The Trials, Tribulations, and Treatment of PTSD

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Conflict of Interest Slide

• Dr. Boggs has no actual or potential conflict of interest associated with this presentation
Off Label Disclosures

• This presentation will discuss substances / medications that are not FDA approved for the treatment of PTSD

Objectives

• Define the symptoms of PTSD

• Describe the different theories for the pathogenesis of PTSD

• List the evidence based pharmacologic treatments for PTSD
DSM 5 Criteria PTSD

**Criterion A:** (one required) The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s):

- Direct exposure
- Witnessing the trauma
- Learning that a relative or close friend was exposed to the trauma
- Indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics)

**DSM 5 Criteria PTSD**

**Criterion B:** (one required) The traumatic event is persistently re-experienced, in the following way(s):

- Intrusive thoughts
- Nightmares
- Flashbacks
- Emotional distress after exposure to traumatic reminders
- Physical reactivity after exposure to traumatic reminders
DSM 5 Criteria PTSD

**Criterion C**: (one required) Avoidance of trauma-related stimuli after the trauma, in the following way(s):

- Trauma-related thoughts or feelings
- Trauma-related reminders

DSM 5 Criteria PTSD

**Criterion D**: (two required) Negative thoughts or feelings that began or worsened after the trauma, in the following way(s):

- Inability to recall key features of the trauma
- Overly negative thoughts and assumptions about oneself or the world
- Exaggerated blame of self or others for causing the trauma
- Negative affect
- Decreased interest in activities
- Feeling isolated
- Difficulty experiencing positive affect
DSM 5 Criteria PTSD

**Criterion E**: (two required) Trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s):

- Irritability
- Risky or destructive behavior
- Hypervigilance
- Heightened startle reaction
- Difficulty concentrating
- Difficulty sleeping

**Criterion F**: (required) Symptoms last for more than 1 month.

**Criterion G**: (required) Symptoms create distress or functional impairment (e.g., social, occupational).

**Criterion H**: (required) Symptoms are not due to medication, substance use, or other illness.
Mr. A is an Operation Enduring Freedom (OEF) Army Veteran who was involved in active combat in Afghanistan where several of his fellow troops lost their lives. Since returning to the USA he reports difficulties adjusting to civilian lifestyle. For the past 3 years he reports having nightmares 3-4 times a week, often “destroying” the bed. Reports staying away from crowds and explosions such as fireworks. His affect is very blunted and Mr. A reports having no close friends because “people cannot be trusted”. Mr. A reports sleeping with a knife under his pillow because he is hearing sounds at night that wake him up.

Question #1

• Which of the following characteristics are most consistent with PTSD?

A. Military veteran, maintains a few close friendships, reports three nightmares related to upcoming deployment over the last month
B. Combat veteran that lost friends in armed conflict, deep distrust in society, extensive history of nightmares for past three years
C. Combat veteran, socially awkward, no reported difficulty sleeping
Learned Stress & Extinction Learning

CS – conditioned stimuli
US – unconditioned stimuli


Pathogenesis of PTSD

• Noradrenergic Etiology
• Serotonin Etiology
Pathogenesis of PTSD

- Noradrenergic Etiology
Pathogenesis of PTSD

- Serotonin Etiology
Question #2

Prazosin, an $\alpha_1$ antagonist, is used in the treatment of PTSD. Based on the purposed pathophysiology of PTSD, prazosin would be beneficial

A. to decrease the hyperserotonergic state in the brain.
B. to decrease the hypernoradrenergic state in the brain.
C. to increase the hyposerotonergic state in the brain.
D. to block the effects of the hypernoradrenergic state of the brain.
E. to increase dopamine by blocking serotonergic receptors.

