The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Posttraumatic Stress Disorder

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Background: This project aimed to provide an organized, sequential, and evidence-supported approach to the pharmacotherapy of posttraumatic stress disorder (PTSD), following the format of previous efforts of the Psychopharmacology Algorithm Project at the Harvard South Shore Program. *Method:* A comprehensive literature review was conducted to determine the best pharmacological choices for PTSD patients and to update the last published version (1999) of the algorithm. We focused on optimal pharmacological interventions to address the prominent symptoms of PTSD, with additional attention to the impact that common comorbidities have on treatment choices. *Results:* We found that SSRIs and SNRIs are not as effective as previously thought, and that awareness of their long-term side effects has increased. New evidence suggests that addressing fragmented sleep and nightmares can improve symptoms (in addition to insomnia) that are frequently seen with PTSD (e.g., hyperarousal, reexperiencing). Prazosin and trazodone are emphasized at this initial step; if significant PTSD symptoms remain, an antidepressant may be tried. For PTSD-related psychosis, an antipsychotic may be added. In resistant cases, two or three antidepressants may be used in sequence. Following that, or with partial improvement and residual symptomatology, augmentation may be tried; the best options are antipsychotics, clonidine, topiramate, and lamotrigine. *Conclusion:* This heuristic may be helpful in producing faster symptom resolution, fewer side effects, and increased compliance. (Harv Rev Psychiatry 2011;19:240–258.)

Keywords: algorithms, posttraumatic stress disorder, psychopharmacology, stress disorders

INTRODUCTION

There has been considerable interest in finding effective psychopharmacological strategies for treating posttraumatic stress disorder (PTSD). It is assumed that biological treatment may have an important role, given the abnormalities in neurotransmitter, neuroendocrine, and neuroanatomical systems that have been identified in patients with PTSD.[1–3]

In this article the authors present a heuristic for selecting medication treatments for PTSD. This version updates a previous PTSD algorithm from the Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS).[4] It was also influenced by the International Psychopharmacology Algorithm Project PTSD algorithm, to which one of the authors (DNO) contributed as a consultant.[5]

Although psychosocial interventions are effective for many patients with PTSD,[6] this algorithm focuses on

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medication usage and is meant to be applied if and when the prescribing clinician and patient determine that medication may be appropriate. We did not evaluate the efficacy of psychotherapy and when it should be offered, though we acknowledge that some guidelines consider psychosocial interventions as a first-line treatment for PTSD.[7–9]

At present, the only medications that the Food and Drug Administration (FDA) has approved for PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine. These medications are widely recommended and used in clinical practice. In this review, we focus on the quality of the evidence for the efficacy of SSRIs and other medications used to treat PTSD. Recent systematic reviews have questioned whether standard medication treatments (e.g., SSRIs) produce results that are clinically robust and whether it is time to revisit the usual sequence of medication choices. A novel approach may be justifiable, at least for certain subpopulations of PTSD patients.[7,10,11]

Method

The PAPHSS method of algorithm development has been described in previous publications.[12–14] These algorithms model the cognitive process involved in a psychopharmacology consultation, with focus on the evidence base. Each is structured as a series of questions about the patient's diagnosis and past treatment history. If the patient has not been tried on one of the medications that is best supported by the evidence pertaining to the clinical circumstances, the algorithm suggests trying that medication. The evidence is cited and appraised, and other options that might be considered are also discussed. When the evidence for treatment at a "node" is inadequate or contradictory, this situation is acknowledged, and any recommendations offered are more tentative and flexible. For more treatment-resistant patients (higher-numbered nodes), there is greater uncertainty, more focus on treatment of residual symptoms, and more deference to the prescriber's clinical experience. The PAPHSS proposes that, as a core value, consideration of the scientific evidence is necessary, but not sufficient, for clinical decision making. The prescriber's clinical experience can support or contradict the research data and should contribute to treatment decisions.

Since PTSD is a chronic illness, and the treatment selected is likely to be continued over an extended period, factors such as short- and long-term side-effect profiles and the risks for drug/drug interactions are weighed strongly in deciding whether and at what point in treatment to include a medication.

After reviewing the previous (1999) PAPHSS algorithm, as well as other algorithms and guidelines, the authors conducted literature searches in PubMed to identify studies and reviews published since 1999. Proposed psychopharmacological agents for PTSD were entered in Boolean (AND) searches with the keywords "posttraumatic stress disorder." Resultant studies in English were selected. Other studies or reviews referenced in the selected articles were also examined. The algorithm was updated based on 103 studies and reviews published since 1999 identified in this manner.

Demographics, Symptom Clusters, and Tailoring of Treatment Approaches

The criteria for PTSD in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (DSM-IV) include the symptom clusters of reexperiencing, avoidance, and hyperarousal.[15] These symptom clusters may differ in their responses to psychopharmacological treatment. It is less clear whether these differences depend on the nature of the trauma—for example, combat veterans versus survivors of rape or domestic abuse. Recently traumatized individuals may respond better than those with distant trauma, such as Vietnam veterans.[16,17] The evidence also suggests that SSRIs may be more effective with female civilian survivors of sexual or domestic violence.[16,17] It is not clear, however, whether these differences are due to gender, age at initial traumatization, possible influence of compensation for combat veterans with PTSD, or other characteristics. Unfortunately, the available evidence is insufficient to support targeting treatments based on these variables. The evidence base on psychopharmacological treatment of child and adolescent PTSD is also scant and devoid of positive controlled studies.[18]

Flowchart for the Algorithm

A summary and overview of the algorithm appears in Figure 1. Each numbered "node" represents a decision point delineating patient populations ranging from treatment naive to highly resistant. The questions, evidence analysis, and reasoning that support the recommendations at each node will be presented below.

NODE 1: DOES THE PATIENT MEET DSM-IV CRITERIA FOR POSTTRAUMATIC STRESS DISORDER?

First, confirm a diagnosis based on DSM-IV criteria, and note any co-occurring psychiatric and medical symptoms and diagnoses that may be important, including substance abuse, depression, bipolar disorder, dissociative symptoms, anger, impulsivity, and psychosis. In treating female patients of childbearing age, the potential impact of medication on pregnancy should also be considered. Table 1 provides a brief overview of treatment considerations for these situations. A more thorough description of this important material is beyond the scope of this review, but the reader is encouraged to consult the associated references.

