.cdc.gov/traumaticbraininjury/data/rates.html
TBI Defined

• A traumatically induced:
  – Structural injury or
  – Physiological disruption of brain function as a result of an external force.
Is it a TBI?

• New onset or worsening of:
  – Loss of or a decreased level of consciousness
  – Loss of memory for events immediately before or after the injury (posttraumatic amnesia)
  – Altered mental state at the time of the injury
Is it a TBI?

• Confusion, disorientation, slowed thinking, alteration of consciousness/mental state)

• Neurological deficits (e.g., weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia) that may or may not be transient.

• Intracranial lesion
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

PTSD
- Reexperiencing symptoms
- Shame
- Guilt

TBI
- Depression/anxiety
- Insomnia
- Irritability/anger
- Trouble concentrating
- Fatigue
- Hyperarousal
- Avoidance

PPCS
- Headache
- Sensitivity to light (and sound)
- Memory deficit
- Dizziness
TBI = Physical S/S

• PTSD
• =
• Psychologic Diagnosis

PTSD
Flashbacks
Avoidance
Hypervigilance
Nightmares
Re-Experiencing Phenomenon

PTS is a Continuum of untreated TBI.
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

Most likely to Sustain TBI:
- Age 0-4
- 15-19
- 65 and Up

Children Ages 0-14 account for 500,000 ER visits/yr.

Males account for > 2x the # of TBI’s vs. females

Adults > 75 have the highest rates of death and hospitalization due to TBI

Children Ages 0-14 account for 500,000 ER visits/yr.
Traumatic Brain Injury by External Cause

- Fall: 35.20%
- MVA: 17.30%
- Struck by Object: 16.50%
- Assault: 10%
- Misc.: 21%
TBI Demographics

1. Sports Injuries - 1.6-3.8 million/yr.
2. Alzheimer’s Risk - increased by 2.3-.4.5 x risk than with no TBI
3. Blast Exposure - Leading cause of TBI in Military Personnel
4. 30% of Military Personnel Diagnosed with TBI
Department of Defense

Represents 6.8% of entire armed forces of the US

Increase from 4.2% after 2011 census

TBI Severity

DoD Numbers for Traumatic Brain Injury
Worldwide – Totals

2000 - 2017 (Q1-Q2)

- Penetrating: 5,131
- Severe: 3,895
- Moderate: 34,926
- Mild: 305,140
- Not Classifiable: 21,596

Total - All Severities: 370,688

Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSC)

Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

*Percentages do not add up to 100% due to rounding

2000-2017 (Q1-Q2), as of August 10, 2017
TBI Demographic Pearls

• 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
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%)
Traumatic Brain Injury

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

Clinical Assessment:

PHQ-2 (Pt. Health Questionnaire-2)
PHQ-9 (Pt. Health Questionnaire-9)
GAD 2 (Generalized Anxiety Disorder 2)
GAD 7 (Generalized Anxiety Disorder 7)
PTSD Screener
The Patient Health Questionnaire-2 (PHQ-2)

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Date of Visit</th>
</tr>
</thead>
</table>

Over the past 2 weeks, how often have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th></th>
<th>Not At all</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
# PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use ✔️ to indicate your answer)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

For office coding: 0 + _____ + _____ + _____

= Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult
<table>
<thead>
<tr>
<th>Mental/psychological/emotional status.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>I have noticed an increase in Mental Energy.</em></td>
</tr>
<tr>
<td><em>My sleep has improved in __________________________ quantity, __________ quality, __________ less interruption.</em></td>
</tr>
<tr>
<td><em>I am sleeping less and wake up feeling more refreshed</em></td>
</tr>
<tr>
<td><em>My over-all emotional status has improved.</em></td>
</tr>
<tr>
<td><em>My memory has improved.</em></td>
</tr>
<tr>
<td><em>My libido (sex drive) has increased.</em></td>
</tr>
<tr>
<td><em>My erections have improved. (male)</em></td>
</tr>
<tr>
<td><em>My orgasms have improved</em></td>
</tr>
<tr>
<td><em>I have an increased sense of well-being.</em></td>
</tr>
<tr>
<td><em>I feel calmer under stress.</em></td>
</tr>
<tr>
<td><strong>Physical Status</strong></td>
</tr>
<tr>
<td><em>I have generally more physical energy.</em></td>
</tr>
<tr>
<td><em>When I exercise I have more energy and feel stronger.</em></td>
</tr>
<tr>
<td><em>I can perform physically longer without the expected fatigue.</em></td>
</tr>
<tr>
<td><em>My athletic performance has improved over-all.</em></td>
</tr>
<tr>
<td><em>I recover faster after exercise.</em></td>
</tr>
<tr>
<td><em>Joint aches and pains are less.</em></td>
</tr>
<tr>
<td><em>My hair is growing faster.</em></td>
</tr>
<tr>
<td><em>The color of my hair is darkening.</em></td>
</tr>
<tr>
<td><em>My nails are harder or growing faster.</em></td>
</tr>
<tr>
<td><em>Facial texture has improved.</em></td>
</tr>
<tr>
<td><em>Wrinkles have decreased.</em></td>
</tr>
<tr>
<td><em>Skin thickness has increased.</em></td>
</tr>
<tr>
<td><em>The numbers of cold or illnesses I experience a year have decreased.</em></td>
</tr>
<tr>
<td><em>Colds, flu-symptoms are less intense and last less time.</em></td>
</tr>
</tbody>
</table>
Physical Diagnosis:

Glasgow Coma Scale
(Acute Field Assessment Rating)
# Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Opening</td>
<td>1. No response</td>
</tr>
<tr>
<td></td>
<td>2. To pain</td>
</tr>
<tr>
<td></td>
<td>3. To speech</td>
</tr>
<tr>
<td></td>
<td>4. Spontaneously</td>
</tr>
<tr>
<td>Verbal</td>
<td>1. No response</td>
</tr>
<tr>
<td></td>
<td>2. Incomprehensible sounds</td>
</tr>
<tr>
<td></td>
<td>3. Inappropriate words</td>
</tr>
<tr>
<td></td>
<td>4. Confused</td>
</tr>
<tr>
<td></td>
<td>5. Oriented to time, person and place</td>
</tr>
<tr>
<td>Motor</td>
<td>1. No response</td>
</tr>
<tr>
<td></td>
<td>2. Abnormal extension</td>
</tr>
<tr>
<td></td>
<td>3. Abnormal flexion</td>
</tr>
<tr>
<td></td>
<td>4. Flex to withdraw from pain</td>
</tr>
<tr>
<td></td>
<td>5. Moves to localised pain</td>
</tr>
<tr>
<td></td>
<td>6. Obey command</td>
</tr>
</tbody>
</table>

**Total Score**

- Best score - 15
- Comatose - ≤8
- Unresponsive - 3
Interpreting the Glasgow Coma Score

- Mild: Glasgow Score < 1
- Moderate: Glasgow Score 1-9, Lose Consciousness 1-24 hours, Post Traumatic Amnesia 1-7 days
- Severe: Glasgow Score > 9, Lose Consciousness > 24 hours, Post Traumatic Amnesia > 7 days
Repetitive Head Injury Sequelae

• 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

• 50% Greater Rate of Suicide in Military than Civilian Population
  
  Reuters, US Military Veteran Suicides Rise. One Dies Every 65 Minutes, 2/1/2013
  C Span, June 2016
Many seemingly innocuous head injuries do not manifest themselves weeks, months or even years after the fact.

Severity of Injury Does Not = Severity of Long Term Sequelae
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.)

