The 2017 Revised Clinical Practice Guideline for PTSD: Recommendations for Medications

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PTSD Consultation Program Lecture Series, October 2017
Overview

1. Describe guideline development process
2. Review medication recommendations
3. Discuss clinical implications and practice changes
VA/DoD Clinical Practice Guideline (CPG) for the Management of Posttraumatic Stress Disorder (PTSD) and Acute Stress Disorder (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
Stages of Guideline Development

1. Formulate and prioritize Key Questions
2. Convene a patient focus group
3. Conduct systematic review
4. Convene face to face meeting with workgroup
5. Draft CPG recommendations
6. Release for external comment
7. Finalize and submit to Evidence Based Practice Work Group
2017 CPG is an update of the 2010 CPG

Methodology for 2017 based on Guide for Guidelines

Two levels of evidence appraisal:

- US Preventive Services Task Force (USPSTF) method for appraising the quality of individual studies

- Grading of Recommendations Assessment, Development and Evaluation (GRADE) method for appraising the quality of a body of evidence
Strength of a Recommendation Based on 4 Domains

1. Confidence in the quality of the evidence
   - (i.e., high, moderate, low, very low)

2. Balance of desirable and undesirable outcomes
   - (i.e., benefit v. harm analysis)

3. Values and preferences
   - (i.e., similar values, some variation, large variation)

4. Other implications, as appropriate, e.g.:
   - (e.g., Resource use, equity, acceptability, feasibility, subgroup considerations)

# Strength of a recommendation on a continuum:

- **Strong For**
  - “We **recommend** offering this option...”

- **Weak For**
  - “We **suggest** offering this option...”

- **Weak Against**
  - “We **suggest not** offering this option...”

- **Strong Against**
  - “We **recommend against** offering this option...”

- **Insufficient**
  - used when there was a common practice (or a practice getting a lot of attention) on which the committee wanted to comment

A  **Strongly Recommend** to offer or provide ...  
*There is *good* evidence that the intervention improves important health outcomes -- *benefits substantially outweigh harm.*

B  **Recommend** to offer or provide ...  
*There is *fair* evidence that the intervention improves health outcomes -- *benefits outweigh harm.*

C  **Consider** offering or providing ....  
*There is *poor* evidence that the intervention can improve health outcomes -- *balance of benefit and harm is too close* to justify a general recommendation.

I  **Insufficient Evidence is to recommend for or against** providing ...  
*Evidence that the intervention is effective is lacking or of poor quality, or conflicting, - *balance of benefits and harms cannot be determined.*
| 1. | What is the effectiveness and safety of pharmacotherapy treatments for PTSD? |
| 2. | What is the effectiveness and safety of psychotherapy treatments for PTSD? |
| 3. | What is the effectiveness and safety of non-pharmacologic biological treatments, (e.g. stellate ganglion block, hyperbaric oxygen, TMS, etc.) for PTSD? |
| 4. | Are complementary and integrative treatments (e.g., mind-body practices, natural products, animal-assisted therapy, and creative therapy) safe and effective either as primary treatments or adjunctive to standard treatments? |
| 5. | What combined treatment approaches are safe and effective in enhancing treatment response (e.g. 2 meds, med plus psychotherapy)? |
### Key Questions for the 2017 CPG, cont’d

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
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</thead>
<tbody>
<tr>
<td>6.</td>
<td>What is the comparative effectiveness of medication and psychotherapy?</td>
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<tr>
<td>7.</td>
<td>What is the effectiveness and safety of psychotherapy treatments delivered in a group therapy setting?</td>
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<td>8.</td>
<td>What is the effectiveness and safety of collaborative care interventions?</td>
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<td>9.</td>
<td>What is the effectiveness and safety of treatment delivered via technology based modalities?</td>
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<tr>
<td>10.</td>
<td>What treatments are safe and effective for acute stress disorder or acute stress reaction?</td>
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<tr>
<td>11.</td>
<td>Is PTSD treatment safety and effectiveness altered by presence of comorbidities?</td>
</tr>
<tr>
<td>12.</td>
<td>What is the safety and effectiveness of peer support approaches?</td>
</tr>
</tbody>
</table>
40 RECOMMENDATIONS

A. General Clinical Management
B. Diagnosis and Assessment of PTSD
C. Prevention of PTSD
D. Treatment of PTSD
   1) Treatment Selection
   2) Psychotherapy
   3) Pharmacotherapy
   4) Augmentation Therapy
   5) Prazosin
   6) Combination Therapy
   7) Non-pharmacologic Biological Treatments
   8) Complementary and Integrative Treatments
   9) Technology-based Treatment Modalities
E. Treatment of PTSD with Co-occurring Conditions
1. We recommend engaging patients in shared decision making (SDM), which includes educating patients about effective treatment options.

