Medication in the Treatment of PTSD

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Research Advisory Committee on Gulf War Veterans Illness

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Overview

• Background on PTSD
• Meta-analytic findings on PTSD treatment
• VA/DoD Practice Guideline for PTSD
• Ongoing research
DSM-5 PTSD Diagnostic Criteria

• Exposure to a traumatic event in which the person:
  – Experienced, witnessed, or was confronted by death or serious injury to self or others
  – Includes occupational exposure, e.g., first responders

• Symptoms
  – 20 symptoms in 4 clusters: intrusion, avoidance, changes in cognition and mood (e.g., numbing, guilt), hyperarousal
  – Last > 1 month
  – Cause clinically significant distress or impaired functioning

– American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 2014
DSM-5 PTSD Prevalence in the United States

Lifetime PTSD Current PTSD

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime</td>
<td>4.1%</td>
<td>8.0%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Current</td>
<td>3.2%</td>
<td>6.1%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

US General population estimates from NESARC-III; Goldstein et al., 2016
DSM-5 PTSD Prevalence in Veterans

VA Healthcare Users

- **OEF/OIF/OND**
  - Overall: 26.5%
  - Women: 20.0%
  - Men: 30.0%

- **All eras**
  - Overall: 12.1%
  - Women: 10.0%
  - Men: 20.0%

All Veterans

- **Lifetime**
  - Overall: 6.9%
  - Women: 5.0%
  - Men: 9.0%

- **Current**
  - Overall: 3.0%
  - Women: 2.0%
  - Men: 4.0%

DSM-5 PTSD Prevalence in Veterans

Current PTSD in Gulf War and Gulf War era Veterans

- Gulf War era: 11.5% (Overall, Women, Men)
- Gulf War: 20.9% (Overall, Women, Men)

All Veterans

- Lifetime: 6.9% (Overall, Women, Men)
- Current: Men (4.7%), Women (12.0%), All Veterans (6.9%)

Gulf War estimates from Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans: Dursa et al., 2016, 2019. All Veterans estimates from NESARC-III: Lehavot et al., 2018; Smith et al., 2016.
Figure 3: Percentage of Veterans in VHA with a diagnosis of PTSD, by year

(Some types of) Medication, Psychotherapy, and Somatic Treatments are Effective for PTSD

- Watts, Schnurr et al. (2013). Effect sizes are represented as a modified Hedges $g$, indicating benefit relative to a control group. $N =$ number of comparisons. 1st and 2nd level significant effects are shown.
Psychotherapy is More Effective Than Medication

** Psychotherapy waitlist control v. medication, $p<.01$

* Psychotherapy treatment control v. medication, $p<.05$

– Watts, Schnurr et al. (2013). Effect sizes are represented as a modified Hedges $g$, indicating benefit relative to a control group.
VA/DoD PTSD Guideline (2017)

- Guidelines are designed to provide information and assist decision making
- Guidelines are not intended to define a standard of care

www.healthquality.va.gov/guidelines/MH/ptsd/
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Criteria

- **Strong For** (or “We recommend offering this option …”)
- **Weak For** (or “We suggest offering this option …”)
- **Weak Against** (or “We suggest not offering this option …”)
- **Strong Against** (or “We recommend against offering this option …”)

**Insufficient** is used when there was a lack of evidence or the evidence did not permit a definitive conclusion.

We recommend individual, manualized trauma focused psychotherapy over other pharmacologic and non-pharmacologic interventions for the primary treatment of PTSD.

When individual trauma focused psychotherapy is not readily available or not preferred, we recommend pharmacotherapy or individual non-trauma-focused psychotherapy. There is insufficient evidence to recommend one over the other.
Recommended Trauma-Focused Psychotherapy

We recommend individual, manualized trauma-focused psychotherapies that have a primary component of exposure and/or cognitive restructuring to include Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), Eye Movement Desensitization and Reprocessing (EMDR), specific cognitive behavioral therapies for PTSD, Brief Eclectic Therapy (BEP), Narrative Exposure Therapy (NET), and written narrative exposure.
Evidence-Based Psychotherapy is More Effective than Evidence-Based Medication