Glasgow 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
10 Most Common Symptoms of mTBI

1. Fatigue (100% of patients)
2. Excessive sleepiness +/- disturbed sleep patterns.
3. Inattention with difficulty concentrating
4. Impaired memory
5. Faulty judgment with slowed thinking.
6. Depression w/wo Anxiety and Panic Attacks.
7. Irritability with emotional outbursts of Anger.
8. Diminished libido.
9. Difficulty switching between two tasks.
10. Alcohol Abuse w/wo Drugs.
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
- Slowed thinking
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.
Focal Areas of Damage Extend Phase I into Phase II

**Thalmus:**
(Damage=Coma)
- Regulates Sleep, Wakefulness
- Processes and relays sensory information to cerebral cortex
- Regulates consciousness, arousal, awareness, activity

**Hypothalamus**
(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
Figure 1
Proportions of patients (n = 45) presenting hormone values above or below laboratory reference interval day 1 and day 4 after sTBI. Reference intervals are given in Table 1.
“Traditional Management of TBI”

• **Antihypertensives** - Prevent exacerbation of intracerebral hemorrhage in hypertensive encephalopathy. E.g. 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/neck pain caused irritative effect of the subarachnoid blood. Reduces Cerebral Edema
“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 with Neuroinflammation Leading to Brain Hormone Disruption

Difficulty reading
Fatigue worsening
“Depressed”
Easily provoked, hypersensitive.
Cries easily.
Sent home from school for disruptive behavior.
Corrective lenses prescribed
“I hate them.”

PE: General: Normotensive
Appears subdued.

Plan: Rx by Psychiatry,
Rx: Mirtazapine 30 mg. 1 @ bedtime
FDA warning: Suicide risk

- This drug has a black box warning. This is the most serious warning from the Food and Drug Administration (FDA). A black box warning alerts doctors and patients about drug effects that may be dangerous.
- Mirtazapine may cause an increase in suicidal thoughts or actions. This risk is higher in children, teenagers, and young adults. It’s also higher within the first few months of treatment and during dosage changes. You and your family members, caregivers, and doctor should watch for any new or sudden changes in your mood, behaviors, thoughts, or feelings. Call your doctor right away if you notice any of these changes.
Long Term Sequelae of TBI

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

<table>
<thead>
<tr>
<th>Axis I</th>
<th>48.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>26.7%</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>11.7%</td>
</tr>
<tr>
<td>Phobias</td>
<td>8.3%</td>
</tr>
<tr>
<td>Panic Disorders</td>
<td>8.3%</td>
</tr>
<tr>
<td>Paranoia</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
### Axis II Psychopathology in TBI

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline Personality Disorder</td>
<td>34%</td>
</tr>
<tr>
<td>Obsessive-Compulsive Syndrome</td>
<td>27%</td>
</tr>
<tr>
<td>Paranoia</td>
<td>26%</td>
</tr>
<tr>
<td>Avoidance</td>
<td>26%</td>
</tr>
<tr>
<td>Antisocial Personality</td>
<td>21%</td>
</tr>
</tbody>
</table>

What Are Missing?

Functional Areas of the Brain

- **Motor Area**: control of voluntary muscles
- **Sensory Area**: skin sensations (temperature, pressure, pain)
- **Frontal Lobe**: movement, problem solving, concentrating, thinking, behaviour, personality, mood
- **Occipital Lobe**: vision, perception
- **Parietal Lobe**: sensations, language, perception, body awareness, attention
- **Wernicke’s Area**: language comprehension
- **Broca’s Area**: speech control
- **Temporal Lobe**: hearing, language, memory
- **Cerebellum**: posture, balance, coordination of movement
- **Brain Stem**: consciousness, breathing, heart rate
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 right 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 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.
HOW TRAUMATIC BRAIN INJURY (TBI) AFFECTS DAILY LIFE

**HEALTHY**
- Frontal: Concentration, Problem Solving, Speech
- Parietal: Sense of Touch, Pain, Temperature
- Occipital: Healthy Vision
- Temporal: Memory, Organization
- Cerebellum: Balance & Coordination
- Brainstem: Breathing, Steady Heart Rate

**TBI**
- Frontal: Lack of Focus, Irritability, Language Difficulty
- Parietal: Difficulty with Reading, Spatial Misperception
- Occipital: Blind Spots, Blurred Vision
- Temporal: Problems with Short- & Long-Term Memory
- Cerebellum: Difficulty Walking, Slurred Speech
- Brainstem: Changes in Breath, Difficulty Swallowing

Data © Mayfield Clinic
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.
IMPORTANT WARNING:

A small number of children, teenagers, and young adults (up to 24 years of age) who took antidepressants (‘mood elevators’) such as venlafaxine during clinical studies became suicidal (thinking about harming or killing oneself or planning or trying to do so). Children, teenagers, and young adults who take antidepressants to treat depression or other mental illnesses may be more likely to become suicidal than children, teenagers, and young adults who do not take antidepressants to treat these conditions. However, experts are not sure about how great this risk is and how much it should be considered in deciding whether a child or teenager should take an antidepressant. Children younger than 18 years of age should not normally take venlafaxine, but in some cases, a doctor may decide that venlafaxine is the best medication to treat a child’s condition.

You should know that your mental health may change in unexpected ways when you take venlafaxine or other antidepressants even if you are an adult over 24 years of age. You may become suicidal, especially at the beginning of your treatment and any time that your dose is increased or decreased. You, your family, or your caregiver should call your doctor right away if you experience any of the following symptoms: new or worsening depression; thinking about harming or killing yourself, or planning or trying to do so; extreme worry; agitation; panic attacks; difficulty falling asleep or staying asleep; aggressive behavior; irritability; acting without thinking; severe restlessness; and frenzied abnormal excitement. Be sure that your family or caregiver knows which symptoms may be serious so they can call the doctor if you are unable to seek treatment on your own.
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

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 with 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 = 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

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
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 R. Hatcher, Ph.D.,
Associate Dean
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.”
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
Treatment Resistant Depression/Anxiety

**Traditional Rx. of Treatment Resistant Depression/Anxiety**

1. 2 SSRI’s + 1 SNRI + CBT  
2. Psychiatric Referral  
3. Evaluate for Comorbidities  
4. Add Tricyclic Antidepressant + Atypical Antidepressants  
5. Add atypical antipsychotics  
   a. Pregabalin  
   b. Gabapentin
Ah Ha! Moment

Figure. Treatment algorithm for treatment-resistant depression

Lack of response to current antidepressant

- No improvement at all or intolerable adverse effects

“True TRD”

- Switch to another antidepressant drug of the same class or another class

Partial and unsatisfying improvement

Augmentation strategies (eg, other antidepressant, lithium, atypical antipsychotic) or combination with psychotherapy (CBT)

Nonresponse to 2 or 3 adequate antidepressant trials

Neurostimulation (eg, rTMS or ECT), antidepressants with innovative mechanism of action

“Pseudo-TRD” (eg, hypothyroidism, nonadherence, “latent” bipolarity)

TRD, treatment-resistant depression; CBT, cognitive-behavioral therapy; rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsant therapy.
33% of TBI Patients have Abnormal Prolactin Levels 3 Mo Post Injury
A Major side effect of antidepressant therapy is Abnormal Prolactin Levels

- **Low Prolactin=**Treatment Resistant Depression/Anxiety

- Increased dopamine suppresses *Prolactin Inhibiting Factor*
  =Decreased production of Prolactin from the Anterior Pituitary.

**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
The Missing Link?

TBI

Comorbid Affective Disorders

Disruption of the Normal Hormonal Symphony

Peripheral Hormone Insufficiencies and Deficiencies

YES
S/S 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/
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.

Major Hormonal Deficits in Treatment Resistant Depression

- Growth Hormone
- Testosterone
- Thyroid Hormone
- Cortisol (Elevated)
- Prolactin
### What Does the Literature Say?

<table>
<thead>
<tr>
<th>Hormones and Depression</th>
<th>Google Scholar “Hits” 2000-2012</th>
<th>Google Scholar “Hits” 2000-2016</th>
<th>Google Scholar “Hits” 1/2/2017-9/15/2018</th>
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<tr>
<td>Testosterone and Depression</td>
<td>70,400</td>
<td>128,000</td>
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<tr>
<td>Estrogen and Depression</td>
<td>51,000</td>
<td>59,700</td>
<td>15,200</td>
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<tr>
<td>Cortisol and Depression</td>
<td>80,300</td>
<td>132,000</td>
<td>17,200</td>
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<tr>
<td>Thyroid and Depression</td>
<td>77,600</td>
<td>123,000</td>
<td>18,000</td>
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<tr>
<td>Prolactin and Depression</td>
<td>23,800</td>
<td>26,500</td>
<td>5830</td>
</tr>
<tr>
<td>GH and Depression</td>
<td>111,000</td>
<td>153,000</td>
<td>17,600</td>
</tr>
</tbody>
</table>
So, What’s Going On? What Are We Missing?

