Summary
PTSD Pharmacotherapy Algorithm

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Algorithm Flowchart

(1) Diagnosis of Posttraumatic Stress Disorder

(2) Is Sleep Disturbed?

No

(2a) Yes—nightmares or nighttime hyperarousal

Try prazosin

Was sleep improved?

Yes

(2b) Yes—but only initiation

No. Or nightmares/nighttime hyperarousal improved, but sleep onset impaired

Consider trazodone

Are there significant remaining PTSD symptoms?

Yes

No

Maintenance

(3) Have You Given a Trial of an SSRI?

No

Try an SSRI or alternative

Yes

What was the response?

No response and no psychosis present

(4) Have you tried a second SSRI, SNRI, or mirtazapine?

Choose one

Was there any response?

No

Yes. Partial response

(5) Have you tried a third medication among SSRIs, SNRIs, mirtazapine, and nefazodone?

(5a) If no response or partial response, consider augmentation (depending on residual symptoms) or try more monotherapies

Hyperarousal symptoms: Consider clonidine, quetiapine, risperidone

Reexperiencing symptoms: Consider aripiprazole, lamotrigine, quetiapine, risperidone, topiramate

Avoidance symptoms: Consider aripiprazole, lamotrigine

Options with possible global benefit: Levetiracetam, phenelzine, prazosin

Partial response and no psychosis is present

(3a) No response or partial response, and psychosis is present

Try adding an antipsychotic

(3b) Partial response and partial psychosis is present

No response or psychosis is present

Try switching to an alternative SSRI

Partial response and psychosis is present

Try adding an antipsychotic

(3a) No response or partial response, and psychosis is present

Try adding an antipsychotic

No response or psychosis is present

Try switching to an alternative SSRI
Comorbidity Assessment

The diagnosis of comorbidities is important because if present, these could change the basic algorithm.

It is important to look for:

- Substance use disorders
  - Avoid benzodiazepines
- Depression
- Bipolar disorder
- Psychosis
- Impulse control disorders

Sleep Assessment

- Sleep impairment is a core symptom of PTSD
- Common sleep disturbances include:
  - Hyperarousal linked to difficulties initiating or maintaining sleep
  - Trauma-related nightmares
  - Disturbed awakenings without nightmare recollection
  - Prolonged sleep latency (often due to fear of nightmares)
- For many patients, improving sleep symptoms can improve core daytime PTSD symptoms (hypervigilance, avoidance, re-experiencing).
- Look for other causes of insomnia: sleep apnea, restless legs syndrome, periodic limb movements of sleep, sleep hygiene issues, excess caffeine consumption, medical problems

Consider Prazosin for Nightmares or Disturbed Awakenings (Node 2a)

Rationale

- Pathophysiology of sleep disturbances in PTSD
  - Increased noradrenergic activity during sleep and while trying to fall asleep
- Prazosin MOA
  - Non-sedating $\alpha_1$ antagonist

Evidence of efficacy

- Five placebo-controlled RCTs
  - 4 published trials
    - 2003-2013
  - 1 unpublished study
    - ClinicalTrials.gov
- Effect sizes from published studies
  - General PTSD symptoms: around 1
  - Nightmares reduction: around 2
- Unpublished study
  - No difference from placebo
Dosing

- Goal of treatment: eliminate disturbed awakenings

Protocol for men (Raskind, 2013)

- Mean average dose: 16 mg (15.6 mg)
- Maximum dose: 25 mg

<table>
<thead>
<tr>
<th>Dose at bedtime</th>
<th>Mid-morning dose (10-11 AM)</th>
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<tbody>
<tr>
<td>• 1 mg HS for 2 nights</td>
<td>• Week 2: 1 mg</td>
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<tr>
<td>• 2 mg for 5 nights</td>
<td>• Week 3–4: 2 mg</td>
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<tr>
<td>• 4 mg for 7 nights</td>
<td>• Week 5-6: 6 mg</td>
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<tr>
<td>• 6 mg for 7 nights</td>
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<tr>
<td>• 10 mg for 7 nights</td>
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<tr>
<td>• 15 mg for 7 nights</td>
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<tr>
<td>• 1 mg for 2 nights</td>
<td>• Week 2-3: 1 mg</td>
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<tr>
<td>• 2 mg for 5 nights</td>
<td>• Week 4–5: 2 mg</td>
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<tr>
<td>• 15 mg for 7 nights</td>
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</table>

Protocol for women (Raskind, 2013)

- Median dose: 7 mg
- Maximum dose: 10 mg

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<td>• 15 mg for 7 nights</td>
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Consider Trazodone if Sleep Initiation is Disturbed (Node 2b)

About trazodone

- Sedating antidepressant
- Efficacy for sleep disturbances shown in open-label studies
- Pharmacodynamic properties:
  - 5-HT₂A antagonist
  - α₁ antagonist
  - H₁ antagonist

Adverse effects

- Sedation
Dizziness
- Orthostatic hypotension
- Syncope
- Priapism (infrequent, but risk may be increased if combined with prazosin)

**Role in PTSD**

Consider prescribing trazodone when:

- The patient has sleep initiation difficulties without nightmares or nocturnal hyperarousals
- The patient still has initial insomnia, even after prazosin was effective for nightmares and nocturnal hyperarousals

There is minimal evidence for treating nightmares and nocturnal hyperarousals with trazodone in case prazosin was not effective.

