Evidenced-Based Prescribing Practices in Treating Post-Traumatic Stress Disorder in Military Combat Veterans

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DISCLOSURES

• The opinions or assertions contained herein are the sole views of the author and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.
• Discussion of use of medications include non-FDA or “off-label” indications; prescribers are advised to use their own clinical judgment in assessing risks, benefits, adverse effects and treatment alternatives when using medications “off-label.”
• The speaker has no conflicts of interest to disclose.

Learning Objectives

• Describe prevalence data for PTSD in the military population
• Examine the neurobiological underpinnings of PTSD
• Identify evidence-based pharmacological interventions for treating PTSD in military combat veterans
• Identify standardized tools to evaluate outcomes in military combat veterans with PTSD
Behavioral Health Disorders in the Military Population

- PTSD 8.5% (Significant Impairment) vs 3.5% in the general US population (18 years or older)
- Vietnam Vets 19%
- PTSD 23.2% (Some Impairment)
- Alcohol or Aggressive Behavior in 50% of cases

PTSD in the Military Population

- Operational Context (Infantry vs. Support Elements)
- Overall prevalence 2-6% immediately post-deployment and 11% 3-6 months later
- Infantry units weighted prevalence rate of 13%

DSM 5: Trauma- & Stress-Related Disorders

- Acute Stress Disorder
- Post-Traumatic Stress Disorder
- Reactive Attachment Disorders
- Disinhibited Social Engagement Disorder
- Adjustment Disorders
- Other Specified or Unspecified
DSM 5 Diagnostic Criteria

• Criterion A:
  • Experienced (directly or indirectly), witnessed or confronted with an event involving actual or threatened death or serious injury, or threat to the physical integrity of self or others.

• Criterion B: Re-experiencing in one or more of the following:
  • Recurrent and intrusive recollections (repetitive play in children with themes of the trauma)
  • Recurrent dreams (frightening dreams without recognizable content in children)
  • Dissociation: acting or feeling the event were recurring (re-enactment in young children)
  • Intense psychological distress at exposure to internal and external cues that resemble even
  • Marked physiological reactions to internal or external cues that symbolize the event

• Criterion C: Avoidance as indicated by three or more of the following:
  • Avoids thoughts, feelings, or conversations associated with trauma
  • Avoids activities, places, or people that arouse recollections

• Criterion D:
  • Inability to recall important aspects of the trauma (dissociative amnesia, not due to an organic cause)
  • Persistent and exaggerated negative beliefs or expectations about the world
  • Persistent, distorted cognitions about the cause or consequences of the lead to blame or guilt
  • Persistent negative emotional state
  • Anhedonia
  • Feelings of detachment
  • Persistent inability to experience positive emotions
**DSM 5 Diagnostic Criteria**

- **Criterion E**
  - Difficulty falling or staying asleep
  - Irritability or anger outbursts
  - Difficulty concentrating
  - Hypervigilance
  - Exaggerated startle response
  - Reckless or self-destructive behavior
- **Criterion F**: Duration of B, C, D, E is **more than one month**
- **Criterion G**: Causes significant distress or impairment in functioning
- **Criterion H**: Not attributable to effects of substances or another medical condition

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**Response to Trauma**

- Response serves an evolutionary purpose to protect you from a life-threatening event:
  - Physiological (“fight or flight”)
  - Cognitive (memories, avoidance)
  - Emotional (fear, anxiety, guilt, shame)
- These are normal, expected reactions to help you adapt to the situation.
- However, if these reactions persist and interfere with functioning they are no longer adaptive.

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**Adaptive Recovery**

- Recollections become less intense and frequent, and more precisely cued.
- Avoidance lessens as individual is re-exposed to situations and nothing bad happens.
- Acute physiological response decreases.
- Gradual relearning that world is not always such a dangerous place and decrease in guilt and shame.
Maladaptive Non-Recovery

• Initial reaction persists for more than a few weeks.
• Individual continues to experience symptoms that are distressing and **significantly interfere with functioning.**
• Symptoms get worse rather than better over time.

Maladaptive Non-Recovery (cont.)