Trauma to the body or directly to the skull → neurotrauma.

Neurotrauma has two components:

1. Tissue damage
2. Neuro-inflammation

The combination of tissue damage and inflammation =

• Alteration in the molecular biochemistry of the brain
• Alteration the physiology of neuronal functioning

“OXIDATIVE STRESS”
Phase II: Oxidative Stress

Oxidative Stress
- Reactive Oxygen
- Reactive Nitrogen
- Lipid Peroxidase

Neurosteroids
- Deficiencies
- Enzyme Inhibition
- Retarded production

Inflammation
- TH1
- Cytokines
- Chemokines

Disruption of BBB
- Hypoxia
- Ischemia
- Cerebral Edema

Secondary Phases of Trauma

Mitochondrial Dysfunction
BAX ▶ AIF, CytoC.

Excitotoxicity
- Glutamate
- Calcium

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

Cell Death
- Necrosis
- Apoptosis
- Cavitation
- Loss of Brain
**What the Heck Is a “Neurosteroid?”**

**Neurosteroids**-Hormones regionally in the manufactured in the brain.

**Neuroactive Steroids**-Traditional Concept of Hormones produced in Peripheral glands

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

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

Steroidogenic Pathways

Cholesterol
- Congenital adrenal hyperplasia (CAH), smoking, E2, progesterone, azole antifungals, spironolactone

Pregnenolone
- Hypergycemia, azole antifungals, aging, smoking, dioxin toxicity, HIV, licorice, etomidate, barbezoate

17-Hydroxylase
- PCB toxicity, DHEA, antiepileptics

17,20-Lyase
- CAH, chronic ETOH ingestion, PCOS (ovary), stress, alcohol, antiepileptics

DHEA
- CAH, chronic ETOH ingestion, PCB toxicity, progesterone, isoflavonoids, metformin, troglitazone, triostane

Androstenediol
- Hyperadrenalinism, hyperthyroidism, hypergycemia, PCOS, IL-4 and IL-13, IGFl-3, forskolin

Testosterone
- Smoking, dioxin, isoflavonoids, flavonoids, EGCG, epilobiol, vitamin C, antianzole, etc.
- Chrystin, stingit neltals, and other flavonoids, ketomazone, metformin

More cortisol:
- Obesity (esp. visceral), metabolic syndrome, hypothyroidism, inflammation, essential HT, cortisol resistance, cholesterol, hypoxia, licorice, vitamin D, cortisol, forskolin

Less cortisol:
- Good insulin sensitivity, hypothyroidism, reduced insulin resistance, Na restriction, HGH (via IGF-1), E2, coffee, rosiglitazone, ketoconazole

Cortisol (active)
- CAH, DHEA, azole antifungals, etomide, metyrapone

Cortisone (inactive)
- CAH, DHEA, azole antifungals, etomide, metyrapone

Corticosterone
- Sodium depletion, high prolactin

Androsterone
- Alcohol, zinc deficiency, stress, hypothyroidism, inflammation, licorice, vitamin D3 (in osteoblasts), forskolin, isopropenol

Estrone (E1)
- Crucifers, berries, B, C, D, soy, flaxseed, caffeine, rosemary, exercise, thryoxine

Estradiol (E2)
- Excess sugar or n6 fats, citrinone, DOPA

Estriol (E3)
- COMT support: Adequate methionine, Mg, B vitamins, GST, reduce stress, rule out Hg toxicity & oxidative stress
Enzymes Produced in the Frontal Lobe Direct Match to Those in Periphery

Peripheral Enzymes
The Brain Produces Its Own Hormones!

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

Intracranially Produced Hormones: Etiology of Hormone Deficiency in TBI

- Neuroactive steroids
  - Endogenous steroids
    - Neurosteroids: Pregnenolone, Pregnenolone sulfate, Allopregnanolone, Dehydroepiandrosterone, Dehydroepiandrosterone sulfate
  - Exogenous steroids
    - Alphaxalone
    - Steroid-3α-hydroxy-5β-pregn-20-one hemisuccinate
  - Hormonal steroids: Estradiol, Progesterone, Testosterone, Glucocorticoid, Dehydroepiandrosterone
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

- Ant-anxiety, antidepressant, anti-aggressive, anti-stress, anti-convulsant behavior effects

- Alzheimer’s and TBI Victims both exhibit a deficiency in allopregnanolone in their frontal lobes
<table>
<thead>
<tr>
<th>Steroids</th>
<th>Plasma (nM)</th>
<th>Brain (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follicular</td>
<td>Luteal</td>
</tr>
<tr>
<td>Progesterone</td>
<td>5.0 ± 0.50 (Wang et al., 1996)</td>
<td>34.7 ± 2.40</td>
</tr>
<tr>
<td>3α-OH-5β-pregnan-20-one</td>
<td>0.6 ± 0.00 (Sundstrom et al., 1998)</td>
<td>1.1 ± 0.50</td>
</tr>
<tr>
<td>3α-OH-5α-pregnan-20-one</td>
<td>0.2–0.6  (Wang et al., 1998; Genazzani et al., 1998)</td>
<td>2–4 (Wang et al., 1996; Genazzani et al., 1998)</td>
</tr>
<tr>
<td>3β-OH-5α-pregnan-20-one</td>
<td>0.3–0.5  (Wang et al., 1996; Sundstrom et al., 1998)</td>
<td>1.5–3.5 (Wang et al., 1996; Sundstrom et al., 1998)</td>
</tr>
<tr>
<td>3β-OH-5β-pregnan-20-one</td>
<td>0.09 ± 0.08 (Havlíkova et al., 2006)</td>
<td>0.26 ± 0.13</td>
</tr>
<tr>
<td>Pregnenolone sulfate</td>
<td>11.2 ± 0.6 (Wang et al., 1996)</td>
<td>15.2 ± 0.8 (Bixo et al., 1997)</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>*2.19     (Kancheva et al., 2007)</td>
<td>–</td>
</tr>
<tr>
<td>3α5α-androstan-3α,17β-diol</td>
<td>*0.475    (Kancheva et al., 2007)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Data cited from references are inserted as indicated. *Concentration in adult men.*
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
**Pregnenolone sulfate** regulates neurotransmission in the hippocampus

*Learning and memory.*


**Pregnenolone** correlates with cognitive performance.
Cognitive Performance is 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.
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
High doses of antianxiety agents and antidepressants suppress hormone production in the brain.

The nerve fibers (axons) that carry serotonin to the target cells seem to change their shape and diminish in number—effects are properly understood as brain damage.

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.

1. Zinc = Aluminum

Alzheimer’s, Cancers, and Chronic Infections result in a zinc deficiency

1. Zinc = 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)

---

**Psychopathology and Neuroactive Steroids in TBI**

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%.