Included only studies with active controls and clinician-rated outcomes

- Lee et al., 2016
<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Recommend For</th>
<th>Suggest For</th>
<th>Suggest Against</th>
<th>Recommend Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Sertraline</td>
<td></td>
<td>Prazosin (exc. Tx of PTSD-assoc. nightmares)</td>
<td></td>
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<tr>
<td></td>
<td>Paroxetine</td>
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<td></td>
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<tr>
<td></td>
<td>Fluoxetine</td>
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<td></td>
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<tr>
<td></td>
<td>Venlafaxine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>Nefazodone</td>
<td>Quetiapine</td>
<td>Divalproex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Olanzapine</td>
<td>Tiagabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Citalopram</td>
<td>Guanfacine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amitriptyline</td>
<td></td>
</tr>
<tr>
<td>Very Low</td>
<td>Imipramine</td>
<td></td>
<td>Lamotrigine</td>
<td>Risperidone</td>
</tr>
<tr>
<td></td>
<td>Phenelzine</td>
<td></td>
<td>Topiramate</td>
<td>Benzodiazepines</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D-cycloserine</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hydrocortisone</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ketamine</td>
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</tbody>
</table>
Table 1. Medications Filled as Prescriptions in the Year Following Initial PTSD Diagnosis, 2004–2013