**Dosing**

- Usually started at 50 mg bedtime, with instructions to reduce to 25 mg if too sedating

**Other options commonly used for improving sleep latency**

- Gabapentin (case reports only)
- Mirtazapine (no evidence, but commonly used, causes weight gain)
- Hydroxyzine (no evidence but commonly used - watch for new PDR max of 100 mg)
- Melatonin (no evidence, but commonly used at 3-10 mg)
- Diphenhydramine (no evidence - hypnotic effect in others dissipates after 3 doses)

**Undesirable initial choices for sleep in PTSD**

**Tricyclic antidepressants**

- Doxepin, Amitriptyline
- Adverse effects:
  - Anticholinergic
  - Antihistaminic (weight gain)
  - Cardiac (not safe in case of overdose)

**Benzodiazepines**

- High potential for abuse in PTSD
  - In patients with or without comorbid substance use disorder
- Might be considered if
  - Past history of clear response without significant abuse or misuse
- Not effective for primary symptoms of PTSD
- May reduce effectiveness of psychotherapies
Quetiapine

- Widely prescribed for sleep in PTSD
- Review paper: “The benefits did not justify the risks. It should not be used as a first-line treatment for insomnia”
- Weight gain
  - Not dose related, can occur at small doses
- More likely to be discontinued than prazosin
## Table - Summary of Selected Recommendations

<table>
<thead>
<tr>
<th>Node</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td><strong>Assessment and Management of Non-Sleep Symptoms: Using SSRIs</strong></td>
<td>• SSRIs are a first-line treatment if:</td>
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<tr>
<td><strong>(Node 3)</strong></td>
<td>o the patient has remaining PTSD symptoms, after sleep symptoms have been managed</td>
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<td></td>
<td>o the patient has no prominent sleep disturbances</td>
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<td></td>
<td>• Evidence of efficacy</td>
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<td>o Below the clinically meaningful threshold, standard mean difference (SMD) of 0.5</td>
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<tr>
<td></td>
<td>▪ Paroxetine and sertraline are FDA-approved</td>
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<td></td>
<td>▪ Sertraline has weaker evidence in male combat veterans</td>
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<td></td>
<td>• Adequate SSRI trial in PTSD:</td>
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<td></td>
<td>o 4-6 weeks</td>
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<td></td>
<td>o Sometimes up to 12 weeks</td>
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<tr>
<td><strong>Management of Psychotic Symptoms in PTSD</strong></td>
<td>• Patients with psychotic symptoms can be considered on a subgroup of PTSD patients in whom early augmentation may be justified</td>
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<tr>
<td><strong>(Node 3a)</strong></td>
<td>o Sometimes PTSD-related symptoms respond to an SSRI alone</td>
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<td></td>
<td>o Consider early augmentation with second-generation antipsychotics</td>
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<td></td>
<td>▪ Risperidone has the best evidence for this use</td>
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<tr>
<td><strong>Management of Non-Response to Initial SSRI Trial</strong></td>
<td>• If the patient is not psychotic and was nonresponsive to the initial SSRI, there are several options:</td>
</tr>
<tr>
<td><strong>(Node 4)</strong></td>
<td>o A different SSRI</td>
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<td></td>
<td>o An SNRI (venlafaxine)</td>
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<td></td>
<td>o An antidepressant with different dual actions (mirtazapine)</td>
</tr>
<tr>
<td><strong>Management of Non-Response to Two SSRI Trials</strong></td>
<td>• If the patient was non-responsive to two antidepressant trials:</td>
</tr>
<tr>
<td><strong>(Node 5)</strong></td>
<td>o Consider nefazodone</td>
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<tr>
<td></td>
<td>▪ Hepatoxicity risk: 1/250,0000</td>
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<tr>
<td></td>
<td>▪ Lack of weight gain or sexual side effects</td>
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<td></td>
<td>▪ Less sedation than trazodone, low priapism risk</td>
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<tr>
<td><strong>Augmentation Strategies: Adding a Second Drug</strong></td>
<td>• Before augmenting:</td>
</tr>
<tr>
<td><strong>(Node 5a)</strong></td>
<td>o Patients who partially respond but are still improving should be continued until the benefits reach a plateau</td>
</tr>
<tr>
<td></td>
<td>• Specific suggestions:</td>
</tr>
<tr>
<td></td>
<td>o Hyperarousal symptoms: consider clonidine, quetiapine, risperidone, doxazosin XL</td>
</tr>
<tr>
<td></td>
<td>o Re-experiencing symptoms: consider aripiprazole, risperidone, quetiapine, lamotrigine, topiramate</td>
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<td></td>
<td>o Avoidance symptoms: consider aripiprazole or lamotrigine</td>
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<tr>
<td></td>
<td>o Looking for global benefit? Consider: phenelzine, levetiracetam, prazosin (if not tried previously).</td>
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