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Pharmacological management of posttraumatic stress disorder

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Posttraumatic stress disorder (PTSD) has been conceptualized as an inability to cope with overwhelming stress that is followed by a distinctive pattern of symptoms. This concept has made it possible to develop therapeutic approaches for PTSD that include medication and psychotherapy options. In this article we summarize research studies on pharmacotherapies for PTSD and review new findings in the neurobiology of PTSD that are promoting the development of targeted treatment options. Research findings that have improved our understanding of psychobiological abnormalities associated with PTSD offer clinicians improved treatment strategies. We review those findings, the developments in the medication management of PTSD and common co-occurring disorders, and new areas of pharmacological research on PTSD treatment.

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Existing pharmacotherapy treatments for posttraumatic stress disorder (PTSD) such as antidepressants and antihypertensives have come from research that tested medications developed for other disorders. These treatments provide symptomatic improvement but lack the specificity to address the unique psychobiology of PTSD. Our goal is to summarize current knowledge of pharmacotherapy for PTSD, with an emphasis on results from randomized clinical trials (RCTs). Developments in our knowledge of the psychobiology of PTSD are only beginning to translate into new medications, yet progress has been made. There is an improved understanding of which individuals are most likely to benefit from recommended medications. We have identified better augmentation strategies for PTSD patients with common co-occurring disorders. This review highlights those advances and exciting areas of current pharmacological research in PTSD.

Antidepressant interventions

Placebo-controlled trials of tricyclics (TCAs) and monoamine oxidase inhibitor (MAOI) antidepressants were conducted in the 1980s primarily among male veterans with PTSD. The studies showed variable results, with more positive effects noted where treatment was given for at least 2 months [1•]. These medications were widely used to treat PTSD at that time. With manufacturers' support, subsequent RCTs testing medications for PTSD concentrated on new antidepressants, selective serotonin re-uptake inhibitors (SSRIs) and to a lesser extent, other antidepressants and drug classes such as antipsychotics, anticonvulsants, and anxiolytics [1•]. The 2010 Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline (CPG) for PTSD concluded that SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) were roughly comparable [2]. These medications were rated as having the highest levels of evidence and were recommended as effective 'first-line' pharmacotherapy treatments. Despite a more complicated side-effect profile and higher levels of risk, older antidepressants such as the TCAs imipramine and amitriptyline, and the MAOI phenelzine were recommended in the CPG as 'second-line' treatments. Mirtazapine and nefazodone were also antidepressants recommended in this group.

Successful trials of paroxetine and sertraline resulted in their classification by the U.S. Food and Drug Administration as the only medications with an indication for PTSD [2]. Unfortunately, success with SSRIs has been limited and despite their benefits, residual symptomatology often remains with their use. Findings now suggest that not all SSRIs are equal in their effectiveness in treating PTSD [1•,3••,4•]. The revised British Association of Psychopharmacology CPG for PTSD recommends as first-line medications two SSRIs (paroxetine and sertraline) and one SNRI (venlafaxine), but fluoxetine was removed [5]. Other PTSD guidelines, including the National Institute of Clinical Excellence (NICE), the World Psychiatric Association (WPA), and the Australian National Health and Research Council followed a stepped-care approach, with psychotherapy endorsed as first-line treatment and medications recommended when psychotherapy has failed, is unavailable, or for individuals with more severe depression [6–8]. In instances where medication is used, these guidelines advocate the use of

any SSRI. The WPA recommends an SSRI or TCA if a medication is to be used but rates the quality of evidence as low.

Two meta-analyses have noted contradictory findings regarding SSRIs as a class. One found efficacy for paroxetine, sertraline, fluoxetine, and venlafaxine [9]. The more recent review found statistically significant effects at 8–12 weeks posttreatment for sertraline, venlafaxine, and paroxetine only, with a particularly large effect for venlafaxine [3••]. Although this effect size appears to differ from the original RCT findings [10], venlafaxine is clearly an effective treatment for PTSD.