*Shared Decision Making* (SDM) is an approach in which providers and patients communicate together using the best available evidence to make decisions.
9. *We recommend* individual, manualized trauma focused psychotherapy over other pharmacologic and non-pharmacologic interventions for the primary treatment of PTSD.

10. 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.
Individual, manualized, trauma-focused psychotherapies:

- Prolonged Exposure (PE)
- Cognitive Processing Therapy (CPT)
- Eye Movement Desensitization & Reprocessing (EMDR)

Additional trauma-focused psychotherapies

- Specific cognitive behavioral therapies for PTSD
- Brief Eclectic Psychotherapy (BEP)
- Narrative Exposure Therapy (NET)
- Written Narrative Exposure

If these therapies are not readily available or not preferred, we recommend:

**Pharmacotherapy**
- Sertraline
- Paroxetine
- Fluoxetine
- Venlafaxine

**Individual, manualized non-trauma-focused therapy**
- Present-Centered Therapy (PCT)
- Stress Inoculation Training (SIT)
- Interpersonal Psychotherapy (IPT)
Lee et al. (2016) Systematic Review

- Included RCTs that used clinical interviews and active controls

<table>
<thead>
<tr>
<th></th>
<th>8-12 wk pre/post</th>
<th>9 month pre/post</th>
<th>9m. Between Group</th>
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<tbody>
<tr>
<td>SSRI/SNRI</td>
<td>1.43 (1.36 to 1.51)</td>
<td>2.51 (2.14-2.82)</td>
<td>.30 (.12-.47)</td>
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<tr>
<td>All TF Therapy</td>
<td>2.19 (2.01-2.37)</td>
<td>3.28 (3.02-3.54)</td>
<td>.75 (.57-.92)</td>
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<td>PE+CPT+EMDR</td>
<td>2.74 (2.50-2.97)</td>
<td>4.54 (4.16-4.91)</td>
<td>.80 (.57-1.03)</td>
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</tbody>
</table>
Both medication and psychotherapy are effective, but psychotherapy is more effective.

For every 100 people who receive the treatment, how many will no longer have PTSD after 3 months?

- **CPT/PE/EMDR**: 53
- **SSRIs**: 42
- **No Treatment**: 9

<table>
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<tr>
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<tr>
<td>Moderate</td>
<td>Sertraline(^\d), Paroxetine(^\d), Fluoxetine, Venlafaxine</td>
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<tr>
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<td>Nefazodone ±</td>
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<td>Risperidone, Benzodiazepines, D-cycloserine, Hydrocortisone, Ketamine</td>
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<td>Buproprion, Desipramine, D-serine, Escitalopram, Mirtazapine</td>
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<td></td>
<td></td>
<td></td>
<td>Antidepressants, Doxepin, Duloxetine,+, Desvenlafaxine, Fluvoxamine,+, Levomilnacipran, Nortriptyline, Trazodone, Vilazodone, Vortioxetine</td>
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*The Work Group determined there was no high quality evidence regarding medication monotherapy.

^FDA approved for PTSD

±Serious potential toxicity, should be managed carefully

†No data were captured in the evidence review (based on the criteria outlined in Conducting the Systematic Review) and were not considered in development of this table

‡Studies of these drugs did not meet the inclusion criteria for the systematic evidence review due to poor quality
17. *We recommend* the following medications as monotherapy for PTSD for patients diagnosed with PTSD who choose not to engage in or are unable to access trauma-focused psychotherapy.

- Sertraline
- Paroxetine
- Fluoxetine
- Venlafaxine
### Medication Monotherapy for PTSD

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**No Data**

*The Work Group determined there was no high quality evidence regarding medication monotherapy
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(VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, page 53)
18. *We suggest* the following as monotherapy for the treatment of PTSD if recommended pharmacotherapy, trauma-focused psychotherapy, or non-trauma-focused psychotherapy are ineffective, unavailable, or not in accordance with patient preference and tolerance. (NOTE: Nefazodone and phenelzine have potentially serious toxicities and should be managed carefully.)

- Nefazodone
- Imipramine
- Phenelzine
# Medication Monotherapy for PTSD

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<td>Topiramate</td>
<td>Risperidone</td>
<td>Benzodiazepines D-cycloserine Hydrocortisone Ketamine</td>
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<td></td>
<td></td>
<td>Antidepressants Doxepin Duloxetine(\wedge) Desvenlafaxine Fluvoxamine(\wedge) Levomilnacipran Nortriptyline Trazodone Vilazodone Vortioxetine</td>
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*The Work Group determined there was no high quality evidence regarding medication monotherapy
\(^\wedge\)FDA approved for PTSD
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(VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, page 53)
19. *We suggest against* treatment of PTSD with the following medications as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks.

