CME

Pharmacotherapy of PTSD: Current Status and Controversies

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CME EDUCATIONAL OBJECTIVES

1. Review the evidence from the literature for the pharmacologic treatment of posttraumatic stress disorder (PTSD).
2. Explain the progress in research on the pharmacologic prevention of PTSD for those who are exposed to trauma.
3. Review the pharmacologic treatment of selected symptoms of PTSD.

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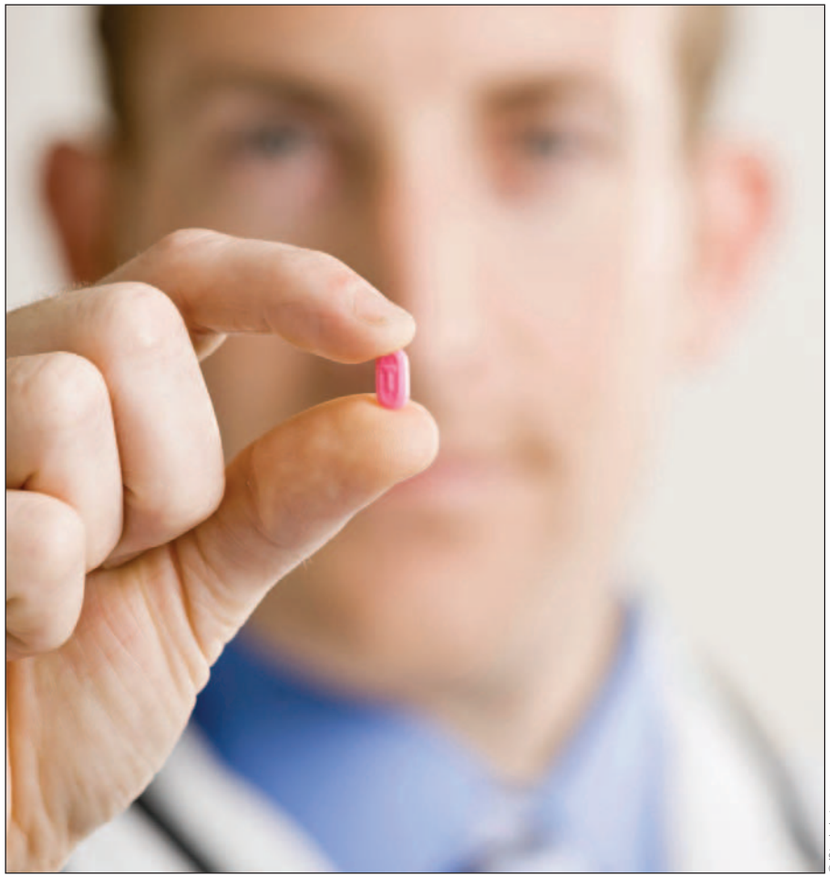
Posttraumatic stress disorder (PTSD) is a common psychiatric disorder in populations exposed to trauma, and it is among the most functionally-impairing, similar in scope to that observed in mood disorders. Recent years have seen many treatment studies assessing efficacy of diverse pharmacotherapies for PTSD. This article reviews the established, evidence-based pharmacotherapeutic treatments for PTSD and highlights current recommendations and controversial areas. The article primarily focuses on published randomized clinical trials that tested overall symptom reduction in PTSD compared to placebo. We also briefly review efforts to target particular symptoms commonly associated with PTSD (eg, sleep disturbance; psychotic symptoms) and at preventing PTSD among populations recently exposed to trauma. Where appropriate, recommendations are made for use of particular agents as first-line pharmacotherapies.

To date, there are no validated sensitive and specific biomarkers of PTSD that can



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aid in diagnosis, treatment selection, or monitoring of clinical progress. Notable biological findings in PTSD[1] include derangements in the two main branches of the stress response system, the noradrenergic/sympathetic brain systems and the hypothalamic-pituitary-adrenal (HPA) axis;[2] increased cerebrospinal fluid concentrations of corticotropin-releasing factor (CRF);[3,4] reduced volume of the hippocampus;[5-7] functional differences in responding of fear system brain regions, such as hyperactivation of the amygdala and hypoactivation of the prefrontal cortex;[8-10] sleep disturbances;[11] measures of hyperarousal in response to stimuli and of delayed habituation to loud noises;[12] and evidence for impaired conditioned fear extinction recall.[13,14] Such findings have firmly grounded the psychopathology of PTSD in neurobiological dysfunctions, thereby suggesting routes of pharmacotherapeutic interventions.[15]