Because of limited research, little guidance regarding the use of TCAs or phenelzine can be offered other than that they are usually recommended as second-line treatments [1•]. Nefazodone is another effective treatment option [3••] but clinicians must consider the risk of liver failure with its use [2]. Given that SSRIs alone do not achieve complete remission for approximately 70% of patients suffering from PTSD [11], the effectiveness and safety of TCAs to treat PTSD should be reassessed [1•].

Factors such as age, gender, chronicity, resilience, type and length of previous treatments, and veteran status all appear to impact antidepressant treatment response in PTSD [1•,12•]. Vietnam veterans with chronic PTSD treated in VA hospitals appear to be a particularly treatment refractory group [1•,13,14]. Their reduced treatment response may be due to selective factors because veterans recruited for studies have often continued to seek treatment after failure to respond to a variety of previous PTSD treatments over the course of several decades.

Other monotherapy approaches

More recently, RCTs of monotherapy approaches have included other classes of medications. Much of this work, however, has been on medications that are not recommended for PTSD monotherapy, including bupropion, benzodiazepines, prazosin, and anticonvulsants. In small placebo-controlled trials, the anticonvulsant topiramate has not shown efficacy as a primary treatment for PTSD, despite early promise [3••]. Similarly, after initial promise for the use of prazosin as a monotherapy for PTSD [15], recent results have been disappointing [16]. Guidance does not support the use of antipsychotic medications as monotherapy, although a small recent study suggests that quetiapine monotherapy may be beneficial in combat-related PTSD [17]. More work is needed to determine the most appropriate use of atypical antipsychotics as monotherapy treatment. Furthermore, consideration must be given to their serious side effects, such as weight gain, risk of metabolic syndrome, and cardiotoxicity.

Augmentation strategies for SSRI partial responders

Monotherapy with the currently recommended antidepressant options does not appear to help most patients achieve remission from PTSD; the magnitude of benefits is a small-medium effect size [4•]. This highlights the need to find effective augmentation strategies for SSRI partial responders. Unlike their positive findings in major depressive disorder [18], atypical antipsychotics as adjunctive treatment for SSRI non-responders have shown mixed results in PTSD [1•]. Risperidone has been evaluated as adjunctive to antidepressant PTSD treatment in five small single-site RCTs, three showing positive effects and two showing no benefit [19]. A small study ($N = 19$) compared olanzapine with placebo for augmentation of SSRI-resistant PTSD symptoms and showed a decrease in total PTSD symptoms as well as in sleep problems [20]. Weight gain in the olanzapine group, however, was substantial. Krystal *et al.* [21] conducted a large multi-site RCT ($N = 247$ veterans) in which antidepressant partial responders were randomized to adjunctive risperidone or placebo. After six months of treatment, the changes from baseline PTSD scores did not differ between the two treatment arms. As a result of this trial, the 2010 VA/DoD PTSD CPG was changed to recommend against risperidone use for SSRI non-responders and other atypical antipsychotics are not recommended as adjunctive agents [2]. A promising finding with regard to adjunctive pharmacotherapy was with the antidepressant mirtazapine, rather than with an atypical antipsychotic. It was a trial in which patients receiving the SSRI sertraline who also received mirtazapine, a tetracyclic antidepressant, exhibited significant and clinically meaningful improvement in PTSD symptom severity, compared to sertraline treatment alone [22••].

Psychotherapy treatment augmentation strategies

In line with the stepped care approach of other CPGs, a recent review concluded that PTSD patients who are partial responders to recommended antidepressant medications should initially be referred for adjunctive first-line trauma-focused psychotherapy rather than prescribed an adjunctive medication [3••]. Unfortunately, research in this area is limited. One study examined whether augmenting sertraline with Prolonged Exposure (PE) psychotherapy would result in greater improvement than continuation with sertraline alone. After a 10-week sertraline trial, patients were randomly assigned to 5 additional weeks of sertraline alone or sertraline plus 10 sessions of twice-weekly PE. After the first 10 weeks, sertraline significantly reduced PTSD severity but no further improvements were noted after the 5 additional weeks of treatment. On the other hand, the patients who received twice-weekly PE augmentation did show further reduction in PTSD severity over the five additional weeks [23]. An exploratory analysis found this