- Quetiapine, Olanzapine, and other Atypical Antipsychotics (except for Risperidone, which is a Strong Against)
- Citalopram
- Amitriptyline
- Lamotrigine
- Topiramate
## Medication Monotherapy for PTSD

### Quality of Evidence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
<th>No Data+</th>
</tr>
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<tbody>
<tr>
<td><strong>Recommend For</strong></td>
<td>Sertraline^</td>
<td>Nefazodone ±</td>
<td>Imipramine, Phenelzine±</td>
<td>Antidepressants</td>
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<tr>
<td><strong>Suggest For</strong></td>
<td>Paroxetine^</td>
<td>Quetiapine, Olanzapine, Citalopram, Amitriptyline</td>
<td>Lamotrigine, Topiramate</td>
<td>Doxepin, Duloxetine‡, Desvenlafaxine</td>
</tr>
<tr>
<td><strong>Suggest Against</strong></td>
<td>Prazosin (excluding the treatment of PTSD associated nightmares)</td>
<td>Divalproex, Tiagabine, Guanfacine</td>
<td>Risperidone, Benzodiazepines, D-cycloserine, D-serine, Escitalopram, Mirtazapine</td>
<td>Bupropion, Desipramine, Hydroxyzine</td>
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<tr>
<td><strong>Recommend Against</strong></td>
<td>Prazosin for the treatment of PTSD associated nightmares</td>
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<td></td>
<td>Levomilnacipran, Trazodone, Vortioxetine</td>
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<tr>
<td><strong>No Recommendation For or Against</strong></td>
<td></td>
<td></td>
<td></td>
<td>Anxiolytic/Hypnotics</td>
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^FDA approved for PTSD

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‡Studies of these drugs did not meet the inclusion criteria for the systematic evidence review due to poor quality

(VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, page 53)
20. We recommend against treating PTSD with the following medications as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks.

- Divalproex
- Tiagabine
- Guanfacine
- Risperidone
- Benzodiazepines
- Ketamine
- Hydrocortisone
- D-Cycloserine
**Benzodiazepines are ineffective for the treatment and prevention of PTSD and any potential benefits are outweighed by the risks.**

**Specific Risks of Benzodiazepine use in PTSD**

- Increased PTSD severity
- Increased aggression
- Increased risk of depression
- Increased risk of substance use
- Difficult withdrawal
- Cognitive blunting

Benzodiazepine Risks: Abuse and Dependence

• Among 20,041 patients with PTSD: (Hermos 2007)
  • Pre-existing diagnosis of drug abuse increased the risk of being prescribed very high daily doses of BZD for extended periods of time.
  • Being prescribed a high-dose BZD was associated with a simultaneous oxycodone prescription.

• OIF/OEF veterans with PTSD are significantly more likely to receive: opiates for pain, higher doses of opiates, 2 or more opiates, sedative hypnotics concurrent with opiates, and to obtain early refills. (Seal, 2012)
21. *We recommend against* treating PTSD with cannabis or cannabis derivatives due to the lack of evidence for their efficacy, known adverse effects, and associated risks.

- Preliminary evidence that cannabis could improve PTSD symptoms, particularly nightmares, is offset by the significant side effects.
- The lack of well-designed RCTs evaluating the efficacy of cannabis in large samples of patients with PTSD combined with the serious side effects, does not support the use of natural or synthetic cannabinoids as a treatment for PTSD.
# Medication Monotherapy for PTSD

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<td>Prazosin for the treatment of PTSD associated nightmares</td>
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<tr>
<td>Low</td>
<td>Nefazodone ± Quetiapine Olanzapine Citalopram Amitriptyline</td>
<td>Divalproex Tiagabine Guanfacine</td>
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<td>Eszopiclone</td>
</tr>
<tr>
<td>Very Low</td>
<td>Imipramine Phenelzine± Lamotrigine Topiramate</td>
<td>Risperidone Benzodiazepines D-cycloserine D-serine Escitalopram Mirtazapine</td>
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<td></td>
<td>Bupropion Desipramine Hydroxyzine Ketamine</td>
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<tr>
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<td></td>
<td></td>
<td>Antidepressants Doxepin Duloxetine‡ Desvenlafaxine Fluvoxamine‡ Levomilnacipran Nortriptyline Trazodone Vilazodone Vortioxetine Anxiolytic/Hypnotics Buspirone‡ Cyproheptadine Hydroxyzine Zaleplon Zolpidem</td>
</tr>
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*The Work Group determined there was no high quality evidence regarding medication monotherapy.

