Pharmacologic Treatment of Acute and Chronic Stress Following Trauma: 2006

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This article reviews pharmacologic treatment options for posttraumatic stress disorder (PTSD), focusing on goals of pharmacotherapy and the clinical trial evidence for drug treatments available for PTSD. The selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line therapy for PTSD; the roles of these and other drug classes including anticonvulsants, mood enhancers, atypical antipsychotic agents, benzodiazepines, α_1-adrenergic antagonists, and β-blockers in achieving improvement in PTSD symptom and outcome scores, achieving remission, and avoiding relapse are discussed. Treatment of PTSD in association with other comorbid conditions is addressed, and the role of pharmacotherapy in treating early PTSD and acute stress disorder is examined. Dosing strategies for the SSRIs sertraline and paroxetine are provided, and an algorithm for PTSD pharmacotherapy is discussed. *(J Clin Psychiatry 2006;67[suppl 2]:34–39)*

Posttraumatic stress disorder (PTSD) can be a severe, chronic, and disabling condition with major consequences for the individual and society in terms of morbidity, mortality, impact on economic productivity, and health-care/welfare costs. Effective treatment is critical, and it is fortunate that well-controlled, double-blind trials over the past decade have demonstrated superiority of selective serotonin reuptake inhibitor (SSRI) drugs over placebo. It is reasonable to believe that the use of these, and related compounds, can become an effective tool in promoting the long-term psychological and psychosocial health, and economic recovery, of those in the region affected by the tsunami on December 26, 2004.

PRINCIPAL GOALS OF PHARMACOTHERAPY FOR PTSD

The objectives of medical treatment for PTSD are to reduce its core symptoms (i.e., reexperiencing via intrusive thoughts, nightmares, and flashbacks; avoidance of trauma-related situations and activities; emotional numbing; and hyperarousal); to improve function, including social functioning; to strengthen resilience, or the ability to cope and thrive in adversity; to relieve comorbid disorders commonly associated with PTSD, including depression and panic disorder; and to prevent relapse. While there is no single gold standard by which outcomes in PTSD treatment are measured, scales such as the Davidson Trauma Scale,[1] the Clinician-Administered PTSD Scale (CAPS),[2] the Short PTSD Rating Interview (SPRINT),[3] and the 8-item Treatment Outcome Posttraumatic Stress Disorder Scale (TOP-8)[4] provide measures by which the changes achieved by pharmacotherapy can be quantified.

FIRST-LINE PHARMACOLOGIC TREATMENT OPTIONS FOR PTSD

The SSRIs are currently recommended as first-line therapy for the treatment of PTSD,[5] and the SSRIs sertraline and paroxetine are licensed for treatment of PTSD in the United States and elsewhere. Following recognition of PTSD as a distinct clinical entity in the 1980s, efficacy data from well-controlled, double-blind trials of pharmacotherapy were initially slow to accumulate, but have become available more recently. SSRIs are effective across all PTSD symptom clusters and improve quality of life and functional impairment, though sleep disturbances and nightmares may respond less well in some cases.[6,7]

Acute Efficacy Studies

Fluoxetine. Three randomized, double-blind, placebo-controlled trials[8–10] have confirmed a significantly higher response in patients with PTSD receiving fluoxetine versus placebo for up to 3 months. In a 5-week study[8] com-

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paring fluoxetine at up to 60 mg per day (N = 33) versus placebo (N = 31), fluoxetine significantly reduced overall PTSD symptomatology assessed using CAPS-2 ($p = .01$). Changes were most marked in the arousal and numbing symptom subcategories. A 12-week trial[9] comparing fluoxetine up to 60 mg per day (N = 27) versus placebo (N = 27) demonstrated that fluoxetine was more effective on most measures using the Duke Global Rating for Post-Traumatic Stress Disorder and the Structured Interview PTSD measure at week 12, including global improvement ($p < .06$), with the effects of therapy evident using the Duke scale as early as week 2. In a larger-scale, 12-week study[10] comparing fluoxetine at 20 to 80 mg per day (N = 226) and placebo (N = 75), fluoxetine was associated with a greater improvement from baseline in TOP-8 scale total score versus placebo at week 12 ($p = .006$).