• Individual has continued and excessive:
  • Re-experiencing (flashbacks, nightmares)
  • Avoidance of people, places and thoughts
  • Arousal (e.g. hypervigilance, insomnia, irritability)
  • Feelings of shame and guilt (need to assess for suicide)

Emotional Memory Review

• Limbic System
  • Cingulate gyrus: receives information
  • Hippocampus: short term memory, spatial coding
  • Thalamus: translator, relay station
  • Amygdala: emotional coding of memories
  • Performs high level processing of sensory information
  • Structures involved with Long-term potentiation
  • Attaches behavioral significance and response to stimulus
**Stress and HPA Axis**

- Hippocampus, Amygdala & HPA axis involved in stress circuits
- Normal Stress Response of HPA axis: release of CRF → ACTH → glucocorticoids → negative feedback on CRF → stop stress response
- Resulting neurotransmitter cascade: release of glutamate and norepinephrine → “fight or flight” response → GABA attenuates Glutamate and Norepinephrine → “fight or flight” stops


**Neurobiological Underpinnings of PTSD**

- Hypothalamic-Pituitary-Adrenal Axis
  - Negative feedback loop is dysregulated
  - Hypercortisolism (near term) then, Hypocortisolism (chronic)
  - Cortico-Releasing Factor over activity in the brain leading to release of norepinephrine from the locus coeruleus
  - Anatomical changes in the brain region that inhibits the HPA axis
- Neurotransmitters alterations
  - Serotonin
  - Norepinephrine
  - GABA
  - Glutamate


**Emerging Neurobiological Theories**

- Physiological processes involved with fear extinction
  - Potential Target: Endocannabinoid system and GABA-B receptors
- Other Substances
  - Potential Target: Brain-Derived Neurotrophic Factor (BDNF), Oxytocin, Substance P

Challenges with Pharmacotherapy
- Heterogeneous symptom presentation
- Most recent FDA approval was 10 years ago
- Co-morbid disorders
- Presence of previous trauma (i.e. Adverse Childhood Events)
- Cost/Formulary vs. non-formulary medications
- Limited evidence-base
- Provider knowledge with existing evidenced-based interventions and clinical practice guidelines

General Pharmacological Treatment Interventions
- Medications
  - SSRIs (Prozac, Paxil, Celexa, Zoloft, Lexapro)
  - SNRIs (Effexor, Cymbalta, Prixis)
  - Mood-Stabilizers (Depakote, Lamotrigine, Topiramate)
  - Atypical Antipsychotics (Seroquel, Zyprexa, Risperidone, Abilify)
  - Benzodiazepines (Valium, Ativan, Klonopin, Xanax)
  - Other Sedating Medications (Ambien, Lunesta, Trazodone, Amitriptyline, Nortriptyline)
  - Beta Blockers (Propranolol)
  - Alpha Blockers (Clonidine and Prazosin)

Evidence-Base: Antidepressants
- Most RCT studies are industry sponsored, however meta-analyses have confirmed efficacy
- Focus generally on Prozac, Zoloft, Paxil and Effexor XR
- Zoloft, Paxil and Effexor XR are only antidepressants FDA approved for PTSD
- Chronicity of symptoms may influence treatment response
- TCAs (particularly Desipramine and Imipramine) also demonstrate efficacy but are not superior to SSRIs and SNRIs
- SSRIs and SMRIs are first-line treatments
- SNRIs demonstrate efficacy for aggression and anger
- Longer treatment trials of medication may be needed

Petrakis, I. et al., (2012)
Evidence-Base: Antipsychotics

- Mixed-results adjunctive antipsychotic treatment with second-generation or atypical antipsychotics
- Atypical antipsychotics used for:
  - Sleep/Sedation
  - Anger/Aggression
  - Psychosis
- No evidence to support monotherapy use
- Recommended only for psychotic sx’s

Department of Veteran Affairs. (2010).

Evidence-Base: Mood Stabilizers

- Limited evidence to support use
- Topiramate and SSRIs/SNRIs have same efficacy and some evidence suggests efficacy for co-morbid Alcohol Use Disorders
- Lamotrigine may be helpful in treating refractory depressive sx’s
- Gabapentin may be helpful in managing hyperarousal symptoms

Batki, S. et al., (2014)

Evidence-Base: Benzodiazepines

- DO NOT USE, NO EVIDENCE TO SUPPORT USE

Lader, M. (2011)
Bernard, N. and Friedman, J. (2015)
Potential Pharmacological Interventions

• Ketamine
• Guanfacine
• GABA-B Receptors
• NMDA
• Endocannabinoid agonists

Fox, H. et al., (2012)
Feder, A. et al., (2014)
Bernardi, N. and Friedman, J. (2015)

Evidence-Base: Hypnotics

• Small study suggestive that Lunesta may be effective for sleep disturbance related to PTSD
• Trazodone helpful sedation