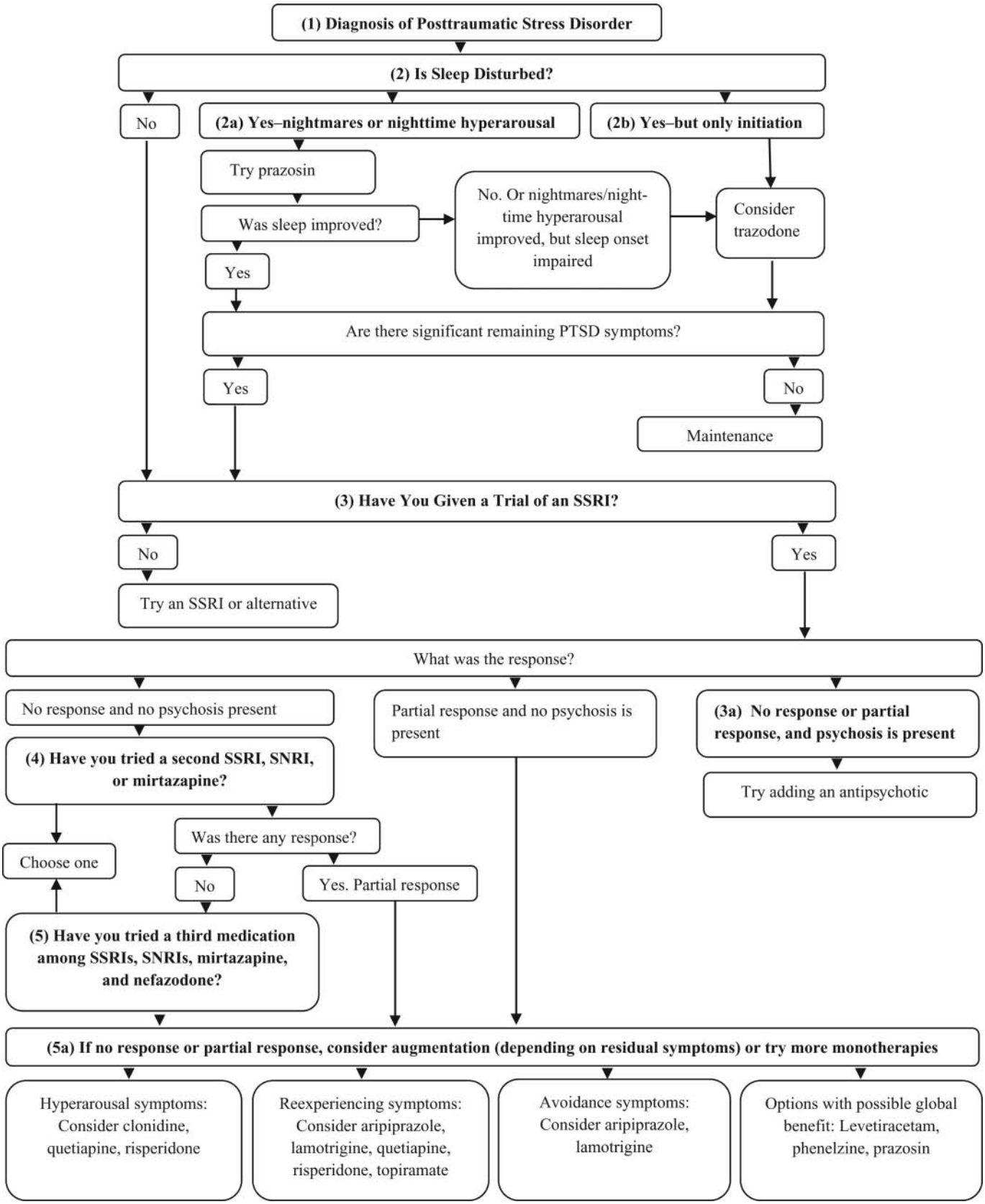

Figure 1. Flowchart of the algorithm for posttraumatic stress disorder. Nodes are indicated in bold.

Table 1. Comorbidity and Other Features in PTSD and How They Affect the Algorithm

Comorbidity	Considerations	Recommendations
Substance abuse	Comorbidity of substance abuse is very high in PTSD patients[4]	Screen for substance abuse in PTSD patients Avoid benzodiazepines
	PTSD patients are at increased risk of abusing prescription medications[19]	Ideally, a patient should be clean & sober at least a week before attempting to apply this algorithm[20]
	Algorithm recommendations do not apply to patients who are actively abusing substances[4]	
Bipolar disorder	Lifetime risk for PTSD approximately double in patients with bipolar disorder, who may be exposed to more trauma & have fewer resources & social supports[21]	Treat nightmares & disturbed awakenings with prazosin
	SSRIs & other antidepressants may pose risks of destabilizing the bipolar disorder[13]	Be more reluctant to use antidepressants for patient dually diagnosed with bipolar disorder & PTSD than in the standard algorithm
Psychosis	Psychotic symptoms in PTSD patients could indicate a comorbid psychotic disorder or could be part of the PTSD[22]	Consider skipping node 2 (sleep management) If primary psychosis, treat first with an antipsychotic
Major depressive disorder	History of major depression increases risk of developing PTSD, & PTSD diagnosis increases risk of depression[23]	Screen for depression in PTSD patients Use antidepressants earlier in the algorithm but know that prognosis is guarded
	Dysregulation of HPA axis may cause above associations[2,24,25]	Know that patients with both diagnoses may not respond to antidepressants as well as those with only PTSD respond
	Responsiveness to antidepressants is diminished in PTSD patients with comorbid depression in some studies[26–28]	If psychotic depression, treat with antidepressant & antipsychotic[12]
	Children/adolescents with PTSD show more variability in response to antidepressants than those with only depression[29]	
Dissociation	Associated with more traumatic events & more serious PTSD pathology[30]	Screen for dissociative symptoms Know that dissociation indicates more serious pathology & less predictable response to pharmacotherapy
	Paroxetine found slightly better than placebo in one study with small *n* & high dropout rates[31]	
	Some recommend psychotherapy as first-line treatment for the dissociative symptoms of PTSD[32]	Consider psychotherapy to address these specific symptoms
Pregnancy	Physiological changes of pregnancy (e.g., decreased drug-protein binding, enhanced hepatic metabolism & renal clearance, & delayed gastric emptying) may affect drug levels in ways that are difficult to predict[33]	Expect altered drug effects in pregnant patients, & monitor them more closely Avoid paroxetine & valproic acid
	Medications with teratogenic risks should be avoided during the first trimester, particularly weeks 3 through 9[33]	
	Paroxetine is only SSRI categorized by FDA as "Category D" due to reports of cardiac septal malformations[33]	
	Valproate has severe teratogenic effects[33]	
Smoking	Rates of smoking were increased in veterans with PTSD returning from Iraq & Afghanistan[34,35]	Bupropion was found to be effective for smoking-cessation efforts in one study of patients with chronic PTSD[36]
		One study found smoking-cessation efforts to be more successful in PTSD patients if smoking was addressed by the patients' psychiatric team rather than by referral to separate clinic[34]

FDA, Food and Drug Administration; SSRI, selective serotonin reuptake inhibitor; VA, Department of Veterans Affairs.

NODE 2: IS SLEEP DISTURBED?

Mounting evidence has implicated sleep impairment as a core symptom in PTSD and a primary source of distress and dysfunction for patients with this disorder.[37,38] It is therefore proposed that sleep problems be assessed initially and reassessed after each algorithm step if they persist and overall response remains unsatisfactory.[38] For many patients,

sleep deprivation may exacerbate core daytime PTSD symptoms (hypervigilance, avoidance, reexperiencing), and these symptoms may improve when sleep improves.[39] Another justification for treating sleep difficulties first is the availability of prazosin, a psychopharmacology option that targets impaired sleep in PTSD patients and that has demonstrated substantially larger effect sizes than medications commonly thought to be effective for the general symptom profile in PTSD (SSRIs and serotonin-norepinephrine reuptake inhibitors [SNRIs]). To our knowledge, none of the previous guidelines or algorithms has placed sleep evaluation and treatment first, before the use of an SSRI.

Sleep disturbances common in PTSD include the following: hyperarousal linked to difficulties initiating or maintaining sleep; trauma-related nightmares; awakenings without nightmare recollection; and prolonged sleep latency.[40,41] Increased noradrenergic activity during sleep and while trying to fall asleep is thought to be an important mechanism.[41–43] Notably, SSRIs can sometimes exacerbate these symptoms.[39,44,45]

Other causes of insomnia may contribute to the sleep difficulties of patients with PTSD. These include sleep apnea, restless leg syndrome, periodic limb movements of sleep, sleep hygiene issues, nicotine withdrawal, and medical problems associated with sleep fragmentation (e.g., pain and nocturia). Caffeine, though frequently employed as a method of coping with daytime symptoms of sleep deprivation secondary to PTSD and other causes of insomnia, can at times become a major independent contributor. Assessment of these factors is essential in the sleep evaluation before applying the algorithm recommendations.

