

# Summary

## PTSD Pharmacotherapy Algorithm

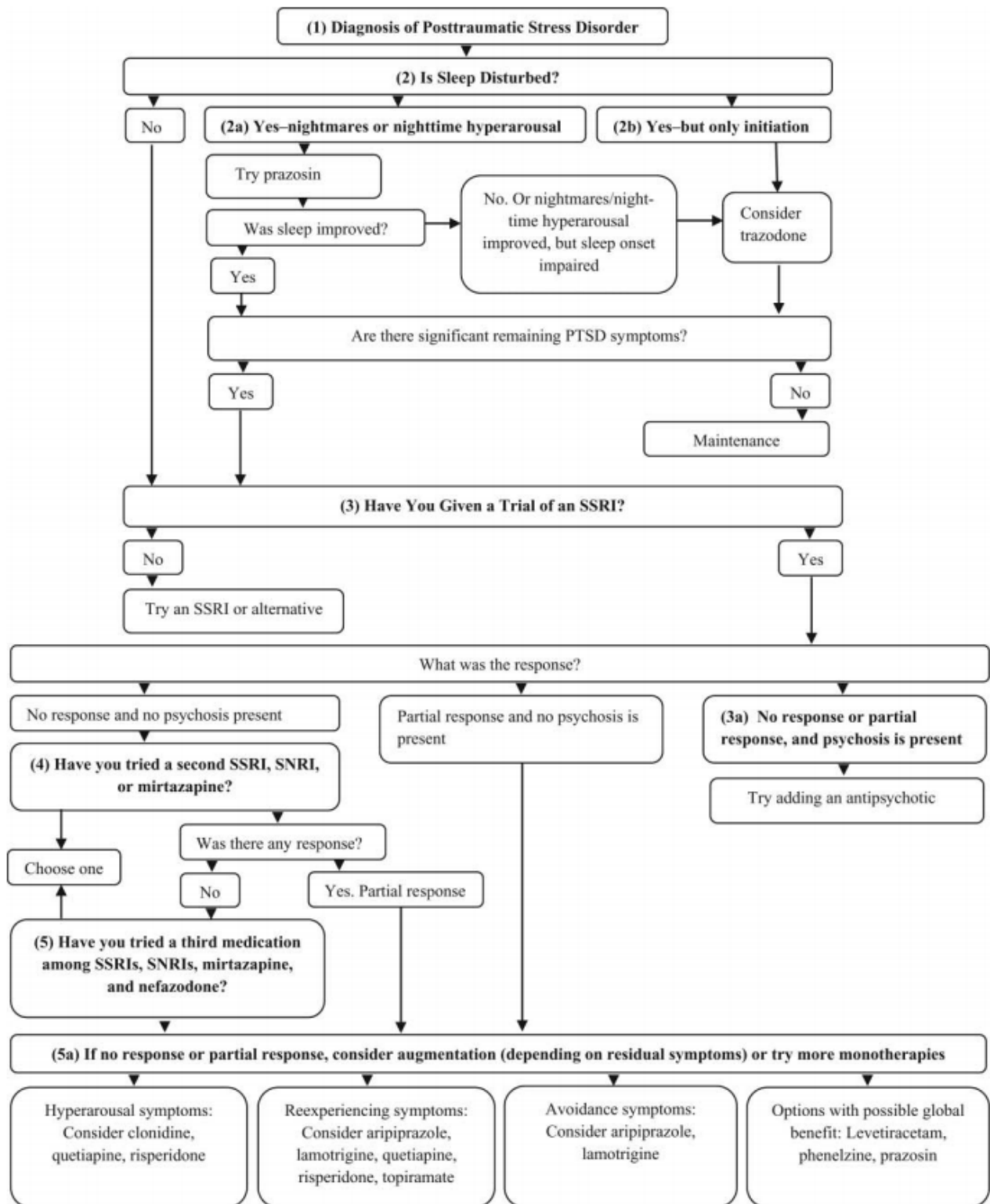
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### Document Contents

Algorithm Flowchart .....	2
Comorbidity Assessment .....	3
Sleep Assessment.....	3
Consider Prazosin for Nightmares or Disturbed Awakenings (Node 2a) .....	3
Rationale .....	3
Evidence of efficacy .....	3
Dosing .....	4
Consider Trazodone if Sleep Initiation is Disturbed (Node 2b).....	4
About trazodone .....	4
Adverse effects .....	4
Role in PTSD .....	5
Dosing .....	5
Other options commonly used for improving sleep latency .....	5
Undesirable initial choices for sleep in PTSD .....	5
Tricyclic antidepressants.....	5
Benzodiazepines .....	5
Quetiapine .....	6
Table - Summary of Selected Recommendations .....	7



