

# It is illegal to post this copyrighted PDF on any website. Are There Effective Psychopharmacologic Treatments for PTSD?

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Posttraumatic stress disorder (PTSD) is a common and debilitating condition that develops in certain individuals after exposure to traumatic events, with a lifetime prevalence of 6.4% in the United States.<sup>1</sup> PTSD is typically characterized by a chronic and often severe time course, with a substantial symptom burden and rate of disability.<sup>1</sup>

PTSD symptomatology is multifaceted, with symptom dimensions that include re-experiencing, avoidance of trauma-related stimuli, negative thoughts and feelings, and arousal and reactivity. Further, PTSD co-occurs with other psychiatric disorders more often than not (eg, depression, anxiety, and substance use).<sup>1</sup> Despite notable recent advances, the pathophysiology of PTSD remains poorly understood, but it is thought to involve dysfunction in multiple biological systems, including synaptic dysregulation/neurocircuitry, neuroendocrine, neurotransmitter, and inflammatory.<sup>2-4</sup>

Despite this dire need for effective treatments, only 2 medications are currently approved by the US Food and Drug Administration (FDA) for the treatment of PTSD: paroxetine and sertraline—both belonging to the same class of selective serotonin reuptake inhibitors (SSRIs).<sup>5</sup> Polypharmacy and off-label prescriptions are common in PTSD, likely driven by the suboptimal response to treatment and the high prevalence of psychiatric comorbidities.<sup>6</sup> In this brief article, we review commonly used pharmacologic interventions and summarize the evidence supporting each. We also review investigational agents that have shown promise in translating to clinical practice. A comprehensive review of pharmacotherapy is beyond the scope of this focused report; for systematic reviews, we suggest refs.<sup>5,7,8</sup>

## OVERVIEW OF PHARMACOTHERAPY IN PTSD

**Slow-acting antidepressants.** A number of organizations including the US Veterans Affairs/Department of Defense (VA/DoD) and the American Psychiatric Association (APA) recommend SSRIs as the first-line pharmacologic intervention.<sup>9</sup> They have been found to be effective in a number of randomized control trials (RCTs) and meta-analyses, and the improvement in symptomatology appears to occur across all PTSD symptom clusters without particular selectivity.<sup>7,8</sup> The effect sizes compared to placebo are low and are somewhat similar to those observed in the treatment of major depressive disorder.<sup>7</sup> The serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine has also been studied in a small number of studies and found to have a relatively comparable effect to SSRIs,<sup>7</sup> although one study suggests that it may be less effective for hyperarousal symptoms.<sup>10</sup>

While only paroxetine and sertraline are approved by the FDA, there does not seem to be a meaningful difference in the SSRI/SNRI

classes at a meta-analytic level in terms of efficacy, as evident by the disagreement in intraclass comparisons across meta-analyses.<sup>5,7,8</sup> Despite the efficacy of this medication class, less than 60% of patients achieve a meaningful clinical response, and remission is achieved in only 20%–30%.<sup>5,7,8</sup> Further, the therapeutic effects are often delayed by several weeks.<sup>5,7,8</sup>

Atypical antidepressants such as mirtazapine, trazodone, and nefazodone are also commonly used, partly for their sedative properties. While some small studies have reported encouraging results with effect sizes comparable to SSRIs,<sup>5,8</sup> evidence for their efficacy is less compelling.<sup>5,7,8</sup> Likewise, the evidence for older tricyclic and monoamine oxidase inhibitor antidepressants has been less consistent than that for SSRIs, perhaps due to lack of large studies testing these drugs.<sup>5,7,8,11</sup>

**$\alpha$ -Adrenoreceptor antagonists.** The  $\alpha_1$ -adrenoreceptor antagonist prazosin was found to be effective in reducing nightmares and overall PTSD symptoms in several early small RCTs and a meta-analysis, showing a medium-to-large effect size for improvement of sleep and overall PTSD symptoms.<sup>12</sup> However, a more recent large trial<sup>13</sup> did not find prazosin to be helpful in the primary outcome of sleep and nightmare symptoms or in the secondary outcomes including overall PTSD symptoms. One possible explanation is the discrepancy in the studied population: the negative study comprised patients that are more clinically stable and excluded patients who were unwilling to discontinue trazodone (ie, possibly those who respond well to sleep-enhancing medications).<sup>13</sup> Further, potential responders to prazosin may have been underrepresented in this sample given the high rate of its use in this population,<sup>6</sup> as those whose symptoms have improved may have been ineligible/unmotivated to participate.

Interestingly, in contrast to VA/DoD and APA, the International Society for Traumatic Stress Studies (ISTSS) guidelines include prazosin on the list of first-line pharmacologic interventions (alongside SSRIs/SNRIs, mirtazapine, and nefazodone).<sup>9</sup> Here, the disagreements across the different guidelines stem partly from the criteria according to which studies were included in the assessment (eg, for prazosin, ISTSS included studies with small samples most of which happened to be positive, while the VA/DoD guidelines excluded small studies).<sup>9</sup>

**Atypical antipsychotics.** Perhaps the most extensively studied atypical antipsychotic in PTSD is risperidone, which in some early studies has shown some potential for use as either monotherapy or as an adjunct to antidepressants.<sup>5,7,8</sup> However, a large RCT later found no benefit in augmenting SSRI therapy with risperidone compared to placebo,<sup>14</sup> and no statistically significant effect was observed at a meta-analytic level.<sup>5,7,8</sup> On the other hand, a recent RCT of quetiapine monotherapy showed improvement in PTSD symptoms compared to placebo.<sup>15</sup>