Wright, D.W., Randomized Clinical Trial of Progesterone for Acute Brain Injury, Annals of Emergency Medicine; 2006 07; 932
Figure 1
Proportions of patients (n = 45) presenting hormone values above or below laboratory reference interval day 1 and day 4 after sTBI. Reference intervals are given in Table 1.
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
Growth Hormone-Brain Affects

- Memory
- Concentration
- Mental clarity
- OCD

Dark moods
Paranoia
Poor Concentration
Anxiety
Growth Hormone

- TBI with GHD

  • Rapid weight gain
  • Excessive anxiety
  • Depression along

  • Deficits in:
    - Attention
    - Executive Functioning
      - Cognitive & Mental Abilities to Achieve Goals
    - Memory
    - Emotion
    - Mood Anxiety/Depression

  • Poor overall physical health and quality of life
Growth Hormone

TBI =

• Rapid weight gain
• Excessive anxiety
• Anxiety/Depression

Deficits In:

Attention
Executive Functioning
Cognitive & Mental Abilities to Achieve Goals
Memory
Emotion, Mood
Growth Hormone

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

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 SQ 5-7 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)

<table>
<thead>
<tr>
<th></th>
<th>Olivia</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone</td>
<td>0.6 ng/ml</td>
<td>5 ng/ml</td>
</tr>
<tr>
<td>IGF-1</td>
<td>78 ng/ml</td>
<td>&gt; 200 ng/ml</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>2950 ng/ml</td>
<td>&gt; 4000 ng/ml</td>
</tr>
</tbody>
</table>

**IGF-1 as proxy**

**IGFBP 3 logarithmic relation to GH Pulse**

*Estrogen and Quercetin can stimulate IGf BP 3*
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

• RX w T3/T4 combination
  – improved weight loss
  – overall sense of well being
  – cognition
  – functionality
Thyroid Dysfunction

**Hypothyroidism**
- DRY, COARSE HAIR
- LOSS OF EYEBROW
- HAIR
- PUFFY FACE
- ENLARGED THYROID (GOITER)
- SLOW HEARTBEAT
- ARTHRITIS
- COLD INTOLERANCE
- DEPRESSION
- DRY SKIN
- FATIGUE
- FORGETFULNESS
- HEAVY MENSTRUAL PERIODS
- INFERTILITY
- MUSCLE ACHES
- WEIGHT GAIN
- CONSTIPATION
- BRITTLE NAILS

**Hyperthyroidism**
- HAIR LOSS
- BULGING EYES
- SWEATING
- RAPID HEARTBEAT
- DIFFICULTY SLEEPING
- HEAT INTOLERANCE
- INFERTILITY
- IRRITABILITY
- MUSCLE WEAKNESS
- NERVOUSNESS
- SCANT MENSTRUAL PERIODS
- WEIGHT LOSS
- FREQUENT BOWEL MOVEMENTS
- WARM, MOIST PALMS
- TREMOR OF FINGERS
- SOFT NAILS
• Among those with MCI, Total T3 levels are inversely associated with cognitive performance across all domains.

• Those with relatively high TT3 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 poorly compared to healthy controls.
Psychosis
(Thyroid Component)

– 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
ACTH and Cortisol

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

\[
\text{CRH} = \text{ACTH} = \text{Cortisol}
\]

\[
\text{LH, TSH}
\]

- **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.
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)

---

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
Testosterone Brain Affects

Cognitive Functions
• Mood Stabilization
• Motivation
• Strength
• Energy

Deficiency
• Depression
• Fatigue
• Suicidal ideation.
Testosterone Brain Affects

- Attenuates inflammatory cytokines
  - Increases IL-10 (which inhibits pro-inflammatory cytokines IFN-gamma, IL3, TNF alpha, GM-CSF)

- Protects against mitochondrial dysfunction

- Controls neuronal excitability

- Improves Seizure Control
  - Aromatase inhibition
  - Maintaining therapeutic levels of DHT

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 decreases pain, anxiety and improves cognitive function by converting to DHT
- Modulates Anorexia Nervosa
- Testosterone Levels Inversely Proportional to Degree of Depression
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
TBI $\rightarrow$ Low T $\rightarrow$ Depression $\rightarrow$ Suicide

- 10th leading cause of death in US
  - (37,000 successful, 1 million attempts in 2009)

- Direct Relationship between Depression and Suicide

- Men Have 4X Suicide Risk of Women

- Suicide Attempts are Inversely Related to Testo Levels

- Peak Years Men 80-90, Women 50-65
  - (UCSF-Attributed to Loss of Estrogen)
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.
Estrogen

Neuroprotective

- Maintains cerebral blood flow, lactate production
- Lowers risk of PTSD after trauma.
- Modulates pain.
- Increases under stressful conditions i.e. critical illness and trauma.
- Prevents apoptosis (cell death), and acts like a growth factor.
- Prevents neuronal loss in CNS
- 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.


Dr. Seeman, Clarke Psychopathology in Women and Men: Focus on Female Hormones Am J Psychiatry, Toronto, Canada 1997; 154:1641–1647.
Estradiol has properties similar to those of atypical antipsychotic drugs.

The theory that many serious mental illnesses, specifically schizophrenia, may have a significant hormonal etiological component is fast gaining popularity and the support of scientific evidence.

Influences:
- Dopamine
- Serotonergic
- Glutaminergic

The Role of Estrogen and Other Hormones in the Pathophysiology and Treatment of Schizophrenia, Schizophrenia Research and Treatment Volume 2012, Article ID 540273. Emily Hayes, Emorfia Gavrilidis, and Jayashri Kulkarni Monash Alfred Psychiatry Research Centre, The Alfred Hospital and Monash University School of Psychology, Psychiatry and Psychological Medicine, Melbourne, VIC 3004, Australia.
Estrogens

• Estradiol leads to decrease production of:
  – Testosterone
  – DHEA
  – Progesterone
  – Pregnenolone

• E2 supplementation leads to transient increase in Cholesterol
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
Progesterone and TBI

Calming, Anti-inflammatory

Deficit:
Agitation
Irritability
Insomnia
Headaches
Poor Libido
Snapping at Others, Especially Those Most Intimate

Levels Diminished in:
Parkinson’s Disease
Dementia
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 with 7 Keto-DHEA
### Estrogen/Progesterone Ratio

(Gordon, M. TBI, San Diego, 2015)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>&lt;250</th>
<th>250-1000</th>
<th>1000-5000</th>
<th>&gt;5000</th>
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<tbody>
<tr>
<td>Headaches</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Sleep Issues</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
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<tr>
<td>Sleep Deprivation</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bloating</td>
<td>NP</td>
<td>NP</td>
<td>Mild</td>
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</tr>
<tr>
<td>Mood Swings</td>
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<tr>
<td>Anxiety</td>
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</tr>
<tr>
<td>Depression</td>
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<td>Severe</td>
</tr>
<tr>
<td>Panic Attacks</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Mastalgia</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>
DHEA

Antidepressant, mood regulator, builds energy, confidence, and improved sense of wellbeing

Builds and protects against cortisol catabolism.

Decreases visceral & subcutaneous fat in elderly persons.

Reduces serum low density lipoprotein levels and body fat.

Improved Bone Density

Symptoms Relieved: Fatigue, Dry Eyes, Dry Skin

Supports the immune system, improves myelin sheath

Improves Insulin Sensitivity


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
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\textsubscript{A} receptors.

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

- Social Phobias
**Pregnenolone sulfate** regulates neurotransmission in the hippocampus—Learning and memory.


**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.
Allo-Pregnenolone (Hint a Metabolite)

- **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 $\downarrow$ 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
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 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

<table>
<thead>
<tr>
<th>Pregnenolone Steal</th>
<th>Result</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnenolone</td>
<td><strong>131 ng/dL</strong></td>
<td>110 ng/dL</td>
</tr>
<tr>
<td>Progesterone</td>
<td><strong>2.1 ng/ml</strong></td>
<td>0.8 ng/ml</td>
</tr>
<tr>
<td>ACTH</td>
<td>35.8 pg/ml</td>
<td>35 pg/ml</td>
</tr>
<tr>
<td>Cortisol</td>
<td><strong>3.41 ug/dL</strong></td>
<td>15 ug/dL</td>
</tr>
<tr>
<td>DHEA</td>
<td>106.2 ug/dL</td>
<td>245 ug/dL</td>
</tr>
<tr>
<td>free Testosterone</td>
<td><strong>8.76 ng/ml</strong></td>
<td>14 ng/ml</td>
</tr>
<tr>
<td>Hormone</td>
<td>Functions</td>
<td>S/S Deficiency</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Mood, Motivation, Strength</td>
<td>Fatigue, Depression, Suicide</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Blood Flow to Brain</td>
<td>PTSD, Pain, Depression</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Anti-inflammatory, Calming</td>
<td>Depression, Anxiety, Aggression</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Energy, Mental Clarity</td>
<td>Poor Cognition, Depression, Psychosis</td>
</tr>
<tr>
<td>DHEA</td>
<td>Regenerates Myelin, Protects Brain Cells</td>
<td>Aging, Poor Memory, Infections</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Memory, Concentration, Mental Clarity</td>
<td>Paranoia, Poor Concentration, Dark Mood</td>
</tr>
</tbody>
</table>
Hormones Used to Treat Depression