Node 2a

If the patient has PTSD-related nightmares or disturbed arousals, we recommend consideration of a trial of prazosin as the first-line medication treatment. Prazosin is a generic alpha-1 adrenergic antagonist previously used to treat hypertension and symptoms of benign prostatic hyperplasia. Murray Raskind and colleagues at the University of Washington reasoned that alpha antagonists might be effective for the hyperarousal symptoms of PTSD. They selected prazosin for study as it is the only commercially available alpha-1 agent that crosses the blood-brain barrier, with the consequence that it would be the most likely to have activity in the brain. To date, they have conducted three randomized, placebo-controlled studies.[42,43,46] Efficacy was demonstrated for trauma-related nightmares, overall quality of sleep, and, to some extent, general PTSD symptoms in patients with either military and civilian trauma. All studies found large effect sizes (Cohen's $d > 1.0$) on the various measures of sleep impairment.These results are summarized in Table 2.

Prazosin was well tolerated in these studies. Hypotension risks were minimized by slowly titrating the dose upward over several weeks, allowing tolerance to the blood pressure effects to develop. Details of the dosing protocols are provided in Table 2 and may be used as guidelines for clinical use. In the largest study, 2 of 20 (10%) dropped out due to subjective dizziness possibly related to blood pressure. Both studies by Raskind and colleagues[42,43] involved male veterans, whereas the study by Taylor and colleagues[46] involved civilian females. Though the reason is unclear, the dosage requirements for men and women differed, with the male veterans often requiring 10 mg or more, compared to the mean of 3 mg needed by women.

In a more recent observational study with mostly male veterans in a Department of Veterans Affairs (VA) setting ($n = 62$), the mean dose of prazosin after initial titration was 3 mg, which increased to 6 mg after up to six years of follow-up.[47] This dose is much lower than in the two controlled studies and may reflect clinicians' unawareness of the doses used in those studies. The rate of dropout due to hypotension at these doses was less than 2%.

Infrequent side effects include dizziness, drowsiness, headache, constipation, loss of appetite, fatigue, nasal congestion, dry eyes, and priapism. Noncardiac chest pain has occurred, but cardiac ischemia must be ruled out.[48] If the patient is hypertensive, coordination with the primary care clinician is advised.

Thompson and colleagues[39] showed in a small chart-review study of 22 combat veterans that disturbed awakenings without nightmare recollection were also significantly reduced ($p < 0.01$) following treatment with prazosin. Although this finding needs to be confirmed in randomized, controlled trials (RCTs), the study suggests that it would be reasonable to employ prazosin in patients with these awakenings.

The study data currently available for prazosin are limited. It should be emphasized that the studies were mostly small, that they were done mostly by one group, and that the RCTs did not use monotherapy in previously untreated patients. Furthermore, dosing with prazosin is somewhat complex. Though the effect sizes with prazosin were large, it has been observed that small studies can generate higher effect sizes; such results should be interpreted with caution.[49] Nevertheless, we are proposing the consideration of prazosin for first-line use for patients with prominent nightmares and related sleep disturbances.

In support of this recommendation, we would first cite again the exceptional effect size relative to placebo of around 1.0 for significant improvement in sleep. As we will be showing later, all other medications, whether used as first-line (e.g., SSRIs) or as add-on interventions for

Table 2. Effect of Prazosin on Sleep and PTSD Symptoms in Three Placebo-Controlled, Randomized Trials

Study	*n*	Dropouts	Outcome variables	Effect size (Cohen's *d*)	Dosing protocol
Raskind et al.(2003)[42]	10	0	CAPS subscales:		Start at 1 mg at bedtime x 3 days
			Recurrent distressing nightmares	1.9	Increase as follows, as tolerated:
			Difficulty falling/staying asleep	1.6	2 mg for 4 nights
			Reexperiencing /intrusion	0.7	4 mg for 7 nights
			Avoidance/numbing	0.6	6 mg for 7 nights
			Hyperarousal	0.9	4 mg at 3 pm & 6 mg at bedtime
			Total CAPS score	0.7	Mean final daily dose = 9.3 mg
			Clinical Global Impression	1.4	
Raskind et al. (2007)[43]	40	6	CAPS recurrent distressing nightmares subscale	0.94	Same as above, except: Day 21: one 10 mg dose at bedtime
			Pittsburg Sleep Quality Index	1.00	Day 28: one 15 mg given at bedtime
			Clinical Global Impression	1.08	Mean final dose = 13 mg
Taylor et al. (2008)[46]	13	0	Recurrent distressing nightmares	0.96	Begin with 1 mg at bedtime
			Difficulty falling/staying asleep	0.50	Increase 1 mg weekly, as tolerated
			Non-nightmare distressed awakenings	1.20	Maximum recommended dose = 4 mg Mean final dose = 3.1 mg
			Clinical Global Impression	1.50	
			PTSD Dream Rating Scale	1.40	

CAPS, Clinician-Administered PTSD Scale.

treatment-resistant patients, fail to achieve even close to this effect size for PTSD symptoms. Next, we have emphasized the importance of sleep impairment in PTSD and the central role that it may have in the pathology of this disorder—and to that may be added the medical risks of leaving sleep problems untreated.[50] Finally, the acceptable side-effect profile of prazosin and low dropout rate that has been found in the studies to date have a favorable appearance compared to the SSRIs, with their common unacceptable sexual side effects and the high dropout rates that meta-analyses have noted.

Clearly, we need larger studies with prazosin, and we need to know if alpha-1 adrenergic agents can be effective for the full spectrum of PTSD symptoms. Some studies are under way: one involving 320 veterans across 13 VA medical centers, and another studying 120 active-duty soldiers at Fort Lewis, Washington. These studies are expected to be completed in late 2012. In the interim, our view is that the current evidence is sufficiently strong to consider employing this agent as a first-line intervention.

Other alpha-1 blocking agents such as doxazosin (4–8 mg/day) and terazosin (3–7 mg/day) may have similar effects on PTSD symptoms, according to brief reports of 12 and 20 patients, respectively.[51,52] Although these products apparently do not cross the blood-brain barrier, the investigators propose that reduction of peripheral adrenergic activity, including tachycardia, may secondarily attenuate central nervous system manifestations of hyperarousal. This hypothesis requires further investigation.

If sleep has improved to an acceptable level, the patient may be maintained on prazosin. The long-term observational follow-up study of prazosin use in 62 patients for up to six years mentioned above found that almost 50% of patients took prazosin until the end of the study period, usually without adding other medications for PTSD.[47]

Node 2a, Continued: The Use of Trazodone

If prazosin fails to improve insomnia, or if it improves nightmares but without eliminating problems with sleep onset—and if other causes unrelated to PTSD have been addressed—then it may be worth considering a trial of low-dose trazodone (see Figure 1). It can be added or substituted, depending on whether prazosin is perceived to offer benefit.

Trazodone, a sedating antidepressant, has shown some effectiveness for sleep difficulties in PTSD patients in open-label studies.[53] It was the most widely prescribed medication used for hypnotic purposes in the United States in 2005.[54] Excess sedation, dizziness, and orthostasis occur frequently, and syncope occasionally. In males, priapism is a concern.[55] Milder erectile stimulation is apparently much

more common; before the advent of medications such as sildenafil, trazodone was recommended for patients with erectile dysfunction.[56]

Trazodone has recently been described as an "ideal hypnotic agent." It has triple sleep-promoting actions (at the 5-HT2A, alpha-1, and H1 receptors), a short half-life, and a low risk of dependence.[57] Although it has not received FDA approval for primary insomnia, in a placebo-controlled RCT of trazodone 50 mg and zolpidem 10 mg in 278 patients with primary insomnia, the two medications had similar efficacy at two weeks, and both had a low incidence of adverse effects. The study was sponsored by the manufacturer of zolpidem.[58]

If trazodone is used, side effects should be actively reviewed and monitored. Since other medications can cause priapism, including prazosin and phosphodiesterase inhibitors (e.g., sildenafil), combining trazodone with these agents demands extra caution regarding this side effect. The combination of trazodone and prazosin may also produce additive problems with blood pressure. Trazodone is usually started at 50 mg at bedtime, with instructions to reduce to 25 mg if too sedating. The dosage of trazodone for sleep has ranged from 12.5 to 300 mg.