Paroxetine. A 12-week study[11] comparing paroxetine (20–50 mg per day; N = 151) and placebo (N = 156) showed significantly greater improvement in CAPS-2 total score from baseline beginning at week 4 ($p < .05$ vs. placebo), with significantly greater proportions of paroxetine-treated patients achieving a response ($p < .001$ vs. placebo) and remission ($p = .008$) by week 12 on the Clinical Global Impressions-Improvement scale. In a second 12-week study[12] comparing paroxetine 20 mg per day (N = 183), 40 mg per day (N = 182), and placebo (N = 186), paroxetine-treated patients in both dose groups demonstrated significantly greater improvement on the CAPS-2 ($p < .001$). A pooled analysis of these trials plus a third 12-week, placebo-controlled study of paroxetine confirmed that treatment resulted in significantly better response and remission rates, improvement in sleep disturbance, and a reduction in symptom clusters in PTSD compared with placebo.[13]

Sertraline. A 12-week study[14] with sertraline at 50 to 200 mg per day (N = 94) versus placebo (N = 93) showed that sertraline produced a significantly greater improvement from baseline at endpoint in CAPS-2 total score ($p = .02$). In a second 12-week study[15] with sertraline (50–200 mg per day; N = 100) or placebo (N = 108), Davidson et al. reported significantly greater benefit for this drug, relative to placebo, on most measures.

EFFECTS ON RESILIENCE

Treatment with fluoxetine and sertraline and with the serotonin/norepinephrine reuptake inhibitor (SNRI) venlafaxine extended release (XR) has been shown to improve resilience in PTSD patients. Open-label treatment with fluoxetine (N = 25) and sertraline (N = 54) resulted in significant changes from baseline in Connor-Davidson Resilience Scale (CD-RISC) scores ($p < .001$ and $p < .0001$, respectively).[7] A long-term (24-week) study[16] comparing the effects of venlafaxine (N = 151) and placebo (N = 161) on all aspects of PTSD showed a resilience-enhancing effect, as well as overall benefit in PTSD: a significantly greater improvement in CD-RISC scores was seen at endpoint for venlafaxine XR versus placebo ($p < .05$).

TIME TO ONSET OF TREATMENT EFFECT AND LONG-TERM TREATMENT WITH SSRIs

Early onset of action of SSRI therapy in PTSD was confirmed by a study featuring mixed-models analysis of 2 twelve-week, placebo-controlled trials of sertraline treatment.[17] Sertraline was found to markedly improve anger by week 1, an effect that was sustained throughout the remainder of the treatment period and that largely explained the ensuing improvement on intrusive symptoms. Other symptoms improved later, such as emotional upset at reminders, anhedonia, and detachment at week 6 and avoidance of trauma-related activities by week 10. While it is clear that onset of SSRI action may be rapid, and the majority of SSRI efficacy trials in PTSD have been of 3 months' duration or less, short-term therapy is insufficient for full recovery, and optimal results may not be seen until after 6 to 9 months of treatment.

There is evidence that continuation of SSRI therapy brings about sustained improvement in PTSD: in an open-label continuation phase of a 12-week acute study,[18] patients treated with sertraline showed continued improvement up to 9 months. The mean CAPS-2 score was reduced from 45 (representing mild PTSD) at 3 months to 20 (equivalent to minimal or no PTSD symptoms and high-end functional state) at 9 months.

OTHER TREATMENT OPTIONS

The noradrenergic and specific serotonergic antidepressant mirtazapine was effective in treating PTSD in an 8-week, placebo-controlled, double-blind pilot study (N = 29) in which response rates on the Short Posttraumatic Stress Disorder Rating Interview Global Improvement measure were 60% for mirtazapine versus 22% for placebo ($p < .05$).[19] Mirtazapine also helps to alleviate sleep disturbance in PTSD patients; its main disadvantages are side effects of weight gain and somnolence.

The SNRI venlafaxine XR has demonstrated efficacy in PTSD.[16,20]

Mood stabilizers and anticonvulsants can also be useful for treating PTSD symptoms. There is, however, a limited database regarding their efficacy and safety; most published studies are open label, and as these agents produce troublesome or serious side effects or require closer monitoring, they should be classed as second- or third-line treatments. In a small double-blind trial of lamotrigine in 1999, Hertzberg et al.[21] showed preliminary evidence, based on 1 out of several rating measures, that lamotrigine may be effective. A single-center trial of topiramate and

placebo presented by Tucker[22] provided mixed but encouraging results for the drug. Carbamazepine and divalproex sodium both require regular blood tests, and topiramate produces cognitive side effects. One positive, placebo-controlled trial of nefazodone exists,[23] as does a negative placebo-controlled study of bupropion.[24] Interestingly, bupropion appeared to aggravate dissociative symptoms. Both of these trials by Davis and colleagues[23,24] were conducted in combat veterans.