Treatment
Psychotherapy

• First Line: VA / DoD
  – Exposure Therapy
  – Cognitive Therapy
  – Eye Movement Desensitization and Reprocessing (EMDR)
  – Stress Inoculation

• Second Line: VA / DoD
  – Imagery Rehearsal Therapy
  – Psychodynamic psychotherapy
  – Brief Cognitive Behavioral Therapy (CBT)

Forbes et al J Trauma Stress 2010

Interpretation of Cohen’s $d$

<table>
<thead>
<tr>
<th>Calculated Effect Size</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>&gt; 0.5</td>
<td>Large Effect</td>
</tr>
<tr>
<td>0.5 – 0.3</td>
<td>Medium Effect</td>
</tr>
<tr>
<td>0.3 – 0.1</td>
<td>Small Effect</td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>Miniscule Effect</td>
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</table>

Efficacies of Selected Psychotherapies for PTSD

<table>
<thead>
<tr>
<th>Psychotherapy Type</th>
<th>PTSD Symptoms (CAPS)</th>
<th>Effect Size (d)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Therapy</td>
<td>-1.36</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>CBT Exposure</td>
<td>-1.27</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Narrative Exposure Therapy</td>
<td>-1.25</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>EMDR</td>
<td>-1.08</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

CAPS – Clinician-Administered PTSD Scale

*Cusack et al Clin Psychol Rev 2016*

Pharmacotherapy
Mirror, Mirror on the Wall……

2010 VA / DoD Pharmacological Practice Guidelines

<table>
<thead>
<tr>
<th>SR</th>
<th>Significant</th>
<th>Some Benefit</th>
<th>Unknown</th>
<th>No Benefit</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>SSRI SNRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Mirtazapine</td>
<td>Prazosin (sleep/nightmares)</td>
<td>TCAs</td>
<td>Nefazodone [Caution*]</td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SSRI- Selective Serotonin Reuptake Inhibitor; SNRI- Serotonin Norepinephrine Reuptake Inhibitor; TCA- Tricyclic Antidepressant; MAOI- Monoamine oxidase Inhibitor

SR = Strength of recommendation
## 2010 VA / DoD Pharmacological Practice Guidelines

<table>
<thead>
<tr>
<th>SR</th>
<th>Significant</th>
<th>Some Benefit</th>
<th>Unknown</th>
<th>No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
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</table>

**Response by Drug Class**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medication</th>
<th>Global Improvement</th>
<th>Re-Experiencing (B)</th>
<th>Avoidance / Numbing (C)</th>
<th>Hyperarousal (D)</th>
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</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Fluoxetine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>MAOI</td>
<td>Phenelzine</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sympathomlytics</td>
<td>Prazosin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Other Antidepressants</td>
<td>Mirtazapine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**SR = Strength of recommendation**
SSRI / SNRI

- No recommendation for specific medication
- No head-to-head studies
- Best evidence for paroxetine, sertraline, fluoxetine, venlafaxine

Efficacies of Selected Pharmacotherapies for PTSD

<table>
<thead>
<tr>
<th>Medication</th>
<th>PTSD Symptoms Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinician-Rated</td>
</tr>
<tr>
<td>Paroxetine*</td>
<td>-0.43**</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-0.24**</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>-0.20**</td>
</tr>
<tr>
<td>Sertraline*</td>
<td>-0.16**</td>
</tr>
</tbody>
</table>

* - FDA approved for PTSD; ** - p < 0.05

Hoskins et al Br J Psychiatry 2015
**Adrenergic Medications**

- **α<sub>1</sub> Antagonist**
  - Prazosin

- **α<sub>2</sub> Agonist**
  - Guanfacine
  - Clonidine

- **β – Blockers**
  - Propranolol
Prazosin

**Dosing**
- Start 1 mg at bedtime and increase as blood pressure allows
- Target: 6 – 10 mg daily

**Side effects:**
- First dose syncope
- Orthostatic hypotension
Cooperative Studies Program #563
Prazosin and Combat PTSD (PACT)

ClinicalTrials.gov Identifier: NCT00532493

- 26 weeks
- Flexible Dosing: (1 – 20mg)

Prazosin and Combat PTSD (PACT) Demographics

<table>
<thead>
<tr>
<th></th>
<th>Prazosin Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>152</td>
<td>152</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>52.3 (13.8)</td>
<td>51.4 (13.8)</td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td>146 / 6</td>
<td>151 / 1</td>
</tr>
<tr>
<td>Major Depressive Disorder (yes)</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>Maintained on antidepressant (yes)</td>
<td>119</td>
<td>117</td>
</tr>
<tr>
<td>Maintained on SSRI (yes)</td>
<td>113</td>
<td>113</td>
</tr>
</tbody>
</table>
Prazosin and Combat PTSD (PACT) – Results

Second Generation Antipsychotics

- Aripiprazole
- Asenapine
- Brexpiprazole
- Cariprazine
- Clozapine
- Iloperidone
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone
Receptor Binding Profiles of Selective Antipsychotics

Data with cloned human receptors.