Node 2b

If the patient presents with difficulty falling asleep but not with nightmares or nocturnal hyperarousal, trazodone may again be considered after identifying and managing other contributing factors. Since prazosin is generally nonsedating, it may be less useful in this situation. At this early point in the algorithm, trazodone might work well enough to eliminate the need for further pharmacotherapy for a patient with sleep-onset difficulties, but the evidence for its use in these circumstances is much less compelling than for the use of prazosin in patients with nightmares.

Trazodone may also be a good choice for patients who request a sleep aid for the short term while waiting for medications (e.g., SSRIs) targeting general symptoms of PTSD to take effect. Trazodone does appear to have efficacy for SSRI-induced insomnia and nightmares, as demonstrated in two small, placebo-controlled RCTs and some open-label studies.[53,55,59,60] If, during any subsequent steps of the algorithm when SSRIs and SNRIs are employed, insomnia/nightmares either fail to improve or emerge de novo, the addition of trazodone should be considered.

Other Medications for Insomnia?

If prazosin and trazodone are not effective or not tolerated in nodes 2, 2a, and 2b, other medications with hypnotic properties may be considered—and are often used in clinical practice. The authors did not find sufficient evidence to support their use at this early point in the algorithm. We will comment briefly on several.

The tricyclic antidepressants (TCAs) imipramine and amitriptyline have some evidence of usefulness in PTSD.[61,62] However, their side effects, especially at full doses, include anticholinergic, cardiac, and seizure risks. TCAs are also undesirable in suicidal patients, who might overdose on them.

Doxepin is a TCA that has recently been studied in large, placebo-controlled RCTs as a treatment for primary insomnia in very low doses of 1–6 mg; one study included geriatric patients.[63] It was found to be safe and effective for transient or chronic insomnia and received FDA approval as a hypnotic in March 2010. It has been marketed at these doses under the new brand name Silenor, but it will still be available as a generic capsule in doses as low as 10 mg. Its mechanism of action at these doses appears to be histamine H1 blockade.[63] It may not provide any advantage over sedating antihistamines such as diphenhydramine or hydroxyzine. Tolerance to the sedative effects of antihistamines has been shown to occur quickly, making them impractical for the long-term use usually required in PTSD.[64]

Benzodiazepines (BZs) are frequently used by clinicians for sleep problems in PTSD. However, in the only placebo-controlled RCT with a BZ ($n = 10$), alprazolam demonstrated no efficacy for core PTSD symptoms.[65] When used in PTSD patients who have problems with substance use, BZs have a high potential for abuse.[19] As with the use of antidepressants in bipolar disorder, the use of BZs in patients with PTSD (with or without substance abuse) represents an area of significant difference between common practice and guideline recommendations.[5,8,66] In both cases, clinicians may perceive that patients improve in the short term while not suspecting placebo effects and without anticipating the potential for harm over the long term. BZs might be considered when a past history of clear response without significant abuse or misuse is present.[4] If the patient has a history of substance abuse, one possibility is to prescribe a small quantity to test the patient's ability to use appropriately.

Recently, eszopiclone, a GABA-A/benzodiazepine receptor agonist, was administered for insomnia associated with PTSD in 24 patients, mostly women with civilian trauma and no history of substance abuse. Efficacy was demonstrated over three weeks in this placebo-controlled RCT. Further research on the use of this class of agents is warranted.[67]

Quetiapine is also widely prescribed for sleep in PTSD. However, a review of reports of using quetiapine for sleep in various patient populations concluded that the benefits did not justify the risks and that it should not be used as a first-line treatment for insomnia.[68] Notably, the weight gain from quetiapine is not dose related and can occur even at low

doses.[69,70] A recent observational study mentioned earlier compared results with quetiapine and prazosin for PTSD in a VA setting between 2002 and 2005 ($n = 62$ on prazosin; $n = 175$ on quetiapine).[47] Quetiapine at a low mean dose of 64 mg was much more likely than low-dose prazosin (3 mg) to be discontinued due to intolerable side effects (35% vs. 18%, $p = 0.008$). Sedation and metabolic effects were the most common reasons for discontinuing quetiapine. The authors' concluding recommendation was that "prazosin be used first-line for treating nighttime PTSD symptoms in veterans." One RCT of low to moderate doses of quetiapine monotherapy versus placebo for PTSD with prominent insomnia has been presented in poster format.[71] Some uncontrolled evidence also suggests that quetiapine be added to SSRI therapy after the latter has proved unsatisfactory.[47,72] These reports will be discussed at a later node in the algorithm—in particular, when we consider augmentation strategies for SSRIs.

Other hypnotics (e.g., zolpidem) and other sedating psychotropic agents (e.g., gabapentin) are occasionally used in clinical practice for PTSD-related sleep problems, but the evidence base for them is too small to consider them in this algorithm as options for initial treatment.

NODE 3: HAVE YOU GIVEN A TRIAL OF AN SSRI?

If the patient does not have prominent sleep disturbance, or if prazosin or trazodone was not tolerated or only partially effective for residual PTSD symptoms such as hyperarousal, reexperiencing, and avoidance, the next step in the algorithm would generally be to consider an SSRI trial. The evidence supporting the use of SSRIs is weak, however, which is one reason that they are not at the top of this algorithm for patients with prominent insomnia. Also, as noted earlier, SSRIs often fail to treat insomnia associated with PTSD, can sometimes aggravate it,[59] and can produce intolerable sexual dysfunction.[73]

Several recent comprehensive reviews and meta-analyses focus on using SSRIs for PTSD. The first was a Cochrane Review.[74] Overall, the authors found a number needed to treat (NNT) of about 5, which is reasonable. The calculated NNT was based on the number of patients across all studies found to be "responders" to medication. "Response" was defined for purposes of that review as having either a final rating of "much improved" or "improved" as measured by the Clinical Global Impression of Improvement (CGI-I) or, for a small number of studies, similar outcomes on the Duke Global Rating for PTSD or on other validated scales. The authors noted, however, that many of the studies were flawed because of relatively small numbers, low effect sizes, and short trial periods. Positive clinical outcomes were less convincing because of high dropout rates (27% to 40%).[26,28,75,76] Also, problems were also noted with tolerability. A separate concern was that many trial subjects came from primary care populations that are "less sick" than patients seen in a psychiatric setting.

Another major review of PTSD treatment data, published in 2008, was commissioned by the VA and conducted by an eight-expert panel from the Institute of Medicine of the U.S. National Academy of Sciences.[11] This review examined data from 14 SSRI studies conducted between 1991 and 2007. Seven of these studies were deemed to be "weakly informative with respect to efficacy because of study limitations." The committee reached the overall conclusion that "the evidence is inadequate to determine the efficacy of SSRIs in PTSD."

Another detailed meta-analysis was conducted by the National Institute for Clinical Excellence (NICE), part of the British National Health Service.[7] That review, which employed a more intensive and statistically rigorous analysis than many qualitative reviews of this literature, also raised concern that SSRIs might be significantly less effective than commonly thought for the treatment of PTSD. The NICE analysis examined data for the SSRIs citalopram, fluoxetine, paroxetine, and sertraline, as well as for amitriptyline, brofaromine, imipramine, mirtazapine, olanzapine, phenelzine, risperidone, and venlafaxine. Data from unpublished studies were included when obtainable from pharmaceutical companies.