There is a growing literature on the use of atypical antipsychotic agents as adjunctive therapy in PTSD. Olanzapine was shown to be a successful adjunct treatment in a study population with combat-related PTSD who were nonresponsive to 12 weeks of SSRI therapy.[25] Patients who received adjunctive olanzapine for a further 8 weeks (N = 19) showed greater improvement in CAPS-2 scores ($p < .05$) and sleep disorder symptoms (assessed by the Pittsburgh Sleep Questionnaire; $p = .01$) than those who were given placebo.

Similarly, Bartzokis et al.[26] showed that the use of adjunctive risperidone in combat veterans with PTSD achieved significantly better improvement than placebo in a broad range of psychiatric symptoms as measured by the CAPS-total scale and subscales (reexperiencing, avoidance, and arousal). In a 5-week, double-blind, placebo-controlled trial of 40 combat veterans, those receiving adjunctive risperidone showed a significantly greater improvement in psychotic symptoms, measured by the Positive and Negative Syndrome Scale, than those given placebo ($p < .05$), as well as a greater improvement in CAPS reexperiencing subscale score at the study endpoint ($p < .05$).[27] The potential risk of side effects with the atypical antipsychotic agents, including weight gain, postural hypotension, extrapyramidal symptoms, hyperglycemia, and diabetes,[28] does however need to be taken into account when selecting therapy.

Several studies have demonstrated the efficacy of the α_1-adrenergic antagonist prazosin in PTSD. In a 20-week, placebo-controlled crossover, add-on study of Vietnam veterans, in which participants received a mean dose of 9.5 mg per day of prazosin (N = 10) or placebo (N = 10), prazosin produced a greater improvement in nightmares, sleep disturbance, and global change in PTSD severity and functional status than placebo, measured using CAPS and Clinical Global Impression of Change scale (CGIC).[29] Total score and symptom cluster scores for reexperiencing, avoidance/numbing, and hyperarousal were also significantly more improved with prazosin. In a small 6-week, open-label trial involving non–combat-related PTSD, in which 5 individuals received prazosin at increasing doses, all subjects experienced moderate-to-marked improvement on the CGIC, as well as an improvement in Clinical Impression of Change-Nightmares score and CAPS One Week Symptom Version PTSD nightmare and sleep category scores.[30]

Psychotherapy has been shown to benefit patients with only a partial response to SSRIs. In a psychotherapy augmentation study, 60 patients received sertraline for 10 weeks.[31] Those not achieving complete clinical remission were randomly assigned to receive 10 sessions of prolonged exposure therapy over a further 5 weeks in addition to sertraline or to receive drug alone. Patients who initially showed only a partial response benefited greatly from the addition of prolonged exposure therapy to sertraline treatment.

ACHIEVING REMISSION IN PTSD

Although SSRIs are recommended as first-line therapy for PTSD, approximately 20% to 40% of PTSD patients fail to respond to treatment as well as one might hope. Remission rates with SSRIs after 12 weeks are relatively low, at 30% or less,[32] though better than might be expected given the severity and chronic nature of PTSD. Many patients discontinue SSRIs because of side effects, including gastrointestinal symptoms, sleep impairment, agitation, insomnia, sexual side effects, and weight gain. As many as half of all U.S. patients stop taking antidepressants within 3 to 4 months of initiating therapy,[33] for a variety of reasons including cultural and social factors, and this impacts negatively on response and remission rates in PTSD.

One strategy to move PTSD patients from partial response to full response, and to achieve higher remission rates, is long-term drug therapy.[34,35] Treatment can also be augmented with another drug or with psychotherapy, and high side effect rates can be avoided by using a low starting dose and titrating steadily upward. Physicians can encourage patients to persist with taking their medication by providing them with information and education on PTSD and the treatment options.

PREVENTION OF PTSD RELAPSE

SSRI therapy appears to protect against PTSD relapse. When a 6-month, open-label study with fluoxetine was followed by 6 months of double-blind, randomized treatment with fluoxetine or placebo, 50% of patients receiving placebo suffered a major relapse versus 22% treated with fluoxetine ($p < .05$).[36] In a relapse prevention study with sertraline, patients who completed a 12-week, double-blind, placebo-controlled study and a subsequent 24-week, open-label continuation phase were randomly assigned to 28 weeks of maintenance treatment with sertraline (N = 46) or placebo (N = 50).[37] The rates of relapse (including discontinuation due to clinical deterioration) were 48% with placebo versus only 16% with sertraline ($p = .005$). In a double-blind, placebo-controlled study of positive responders to 12 weeks of fluoxetine treatment, patients randomly assigned to receive a further 24 weeks of fluoxetine therapy (N = 69) were found to be

less likely to relapse than those given placebo (N = 62; p = .027).[38]

It is currently recommended that treatment should be tried initially for at least 3 months,[5,38] with effective pharmacotherapy continued for at least 1 year. Discontinuing medication after 6 months exposes patients to a higher risk of relapse. There are currently no published PTSD relapse prevention studies using agents other than SSRIs.