Evidenced-Based Treatment for Combat-Related Nightmares
“Sleep that knits up the raveled sleeve of care, the death of each day’s life, sore labor’s bath, balm of hurt minds, great nature’s second course, chief nourisher in life’s feast.”
“William Shakespeare, Macbeth

“A good laugh and a long sleep are the best cures in the doctor’s book.”
“Irish Proverb

“Some people talk in their sleep. Lecturers talk while other people sleep.”
“Albert Camus

http://www.quotegarden.com/sleep.html

Combat-Related Nightmares

- Sleep disturbance is a core symptom of PTSD
- A foundational component that significantly influences functional impairment
- Reported by 50-70% of Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF) combat veterans with PTSD³

Neurobiological Underpinnings of Combat-Related Nightmares

- The locus coeruleus “shuts down” during normal REM sleep with no norepinephrine release.
- In PTSD, locus coeruleus remains “active” norepinephrine is released during REM sleep, disrupting REM.

Prazosin

- Background
  - One of the few lipid soluble alpha-1 antagonist
  - A non-sedating generic that has been used for decades to treat hypertension and BPH
  - Decreases/eliminates the effect of norepinephrine during REM sleep
  - Initially found effective for trauma nightmares in Vietnam veterans\(^1\)
    - reports of improved sleep quality and duration
    - marked decrease in frequency intensity of nightmares
    - well tolerated, improvement is dose related
    - discontinuing medications after improvement associated with return of nightmares
    - potential to reduce co-morbid alcohol abuse

Evidence of Prazosin Efficacy for Trauma Nightmares and Global Function

- In Vietnam veterans, a crossover placebo-controlled study (\(n = 10\))\(^2\)
  and a parallel group placebo-controlled study (\(n = 34\))\(^2\)
  positive improvement in sleep duration and quality, reduction in nightmares
- In civilians, a crossover study (\(n = 13\)) positive and sleep duration 90 minutes longer than with placebo\(^3\)

\(^3\)Taylor F. et al., (2008).
Evidence of Prazosin Efficacy for Trauma Nightmares and Global Function

- In OIF deployed in a combat zone, a prospective study \( n = 13 \) positive improvement in sleep duration and quality, reduction in nightmares and improved overall level of functioning.\(^1\)
- In OIF/OEF combat veterans, a double-blind placebo RCT \( n = 56, 29 \) placebo and 27 prazosin) positive improvement in sleep duration and quality, reduction in nightmares and improved overall level of functioning.
- Prazosin vs. Quetiapine \( (N=237, 62 \text{ prazosin and } 175 \text{ quetiapine}) \) similar efficacy, however prazosin is much better tolerated.

\(^1\)Calohan, J. et al., (2010).
\(^3\)Byers, M. et al., (2010)

Prescribing Prazosin

- Prazosin (Minipress) 1mg-20mg
- Dose initially at 1mg for two nights to assess for "first-dose effect." Has been associated with orthostatic hypotension with first dose. Also possibility of reflex tachycardia in the AM upon exertion
- If pt is tolerates medication and no improvement in nightmares, then increase dose to 2mg HS for four nights. Continue titrating dose upwards by 2mg q 4 days to effect
- Monitoring: initial orthostatic and ongoing BP monitoring
- Also can consider low-dose during the day (mid-AM) 2-6mg to address residual hyperarousal symptoms
- Outcome Evaluation Tools
  - Clinician Administered Post-Traumatic Stress Scale
  - Clinical Global Impression of Change

CAPS Sleep Items (B2)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Question</th>
</tr>
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<tbody>
<tr>
<td>Sleep</td>
<td>How much of a problem did you have with your sleep?</td>
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<tr>
<td>N</td>
<td>How long did it take you to fall asleep?</td>
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CAPS Nightmare Items (D2)

- Have you ever had unpleasant dreams about (EVENT)?
  - How often have you had these dreams in the past month?
  - How much distress did these dreams cause you?
  - Did you ever wake up in distress?
  - How long did it take you to get back to sleep?

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<th>Description/Examples</th>
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<td>Intensity</td>
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<td>How much distress or discomfort did these dreams cause you? Did you ever wake up in distress? How long did it take you to get back to sleep?</td>
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Clinical Global Impression of Change

- Considerations in Selecting Pharmacological Agents

  - Symptom presentation
  - Meet patient/client where they are at
  - Collaborative goal-setting
  - Expectations management
Questions?

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