The NICE guidelines proposed definitions of levels of efficacy that could be considered "clinically meaningful" or "clinically important." Setting a conservative standard, an effect size compared to placebo of a standard mean difference (SMD) of 0.5 or better was considered "clinically meaningful," and an SMD of 0.8 or more was considered "clinically important." They found that none of the SSRIs were beneficial for PTSD symptoms at an effect size of 0.5 and thus that the benefits were not clinically meaningful. Furthermore, reported effect sizes were considered to be overestimated because of the use of intent-to-treat analyses with last-observation-carried-forward in studies that had high dropout rates.

Some details of the NICE data on individual SSRIs will be briefly reviewed.

Paroxetine was evaluated in four RCTs, two of which were unpublished. One was a placebo-controlled study by Marshall and colleagues in 2001 that reported positive outcomes using the Clinician-Administered PTSD Scale (CAPS).[28] The specific PTSD symptom clusters of reexperiencing, hyperarousal, and numbing/avoidance were included. Marshall and colleagues replicated those results in a second RCT in 2007.[31]

The NICE meta-analysis of these paroxetine studies found that efficacy on the CAPS (effect size = 0.42) and on the Davidson Trauma Scale (DTS) (0.41) approached

the 0.5 benchmark for clinical meaningfulness. In one *unpublished* study, however—a maintenance trial carried out in patients who responded to paroxetine in a 12-week acute study and then were assigned to either placebo or continuation of paroxetine for 24 weeks—there was no efficacy and actually a trend in favor of placebo on the CAPS (effect size = 0.19). This surprising result suggests that something may have been irregular about the patient sample of this unpublished study.

Sertraline, the other FDA-approved SSRI, was studied in four large RCTs, two with positive results and two showing no efficacy. Three are published. Brady and colleagues[75] showed positive drug-versus-placebo differences for three of four primary outcome measures (CAPS, CGI of change, and CGI of severity) in a population of mostly women with sexual and other civilian trauma. Davidson and colleagues[26] used a similar design and population, and found sertraline to be statistically superior to placebo using four primary outcome measures. In the RCT by Friedman and colleagues,[17] however, which involved chronically ill combat veterans, sertraline produced no efficacy versus placebo as measured by the CAPS, CGI, or Impact of Event Scale. The fourth study, which is unpublished but was included in the NICE meta-analysis discussed earlier,[7] found no efficacy—possibly related, it was speculated, to the chronicity of symptoms, gender, or the type of trauma that subjects endured.

In the NICE meta-analysis of these sertraline data,[7] it was found that sertraline was "unlikely" to be beneficial by self-report measures of the DTS or the Impact of Event Scale, because of very small effect sizes of 0.18 and 0.06, respectively. The effect size on the CAPS (0.26) was rated as "inconclusive."

After evaluating the sertraline studies, licensing authorities in England approved sertraline only for women with PTSD. In the United States the FDA approved sertraline for PTSD patients of both genders. However, the FDA imposed a fine on the corporate sponsor of the trial by Friedman and colleagues[17] for withholding the study's negative data for almost ten years.

Fluoxetine was the subject of three major studies, with mixed results.[77–79] Two of the studies, which involved RCTs of 12 weeks followed by a 24-week maintenance phase, showed fluoxetine to be effective and well tolerated for the initial 12-week period and for the relapse-prevention phase. Subjects were mostly combat veterans, though some had civilian trauma, and the overall effect size for fluoxetine was about 0.4. The largest study, however—involving 411 civilian women—found fluoxetine to be equivalent to placebo on the CAPS.[79] An earlier, smaller study found no efficacy for fluoxetine in older, chronically ill combat veterans.[16] The NICE meta-analysis of fluoxetine, which looked at the above studies and some unpublished data, found the overall evidence for fluoxetine "inconclusive" on the DTS or CAPS (effect size = 0.28). They found no efficacy (effect size = 0.02) on the self-report measure of the Treatment Outcome PTSD Scale.[7]

Citalopram has been employed in one published RCT and several open-label studies. In an open trial ($n = 38$, mostly children and adolescents), citalopram improved total CAPS-2 scores and subscale ratings for reexperiencing, hyperarousal, and avoidance.[80] English and colleagues[81] conducted an eight-week, open-label study of citalopram in eight combat veterans. They found improvement on the CAPS, Hamilton Rating Scale for Anxiety, and CGI (among others) at week 4 but not at week 8. Tucker and colleagues[76] conducted a double-blind study of citalopram versus sertraline versus placebo for PTSD patients ($n = 25$, 23, and 10, respectively). Using an intent-to-treat analysis, the authors found significant improvement in total symptoms of PTSD measured by the CAPS, as well as for all three symptom clusters and sleep time, in all three groups, including placebo.

Robert and colleagues[82] published an open-label study with *escitalopram* in 25 patients, finding significant improvement for the CAPS-C (avoidance/numbing) and CAPS-D (hyperarousal) subscales, but only trend improvement for the CAPS-B (reexperiencing) subscale.

Alternatives to SSRIs at Node 3

As noted, side effects such as sexual dysfunction may make SSRIs unacceptable to some patients. Options that might be considered at node 3 include bupropion, mirtazapine, and certain antipsychotics. Nefazodone also has few sexual side effects and some evidence of efficacy in PTSD, but due to the risk of liver toxicity, it is not considered until later in the algorithm. Venlafaxine has efficacy for PTSD, but it has sexual side effects, and for other reasons (to be discussed) it seems better as a second-line option.

Bupropion showed some promise in an open-label trial in 17 combat veterans, but those results were not confirmed in an eight-week, placebo-controlled RCT in 30 patients with mixed civilian and military trauma.[83,84] Some patients had bupropion added to an SSRI. A trend toward better outcomes was evident in younger patients and those on monotherapy. More research is needed to determine if bupropion is effective for PTSD.

The evidence for using mirtazapine is more favorable, although its desirability is limited by the risk of weight gain. Bahk and colleagues[85] published a small study ($n = 15$) of the effectiveness and tolerability of mirtazapine in an eight-week trial in Korean patients with chronic PTSD. The dosing regimen was flexible, and patients were evaluated at four and eight weeks on several rating scales. At eight weeks, scores on all scales showed significant improvement. The medication was well tolerated. An open-label study by

Chung and colleagues in 2004,[86] also in Korean veterans, compared mirtazapine to sertraline. Both were well tolerated and seemed effective.

Davidson and colleagues[87] conducted a placebo-controlled, double-blind RCT of mirtazapine in 29 patients, with impressive results. The dose ranged up to 45 mg per day for eight weeks, with the DTS used as the primary outcome measure. Rates of response were 65% and 20% for mirtazapine and placebo, respectively (NNT = 2.2). The medication was well tolerated.

A long-term (24-week) study of mirtazapine was published by Kim and colleagues in 2005.[88] Twelve of 15 participants completed the study. The results suggested that mirtazapine might be effective for continuation treatment.

Certain antipsychotics are another alternative to SSRIs at node 3. For example, as noted at node 2, some clinicians use quetiapine as a monotherapy, first-line treatment for the global symptoms of PTSD, although the published evidence to support this practice is minimal. As noted earlier, the side-effect risks are considerable, making the product appear unsuitable for early selection in the algorithm.