Quetiapine Monotherapy for PTSD

FIGURE 2. Clinician-Administered PTSD Scale (CAPS) Scores for PTSD Patients in Study of Quetiapine

Quetiapine (mean, range): 258mg, 50 – 800mg

Villarreal et al Am J Psychiatry 2016
Benzodiazepines in Fear Extinction

FIGURE 1. Effect of Treatment on Clinician-Rated Symptoms and Extinction Learning in Iraq and Afghanistan Veterans With PTSD Treated With Virtual Reality Exposure Plus n-Cycloserine, Alprazolam, or Placebo

Rothbaum et al Am J Psychiatry 2014

Benzodiazepines for PTSD

Level of Evidence for BZD

Efficacy D
Inefficacy A
Worsened outcomes B

Guina et al J Psychiatric Practice 2015
Eszopiclone for PTSD and Insomnia

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Eszopiclone Baseline (mean ± SD)</th>
<th>Placebo Baseline (mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>11.52 ± 3.50</td>
<td>11.13 ± 3.33</td>
<td>0.011</td>
</tr>
<tr>
<td>Subjective sleep quality</td>
<td>2.0 ± 0.66</td>
<td>1.88 ± 0.80</td>
<td>0.015</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>2.08 ± 1.10</td>
<td>2.0 ± 0.98</td>
<td>0.007</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>1.83 ± 0.87</td>
<td>1.67 ± 0.76</td>
<td>0.103</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>1.96 ± 1.20</td>
<td>1.96 ± 1.27</td>
<td>0.177</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>1.57 ± 0.66</td>
<td>1.54 ± 0.66</td>
<td>0.034</td>
</tr>
<tr>
<td>Use of sleep medication</td>
<td>0.54 ± 1.10</td>
<td>0.46 ± 1.06</td>
<td>0.933</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>1.63 ± 0.77</td>
<td>1.54 ± 0.93</td>
<td>0.018</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>65.71 ± 67.15</td>
<td>49.17 ± 29.51</td>
<td>0.044</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>319.38 ± 79.18</td>
<td>338.09 ± 57.41</td>
<td>0.061</td>
</tr>
<tr>
<td>PTSD measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRINT score</td>
<td>22.13 ± 3.50</td>
<td>21.92 ± 5.46</td>
<td>0.032</td>
</tr>
<tr>
<td>CAPS score</td>
<td>75.08 ± 14.43</td>
<td>68.08 ± 21.67</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Pollack et al J Clin Psychiatry 2011

Cannabis for PTSD

- Approved for treatment of PTSD in Connecticut
- No well controlled studies for treatment of PTSD\(^1\)
- Veterans report improved sleep with cannabis\(^2\)
- Recent evidence suggesting poorer outcomes with PTSD\(^3\)

Question #3
Mr. A comes in for a second visit and will not agree to psychotherapy but agrees to start medications for treatment of PTSD. However, Mr. A states “I don’t want to be experimented on”. Which of the following medications has the best evidence for treatment of core symptoms of PTSD?