# Algorithm Flowchart



# 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  - 1 unpublished study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- Unpublished study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

Dose at bedtime	Mid-morning dose (10-11 AM)
<ul style="list-style-type: none"><li>• 1 mg HS for 2 nights</li><li>• 2 mg for 5 nights</li><li>• 4 mg for 7 nights</li><li>• 6 mg for 7 nights</li><li>• 10 mg for 7 nights</li><li>• 15 mg for 7 nights</li></ul>	<ul style="list-style-type: none"><li>• Week 2: 1 mg</li><li>• Week 3–4: 2 mg</li><li>• Week 5-6: 6 mg</li></ul>

### Protocol for women (Raskind, 2013)

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

Dose at bedtime	Mid-morning dose (10-11 AM)
<ul style="list-style-type: none"><li>• 1 mg HS for 2 nights</li><li>• 2 mg for 5 nights</li><li>• 4 mg for 7 nights</li><li>• 6 mg for 7 nights</li><li>• 10 mg for 7 nights</li><li>• 15 mg for 7 nights</li></ul>	<ul style="list-style-type: none"><li>• Week 2-3: 1 mg</li><li>• Week 4–5: 2 mg</li></ul>

## 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-HT<sub>2A</sub> antagonist
  - $\alpha_1$  antagonist
  - H<sub>1</sub> 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

Node	Recommendation
Assessment and Management of Non-Sleep Symptoms: Using SSRIs (Node 3)	<ul style="list-style-type: none"> <li>SSRIs are a first-line treatment if: <ul style="list-style-type: none"> <li>the patient has remaining PTSD symptoms, after sleep symptoms have been managed</li> <li>the patient has no prominent sleep disturbances</li> </ul> </li> <li>Evidence of efficacy <ul style="list-style-type: none"> <li>Below the clinically meaningful threshold, standard mean difference (SMD) of 0.5 <ul style="list-style-type: none"> <li>Paroxetine and sertraline are FDA-approved</li> <li>Sertraline has weaker evidence in male combat veterans</li> </ul> </li> </ul> </li> <li>Adequate SSRI trial in PTSD: <ul style="list-style-type: none"> <li>4-6 weeks</li> <li>Sometimes up to 12 weeks</li> </ul> </li> </ul>
Management of Psychotic Symptoms in PTSD (Node 3a)	<ul style="list-style-type: none"> <li>Patients with psychotic symptoms can be considered on a subgroup of PTSD patients in whom early augmentation may be justified <ul style="list-style-type: none"> <li>Sometimes PTSD-related symptoms respond to an SSRI alone</li> <li>Consider early augmentation with second-generation antipsychotics <ul style="list-style-type: none"> <li>Risperidone has the best evidence for this use</li> </ul> </li> </ul> </li> </ul>
Management of Non-Response to Initial SSRI Trial (Node 4)	<ul style="list-style-type: none"> <li>If the patient is not psychotic and was nonresponsive to the initial SSRI, there are several options: <ul style="list-style-type: none"> <li>A different SSRI</li> <li>An SNRI (venlafaxine)</li> <li>An antidepressant with different dual actions (mirtazapine)</li> </ul> </li> </ul>
Management of Non-Response to Two SSRI Trials (Node 5)	<ul style="list-style-type: none"> <li>If the patient was non-responsive to two antidepressant trials: <ul style="list-style-type: none"> <li>Consider nefazodone <ul style="list-style-type: none"> <li>Hepatotoxicity risk: 1/250,000</li> <li>Lack of weight gain or sexual side effects</li> <li>Less sedation than trazodone, low priapism risk</li> </ul> </li> </ul> </li> </ul>
Augmentation Strategies: Adding a Second Drug (Node 5a)	<ul style="list-style-type: none"> <li>Before augmenting: <ul style="list-style-type: none"> <li>Patients who partially respond but are still improving should be continued until the benefits reach a plateau</li> </ul> </li> <li>Specific suggestions: <ul style="list-style-type: none"> <li>Hyperarousal symptoms: consider clonidine, quetiapine, risperidone, doxazosin XL</li> <li>Re-experiencing symptoms: consider aripiprazole, risperidone, quetiapine, lamotrigine, topiramate</li> <li>Avoidance symptoms: consider aripiprazole or lamotrigine</li> <li>Looking for global benefit? Consider: phenelzine, levetiracetam, prazosin (if not tried previously).</li> </ul> </li> </ul>