- Growth Hormone
- Thyroid Augmentation
- Testosterone
- Estrogen as adjunct (not effective as stand alone)
- DHEA
- Pregnenolone

Howland, MD, J., “Use of Endocrine Hormones for Treating Depression.” Psychosocial Nursing and Mental Health Services Psychopharmacology, Dec 2010, Vol 10, 123-161
Any Insult to the Brain Can Result in Hormonal Disruptions


⅓ CVA Patients Experience Long Term Hypopituitarism

Diagnosis: Treatment Resistant Depression

<table>
<thead>
<tr>
<th></th>
<th>Olivia</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Testosterone</td>
<td>12.72 ng/ml</td>
<td>44 ng/ml</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>0.08 ng/ml</td>
<td>2-4 ng/ml</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>49.2 ug/dL</td>
<td>235 ug/dL</td>
</tr>
<tr>
<td>DHT</td>
<td>4 ng/dL</td>
<td>&lt;30 ng/dL</td>
</tr>
</tbody>
</table>
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)
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.
Laboratory Evaluation in TBI

“The Optimal Physiological Level”

Major National Lab

Total Testosterone Range (264-916) = \( \frac{1180}{2} = 590 \) Median

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

Range lowered due to obesity crisis showing improvement w low testosterone levels
“The Optimal Physiological Level”

Goal is in Upper $\frac{1}{2}$ to $\frac{3}{4}$ of Median
# Lab Studies

<table>
<thead>
<tr>
<th>Central</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>free T3, free T4, reverse T3, TPO, anti thyroglobulin</td>
</tr>
<tr>
<td>GH</td>
<td>IGF-1, IGFBP3</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>Testosterone, (free, total) DHEA-S; Male-DHT, Estradiol</td>
</tr>
<tr>
<td></td>
<td>Female (Estrone, Estradiol, Progesterone)</td>
</tr>
<tr>
<td>ACTH</td>
<td>Cortisol A.M. and P.M. or 4 Point Cortisol Saliva Test</td>
</tr>
<tr>
<td>Others</td>
<td>CBC, Chem Profile, Lipid Profile, cRP, Homocysteine, Insulin, 25-OH Vit D,</td>
</tr>
<tr>
<td></td>
<td>Pregnenolone, PSA (Total and fractionated), Zinc, Prolactin</td>
</tr>
<tr>
<td>Hormone</td>
<td>Median Male</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>200 ug/dL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>690 ng/ml</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>14 ng/ml</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>DHT</td>
<td>&lt;52 ng/dL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>45 pg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone</td>
<td>Median Male</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Estrone</td>
<td>&lt;30 pg/mL</td>
</tr>
<tr>
<td>Estradiol</td>
<td>&lt;25 pg/ml</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.8ng/ml</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>&lt;194 ng/dL</td>
</tr>
<tr>
<td>Vitamin D 3</td>
<td>&gt;60 ng/ml</td>
</tr>
<tr>
<td>Hormone</td>
<td>Median Male</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>LH</td>
<td>5.1 mIU/mL</td>
</tr>
<tr>
<td>FSH</td>
<td>6.95 mIU/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>11.25 ng/ml</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>210 ng/dL</td>
</tr>
<tr>
<td>Insulin</td>
<td>&lt;5 uIU/ml</td>
</tr>
<tr>
<td>Hormone</td>
<td>Median Male</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Growth Hormone (Morning Draw)</td>
<td>5 ng/ml</td>
</tr>
<tr>
<td>IGF-1</td>
<td>&gt;200 ng/ml</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>4000 ng/ml</td>
</tr>
<tr>
<td>ACTH</td>
<td>&lt;35 pg/dL</td>
</tr>
<tr>
<td>Cortisol (AM)</td>
<td>12.8 pg/ml</td>
</tr>
<tr>
<td>Cortisol (PM)</td>
<td>7.4 ug/dL</td>
</tr>
<tr>
<td>Hormone</td>
<td>Median Male</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>TSH</td>
<td>2.5 mIU/ml</td>
</tr>
<tr>
<td>free T4</td>
<td>1.5 ng/dL</td>
</tr>
<tr>
<td>free T3</td>
<td>3.2 pg/ml</td>
</tr>
<tr>
<td>Reverse T3</td>
<td>&lt;15 ng/dL</td>
</tr>
<tr>
<td>TPO</td>
<td>&lt;34 IU/ml</td>
</tr>
<tr>
<td>antithyroglobulin</td>
<td>&lt;1.0 IU/ml</td>
</tr>
</tbody>
</table>
Normal Saliva Cortisol Pattern

Salivary Cortisol and DHEA

Cortisol +
Reference Range
1 Hour After Rising
7AM - 9AM:
0.27-1.18 mcg/dL
11AM - 1PM:
0.10-0.41 mcg/dL
3PM - 6PM:
0.05-0.27 mcg/dL
10PM - 12AM:
0.03-0.14 mcg/dL

DHEA 7am - 9am
Reference Range: 71-640 pg/mL

DHEA:
Cortisol Ratio/10,000
Reference Range: 155-1,180
## Cortisol Excess

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Result</th>
<th>Ref Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASI</td>
<td>Adrenal Stress Index (Original) - Saliva</td>
<td></td>
<td>Adults (M/F):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13-24 nM</td>
</tr>
<tr>
<td>TAP</td>
<td>Free Cortisol Rhythm - Saliva</td>
<td></td>
<td>5-10 nM</td>
</tr>
<tr>
<td>06:00 - 08:00 AM</td>
<td>39 Elevated</td>
<td></td>
<td>3-8 nM</td>
</tr>
<tr>
<td>11:00 - 1:00 PM</td>
<td>24 Elevated</td>
<td></td>
<td>1-4 nM</td>
</tr>
<tr>
<td>04:00 - 05:00 PM</td>
<td>25 Elevated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00 - Midnight</td>
<td>9 Elevated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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](image-url)
## Cortisol Excess - 6 Months Later

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Result</th>
<th>Ref Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP</td>
<td>Cortisol rhythm (saliva)</td>
<td></td>
<td>Adults (M/F):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>06:00 - 08:00 AM</td>
<td>8</td>
<td>Depressed</td>
</tr>
<tr>
<td></td>
<td>11:00 - 1:00 PM</td>
<td>16</td>
<td>Elevated</td>
</tr>
<tr>
<td></td>
<td>04:00 - 05:00 PM</td>
<td>9</td>
<td>Elevated</td>
</tr>
<tr>
<td></td>
<td>10:00 - Midnight</td>
<td>4</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td><strong>Total Cortisol Output:</strong></td>
<td>37</td>
<td><strong>22 - 46 nM</strong></td>
</tr>
</tbody>
</table>

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.