\(^\wedge\)FDA approved for PTSD

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22. There is *insufficient evidence* to recommend for or against monotherapy or augmentation therapy for the treatment of PTSD with the following medications:

<table>
<thead>
<tr>
<th>Antidepressants</th>
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</thead>
<tbody>
<tr>
<td>Bupropion</td>
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<td>Doxepin</td>
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<td>Duloxetine</td>
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<td>Escitalopram</td>
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<td>Hydroxyzine</td>
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<td>Levomilnacipran</td>
<td>Zaleplon and Zolpidem</td>
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<tr>
<td>Quality of Evidence</td>
<td>Recommend For</td>
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<td>---------------------</td>
<td>---------------</td>
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<tr>
<td>Moderate</td>
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</tr>
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<td>Low</td>
<td>Topiramate</td>
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<tr>
<td>Very Low</td>
<td>Baclofen Pregabalin D-cycloserine†</td>
</tr>
<tr>
<td>No Data+</td>
<td>Other atypical antipsychotics</td>
</tr>
</tbody>
</table>

*Combination means treatments are started simultaneously; augmentation means one treatment is started after another treatment (all treatments are augmentation unless otherwise noted)

†Outside of a research setting

‡No data were captured in the evidence review (based on the criteria outlined in Conducting the Systematic Review) and were not considered in development of this table

Recommendations for Prazosin

28a. For global symptoms of PTSD, we suggest against the use of prazosin as mono- or augmentation therapy.

28b. For nightmares associated with PTSD, there is insufficient evidence to recommend for or against the use of prazosin as mono- or augmentation therapy.
Prazosin and Combat PTSD (PACT) – CSP Results

- CAPS Recurrent Distressing Dreams item: Prazosin -1.9, Placebo -1.7
- Pittsburgh Sleep Quality Index: Prazosin -2.3, Placebo -2.1
- Clinical Global Impression of Change: Prazosin 3.3, Placebo 3.3
- Total CAPS Score: Prazosin -14.1, Placebo -16.2
## Medication Augmentation Therapy for PTSD

<table>
<thead>
<tr>
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<th>Suggest Against</th>
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<tr>
<td><strong>Moderate</strong></td>
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<td>Prazosin (excluding the treatment of PTSD associated nightmares)</td>
<td>Risperidone</td>
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<td>Any drug not listed</td>
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</tr>
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*Combination means treatments are started simultaneously; augmentation means one treatment is started after another treatment (all treatments are augmentation unless otherwise noted)*
±The Work Group determined there was no high quality evidence regarding medication augmentation and combination therapy
†Outside of a research setting
‡No data were captured in the evidence review (based on the criteria outlined in Conducting the Systematic Review) and were not considered in development of this table
23. *We suggest against* the use of the following medications as augmentation treatment of PTSD due to insufficient data and/or known adverse effect profiles and associated risks.

24. *We suggest against* combining exposure therapy with D-cycloserine in the treatment of PTSD outside of the research setting.

- Topiramate
- Baclofen
- Pregabalin
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±The Work Group determined there was no high quality evidence regarding medication augmentation and combination therapy
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^Combination treatment
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25. We recommend against using the following medications as augmentation therapy for the treatment of PTSD due to low quality evidence or the absence of studies and their association with known adverse effects.

- Atypical antipsychotics
- Benzodiazepines
- Divalproex
<table>
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<td>Divalproex Olanzapine</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Very Low</td>
<td></td>
<td></td>
<td>Baclofen Pregabalin D-cycloserine†</td>
<td></td>
<td>Mirtazapine and Sertraline^</td>
</tr>
<tr>
<td>No Data+</td>
<td></td>
<td></td>
<td>Other atypical antipsychotics</td>
<td></td>
<td>Any drug not listed</td>
</tr>
</tbody>
</table>

*Combination means treatments are started simultaneously; augmentation means one treatment is started after another treatment (all treatments are augmentation unless otherwise noted)
‡Outside of a research setting
†Combination treatment
‡No data were captured in the evidence review (based on the criteria outlined in Conducting the Systematic Review) and were not considered in development of this table
26. There is **insufficient evidence** to recommend the combination of exposure therapy with **hydrocortisone** outside of the research setting.

27. There is **insufficient evidence** to recommend for or against the use of **mirtazapine** in combination with **sertraline** for the treatment of PTSD.
29. In partial- or non-responders to psychotherapy, there is **insufficient evidence** to recommend for or against augmentation with pharmacotherapy.