Node 3 Conclusion

The FDA has approved the SSRIs sertraline and paroxetine for the treatment of PTSD. Paroxetine has the best evidence of efficacy but has more problems with sexual dysfunction, constipation, sedation, drug interactions, withdrawal syndrome, and weight gain than the other SSRIs.[66] The pregnancy risk rating of D is an issue with women of childbearing potential. Though the evidence supporting sertraline is weaker, especially in male combat veterans, it has fewer side effects than paroxetine. It may be reasonable to consider non-FDA-approved citalopram: although the subject of fewer and less rigorous studies in relation to PTSD, citalopram's efficacy in other anxiety disorders and in major depression suggests that its benefit in treating PTSD might be comparable to that of other SSRIs. It was thought to have the fewest side effects within the SSRI class.[89] However, the FDA just issued a Drug Safety Communication saying that the dose should not exceed 40 mg daily due to QTc prolongation risks.

According to most sources, an adequate trial of an SSRI for treating a PTSD patient would run 4 to 6 weeks, although sometimes up to 12 weeks are required.

Some patients show a partial response to SSRIs or a response that is limited to certain symptom domains in PTSD. Patients who partially respond but are still improving should be continued until the benefits reach a plateau. If improvement stalls for two or three weeks, consider raising the dose or switching to another option (see node 4). Augmentation may be considered (see nodes 3a and 5a) if both clinician and patient are convinced that the partial improvement was not a placebo effect and not attributable to other aspects of the treatment such as psychotherapy—which can be difficult to evaluate. Before proceeding with augmentation, keep in mind the preceding discussion indicating that SSRIs outperform placebo in controlled trials much less than generally assumed. "Augmenting" a likely placebo effect with another medication should be avoided. Also, augmentation introduces risks of increased side effects and drug interactions, reduced compliance due to complexity of regimens, and increased cost. In this algorithm, augmentation for partial response is considered most appropriate at nodes 3a and 5a. A switch is considered at node 4. See Figure 1.

Node 3a: Does the Patient Have PTSD-Related Psychosis?

PTSD-related psychotic symptoms are often present in PTSD patients.[90] Symptoms include phenomena referable to the original trauma—for example, hearing soldiers scream, experiencing visual hallucinations of an enemy, or other combat-related themes. Unrelated—for example, paranoid—delusions can also occur. Delusions related to PTSD are non-bizarre and not associated with disorganized thought or flat or inappropriate affect, and are not related to substance abuse or withdrawal. They do not occur only during dissociative flashbacks.[91] Patients with these psychotic symptoms can be considered one subgroup of PTSD patients for whom early augmentation may be justified. For this purpose, atypical antipsychotics are the medication of choice.

A preliminary study of risperidone (mean dose = 2.5 ± 1.25 mg/day) as an augmentation of antidepressants in 40 combat veterans with chronic PTSD-related psychotic symptoms demonstrated a significant decrease in psychotic symptoms and an improvement in reexperiencing symptoms.[92] A more recent, placebo-controlled RCT of risperidone augmentation for SSRI-resistant civilians with psychotic PTSD found improvement in the positive symptoms and paranoia subscales of the Positive and Negative Symptom Scale.[93]

Open-label studies support the addition of quetiapine and olanzapine, but not the first-generation neuroleptic fluphenazine, for antidepressant-resistant psychotic combat veterans with PTSD.[22,94,95] The quetiapine study involved patients resistant to SSRIs and other medications who were admitted to an inpatient unit for the trial.[22] Without a placebo control it is impossible to exclude that the positive outcome (on all three dimensions of PTSD symptoms) was due to the effects of hospitalization. We could not find any reports of aripiprazole augmentation in patients with PTSD-related psychosis.

Thus, if the patient does not respond satisfactorily to an antidepressant and has PTSD-related psychosis, it seems reasonable to add an antipsychotic. The evidence base points

to risperidone since it has one published, placebo-controlled RCT with favorable results. Quetiapine is widely used, has some evidence as an augmentation in nonpsychotic PTSD,[96] and might also be tried here. If the patient responds well to addition of an antipsychotic, and the SSRI had minimal benefit, gradually removing the SSRI should be considered to determine if it was necessary for the improvement.

NODE 4: HAVE YOU TRIED A SECOND SSRI, SNRI, OR MIRTAZAPINE?

If the patient is not psychotic and was nonresponsive to the initial SSRI chosen in node 3, several prime options are available: trying a different SSRI, an SNRI (especially venlafaxine), or an antidepressant with different dual actions (mirtazapine, evidence for which was discussed under node 3).

Venlafaxine was initially thought less likely to be effective in PTSD because of its noradrenergic component, given that PTSD is characterized by excessive noradrenergic activity.[97,98] An early RCT in combat veterans employing the strong norepinephrine reuptake-blocking tricyclic desipramine ($n = 18$) found no efficacy.[99] However, two large, placebo-controlled RCTs have been conducted to evaluate the efficacy of venlafaxine ER in PTSD, and both demonstrated some efficacy.

One of these venlafaxine studies involved 329 outpatients, mostly female, from international sites.[100] Only 12% had combat-related trauma. In this 24-week trial, CAPS scores improved five points more on venlafaxine than on placebo ($p = 0.06$). Mean daily maximum dose of venlafaxine ER was 222 mg. Reexperiencing and avoidance symptoms improved, but hyperarousal did not, possibly due to the impact of the noradrenergic component of venlafaxine. Overall effect sizes were small and similar to those found in the short-term SSRI studies even after almost six months of treatment.

The second study was a 12-week comparison of venlafaxine ER, sertraline, and placebo in a similar population of 538 patients, with CAPS scores again used as the primary outcome measure.[101] Remission rates at week 12 were 30% with venlafaxine, 24% with sertraline, and 20% with placebo. Mean daily maximum doses with venlafaxine and sertraline were 225 mg and 151 mg, respectively. Venlafaxine demonstrated statistically significant benefits over placebo ($p < 0.05$), but again, effect sizes were generally small on secondary outcome measures (particularly patient satisfaction and quality of life). Sertraline response did not differ from placebo on most measures, consistent with the unimpressive results with sertraline discussed earlier, in node 3. Both medications were similarly tolerated, with 10% attrition from side effects.

In a separate pooled analysis, the authors of these two studies attempted to differentiate response by gender and by trauma type.[102] No consistent predictors were found despite the opportunity presented by the large number of subjects. Venlafaxine offered no benefit for insomnia or nightmares.[103]

Thus, venlafaxine is a reasonable option as a second-choice pharmacotherapy, but the evidence base (despite the better response rate than sertraline in one study) seems to suggest no reason to prefer it to SSRIs for first-line use. It was ineffective for hyperarousal and sleep disturbance. Cardiovascular safety issues might affect certain vulnerable patients.[101]

NODE 5: HAVE YOU TRIED A THIRD MEDICATION AMONG SSRIs, SNRIs, MIRTAZAPINE, OR NEFAZODONE?

If two adequate monotherapy regimens among the SSRIs, SNRIs, or mirtazapine have been tried with no response to either, a third trial seems reasonable. The options may now include nefazodone, which is limited to third-line due to its liver toxicity. Fatal hepatotoxicity has been estimated to occur in about one in 250,000 patients.[104] Despite the rarity of this complication, nefazodone was removed from European formularies in 2003 but remains available in the United States as a generic. The usual side-effect profile of nefazodone actually makes it rather desirable, given the lack of weight gain or sexual side effects, less sedation than trazodone, and low risk of priapism.

Evidence to support the efficacy of nefazodone for PTSD includes two RCTs (one placebo-controlled) and several open-label trials.[105–107] The placebo-controlled RCT, with 41 patients, found benefits on the CAPS, with an impressive effect size of 0.6 ($p = 0.04$).[107] The other RCT was less impressive: it was a comparator study of the effectiveness of nefazodone and sertraline in a 12-week, randomized, double-blind study involving 37 patients, using the CAPS, CGI, and DTS measures.[108] It found no significant difference between groups on any outcome measure, including PTSD cluster symptoms, depression, sleep, and quality of life over time. In an analysis of six open-label trials involving 105 patients, Hidalgo and colleagues[109] found that 46% had an improvement of at least 30% on the CAPS.

