Objectives

By the end of this section, Participants will be able to:

- Identify & describe the brain structures related to trauma & PTSD
- Describe the neuro chemistry related to PTSD & trauma symptom prescribing
- Discuss 3 psychopharmacological agents used to treat symptoms of trauma

Faculty Disclosures

- This presenter has no conflicts of interest or commercial support to disclose.
- Discussion of off-label medication uses will occur in this presentation.
- Presenter may receive royalties for publication of text through the American Psychiatric Association
Neurobiology & Psychopharmacological Treatments for Trauma Disorders

Laura G Leahy, DrNP, APRN, PMH-CNS/FNP, CARNP-AP, FAANP
APNSolutions, LLC
123 Egg Harbor Road
Suite 703, Sewell, NJ 08080
Phone/text: 856.556.0860
Fax: 844.276.7656
Email: LGLeahy@APNSolutions.com
Website: www.APNSolutions.com

Important Abbreviations

- PTSD = Post Traumatic Stress Disorder
- SUD = Substance Use Disorders
- HPA = Hypothalamic-Pituitary-Adrenal Axis
- CNS = Central Nervous System
- CRH = Corticotropin-releasing Hormone
- ACTH = Adrenal Corticotropin Hormone
- 5HT = Serotonin
- NE = Norepinephrine
- DA = Dopamine

Photos courtesy of Wil Okken, Mosul, Iraq 2017
Thomas Eakins depicts subject George Reynolds’ battle scars & hints at deeper wounds of the soul.

PTSD Mnemonic—TRAUMA

- Traumatic Event
- Re-experience
- Avoidance
- Unable to Function
- Month or More of Symptoms
- Arousal Increased

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“Too often only the 20% above the surface is diagnosed & treated; the other 80% remains hidden.”

--William Shryer, LCSW

Major Symptom Clusters in Trauma

▶ Intrusion Symptoms
  ▶ Memories/flashbacks/dreams
  ▶ Physiological reactions

▶ Avoidance Symptoms
  ▶ Isolative behaviors, napping
Negative Cognitions & Mood Symptoms
- Dissociative amnesia
- Negative beliefs about oneself, others, world
- Persistent negative emotional state

Alterations in Arousal & Reactivity Symptoms
- Irritable/angry behavior & outbursts
- Reckless/self-destructive behavior
- Sleep disturbance, hypervigilance, poor concentration

Trauma’s Impact on the Soul
Longitudinal Progression of PTSD: Points for Clinical Intervention

Factors that modify risk:
- Genetic or biological
- Prior trauma or environmental
- Less support, marital discord, or post-trauma reactions

Criteria A1: Stress exposure
Criteria A2: Functional setback
PTSD symptoms:
- Reexperiencing
- Avoidance
- Hyperarousal

Other symptoms:
- Emotional numbing
- Relationship problems

Primary prevention:
- Assess genetic vulnerability
- Increase safety
- Prevent triggers

Secondary prevention:
- Create a trauma-informed environment
- Support systems
- Increase awareness of trauma

Tertiary prevention:
- Psychotherapy
- Pharmacotherapy
- Social support systems
- Health promotion
- Disaster preparedness

Genes

Neurochemistry
Endocrinology

Early life stress
- Associative learning
- Cognition

Vulnerability

Social Support
No PTSD
PTSD
No PTSD

Resilience

What Happens to the Brain During Trauma??

Laura G Leahy, DrNP, APRN, FAANP
LGLeahy@APNSolutions.com

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Developmentally Sensitive Criterion

- PTSD in Children 6 Years & Younger
  - Experienced, witnessed, learned
  - Intrusive Memories
  - Recurrent Distressing Dreams
  - Dissociative Reactions/Flashbacks
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Neurotransmitters & Hormones in PTSD

- **Corticotropin Releasing Hormone**
  - Increased
  - Activates release of cortisol

- **Cortisol**
  - Mixed
  - Stress, Reduced immunity, chronic elevation may reduce sensitivity to danger/threat and exhaust the HPA axis

- **DHEA**
  - Increased
  - Reduced immune response

- **Norepinephrine**
  - Increased
  - Anxiety, insomnia, nightmares, stress, worry

- **Serotonin 1A**
  - Decreased
  - Depression, avoidance

- **Dopamine**
  - Increased
  - Psychosis, flashbacks, arousal

- **Testosterone**
  - Decreased
  - Fatigue, anhedonia, avoidance

- **Neuropeptide Y**
  - Decreased
  - Anxiety, arousal, stress
Role of Serotonergic System

- Mood & Anxiety
- Memory & Aging
- Circadian Rhythms
- Eating & Satiety
- GI & Bowel Issues

Role of Noradrenergic System

- Phenylethylamine
- Tyrosine
- L-Dopa
- Converting by: Vitamin B6
- Dopamines
- Converting by: C-Serper & Vitamin C & O2