**Other classes.** Benzodiazepines are commonly prescribed in PTSD, most likely in response to hyperarousal symptoms.<sup>6</sup> However, in the small number of studies that have examined the use of benzodiazepines in PTSD, no measurable benefit was found.<sup>7,8,16</sup> In fact, some detrimental effects have been reported, such as worsening of PTSD-related symptoms, increased risk of developing PTSD when used following recent trauma, worsened outcome when combined with psychotherapy, and increased risk of substance abuse.<sup>16</sup>

Several anticonvulsive/mood-stabilizing medications including lamotrigine, tiagabine, and topiramate have been tested in PTSD.

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In general, there has been no convincing evidence to support their use,<sup>5,7</sup> though a more recent study showed that topiramate may be efficacious,<sup>17</sup> which calls for further study.

## CONCLUSIONS AND FUTURE DIRECTIONS

In summary, pharmacologic agents that are efficacious for the treatment of PTSD exist, although the clinical effectiveness appears to be modest at best. The most convincing evidence appears to be for the SSRI/SNRI classes. Although certain meta-analytic studies found evidence of superiority of certain agents in intraclass comparisons, the lack of consensus across these studies suggests a nonspecific class effect.<sup>5,7,8</sup> Important practical considerations include the varying side effect profiles of different medications within this class; here, treatment should be individualized and consistent with the desired therapeutic goals/priorities of the patient (eg, concerns of weight gain could influence the decision against agents known to be problematic in that regard, eg, paroxetine). There is also evidence to suggest that certain patient groups (eg, combat veterans, men) may respond less strongly to antidepressant medications.<sup>5,8,11,18</sup> Furthermore, sertraline—although one of only 2 medications that carry FDA approval for PTSD—does not appear to be effective in combat veterans as evidenced by its failure to differentiate from placebo in RCTs that were conducted in this population (eg, Friedman et al<sup>19</sup>) and may be best avoided in this group.

Agents that target the adrenergic system such as prazosin may be helpful in certain patients. Among the encouraging findings are the medium-to-large effect sizes for overall PTSD symptom improvement and sleep symptoms, both statistically significant (such effect sizes are uncommon in other PTSD treatments that are currently used).<sup>5,12</sup> The disappointing negative results from the recent Raskind et al trial<sup>13</sup> in contrast to the earlier studies perhaps underscore the importance of identifying pertinent biotypes in PTSD that would enable the selection of candidate patients who are likely to benefit from this intervention. Notable progress has been made in this regard; a study showed that high blood pressure at baseline predicted response to treatment (possibly because both involve the noradrenergic system).<sup>20</sup> Such efforts are still in infancy and require consistent replication before they can be incorporated into treatment guidelines. Other groups have suggested that PTSD with predominant sleep-related symptoms (related to nighttime hyperarousal or nightmares) may be treated more appropriately with prazosin and have recommended its use on a first-line basis.<sup>21</sup> As such, given the benefit potential, and its relatively benign side effect profile when titrated adequately,<sup>12,21</sup> prazosin should be given due consideration in the clinic (for more detailed discussions of prazosin in PTSD, we suggest Khachatryan et al<sup>12</sup> and Bajor et al<sup>21</sup>).

Antipsychotic medications including the newer atypical agents have substantial side effects.<sup>5</sup> Given their unclear utility in PTSD, it is therefore important to stress the importance of using them judiciously where needed, until future trials yield more definitive answers. Certain classes such as benzodiazepines are best avoided as trials have found insufficient evidence of efficacy and possibly some evidence of harm in certain settings.

Trauma-focused psychotherapies should also be considered; they appear to be at least as effective as current pharmacotherapies.<sup>5,22</sup> However, obstacles limiting more widespread use include that they require the active engagement of patients and their motivation to tolerate bothersome symptoms elicited through therapy. The utility of combining pharmacotherapy and psychotherapy has not been demonstrated in the small number of studies that have been conducted.<sup>5</sup> This necessitates further investigation as a synergistic effect is biologically plausible and is observed in other disorders (eg, depression).

Promising ongoing investigations include the use of the N-methyl-D-aspartate receptor modulator ketamine, which has

recently been found to possess rapid-acting antidepressant properties when used in subanesthetic doses.<sup>23</sup> In a similar paradigm adapted to PTSD, it has shown promise in a pilot study.<sup>23</sup> Other promising approaches include 3,4-methylenedioxymethamphetamine (MDMA)-augmented psychotherapy (currently in phase 3 trials), the effects of which appear to be sustained even at the 1-year assessment timepoint.<sup>24</sup>

Drugs with higher effectiveness and faster onset of action are urgently needed. In PTSD—perhaps more so than in other psychiatric disorders—symptomatology is highly heterogeneous across individuals, which is likely paralleled by distinct neurobiological abnormalities.<sup>3</sup> A possible explanation for the mixed results in the literature could be that certain interventions are effective in certain groups of patients but generalize poorly to the whole population. Here, innovative developments in precision medicine and the identification of PTSD biotypes through biomarkers will be crucial in improving treatment outcomes.<sup>2,20</sup>

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