Although small ($n = 10$), a nefazodone study conducted by Hertzberg and colleagues[110,111] is of interest because subjects were followed for three to four years. Originally conducted as a 12-week study,[110] long-term follow-up was described in 2002.[111] The dose was 400–600 mg, and ten of ten participants were rated as "much improved" on the CGI at 12 weeks. After three years of monitoring, seven of ten were still "much improved," while two were

minimally improved and one was worse than his original baseline.

Another interesting nefazodone case series involved 19 treatment-resistant combat veterans with PTSD. Zisook and colleagues[112] administered doses of 100–600 mg per day for 12 weeks to patients who had failed three previous medication trials. Improvements were noted in intrusive thoughts, avoidance, hyperarousal, sleep, sexual function, and depression. The reduction in PTSD symptoms, as measured by the CAPS, was 32%. Side effects were typically mild and included headaches, dry mouth, and gastrointestinal disturbance.

Node 5a: If No Response or Partial Response, Consider Augmentation (Depending on Residual Symptoms) or Try Other Monotherapies

If the patient failed to respond to the previous interventions, or if the response was partial, not explained by placebo effect, and still unsatisfactory in some respects, various options are available: mood stabilizers (gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, and valproate), antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone), anti-adrenergic agents (alpha-1 antagonists, alpha-2 blockers, and beta-blockers), and monoamine oxidase inhibitors (MAOIs). The supporting evidence ranges from unconvincing to fairly robust.

Some of these treatments appear useful for all of the symptom clusters of PTSD (avoidance, hyperarousal, reexperiencing), whereas others have evidence that they target one or more clusters. As noted earlier, the general principle is that one should try to minimize polypharmacy by critically evaluating partial response and determining if improvement was due to real effects of the medication or to a nonspecific response to other concomitantly administered treatments (including psychotherapy) or to changed circumstances (including hospitalization). If either of the latter is suspected, consider switching rather than augmenting. It must be kept in mind, however, that the constellation of PTSD manifestations is currently thought to include multiple symptom domains with potentially different responses to medication, suggesting that some patients will need more than one agent. We will briefly review some of the options, considering strength of evidence and how the choice might be influenced by comorbid psychiatric or medical problems. Patient preference and formulary availability/cost will also affect choice. Medications are not listed in order of preference, and the list is not complete. The flowchart in Figure 1 organizes these medications by their target symptom clusters, consistent with the evidence to be described below.

Anticonvulsants. In a 1991, open-label trial of *valproic acid* conducted at the Seattle Veterans Affairs Medical Center involving 16 Vietnam veterans with PTSD, 10 improved, mainly in symptoms of hyperarousal.[113] More recently, two placebo-controlled RCTs of divalproex have been reported. The larger study, published in 2008, involved 85 U.S. military veterans. It was conducted at the Tuscaloosa Veterans Affairs Medical Center and supported by the manufacturer. The subjects received a mean dose of 2,300 mg daily, which produced a mean average plasma level of 82 mg/L.[114] For total CAPS scores and for two of the CAPS symptom clusters (reexperiencing, avoidance), the divalproex group showed slightly less improvement than the placebo group. For the hyperarousal cluster, the study and control groups had the same final scores. Depression, anxiety, and CGI of severity likewise showed no differentiation between the study and control groups, with the quantity of improvement similar to that seen in the open-label trial. The other RCT, published in 2009 and conducted at the Ralph A. Johnson VA Medical Center in Charleston, South Carolina, randomized 29 combat veterans to divalproex or placebo and also found no advantages for divalproex. In fact, the placebo group did significantly better for the avoidance symptom cluster and on changes in CGI of severity. Given that all three of these studies involved monotherapy with male combat veterans, it remains to be seen whether this drug might prove more effective for use with veterans in an adjunctive role or when used either as monotherapy or adjunctive therapy for civilian males or for females.

In a double-blind, placebo-controlled study of *lamotrigine* for PTSD, 14 patients with different kinds of trauma were randomized 2:1 to either lamotrigine or placebo.[115] Over eight weeks the medication was titrated to a maximum of 500 mg per day (as tolerated). The study found nonsignificant, but possibly promising, improvement in reexperiencing and avoidance/numbing symptoms with lamotrigine in comparison to placebo.

Two negative studies of *topiramate* for PTSD have been published. In a double-blind, placebo-controlled RCT, 38 subjects with non-combat-related PTSD were studied on doses up to 400 mg per day.[116] Overall results showed a nonsignificant decrease in total CAPS scores. However, the treatment group did have significant reductions in symptoms of reexperiencing and on a secondary global outcome measure. The second study was a seven-week, double-blind, placebo-controlled RCT in 40 subjects, all male veterans in a residential PTSD treatment program.[117] The experimental group received flexible-dose topiramate and had a high dropout rate (40% vs. 10% for placebo recipients). The authors found no significant treatment effects, but the high dropout rate may have been a factor in this outcome.

In an observational study, *levetiracetam* was administered to 23 civilian patients with treatment-resistant PTSD, with the medication used adjunctively in 19 of those cases.[118] Outcome was evaluated retrospectively with several rating

instruments, including the CGI. At a mean dose of 2000 mg for 10 weeks, patients improved significantly on all measures. Fifty-six percent responded, 26% remitted, and the medication was well tolerated.

One small, open-label study and one large, multicenter, double-blind RCT of *tiagabine* have been published. In the former, 29 outpatients were treated for 12 weeks.[119] Responders ($n = 18$) were later entered into a double-blind maintenance study and randomly assigned to continue on tiagabine or placebo. During the extension phase, the placebo-treated patients did not relapse, but the tiagabine patients made further improvements. In the RCT, 232 patients were randomized to tiagabine or placebo for 12 weeks.[120] The experimental group received up to 16 mg daily of tiagabine. No efficacy was found for the anticonvulsant.

Antipsychotics. *Risperidone* has been evaluated in four small, placebo-controlled RCTs in nonpsychotic patients (civilians and veterans) with PTSD[121,122] and in a recent, larger-scale, placebo-controlled RCT studying 247 veterans who had served in combat zones.[123] Many of these patients were "treatment-resistant," and in most, the risperidone was added to other medications. It seemed to have some efficacy on the reexperiencing and hyperarousal symptom clusters, although the effects were small. There was no effect shown for avoidance.

In two open-label trials, *quetiapine* administered as an adjuvant was shown to improve all three clusters of PTSD symptoms and also sleep disturbance.[72,124] One double-blind, placebo-controlled RCT of quetiapine monotherapy in 80 patients with "chronic PTSD" (94% male, mean age = 52) has been completed and is under review, but some results were provided in a poster.[96] Patients were all U.S. combat veterans, and 30% had PTSD-related psychotic features. The doses ranged from 50 to 800 mg per day, with a mean of 258 mg. Reexperiencing and hyperarousal improved significantly ($p = 0.002$ and $p = 0.03$, respectively), but as with risperidone, the avoidance symptom cluster did not ($p = 0.56$). A separate analysis was not provided for the psychotic and nonpsychotic patients. Thus, it is unclear if these results best apply here or at node 3a.

Aripiprazole has been investigated in three uncontrolled studies of PTSD patients from mixed populations, including civilians and veterans. Medication was used as monotherapy in two of these studies[125,126] and as an adjunct to various other treatments in the third.[95] Aripiprazole monotherapy was found effective over 12 weeks in an open-label trial in 22 combat veterans at a mean dose of 13 mg.[125] CAPS scores improved ($p = .01$). Another case series of 32 civilian patients from Brazil experienced good results at a mean dose of 10 mg daily.[126] CAPS scores improved from a mean of 83 at baseline to 51 at the endpoint 16 weeks later ($p = .001$). All studies reported significant improvement in reexperiencing and avoidance/numbing, but marginal benefit for hyperarousal. Doses generally started at 5 mg.