Agents that enhance serotonergic neurotransmission, such as serotonin selective reuptake inhibitors (SSRIs), appear to attenuate several of the prominent symptoms of the PTSD. However, randomized clinical trials (RCTs) published to date have, at best, demonstrated limited efficacy for the constellation of symptoms that make up PTSD.[16,17] In fact, effect sizes (Cohen's d statistic) from the best pharmacotherapy RCTs have been relatively small, prompting the United Kingdom's National Institute for Clinical Excellence to recommend that medication treatments not be used as routine first-line treatments in preference to a trial of a trauma-focused psychological therapy.[18] Yet the overall conclusion of a recent meta-analysis of existing RCTs in PTSD conducted by the Cochrane Collaboration was that medication treatments were superior to placebo in reducing the severity of PTSD symptom clusters as well as comorbid depression and disability.[19] Therefore, both combination psychotherapy and pharmacotherapy and psychotherapy alone should be considered as first line approaches to PTSD while pharmacotherapy alone is generally not recommended, except in the circumstance when proven efficacious psychotherapies are not available.

SEROTONIN SELECTIVE REUPTAKE INHIBITORS (SSRIS)

The SSRIs have been tested for efficacy in randomized clinical trials (RCTs) for PTSD resulting from a variety of trauma types (eg, combat, physical and sexual abuse, assault, accident, and witnessing).[20-30] Common methodological limitations in pharmacotherapy trials have included small sample sizes, high or differential dropout rates, and inadequate statistical methodologies applied for missing data. Yet in the larger RCTs, the SSRIs sertraline ($N = 208$) and paroxetine ($N = 551$) were demonstrated to be more effective in the treatment of PTSD than placebo. Food and Drug Administration approval has been gained for the PTSD indication in both treatments. It is notable that only paroxetine demonstrated superiority over placebo in all three PTSD symptom clusters, re-experiencing phenomena, numbing/avoidance, and hyperarousal symptoms.[24]

Several of the larger RCTs demonstrating therapeutic effects of SSRIs have been conducted in mostly civilian samples,[20,21,26,27] making extrapolation to combat veteran samples perilous. In two of the larger RCTs made up of mostly veterans, SSRIs were not more effective than placebo,[22,30] suggesting the veteran population with chronic PTSD may be less responsive to SSRIs. Also, not all studies in civilians have demonstrated efficacy of SSRI pharmacotherapy.[29]

Despite the efficacy demonstrated for the SSRIs, it has been noted in a recent guideline that overall effect sizes in PTSD medication trials, with rare exceptions, have not been greater than 0.5.[18] Although it is certainly true that effect sizes have generally been small, the choice of 0.5 as a lower limit of clinical effectiveness is arbitrary as there is no direct translation of the effect size statistic to clinical efficacy.[19] Thus, it is the opinion of the authors of this review that SSRIs pharmacotherapy does have a first line role in the treatment of PTSD due to definitive demonstration of significant symptom reduction over placebo.

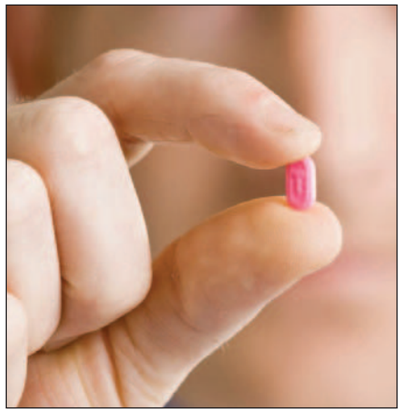
There is a paucity of data on the optimal treatment length when using SSRIs for PTSD, although a number of maintenance studies provide some guidance.[31-34] These data suggest the typical 12-week or shorter trials in PTSD are of inadequate duration for a subset of patients with more severe PTSD symptoms, and, in responders to an SSRI, continuation of treatment for at least 6 months or more appears indicated given the currently available data.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)

To date, there have been only two large published trials in PTSD using the dual-action serotonin and norepinephrine reuptake inhibitor venlafaxine extended release (ER).[35,36] These studies involved 329 patients in one study and 538 in the other. Between the two studies, venlafaxine ER has been shown to be superior to placebo on all three PTSD symptom clusters. As with studies on SSRIs in PTSD, the effect sizes were small. Also, both studies had notably high dropout rates of over 30%.