![Circadian Cortisol Profile](image.png)
### Cortisol Deficiency

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

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.
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)**

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

**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

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

I.R. is Independent of HbA1C

Ex. FBS = 101  
Insulin = 4.8  
I.R. = 1.197
4. Estrogen/Progesterone Ratio

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

\[
\text{E1+E2/Prog.}=\frac{E}{P} \text{ Ratio}
\]

Goal <250

<table>
<thead>
<tr>
<th>E1</th>
<th>Median= &lt;200 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>= 90 pg/ml</td>
</tr>
<tr>
<td>Prog</td>
<td>= 5-7 ng/ml</td>
</tr>
<tr>
<td>P/E</td>
<td>52.2</td>
</tr>
</tbody>
</table>

Estrogen Dominant

<table>
<thead>
<tr>
<th>E1</th>
<th>E2</th>
<th>Prog=0.04</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>112</td>
<td>P/E = 2886</td>
</tr>
</tbody>
</table>

E1= 37

E2= 21
### Estrogen/Progesterone Ratio

(Gordon, M. TBI, San Diego, 2015)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>&lt;250</th>
<th>250-1000</th>
<th>1000-5000</th>
<th>&gt;5000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Sleep Issues</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Sleep Deprivation</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bloating</td>
<td>NP</td>
<td>NP</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mood Swings</td>
<td>NP</td>
<td>Mild</td>
<td>Moderate</td>
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</tr>
<tr>
<td>Anxiety</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Depression</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Panic Attacks</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Mastalgia</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>
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

**Estrogen Dominant**

E2=38  Median=90 pg/ml
Prog.= 0.8 = 0.45
P x1000/E2 =21.05

< 100=Estrogen Dominant
100-500=Normal
> 500=Prog. Excess
6. **Total Testosterone/SHBG**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>T Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Serum tot. testo/SHBG</strong> (free testo index in mmol)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-100</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td><strong>Serum tot. testo/SHBG</strong> (free testo index in mmol)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Male Hormone Testing</td>
<td>Result</td>
<td>Range</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>5ng/ml*</td>
<td></td>
</tr>
<tr>
<td>Somatomedin C (IGF-1)</td>
<td>&gt; 200 ng/ml</td>
<td></td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>&gt; 4000 ng/ml</td>
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</tr>
<tr>
<td>DHEA-S</td>
<td>245 ug/dl*</td>
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<tr>
<td>Estrone (E1)</td>
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<tr>
<td>Progesterone</td>
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</tr>
<tr>
<td>Pregnenolone</td>
<td>110 ng/dl*</td>
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<tr>
<td>EP Ratio</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MALE LABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Free</td>
</tr>
<tr>
<td>Testosterone Total</td>
</tr>
</tbody>
</table>

<p>| | DHT | &lt; 55 ng/dl |
| | SHBG | &lt; 75 pg/ml |
| | FSH | 7 mIU/ml* |
| | LH | 5.1 mIU/ml |
| | Prolactin | 14 ng/ml* |
| | Zinc | 95mcg/dL |
| | Insulin | &lt;30mIU/L |
| | Vitamin D3 | &gt;60 ng/dl* |
| | ACTH | 35 pg/ml * |
| | Cortisol | &lt; 15 ug/dl |
| | TSH | &lt;2.5 mIU/ml* |
| | T3, Free | &gt; 2.5 pg/ml |
| | T4, Free | &gt; 1.5 pg/ml |
| | rT3 | 80-250 pg/ml |
| | T3/rT3 Ratio | &gt;1.06 |
| | TPO | &lt;35 |</p>
<table>
<thead>
<tr>
<th>Female Hormone Testing</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone</td>
<td></td>
<td>5ng/ml*</td>
</tr>
<tr>
<td>Somatomedin C (IGF-1)</td>
<td>&gt; 200</td>
<td>ng/ml</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>&gt;4000</td>
<td>ng/ml</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>195</td>
<td>ug/dl*</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>&lt; 200</td>
<td>pg/ml*</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>90</td>
<td>pg/ml*</td>
</tr>
<tr>
<td>Progesterone</td>
<td>5-7</td>
<td>ng/ml*</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>100</td>
<td>ng/dl*</td>
</tr>
<tr>
<td>EP Ratio</td>
<td>&lt; 250</td>
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</table>

<table>
<thead>
<tr>
<th>Female Labs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Free</td>
<td></td>
<td>2-4 pg/ml*</td>
</tr>
<tr>
<td>Testosterone Total</td>
<td></td>
<td>&lt;44 ng/ml*</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt;2.5</td>
<td>mcu/ml*</td>
</tr>
<tr>
<td>T3, Free</td>
<td>&gt; 2.5</td>
<td>pg/ml</td>
</tr>
<tr>
<td>T4, Free</td>
<td>&gt; 1.5</td>
<td>ng/ml</td>
</tr>
<tr>
<td>rT3</td>
<td>80-250</td>
<td>pg/ml</td>
</tr>
<tr>
<td>T3/rT3 Ratio</td>
<td>&gt; 1.06</td>
<td></td>
</tr>
<tr>
<td>TPO</td>
<td>&lt;35</td>
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</table>
### Female Hormone Testing

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone</td>
<td>0.6</td>
<td>5ng/ml*</td>
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<tr>
<td>Somatomedin C (IGF-1)</td>
<td>78</td>
<td>&gt;200 ng/ml</td>
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<tr>
<td>IGFBP-3</td>
<td>2950</td>
<td>&gt;4000 ng/ml</td>
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<tr>
<td>DHEA-S</td>
<td>49.2</td>
<td>195 ug/dl*</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>274</td>
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<tr>
<td>Estradiol (E2)</td>
<td>191</td>
<td>90 pg/ml*</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.06</td>
<td>5-7 ng/ml*</td>
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<td>Pregnenolone</td>
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<td>100 ng/dl*</td>
</tr>
<tr>
<td>EP Ratio</td>
<td>3457</td>
<td>&lt;250</td>
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</table>

### OLIVIA G.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Free</td>
<td>0.8</td>
<td>2-4 pg/ml*</td>
</tr>
<tr>
<td>Testosterone Total</td>
<td>12.7</td>
<td>&lt;44 ng/ml*</td>
</tr>
<tr>
<td>TSH</td>
<td>0.98</td>
<td>&lt;2.5 mcu/ml*</td>
</tr>
<tr>
<td>T3, Free</td>
<td>3.6</td>
<td>&gt;2.5 pg/ml</td>
</tr>
<tr>
<td>T4, Free</td>
<td>1.8</td>
<td>&gt;1.5 ng/ml</td>
</tr>
<tr>
<td>rT3</td>
<td>168</td>
<td>80-250 pg/ml</td>
</tr>
<tr>
<td>T3/rT3 Ratio</td>
<td>2.14</td>
<td>&gt;1.06</td>
</tr>
<tr>
<td>TPO</td>
<td>19</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>

### Hormone Testing Result Range

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHT</td>
<td>23</td>
<td>&lt;30 ng/Dl</td>
</tr>
<tr>
<td>SHBG</td>
<td>88</td>
<td>&lt;75 pg/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>6.8</td>
<td>7 mIU/ml*</td>
</tr>
<tr>
<td>LH</td>
<td>5.0</td>
<td>5.1 mIU/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>7.2</td>
<td>14 ng/ml*</td>
</tr>
<tr>
<td>Zinc</td>
<td>89</td>
<td>95 mcg/dL</td>
</tr>
<tr>
<td>Insulin</td>
<td>8</td>
<td>&lt;30 mIU/L</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>17</td>
<td>&gt;60 ng/dl*</td>
</tr>
<tr>
<td>ACTH</td>
<td>16</td>
<td>35 pg/ml*</td>
</tr>
<tr>
<td>Cortisol</td>
<td>3.4</td>
<td>&lt;15 ug/dl</td>
</tr>
</tbody>
</table>

---

*Note: * indicates the normal range for the respective hormone.
Psychiatric Issues 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.
Agitated behavior (hurting oneself) is present along a continuum with varying levels of behavioral disturbance:

- Inattention
- Disinhibition
- Emotional Lability
- Impulsivity
- Motor Restlessness

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

• **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
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

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

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

• Elderly males: Low E2, High T=better performance on cognitive testing.

• “Optimal” levels necessary for cognitive functioning

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
**Pregnenolone sulfate** regulates neurotransmission in the hippocampus—Learning and memory.


**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.

- Testosterone, estradiol and IGF-1 have independent and selective effects on cognition.

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.

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 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.