A. Aripiprazole
B. Brexpiprazole
C. Cannabis
D. Duloxetine
E. Venlafaxine

Future Pharmacological Treatment of PTSD?
Added ? mark
Leschak, Andrea, 3/14/2017
Future Pharmacotherapy

- Treatment after trauma to prevent PTSD
- Pharmacotherapy augmentation to pharmacotherapy
- Pharmacotherapy augmentation for psychotherapy
- Treatments for PTSD phenotypes
- Novel treatments
  - Ketamine
- Genomic targets for PTSD

---

Prophylaxis for PTSD

![Figure 2: Standardized effect sizes of pharmacological prevention for PTSD compared with control groups; incidence risk ratio](#)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pharmacotherapy</th>
<th>Timepoints</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
<th>ePTSD n</th>
<th>n Total</th>
<th>Risk of bias</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
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<tr>
<td>Friedman et al. (2013)**</td>
<td>Hydrocortisone</td>
<td>2</td>
<td>0.21</td>
<td>0.07-0.59</td>
<td>0.48</td>
<td>2/34</td>
<td>1/32</td>
<td>- - + - 1</td>
</tr>
<tr>
<td>Hoge et al. (2012)**</td>
<td>SSRI</td>
<td>2</td>
<td>1.06</td>
<td>0.60-1.83</td>
<td>0.89</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
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<tr>
<td>Kolmson et al. (2012)**</td>
<td>Anti-inflammatory</td>
<td>1</td>
<td>0.63</td>
<td>0.22-1.97</td>
<td>0.06</td>
<td>2/20</td>
<td>1/20</td>
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<tr>
<td>Kolmson et al. (2013)**</td>
<td>Chinese herbal medicine</td>
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<td>0.21</td>
<td>0.07-0.59</td>
<td>0.48</td>
<td>2/34</td>
<td>1/32</td>
<td>21/22</td>
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<tr>
<td>Nagy et al. (2013)**</td>
<td>SSRI</td>
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<td>3.46</td>
<td>0.55-21.76</td>
<td>0.13</td>
<td>1/32</td>
<td>1/32</td>
<td>NA NA NA 0</td>
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<tr>
<td>Prineas et al. (2013)**</td>
<td>SSRI</td>
<td>2</td>
<td>1.44</td>
<td>0.64-3.27</td>
<td>0.36</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
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<tr>
<td>Sijbrandij et al. (2015)**</td>
<td>Hydrocortisone</td>
<td>1</td>
<td>0.22</td>
<td>0.09-0.51</td>
<td>0.07</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
</tr>
<tr>
<td>Sijbrandij et al. (2016)**</td>
<td>Hydrocortisone</td>
<td>1</td>
<td>0.22</td>
<td>0.09-0.51</td>
<td>0.07</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
</tr>
<tr>
<td>Share et al. (2013)**</td>
<td>SSRI</td>
<td>1</td>
<td>3.46</td>
<td>0.55-21.76</td>
<td>0.13</td>
<td>1/32</td>
<td>1/32</td>
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<td>Stern et al. (2016)**</td>
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<td>1/32</td>
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<tr>
<td>Stern et al. (2017)**</td>
<td>Benzodiazepine</td>
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<td>1.43</td>
<td>0.69-2.98</td>
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<td>1/32</td>
<td>1/32</td>
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<tr>
<td>Tansel et al. (2017)**</td>
<td>SSRI</td>
<td>1</td>
<td>0.49</td>
<td>0.15-1.60</td>
<td>0.35</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
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<tr>
<td>Vala et al. (2017)**</td>
<td>SSRI</td>
<td>1</td>
<td>0.24</td>
<td>0.09-0.54</td>
<td>0.08</td>
<td>1/32</td>
<td>1/32</td>
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<td>Wintre et al. (2016)**</td>
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<td>0.21</td>
<td>0.06-0.73</td>
<td>0.09</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
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<tr>
<td>Zehet et al. (2017)**</td>
<td>Hydrocortisone</td>
<td>2</td>
<td>0.20</td>
<td>0.05-0.82</td>
<td>0.09</td>
<td>1/32</td>
<td>1/32</td>
<td>- - - - 0</td>
</tr>
</tbody>
</table>

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Sijbrandij et al. *Lancet Psychiatry* 2015
Summary

- PTSD is no longer classified as an anxiety disorder
- Serotonergic and noradrenergic changes in the brain are thought to be related to the pathophysiology of the disorder
- Evidence based psychotherapies have shown good efficacy in the treatment of PTSD
- First line pharmacotherapy treatment of PTSD includes SSRIs and SNRIs
Questions?

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