CLASSIC ANTIDEPRESSANTS: TRICYCLIC ANTIDEPRESSANTS AND MONOAMINE OXIDASE INHIBITORS

RCTs of the tricyclic antidepressants (TCAs) and the irreversible-type of monoamine oxidase inhibitors (MAOIs) were carried out in the late 1980s when pharmacological trials in psychiatry were in relative infancy. Thus, the methodological shortcomings were great, and most also suffered from inadequate sample sizes.[37-40] The reversible MAOI brofaromine has undergone two, large, multi-center RCTs.[41,42] In both, brofaromine failed to demonstrate significant effects for the primary outcome measure of PTSD symptom reduction. Overall, although there is the suggestion that TCAs and irreversible MAOIs may have efficacy in PTSD, the evidence is quite limited.[37,38] Larger, more methodologically sound RCTs are needed to demonstrate this definitively. Given the generally higher risks of adverse events from these classes (and the dietary restrictions necessary for the safe use of the irreversible MAOIs), these agents cannot be recommended as first line treatments for PTSD at this point.



Remarkably little empirical study of benzodiazepines in PTSD has been conducted despite the common clinical use of this class as anxiolytics and hypnotics.

OTHER SECOND-GENERATION ANTIDEPRESSANTS

Although alternatives to SSRIs and mixed SNRIs in PTSD would be desirable, little data supports the use of other antidepressants. An RCT of buproprion sustained release (SR) in a mixed trauma sample with PTSD failed to separate from placebo.[43] Mirtazapine, an alpha-2-adrenergic antagonist with 5-HT2 and 5-HT3 antagonism, produced mixed results. Although it was not found to be significantly better than placebo on total score, the response on the global measure of improvement were better among the drug group (65%) as compared with the placebo group (22%) suggesting indirect effects among patients with PTSD.[44] Although a 12-week RCT of the nefazodone, which is both a serotonin reuptake inhibitor and a 5-HT2A receptor antagonist, demonstrated greater reduction from baseline in CAPS total score and hyperarousal subscale score compared with placebo,[45] post-marketing association between nefazodone and hepatotoxicity makes adoption of nefazodone for first line use in PTSD unlikely.[46]

BENZODIAZEPINES

Remarkably little empirical study of benzodiazepines in PTSD has been conducted despite the common clinical use of this class as anxiolytics and hypnotics. In fact, only one RCT in PTSD was identified by the authors. This study involved 10 subjects in a 5-week crossover design of alprazolam in a mixed trauma population with PTSD,[47] and it failed to show an effect on PTSD-specific symptoms. Yet the large sample sizes required to show an effect of SSRIs would suggest this one study was grossly underpowered. Thus, the paucity of RCT data for benzodiazepine treatment in PTSD does not permit firm conclusions about their role. In a systematic review of controlled trials in anxiety disorders, including PTSD, it was recently observed that despite the absence of

comparative data between newer antidepressants and benzodiazepines, there has been a major change in prescribing pattern from benzodiazepines to newer antidepressants.[48] In PTSD, this may be reasonable simply due to the lack of systematic, methodologically-sound, large trials of benzodiazepines, although it is clear that such trials are needed. Also, given the propensity for abuse of this class in some individuals, judicious employment of benzodiazepines in PTSD should involve careful consideration of comorbid substance use disorders and past history of substance use disorders.

NMDA RECEPTOR MODULATORS

Preclinical studies have implicated roles for amygdala N-methyl-D-aspartate (NMDA) subtype of glutamatergic receptors in fear extinction and reconsolidation.[49] Similar work suggested a potential therapeutic effect of D-cycloserine (a partial agonist at a glycine regulatory site of the NMDA receptor) in anxiety disorders, particularly in combination with psychotherapies that employ extinction. In a small, 4-week trial of D-cycloserine in civilian PTSD, in which it was not specifically employed with psychotherapy, there was no group difference in reduction of CAPS scores.[51] Yet the length of treatment, sample size, and high percentage of non-completers are all deficiencies in the methodology that preclude making conclusions regarding D-cycloserine from this study alone. Current RCTs are investigating whether the effectiveness of CBT/exposure for PTSD can be enhanced by combination with D-cycloserine dosing. Thus, it is not yet possible to suggest a role for this agent alone or in combination PTSD-specific psychotherapies, although results from trials for the latter use should soon be forthcoming.

ATYPICAL ANTIPSYCHOTICS

Several RCTs of the atypical antipsychotic class in PTSD have been reported. Yet in some the use has been adjunctive to an antidepressant,[51,52] and in others the reduction in overall PTSD symptomatology has not been the main outcome.[53] Overall there is little empirical evidence supporting use of atypical antipsychotics as monotherapy in PTSD,[55] and data on use as an augmentation strategy to SSRIs is equivocal.[51,52] Risperidone may be helpful in selected cases in which comorbid psychotic symptoms are present, and some evidence suggests further study of this atypical is warranted for PTSD symptom clusters.[55-57] Given both the lack of empirical evidence as well as the greater propensity for severe side effects, such as obesity and metabolic syndrome, this class cannot be recommended for first line use at this time.