- 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.
• **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.**
Treatment

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

- Testosterone
- Estrogen
- Progesterone
- Thyroid
- Growth Hormone
- ACTH and Cortisol
## Summary of Hormones and Brain Function

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Functions</th>
<th>S/S Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>Mood, Motivation, Strength</td>
<td>Fatigue, Depression, Suicide</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Blood Flow to Brain</td>
<td>PTSD, Pain, Depression</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Anti-inflammatory, Calming</td>
<td>Depression, Anxiety, Aggression</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Energy, Mental Clarity</td>
<td>Poor Cognition, Depression, Psychosis</td>
</tr>
<tr>
<td>DHEA</td>
<td>Regenerates Myelin, Protects Brain Cells</td>
<td>Aging, Poor Memory, Infections</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Memory, Concentration, Mental Clarity</td>
<td>Paranoia, Poor Concentration, Dark Mood</td>
</tr>
</tbody>
</table>
Treatment

• Male: Daily Testosterone production rates range from 4 to 11.8 mg per day.
  – Ave = 28 mg - 80 mg/week.

• Female: Daily Testosterone production rates ranged from .9 mg to 2.8 mg per day.
  – Ave=6.3mg to 20mg/week.

• With Supraphysiologic doses we get elevated Estrogen/DHT.

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: 500-1400 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. $(-) \times (-) = (+)$

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

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

* - 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.
I telephoned 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 an effective and safe alternative to testosterone supplementation in men wishing to preserve their fertility.

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
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.
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.

\[
E1 + E2/P = E/P \text{ Ratio}
\]

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

- If E1 is elevated, control with 7 Keto-DHEA
## Estrogen/Progesterone Ratio

(Gordon, M. TBI, San Diego, 2015)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>&lt;250</th>
<th>250-1000</th>
<th>1000-5000</th>
<th>&gt;5000</th>
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<tbody>
<tr>
<td>Headaches</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Sleep Issues</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Sleep Deprivation</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bloating</td>
<td>NP</td>
<td>NP</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mood Swings</td>
<td>NP</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Anxiety</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Depression</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Panic Attacks</td>
<td>NP</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Mastalgia</td>
<td>Intermittent</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>
Progesterone/Estradiol Ratio

• **Alternative Measurement**
  
  • *Serum*: $\frac{Pg \times 1000}{E^2} = \frac{P}{E^2}$ Ratio
  
  • *Saliva*: $\frac{Pg}{E^2} = \frac{Pg}{E^2}$ Ratio

• **Results**

<table>
<thead>
<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Estrogen Dominant</td>
</tr>
<tr>
<td>100-500</td>
<td>Normal Ratio</td>
</tr>
<tr>
<td>&gt;500</td>
<td>Progesterone Dominant</td>
</tr>
</tbody>
</table>
## Female Hormone Treatment

(Gordon, M. TBI, San Diego, 2015)

<table>
<thead>
<tr>
<th></th>
<th>Estradiol</th>
<th>Estriol</th>
<th>Progesterone</th>
<th>Testosterone</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starter</strong></td>
<td>0.2 mg</td>
<td>2.0 mg</td>
<td>100 mg</td>
<td>1 mg</td>
<td>Vaginal</td>
</tr>
<tr>
<td><strong>Breast Tender</strong></td>
<td>0.1 mg</td>
<td>2.0 mg</td>
<td>100 mg.</td>
<td>1 mg</td>
<td>Vaginal</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>0.2 mg</td>
<td>2.0 mg</td>
<td>50 mg.</td>
<td>1 mg</td>
<td>Vaginal</td>
</tr>
<tr>
<td><strong>Libido</strong></td>
<td>0.2 mg</td>
<td>2.0 mg</td>
<td>100 mg.</td>
<td>2 mg</td>
<td>Transdermal</td>
</tr>
<tr>
<td><strong>Basic</strong></td>
<td>0.2 mg</td>
<td>2.0 mg</td>
<td>100 mg.</td>
<td>No</td>
<td>Transdermal</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td>0.1 mg</td>
<td>2.0 mg</td>
<td>100 mg.</td>
<td>No</td>
<td>Vaginal</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>none</td>
<td>2.0 mg</td>
<td>100 mg.</td>
<td>1-2 mg.</td>
<td>Vaginal</td>
</tr>
</tbody>
</table>
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.
<table>
<thead>
<tr>
<th>Serum TSH: Cut-off points within ref. range above which there is ↑ risks of disease</th>
<th>mU/L</th>
<th>↑ Risks of disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3.5</td>
<td>↑ severe form of depression</td>
<td>Berlin 1 1999 Nylles A 2006</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.3 (higher quartile)</td>
<td>↑ body mass index over 7 years</td>
<td>Nylles A 2006</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.2</td>
<td>↑ waist circumfer., BMI, glucose, TG, systolic BP</td>
<td>Waterhouse DF 2007</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>↑ cardiac abnormalities (pat. + auto-immune thyroiditis)</td>
<td>Zoncu S 2005</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.8 (higher quartile)</td>
<td>↑ post-partum hypothyroidism</td>
<td>Azizi F 2004</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.1</td>
<td>↑ Stenosis, multi-vessel disease (angina patients)</td>
<td>Yun KH 2007</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>↑ homocysteine &amp; CRP (patients + L-thyroxine)</td>
<td>Gursoy A 2006</td>
<td></td>
</tr>
<tr>
<td>≥ 2.0</td>
<td>↑ Familial predisposition to hypertension</td>
<td>Gumieniak O</td>
<td></td>
</tr>
<tr>
<td>≥ 2.0</td>
<td>↑ Hypercholesterolemia (patients + auto-immune thyroid)</td>
<td>Michalopoulou G 1998</td>
<td></td>
</tr>
<tr>
<td>3.0-1.99</td>
<td>↑ overt hypothyroidism (antibodies)</td>
<td>Gual KW 1993</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.98</td>
<td>↑ aggravation of coronary heart disease</td>
<td>Auer J 2003</td>
<td></td>
</tr>
<tr>
<td>≥ 1.9</td>
<td>↑ systolic &amp; diastolic blood pressures (men)</td>
<td>Iqbal A 2006</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.9</td>
<td>↑ auto-Immune thyroid ATPO- (pregnant women)</td>
<td>Sieiro Netto L 2004</td>
<td></td>
</tr>
<tr>
<td>≥ 1.8</td>
<td>↑ systolic &amp; diastolic blood pressures (women)</td>
<td>Iqbal A 2006</td>
<td></td>
</tr>
</tbody>
</table>
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 \( \text{T4 to rT3} \).
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


Any Treatment Other Than Desiccated T4 Is Outside Realm Of Medicine

Doctor’s Solution
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)

<table>
<thead>
<tr>
<th>Cruciferous Vegetables</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bok Choy</td>
<td>Soy</td>
</tr>
<tr>
<td>Broccoli</td>
<td>Pine Nuts, Peanuts</td>
</tr>
<tr>
<td>Brussel Sprouts</td>
<td>Millet</td>
</tr>
<tr>
<td>Cabbage</td>
<td>Strawberries</td>
</tr>
<tr>
<td>Canola</td>
<td>Pears, Peaches</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>Bamboo Shoots</td>
</tr>
<tr>
<td>Chinese Cabbage</td>
<td>Spinach</td>
</tr>
<tr>
<td></td>
<td>Sweet Potatoes</td>
</tr>
<tr>
<td>Collard Greens</td>
<td></td>
</tr>
<tr>
<td>Horseradish</td>
<td></td>
</tr>
<tr>
<td>Kale</td>
<td></td>
</tr>
<tr>
<td>Kohirabi</td>
<td></td>
</tr>
<tr>
<td>Mustard Greens</td>
<td></td>
</tr>
<tr>
<td>Radishes</td>
<td></td>
</tr>
<tr>
<td>Rutabaga</td>
<td></td>
</tr>
<tr>
<td>Turnips</td>
<td></td>
</tr>
</tbody>
</table>
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.*

Shameless Plug to Invite Me Back for “The Thyroid Show”

- Gastrointestinal-Immune-Thyroid Connection
- Autoimmune-Nutrient-Thyroid Connection
- Autoimmune-Iodine-Thyroid Connection
- HPA Axis-Thyroid Connection
- Heavy Metal-Toxin-Thyroid Connection
- Infectious Disease-Thyroid Connection
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, 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


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.
Treatment

- Secondary Hormones
  - Pregnenolone
  - DHEA
  - Prolactin
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
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

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
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.