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2007</th>
<th>2010</th>
<th>2013</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New PTSD Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>731,520</td>
</tr>
<tr>
<td>Mean Number of Psychotics</td>
<td>3.5 ± 2.5</td>
<td>3.5 ± 2.6</td>
<td>3.6 ± 2.7</td>
<td>3.5 ± 2.7</td>
<td>3.5 ± 2.7</td>
</tr>
<tr>
<td><strong>All Antidepressants</strong></td>
<td>85.1 (44,026)</td>
<td>82.7 (57,544)</td>
<td>80.1 (68,001)</td>
<td>78.0 (64,394)</td>
<td>81.0 (592,505)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>5.7 (2948)</td>
<td>4.6 (3195)</td>
<td>3.8 (3221)</td>
<td>3.7 (3074)</td>
<td>4.2 (31,019)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>12.4 (6392)</td>
<td>12.3 (8578)</td>
<td>12.9 (10,973)</td>
<td>13.0 (10,722)</td>
<td>12.6 (92,460)</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1.2 (638)</td>
<td>0.3 (237)</td>
<td>0.1 (116)</td>
<td>0.1 (50)</td>
<td>0.3 (2097)</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>0.0 (20)</td>
<td>0.0 (10)</td>
<td>0.0 (8)</td>
<td>0.0 (8)</td>
<td>0.0 (92)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>33.4 (17,296)</td>
<td>32.3 (22,484)</td>
<td>30.5 (25,847)</td>
<td>29.7 (24,489)</td>
<td>31.0 (226,812)</td>
</tr>
<tr>
<td><strong>Any SSRI or SNRI</strong></td>
<td>70.1 (36,290)</td>
<td>67.6 (47,064)</td>
<td>65.7 (55,740)</td>
<td>63.1 (52,112)</td>
<td>66.3 (485,194)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>13.9 (7212)</td>
<td>11.8 (8246)</td>
<td>9.5 (3022)</td>
<td>11.5 (9481)</td>
<td>11.3 (62,346)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10.3 (5331)</td>
<td>7.0 (4842)</td>
<td>5.0 (4266)</td>
<td>6.0 (4951)</td>
<td>6.6 (48,215)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>26.0 (13,449)</td>
<td>16.3 (11,367)</td>
<td>21.4 (18,145)</td>
<td>31.2 (25,771)</td>
<td>22.9 (167,613)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>9.2 (4770)</td>
<td>8.5 (5882)</td>
<td>8.4 (7121)</td>
<td>11.7 (9680)</td>
<td>9.1 (66,747)</td>
</tr>
<tr>
<td><strong>All Anticonvulsants</strong></td>
<td>21.8 (11,267)</td>
<td>22.8 (15,871)</td>
<td>26.0 (22,080)</td>
<td>29.1 (24,005)</td>
<td>24.9 (182,077)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>11.1 (5739)</td>
<td>12.1 (8399)</td>
<td>15.2 (12,851)</td>
<td>18.2 (15,001)</td>
<td>14.1 (102,791)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2.1 (1072)</td>
<td>2.6 (1832)</td>
<td>3.3 (2764)</td>
<td>4.3 (3517)</td>
<td>3.1 (22,803)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>7.3 (3794)</td>
<td>6.8 (4723)</td>
<td>6.8 (5732)</td>
<td>6.2 (5152)</td>
<td>6.7 (49,197)</td>
</tr>
<tr>
<td>Frazosin</td>
<td>6.1 (3171)</td>
<td>9.5 (6690)</td>
<td>17.3 (14,641)</td>
<td>25.8 (21,291)</td>
<td>15.0 (110,048)</td>
</tr>
<tr>
<td><strong>All Atypical Antipsychotics</strong></td>
<td>29.7 (15,390)</td>
<td>23.8 (16,562)</td>
<td>20.3 (17,185)</td>
<td>16.9 (13,944)</td>
<td>21.8 (159,757)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4.5 (2347)</td>
<td>1.9 (1342)</td>
<td>1.7 (1444)</td>
<td>1.6 (1298)</td>
<td>2.0 (14,691)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>18.9 (9758)</td>
<td>15.8 (10,970)</td>
<td>11.5 (9728)</td>
<td>9.0 (7426)</td>
<td>13.3 (97,542)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>9.9 (5126)</td>
<td>6.1 (4248)</td>
<td>5.1 (4323)</td>
<td>4.7 (3917)</td>
<td>5.8 (42,311)</td>
</tr>
<tr>
<td><strong>All Typical Antipsychotics</strong></td>
<td>1.8 (946)</td>
<td>1.8 (1275)</td>
<td>1.8 (1526)</td>
<td>1.8 (1485)</td>
<td>1.8 (13,304)</td>
</tr>
<tr>
<td><strong>All Sedative Medicines</strong></td>
<td>7.8 (4027)</td>
<td>12.4 (6065)</td>
<td>12.9 (10,984)</td>
<td>12.9 (10,637)</td>
<td>11.9 (87,361)</td>
</tr>
<tr>
<td>All Sedative Hypnotics</td>
<td>38.2 (19,776)</td>
<td>37.9 (26,353)</td>
<td>41.3 (35,085)</td>
<td>35.4 (29,262)</td>
<td>38.9 (284,877)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>4.6 (2404)</td>
<td>7.9 (5532)</td>
<td>18.2 (15,472)</td>
<td>14.3 (11,837)</td>
<td>13.0 (95,086)</td>
</tr>
<tr>
<td>Any benzodiazepine</td>
<td>34.9 (18,066)</td>
<td>32.9 (22,907)</td>
<td>29.4 (24,979)</td>
<td>25.1 (20,756)</td>
<td>30.3 (221,309)</td>
</tr>
<tr>
<td><strong>All Opioids</strong></td>
<td>35.4 (18,325)</td>
<td>37.8 (26,301)</td>
<td>38.3 (32,473)</td>
<td>34.6 (28,564)</td>
<td>36.9 (270,103)</td>
</tr>
<tr>
<td>All Stimulants</td>
<td>1.1 (592)</td>
<td>1.5 (1060)</td>
<td>2.3 (1991)</td>
<td>3.3 (2702)</td>
<td>3.1 (15,690)</td>
</tr>
<tr>
<td>Lithium</td>
<td>1.8 (942)</td>
<td>1.4 (951)</td>
<td>1.4 (1162)</td>
<td>1.5 (1254)</td>
<td>1.4 (10,580)</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5.1 (2565)</td>
<td>4.7 (3241)</td>
<td>4.9 (4168)</td>
<td>6.4 (5269)</td>
<td>5.1 (37,614)</td>
</tr>
</tbody>
</table>

- Krystal et al., 2017; data from B. Shiner
Anticonvulsant Medication Use in Veterans with PTSD in VA

- N = 732,520 VA users entering treatment for PTSD, 2004-2013
  - 24.9% received an anti-convulsant
  - 94.6% had an indication for anticonvulsant use
  - 51.2% initiated anticonvulsant use before PTSD treatment

- Gabapentin was most frequently prescribed and increased most over time

- Shiner et al., 2017
Recommendations from “It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group”

- The urgent need to find effective pharmacologic treatments for PTSD should be considered a national mental health priority.
- There is a need to increase the number of early phase clinical trials through novel collaborations among government, industry, and academia.
- There is a need to develop new trial designs and/or methodologies specifically in the area of PTSD psychopharmacology trials.
- Foundational studies are required to inform the optimal prescription of commonly prescribed medications for the treatment of PTSD.
- The development of a psychopharmacology clinical trials workforce and infrastructure for PTSD would advance the goal of increasing clinical trials in this area.
- Studies exploring the pathophysiology of PTSD will be critical to inform the rational development of novel pharmacologic interventions.
- There is a need to continue to invest in initiatives in translational neuroscience to enhance the expansion of the pipeline of new PTSD pharmacotherapeutics.