Serotonin & PTSD

- Mood & Anxiety
- Migraine Headaches
- Premature Ejaculation
- Pain
- Substance Abuse
- Vasoconstriction & Vasodilation
Role of Dopaminergic System

PTSD Comorbidities by Population

<table>
<thead>
<tr>
<th>Comorbid Disorder</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depressive Disorder</td>
<td>General &amp; Women</td>
</tr>
<tr>
<td>Other Anxiety Disorders</td>
<td>General &amp; Women</td>
</tr>
<tr>
<td>Alcohol Use &amp; Abuse Disorders</td>
<td>Combat Veterans, Rescue Workers, Accident &amp; Assault Survivors &amp; Men</td>
</tr>
<tr>
<td>Other Drug Use &amp; Abuse Disorders</td>
<td>Combat Veterans, Accident &amp; Assault Survivors &amp; Men</td>
</tr>
<tr>
<td>Somatization Disorder</td>
<td>Childhood Abuse Survivors &amp; Women</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>Socioeconomically Disadvantaged &amp; Chronically Ill (disorder is preexisting)</td>
</tr>
</tbody>
</table>

Over 50% men & about 30% women ETOH
About 35% men & 27% women Drugs
May reduce ability to discriminate
between safety & danger → high-risk
behaviors & increased risk for further
trauma exposure

Relationship of PTSD & SUDs

PTSD Arousal Symptoms
- Difficult falling/staying asleep
- Irritability & Angry Outbursts
- Difficulty Concentrating
- Hypervigilance
- Exaggerated Startle Response
- Flashbacks

CNS Depressant Withdrawal Symptoms
- Insomnia
- Psychomotor Agitation
- Anxiety
- Autonomic Hyperactivity
- Increased Hand Tremor
- Transient Hallucinations
- Nausea/Vomiting
- Seizures

They promised that Dreams can come True.
But forgot to mention that Nightmares are Dreams too.

OSCAR WILDE
IRISH WRITER (1854-1900)
PTSD Mnemonic—DREAMS

- Disinterest in Usual Activities
- Re-experience
- Event Preceding Symptoms
- Avoidance
- Month or More of Symptoms
- Sympathetic Arousal


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Sleep Cycles

The sleep cycle
There are two very different types of sleep:

REM Sleep
- Rapid Eye Movement
- Light sleep
- Deep sleep
- Stage 1
- Stage 2
- Sleep paralysis
- Sleep terrors

Deep Sleep
- Sleep deeper
- More sleep
- Restful
- 4 or 5 sleep cycles
- More of a good night’s sleep

Comparing Sleep

**PTSD**
- Chronicity impairs objectivity
- Significant Disruption
- REM sleep broken
- Elevated adrenaline
- Memories stored & attached emotions remain

**NORMAL**
- Fairly objective reporting
- Restful & Refreshing
- REM sleep restorative
- Norepinephrine/adrenaline-free environment
- Memories processed & triggers removed

PTSD Sleep Cycle

**Bedtime**
- Racing thoughts
- Rx dependent
- Restless Legs
- Time Monitoring
- Worry & Stress

**Daytime**
- Sleepiness
- Desire to Nap
- Impairment
- Poor Coping
- Avoidance

**Nighttime**
- Nightmares
- Insomnia
- Lost/Broken Sleep
- Motor Activity
- Sleep Breathing D/Os

**Wake Up**
- Un-refreshed
- Lethargic
- No Motivation
- Inertia
- Low Energy

Post-Traumatic Stress Disorder

**Sleep Disturbance**
- Recurrent Nightmares
- Conditioned Fear of Sleep
- Excessive Nighttime Motor activity

**REM Sleep dysregulation**
- Sleep-Related Breathing Disorders
  - Sleep Apnea
  - Upper Airway Resistance
- Microawakenings

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Lab & Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;, T&lt;sub&gt;4&lt;/sub&gt;, TSH</td>
<td>Restlessness, insomnia, autonomic hyperactivity T&lt;sub&gt;3&lt;/sub&gt; &amp; T&lt;sub&gt;4&lt;/sub&gt; have been elevated in patient with PTSD TSH typically unaffected in PTSD alone</td>
</tr>
<tr>
<td>Drug Screen</td>
<td>High incidence of comorbidity in PTSD</td>
</tr>
<tr>
<td>Head CT or MRI</td>
<td>Comorbid head trauma, amnesia or cognitive deficits</td>
</tr>
<tr>
<td>Neuropsychiatric Testing</td>
<td>Head trauma, memory difficulties &amp; cognitive decline</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>Symptoms preceding trauma, symptoms of 1° sleep disorder (eg: OSA, Idiopathic Hypersomnolence, Restless Leg Syndrome &amp;/or Periodic Limb Movement Disorder)</td>
</tr>
</tbody>
</table>