Based on two small studies, the use of *olanzapine* has minimal support.[127,128] In a case series *ziprasidone* was reported to be effective in nonpsychotic PTSD.[129]

The benefits of atypical antipsychotics must be weighed against their side effects, including weight gain, metabolic syndrome, and cardiac risk.[69] Ray and colleagues,[130] in a large epidemiological survey, found that patients treated with antipsychotics had about double the rate of sudden cardiac death compared to non-treated controls who had similar psychiatric diagnoses and metabolic syndrome symptoms. The relative risk ratio of death was 2.26 (95% CI, 1.88–2.72) with atypical antipsychotics, and it was dose related.[130] The mechanism of death was thought likely to be arrhythmias, perhaps involving QTc prolongations. The authors of this study advised a "sharp reduction" in using these agents in populations for which the evidence of efficacy is limited. There is growing concern that antipsychotics should not be used as primary or adjunctive agents in treating PTSD unless other options with comparable effectiveness and better safety have already been tried.[131]

Medications Targeting Central Noradrenergic Dysregluation. Studies with the alpha-1 adrenergic antagonist prazosin were reviewed earlier. Alpha-2 agonists (clonidine and guanfacine) and beta-adrenergic antagonists have also been used for PTSD, with mixed results.

Two studies, one a placebo-controlled RCT, investigated *clonidine*. Kinzie[132] studied the combination of imipramine and clonidine in 9 traumatized Cambodian refugees with concurrent PTSD and major depression. PTSD global symptoms (CAPS) improved in 6 patients, nightmares improved in 7 patients, and hyperarousal in 4 patients. Avoidance behavior showed no improvement. In the RCT, 18 patients (17 female) with borderline personality disorder, all of whom had prominent hyperarousal symptoms on the CAPS, were treated with clonidine, up to 0.45 mg in divided doses, for two weeks.[133] Most were on other medications, which were maintained, but benzodiazepines were not allowed. Hyperarousal improved significantly versus placebo ($p = 0.003$), irrespective of PTSD comorbidity. Sleep also improved across all subjects.

Guanfacine, a longer-acting alpha-2 agonist, was administered in two recent RCTs, both with negative outcomes. Neylan and colleagues[134] treated 63 chronically ill U.S. veterans with guanfacine at a mean daily dose of 2.4 mg at bedtime (achieved with weekly 0.5 mg increases) or placebo for eight weeks. Most were on one or more other medications. Analysis showed no separation of guanfacine and placebo on the CAPS, the Impact of Events Scale, general mood, or subjective quality of sleep. In a smaller study, Davis and colleagues[135] administered guanfacine or placebo to combat

veterans for eight weeks while continuing their antidepressants. No improvement was shown on the CAPS or DTS.

Beta-blockers have not received substantial study in chronic PTSD. Several studies have explored the use of propranolol immediately after a trauma to prevent the onset of PTSD.[136–139] The findings are variable, and more research is needed before this treatment can be recommended.

Four RCTs have examined the short-term benefits of *monoamine-oxidase inhibitors* in PTSD due to a variety of traumas. Two involved phenelzine.[62,140] In the first, a comparison of phenelzine ($n = 19$), imipramine ($n = 23$), and placebo ($n = 18$), there was significant improvement with both antidepressants compared to placebo, but more so with the MAOI.[62] The dropout rate was about 50%, however, making interpretation difficult. The other phenelzine study was small and showed no benefit.[140] The other two MAOI trials involved brofaromine, a non-selective MAOI not available in the United States.[141,142] Both found no efficacy.

COMPARISON TO OTHER ALGORITHMS AND GUIDELINE RECOMMENDATIONS:

The present algorithm for selecting psychopharmacology treatment for PTSD differs in some respects from earlier versions of the PAPHSS algorithm and other published algorithms and guidelines. The 1999 version of the PAPHSS algorithm recommended initial use of trazodone for managing sleep disturbance, including nightmares, with low-dose doxepin a second choice for patients not at high risk for suicide, seizures, or cardiac events.[4] That algorithm was similar to the present version (and different from other guidelines at that time) in proposing efforts to manage PTSD-related sleep problems before the introduction of an SSRI or other antidepressants. The most recent (2005) NICE guidelines recommended paroxetine and mirtazapine as first-line pharmacotherapy and discouraged sertraline.[7] Similarly, the International Psychopharmacology Algorithm

Table 3. Characteristics of Other Algorithms and Guidelines for the Treatment of PTSD

Algorithm/guideline	Year	Comments
Expert consensus guidelines[144]	1999	First-line: SSRIs, venlafaxine, & nefazodone Second-line: TCAs
Psychopharmacology Algorithm Project at Harvard South Shore Program[4]	1999	Early use of hypnotic agent for sleep; trazodone first-line, followed by SSRI for persistent daytime PTSD symptoms
The United Kingdom's National Institute for Clinical Excellence[7]	2005	SSRIs in PTSD are reviewed & shown to have a more modest effect size then commonly considered Psychotherapy recommended as first-line treatment
Canadian clinical practice guidelines[145]	2005	First-line: one agent among fluoxetine, paroxetine, sertraline, & venlafaxine XR Second-line: mirtazapine, fluvoxamine, phenelzine, & moclobemide, plus adjunctive olanzapine or risperidone
The International Psychopharmacology Algorithm Project[5]	2005	Once diagnosis of PTSD established, SSRI trial recommended as first-line pharmacological intervention, followed by venlafaxine & mirtazapine trials
The International Society of Traumatic Stress Studies[6]	2008	SSRIs recommended as first-line intervention, followed by augmentation with atypical antipsychotics Prazosin considered "promising"
APA Guidelines Watch[10]	2009	Concludes new studies suggest SSRIs are less effective than previously assumed Prazosin considered a promising option for sleep disturbance in PTSD
VA/DoD clinical practice guideline for managing posttraumatic stress[146]	2010	Strongest recommendation is for SSRIs & SNRIs but suggests "some benefit" for prazosin, mirtazapine, & adjunctive atypical antipsychotics Recommends consideration of prazosin for nightmares as adjunctive treatment if trazodone & other hypnotics are insufficient

APA, American Psychiatric Association; DoD, Department of Defense; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VA, Veterans Administration.

Project's 2005 algorithm recommended an SSRI, SNRI, or mirtazapine, whereas the American Psychiatric Association practice guideline (2004) also endorsed SSRIs as first-line treatment.[5,143] However, the association's March 2009 "Guideline Watch" for PTSD noted that more recent studies "suggest that SSRIs may no longer be recommended with the same level of confidence for veterans with combat-related PTSD."[10] It was also noted that prazosin is "among the most promising advances," though without any indication as to when it should be used.

The 2008 assessment by the National Academy of Sciences made no psychopharmacology recommendations; it found the evidence "inadequate to determine efficacy" for all classes of drugs reviewed.[11] See Table 3 for a summary of these and other algorithms and guidelines, with comments on their essential features.

FINAL COMMENT

This heuristic will serve clinicians by offering a summary and interpretation of the current evidence base pertinent to psychopharmacological practice. Nevertheless, despite development of this and other algorithms and guidelines, the treatment of PTSD remains a challenge for physicians and patients. More needs to be learned about the pathophysiology of this chronic, disabling condition and about the comorbidities with which it often presents. Improvements in our understanding of genetics, the neurobiological underpinnings of PTSD, and mechanisms related to each symptom cluster promise to add refinements to the current treatment strategy.

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