30. In partial- or non-responders to pharmacotherapy, there is **insufficient evidence** to recommend for or against augmentation with psychotherapy.

31. There is **insufficient evidence** to recommend for or against starting patients with PTSD on combination pharmacotherapy and psychotherapy.
32. There is **insufficient evidence** to recommend for or against the following somatic therapies:

- Repetitive transcranial magnetic stimulation (rTMS)
- Electroconvulsive therapy (ECT)
- Hyperbaric oxygen therapy (HBOT)
- Stellate ganglion block (SGB)
- Vagal nerve stimulation (VNS)
We recommend that the presence of a co-occurring disorder(s) not prevent patients from receiving other VA/DoD guideline-recommended treatments.

We recommend VA/DoD guideline-recommended treatments for PTSD in the presence of co-occurring substance use disorder (SUD).

We recommend an independent assessment of co-occurring sleep disturbance in patients with PTSD, particularly when sleep problems pre-date PTSD onset or remain following successful completion of a course of treatment.

We recommend Cognitive Behavioral Therapy for Insomnia (CBT-I) for insomnia in patients with PTSD unless an underlying medical or environmental etiology is identified or severe sleep deprivation warrants the immediate use of medications to prevent harm.
## Conclusions - Medication Monotherapy for PTSD

### Quality of Evidence

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Recommend For</th>
<th>Suggest For</th>
<th>Suggest Against</th>
<th>Recommend Against</th>
<th>No Recommendation For or Against</th>
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</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Sertraline(^\wedge)</td>
<td>Prazosin (excluding the treatment of PTSD associated nightmares)</td>
<td>Prazosin for the treatment of PTSD associated nightmares</td>
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<tr>
<td></td>
<td>Paroxetine(^\wedge)</td>
<td><em>Sertraline</em> is FDA approved for PTSD</td>
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<tr>
<td></td>
<td>Fluoxetine</td>
<td><em>Sertraline</em> is FDA approved for PTSD</td>
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<td></td>
<td>Venlafaxine</td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>Nefazodone ±</td>
<td>Quetiapine, Olanzapine, Citalopram, Amitriptyline</td>
<td>Divalproex, Tiagabine, Guanfacine</td>
<td>Eszopiclone</td>
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<tr>
<td>Very Low</td>
<td>Imipramine, Phenelzine±</td>
<td>Lamotrigine, Topiramate</td>
<td>Risperidone, Benzodiazepines, D-cycloserine, Hydrocortisone, Ketamine</td>
<td>Bupropion, Desipramine, D-serine, Escitalopram, Mirtazapine</td>
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</tr>
<tr>
<td>No Data+</td>
<td><em>The Work Group determined there was no high quality evidence regarding medication monotherapy for PTSD.</em></td>
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</tr>
</tbody>
</table>

\(^\wedge\)FDA approved for PTSD

±Serious potential toxicity, should be managed carefully

†No data were captured in the evidence review (based on the criteria outlined in Conducting the Systematic Review) and were not considered in development of this table

‡Studies of these drugs did not meet the inclusion criteria for the systematic evidence review due to poor quality

(VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder, page 53)
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<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles S. Hoge, MD</td>
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<td></td>
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<tr>
<td>Kate McGraw, PhD</td>
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<td>Silver Spring, MD</td>
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<tr>
<td>Jonathon Wolf, MD</td>
<td>MD, MPH, FAPA, CDR, MC USN</td>
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<tr>
<td>Megan J. Ehret, PharmD, MS</td>
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<tr>
<td>Joel T. Foster, PhD</td>
<td>PhD, MAJ, USAF, BSC</td>
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<tr>
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<td>Falls Church, VA</td>
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<tr>
<td>Meena Vythilingham, MD</td>
<td>CDR, USPHS</td>
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<td>Arlington, VA</td>
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<tr>
<td>Lisa Teegarden, PsyD, COL</td>
<td>PsyD, COL, MS, USA</td>
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<tr>
<td>Elaine Stuffel, RN, NSN, MHA</td>
<td>RN, NSN, MHA</td>
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<td>Wendi M. Waits, MD</td>
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<tr>
<td>David Riggs, PhD</td>
<td>PhD, Champion</td>
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<tr>
<td></td>
<td>Professor and Chair, Department of Medical and Clinical Psychology</td>
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<td></td>
<td>Executive Director, Center for Deployment Psychology</td>
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<tr>
<td></td>
<td>Uniform Services University of the Health Sciences</td>
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<tr>
<td>Jeffery Millegan, MD</td>
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<td>CDR MC USN</td>
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<tr>
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<td>San Diego, CA</td>
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