“Over 25% of ALL common medications have genetic information that can be tested and used to personalize medical treatment”

–Frueh and Colleagues, 2008

“Psychopharmacogenetics & PTSD

All images in public domain
Selective Serotonin Reuptake Inhibitors

- Regulate mood, anxiety, depressive symptoms, sleep & appetite
- Reduce hyperarousal & avoidance
- Sertraline (Zoloft)
  - FDA approved, Most evidence
- Paroxetine (Paxil)
  - FDA approved
- Fluoxetine (Prozac)
  - Off-label

Tricyclic Antidepressants (Imipramine)

- Not 1st line 2° side effects (cardiac arrhythmias)
- Global improvement
- Prevented PTSD in Pediatric Burn Patients

Buspirone (BuSpar)

- Used adjunctively to treat hyperarousal symptoms
- Acts on Serotonin & may decrease anxiety
Other Antidepressants

- **Venlafaxine (Effexor)**
  - At lower doses acts as SHT reuptake inhibitor
  - At higher doses also NE reuptake inhibitor
- **Mirtazapine (Remeron)**
  - Treatment of insomnia in PTSD
- **Trazodone (Desyrel)**
  - Treatment of insomnia in PTSD, little evidence

Treatment of insomnia in PTSD

Venlafaxine (Effexor)
- At lower doses acts as SHT reuptake inhibitor
- At higher doses also NE reuptake inhibitor

Mirtazapine (Remeron)
- Treatment of insomnia in PTSD

Trazodone (Desyrel)
- Treatment of insomnia in PTSD, little evidence

Image: https://beyondmeds.com/2014/04/27/antidepressant-drugs/

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Drugs Used Off-Label in PTSD

**Trazodone (disordered sleep), Prazosin (night terrors)**
- Trazodone inhibits serotonin 5HT2a receptors and serotonin reuptake (SAR)
- Prazosin blocks noradrenaline α1 receptors

- Reduces nightmares & improves sleep
- Blocks noradrenergic stimulation of α-1 receptor
- Decreases sensitivity to adrenaline
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• Blocks adrenaline (epinephrine) on organs such as the heart, sweat glands & muscles
• Propranolol (Inderal), Guanfacine (Tenex)

**Mood Stabilizers**

► Block Glutamate or Potentiate GABA or Both
► Carbamazepine (Tegretol)
  ► Induces its own metabolism & may increase metabolism of other drugs (e.g., oral contraceptives)
► Divalproex (Depakote)
  ► Target dosage is 10x's patient's weight in pounds
  ► Monitor for hepatotoxicity & thrombocytopenia

► Gabapentin (Neurontin)
  ► Anticonvulsant that exerts anxiolytic, antinociceptive, and sleep-promoting effects
  ► Works on Calcium channels→ decreased release of NE, 5HT, Glutamate & Substance P
  ► Enhances slow-wave sleep, reduces arousal & increases total sleep time
  ► Normalizes GABA in amygdala
Lamotrigine (Lamictal)
May reduce arousal & reactivity
Requires SLOW titration 2° risk of Steven’s Johnson Syndrome

Topiramate (Topamax)
May reduce nightmares in PTSD
Monitor for glaucoma, sedation, cognitive dulling

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Atypical Antipsychotics

- NOT recommended as Monotherapy
- Inhibit Dopamine & Block Reuptake of Serotonin

---

Risperidone (Risperdal) contraindicated for use as an adjunctive agent due
Potential side effects exceed benefits

Insufficient evidence to recommend any as adjunctive treatments
May be helpful with co-morbid psychosis
Benzodiazepines & PTSD

- Act directly on GABA receptors
- Calms central nervous system, but little impact on core PTSD symptoms
- Potential for disinhibition & addiction
  - Lorazepam (Ativan)
  - Clonazepam (Klonopin)
  - Alprazolam (Xanax)

The Benzodiazepine Controversy

Drugs in the Pipeline for PTSD

- D-cycloserine (DCS)
  - Partial Agonist of Glutamatergic N-methyl-D-aspartate (NMDA) receptor
  - Used in panic disorder to enhance effects of exposure therapy
Memantine (Namenda)
Protects against glutamatergic destruction of neurons

Neuropeptides
Intervene at HPA axis or on Glucocorticoid receptors to modulate effects of stress Substance P & Neuropeptide Y

“While medicine can help control some of the symptoms, psychotherapy is still the gold standard.”

--Dr. Gregory Weiss
Durham VA Medical Center & DUKE University

PTSD Treatment Resources

Images: screen shots of app buttons LGLeahy 2017
PTSD is a whole-body tragedy, an integral human event of enormous proportions with massive repercussions.”

--Susan Pease Banitt

THANK YOU!!

QUESTIONS & ANSWERS