- Krystal et al., 2017
VA Office of Research and Development: PTSD Psychopharmacology Initiative

Accelerating Development of Better PTSD Treatment for Veterans: The VA PTSD Psychopharmacology Initiative (PPI)

Since 2016, VA Research has been working to support the development of new medication treatments through focused clinical trials under our PTSD Psychopharmacology Initiative (PPI). While there are two FDA approved medications for PTSD (both antidepressants), not everyone successfully intolerance or responds to these medications, and thus our clinical trials program has grown to accommodate multiple ongoing studies (described below). It is the goal of the PPI to identify, test, and confirm new effective medications that could become available for PTSD treatments.

In this effort we still need investigators to:

1. Evaluate local interest in serving as a performance sites for PTSD medication studies. Researchers who wish to serve as site investigators should notify their Research Office and assist with the completion of the PPI Site Survey.

2. Conduct research on new compounds. We encourage eligible VA investigators who are interested in testing new medications for PTSD in Veterans to apply for funding through the CSIRAD Clinical Trials program. The first step in this process is to submit a Clinical Trial letter of intent. Instructions and deadlines can be found in Section IV of our Resources For the VA Research Community.

The PPI is an integral part of the Clinical Science Research and Development (CSIRAD) roadmap, Accelerating the Translation of New Medications for Veterans with PTSD. This document illustrates our progress to date as well as future goals related to this important effort.
CSP #2016: The National Adaptive Trial for PTSD-Related Insomnia (NAP)

- Four arms, 12-weeks, of oral medication at bedtime (placebo, trazodone 200 mg, gabapentin 2000 mg, eszopiclone 3 mg)
- 1224 patients from 34 VA Medical Centers; veterans with treatment-resistant PTSD-related insomnia
- Primary outcome: Insomnia Severity Index (self-rated)
- Secondary outcome: CAPS (rated centrally)
  - Additional clinical outcomes (CGI, QOL, etc.)
- Exploratory outcomes: actigraphy, molecular biomarkers
- Adaptive: interim analysis will inform discontinuation of futile arms
  - Discontinuation will not reduce target recruitment, increasing power of remaining comparisons
- PI: J. Krystal
- VACSCC: Palo Alto
Ketamine for Treatment-Resistant Symptoms of Military-Related PTSD

- Funding: Consortium to Alleviate PTSD and NCPTSD (DOD, VA)
- Ongoing trial: 167 randomized patients from three sites (Veterans: VA Connecticut, VA Minneapolis, Active Duty: BAMC)
- 3 arms: placebo, ketamine 0.2 mg/kg, ketamine 0.5 mg/kg
- Design:
  - Primary: twice weekly infusions for 4 weeks
  - Secondary: 4-week follow-up for duration of benefit
- Outcome measure:
  - Primary: PCL-5 (self-rated)
  - Secondary: CAPS, mood, anxiety, CGI, QOL
- Exploratory outcomes: biochemical biomarkers
- PI: J. Krystal
A Promising Direction: Medication-Enhanced Psychotherapy

- Efforts underway to use medication to boost evidence-based psychotherapy with, e.g., ketamine, cannabidiol, oxytocin
  - e.g., VA is currently sponsoring a placebo-controlled randomized clinical trial of cannabidiol with Prolonged Exposure Therapy

- Also research on MDMA with other psychotherapy

- Blinding is a challenge for studying some of these medications
Current State of the Evidence on Medication for PTSD

- Several medications are effective, but the best medications are less effective than the best psychotherapies
- Medication-assisted psychotherapy is promising, but at a preliminary state; placebo control is challenging
- Research is needed, especially to develop novel medications