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
<table>
<thead>
<tr>
<th>Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3</td>
</tr>
<tr>
<td>MVI</td>
</tr>
<tr>
<td>Methylated B6, B12, Folate</td>
</tr>
<tr>
<td>Phosphatidylserine</td>
</tr>
<tr>
<td>L Threonine</td>
</tr>
<tr>
<td>DL-Phenylalanine</td>
</tr>
<tr>
<td>Zinc Citrate</td>
</tr>
<tr>
<td>Omega 3 FA</td>
</tr>
<tr>
<td>Ribose</td>
</tr>
<tr>
<td>Glutathione</td>
</tr>
<tr>
<td>Tocopherols</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
</tr>
<tr>
<td>Carnosine</td>
</tr>
<tr>
<td>Melatonin</td>
</tr>
<tr>
<td>Lipoic Acid</td>
</tr>
<tr>
<td>PQQ</td>
</tr>
<tr>
<td>Coenzyme Q 10</td>
</tr>
<tr>
<td>Quercetin</td>
</tr>
</tbody>
</table>
Supplements: The Magnificent 7

1. *Omega-3’s* (EPA/DHA)-Cognition
2. *MCT Oil*-Energy, Neuroprotection
3. *Vitamin D₃*-Neurotransmitter Production, Memory storage, Synapse density
4. *Probiotics*-Cognition, Learning, Memory
5. *Methylated B Vitamins*-Cognition, Memory, Mood
6. *Magnesium L-Threonate*-Sleep, Focus
7. *Branch Chain Amino Acids*-Enzyme and Hormone Production
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
Vitamin D and TBI

Necessary for Progesterone to Perform Its Anti-Inflammatory Functions in the Brain (Activates TNF, IL 1, IL 6, NF B, p65 cytokines)


Protects against Depression, Alzheimer’s Dx., Dementia

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

Rx: Typically 5000-10,000 IU/d
- Every 1000 IU supplement increases Vit. D3 by 8 ng/dL
Supplements

**Methylated B6, B12, Folate**-Synthesizes neurotransmitters.

Malfunction of the methylation cycle is due to diet deficient in B6, B2, 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
**DL-Phenylalanine**

- Essential amino acid DLP is a precursor to 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

**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).

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, H2O2 and hydroxyl radicals.

Neurovascular-protective effects after TBI.

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

NAC + Vitamin E  \(\downarrow\)  Nf KappaB

**Efficacy of N-Acetyl cysteine 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 1.5 grams 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
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 peroxy 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

---

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**

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

| DHT                    | 23     | < 30ng/Dl   |
| SHBG                   | 88     | < 75 pg/ml  |
| FSH                    | 6.8    | 7 mIU/ml*   |
| LH                     | 5.0    | 5.1 mIU/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  |
| 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         |

OLIVIA G.

Testosterone Free 0.8 2-4 pg/ml*
Testosterone Total 12.7 <44 ng/ml*
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
<table>
<thead>
<tr>
<th>Male Testing</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone</td>
<td>1.7</td>
<td>5ng/ml*</td>
</tr>
<tr>
<td>Somatomedin C (IGF-1)</td>
<td>122</td>
<td>&gt; 200 ng/ml</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>3182</td>
<td>&gt;4000 ng/ml</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>161</td>
<td>245 ug/dl*</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>&lt;5</td>
<td>&lt; 60 pg/ml*</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>68</td>
<td>&lt;25 pg/ml*</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.96</td>
<td>0.8 ng/ml*</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>121</td>
<td>110 ng/dl*</td>
</tr>
<tr>
<td>EP Ratio</td>
<td></td>
<td>&lt; 250</td>
</tr>
<tr>
<td>DHT</td>
<td>33</td>
<td>&lt; 55 ng/Dl</td>
</tr>
<tr>
<td>SHBG</td>
<td>58</td>
<td>&lt; 75 pg/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>5.8</td>
<td>7 mIU/ml*</td>
</tr>
<tr>
<td>LH</td>
<td>8.9</td>
<td>5.1mIU/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>1.3</td>
<td>14 ng/ml*</td>
</tr>
<tr>
<td>Zinc</td>
<td>68</td>
<td>95mcg/dL</td>
</tr>
<tr>
<td>Insulin</td>
<td>19</td>
<td>&lt;30mIU/L</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>99</td>
<td>&gt;60 ng/dl*</td>
</tr>
<tr>
<td>ACTH</td>
<td>42</td>
<td>35 pg/ml *</td>
</tr>
<tr>
<td>Cortisol</td>
<td>22</td>
<td>&lt; 15 ug/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>0.99</td>
<td>&lt;2.5 mcu/ml*</td>
</tr>
<tr>
<td>T3, Free</td>
<td>3.1</td>
<td>&gt; 2.5 pg/ml</td>
</tr>
<tr>
<td>T4, Free</td>
<td>1.8</td>
<td>&gt; 1.5 ng/ml</td>
</tr>
<tr>
<td>rT3</td>
<td>32.6</td>
<td>80-250 pg/ml</td>
</tr>
<tr>
<td>T3/rT3 Ratio</td>
<td>0.95</td>
<td>&gt;1.06</td>
</tr>
<tr>
<td>TPO</td>
<td>199</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Male Testing</th>
<th>Result</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone</td>
<td>4.2</td>
<td>5ng/ml*</td>
</tr>
<tr>
<td>Somatomedin C (IGF-1)</td>
<td>173</td>
<td>&gt; 200 ng/ml</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>4227</td>
<td>&gt;4000 ng/ml</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>244</td>
<td>245 ug/dl*</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>&lt;5</td>
<td>&lt; 60 pg/ml*</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>27</td>
<td>&lt;25 pg/ml*</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.73</td>
<td>0.8 ng/ml*</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>96</td>
<td>110 ng/dl*</td>
</tr>
<tr>
<td>EP Ratio</td>
<td></td>
<td>&lt; 250</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>DHT</td>
<td>47</td>
<td>&lt; 55 ng/Dl</td>
</tr>
<tr>
<td>SHBG</td>
<td>24</td>
<td>&lt; 75 pg/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>7</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>LH</td>
<td>5.1</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>Progesterone</td>
<td>5.6</td>
<td>14 ng/ml*</td>
</tr>
<tr>
<td>Zinc</td>
<td>99</td>
<td>95mcg/dL</td>
</tr>
<tr>
<td>Insulin</td>
<td>5</td>
<td>&lt;30mIU/L</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>82</td>
<td>&gt;60 ng/dl*</td>
</tr>
<tr>
<td>ACTH</td>
<td>31</td>
<td>35 pg/ml *</td>
</tr>
<tr>
<td>Cortisol</td>
<td>9</td>
<td>&lt; 15 ug/dl</td>
</tr>
</tbody>
</table>

**Joel P.**

**3 Mo. Follow-up**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Testosterone Free</td>
<td>11.4</td>
<td>12-14 pg/ml*</td>
</tr>
<tr>
<td>Testosterone Total</td>
<td>902</td>
<td>690 ng/ml*</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>1.48</td>
<td>&lt;2.5 mcu/ml*</td>
</tr>
<tr>
<td>T3, Free</td>
<td>3.2</td>
<td>&gt; 2.5 pg/ml</td>
</tr>
<tr>
<td>T4, Free</td>
<td>1.42</td>
<td>&gt; 1.5 ng/ml</td>
</tr>
<tr>
<td>rT3</td>
<td>12.6</td>
<td>80-250 pg/ml</td>
</tr>
<tr>
<td>T3/rT3 Ratio</td>
<td>2.53</td>
<td>&gt;1.06</td>
</tr>
<tr>
<td>TPO</td>
<td>102</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>
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

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Clomid (CPC)</th>
<th>Testosterone (TPC)</th>
<th>Combination (CPC+TPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>57/1</td>
<td>47</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Population by Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>20s</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution - Percent Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>20-29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group to Percent Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>%</td>
</tr>
</tbody>
</table>
BATTLEFIELD ACUPUNCTURE (BFA)

- Omega 2
- Shen Men
- Point Zero
- Thalamus
- Cingulate Gyrus
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