TREATMENT OF PTSD-ASSOCIATED SYMPTOMS: PSYCHOTIC FEATURES, HYPERAROUSAL, AND SLEEP DISTURBANCE

In a study targeting comorbid psychotic features in PTSD (using adjunctive risperidone versus placebo), a significantly greater decrease in psychotic symptoms was demonstrated, while the reduction in CAPS total score did not differ between groups.[53] Another study in combat veterans targeted hyperarousal symptoms in a small sample with notably high hyperarousal (cluster D) symptoms in a 6-week trial of low dose (0.5-2 mg/d) risperidone or placebo;[58] significantly greater reductions in irritability and intrusive thoughts were reported.

Nightmares and sleep disturbance occur in up to 70% of PTSD patients, and noradrenergic system dysfunction has been suggested to contribute.[59] Prazosin, an alpha-1-adrenergic antagonist that attenuates noradrenergic-mediated suppression of REM sleep in preclinical work,[60] has been tested in several RCTs in PTSD, which have assessed impact on nightmares, insomnia, and global clinical status.[59,61,62] Improvement in all three measures in veterans with chronic PTSD has been reported with prazosin treatment, with minimal adverse events and large effect sizes. Home sleep monitoring indicated the prazosin-induced reductions in nighttime PTSD symptoms are accompanied by increase in total sleep time, REM sleep time, and mean REM period duration; yet this agent does not appear to have a sedative-like effect on sleep onset latency.[62]

PREVENTION OF PTSD DEVELOPMENT

Animal models have demonstrated a central role for noradrenergic signaling in the amygdala in the formation of traumatic memories during acute traumatic stress. This has been suggested to have particular relevance to the goal of preventing PTSD development after severe trauma.[63] An RCT aimed at prevention of PTSD development tested the effect of blockade of such signaling by the beta-adrenergic antagonist propranolol, administered daily starting within 6 hours of the trauma.[64] Neither total PTSD symptom score at 1 month nor PTSD rate at 3 months demonstrated superiority over placebo, although upon exposure to trauma-script-driven imagery the propranolol group evidenced attenuated physiological response. An RCT for the same purpose compared propranolol, the anticonvulsant gabapentin, and placebo, beginning within 48 hours of injury at a surgical trauma center.[65] No significant benefit over placebo was found for either drug on PTSD and depressive symptoms at 1, 4, and 8 months post-injury.

Opiates acutely inhibit the noradrenergic system in brain regions believed to be responsible for traumatic memory consolidation. Therefore, the effects of morphine, administered as an analgesic, on posttrauma emergence of PTSD symptoms, was investigated in children hospitalized for acute burns.[66] An inverse relationship between change in the Child PTSD Reaction Index score and mean morphine dose per hospital day was identified, suggesting that further

investigation of morphine or other opiates in prevention of PTSD post trauma may be warranted.

A small trial of benzodiazepines for PTSD prevention in recently traumatized subjects suggested worse outcome in the benzodiazepine group at 6 months, with a higher rate of PTSD;[67] yet, the methodology was insufficient as there was no randomization, and sample size was small ($N = 13$ per group). A small ($N = 11$ in each group), 1-week RCT of temazepam in recently traumatized individuals failed to demonstrate a group effect on rates of PTSD or PTSD symptoms at 6 weeks' assessment.[68] Thus, the extremely limited data on benzodiazepine use in prevention of PTSD suggest they may be contraindicated for this specific role, but further study of this class is warranted. In summary, there are currently no pharmacotherapy treatments that can be recommended clinically for the prevention of PTSD development posttrauma.

SUMMARY

We reviewed RCTs that aimed to examine efficacy of pharmacological treatments for PTSD and its associated symptoms. Evidence for pharmacotherapy suggests that many of the studies to date were limited by small sample sizes, high dropout rates, and inadequate statistical methodologies applied for missing data. Despite these shortcomings, and especially for civilian's populations, two SSRIs, sertraline (Zoloft) and paroxetine (Paxil) have demonstrated reasonable efficacy in the treatment of PTSD as compared with placebo. Findings among veteran populations, however, suggest that SSRIs are not more effective than placebo, especially among service members with chronic PTSD. Although, testing of SSRIs in more recently traumatized veterans as well as longer treatment trials still hold promise for demonstration of efficacy in the veteran population. Importantly, in addition to SSRIs, venlafaxine ER appears to be efficacious in PTSD. Additionally, the alpha-1-adrenergic antagonist prazosin appears particularly effective for trauma related nightmares and insomnia in veterans with PTSD. It is premature to recommend any particular pharmacological strategies for preventing PTSD in the recently traumatized. Similarly, results of studies testing augmentation of extinction in CBT/PE psychotherapy for PTSD are still awaited.

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