COMORBIDITY IN PTSD

Because PTSD is commonly associated with other psychiatric disorders,[39] and because the SSRIs are recognized as effective broad-spectrum therapy for depression and anxiety disorders, it was expected that these drugs would be effective in treating PTSD with some comorbid conditions. Acute, randomized, double-blind, placebo-controlled studies indicate that both sertraline[40] and paroxetine[13] are effective in treating PTSD both with and without depression, anxiety, or both. An early open-label trial with sertraline (N = 9) suggested that it was effective in treating PTSD in patients with alcohol dependence, with participants showing decreased alcohol consumption.[41] A subsequent 12-week placebo-controlled trial with sertraline in 94 patients failed to show an overall benefit for sertraline, but suggested in a post hoc analysis the possibility that there may be subgroups who respond better to sertraline; those with less severe alcohol dependence and later-onset PTSD had significantly fewer drinks per drinking day (p < .001).[42]

DOSING STRATEGIES

SSRIs should be initiated at a low dose, with slow titration (up to the maximal daily dose if required) until a good response or remission is achieved, or until side effects prevent further dose increases. If side effects are troublesome and the response is poor, other agents should be considered. Suggested dose titration schedules for sertraline and paroxetine are shown in Table 1.

Table 1. Suggested Dose Titration for Sertraline and Paroxetine in Posttraumatic Stress Disorder

	Recommended Dose (mg/d)	
Week	Sertraline	Paroxetine
1	25	10
2	50	20
3	100	30
4–6	150	40
8	200	50

PHARMACOLOGIC PREVENTION OF ACUTE STRESS DISORDER OR EARLY PTSD

Very few studies have investigated pharmacologic prevention of acute stress disorder (ASD) or early PTSD (i.e., occurring within 1 month of trauma). One study[43] in children suggests that short-term antidepressant therapy may be helpful in ASD or early PTSD. In a prospective, randomized, double-blind pilot study in children with severe burns and ASD, treatment with the tricyclic antidepressant imipramine at 1 mg/kg for just 1 week produced an 83% response rate, versus only 38% for control patients who received chloral hydrate to assist sleep.[43] It is unknown for how long successful treatment of ASD should be continued. If symptoms return, then it is advisable to continue treatment for a longer period.

Two studies, one randomized[44] and the other nonrandomized,[45] suggest that treatment with the β-blocker drug propranolol immediately after trauma might prevent some symptoms of PTSD, such as hyperarousal in response to traumatic memories, but may not prevent PTSD overall. Further larger-scale studies are required.

Benzodiazepines are useful in controlling anxiety and agitation and assisting sleep. They are not particularly effective in ASD, however, and may impair learning in a clinical situation and have withdrawal symptoms.[5] They are therefore not recommended for ASD or early PTSD. In 6-week and 6-month studies in trauma patients, more than twice as many patients receiving benzodiazepine still had PTSD compared with controls receiving no treatment or placebo, suggesting a harmful effect (although it is important to remember that assignment to treatment was not randomized in 1 trial, thus leaving open the possibility of important confounding differences between the groups).[46,47] Hypnotic antidepressants may be more useful in treating sleep disturbances in PTSD.[5]

Antipsychotic agents may be useful in the short term for acute agitation, but, in general, experience with these drugs is limited to use as an adjunct to SSRIs in chronic PTSD, mainly if patients exhibit psychotic-like symptoms, bipolar features, lack of impulse control, and aggression, or if there has been lack of response to other treatments.

CHALLENGES FOR PHARMACOLOGIC TREATMENT OF PTSD

Effective pharmacotherapy of PTSD may be complicated by a number of cultural and social factors. It cannot be assumed that treatments are universally accepted in all cultures, and one needs to consider different beliefs, concerns, and taboos surrounding illness and treatment in different settings, and the varying degree to which family members become involved, for example. Skepticism toward medication on the part of patients needs to be addressed by providing more education, increasing patient contact, and offering assistance with problems. Failure to do so may result in high rates of attrition or treatment nonadherence.

A shortage of trained professionals and a lack of resources can also pose challenges, particularly after a major disaster such as the 2004 Asian tsunami. Worldwide, much of the burden of diagnosis and prescription of psychotropic medications falls on the family doctor, and it is therefore necessary to optimize the management of PTSD in the primary care setting.

Ethnic differences in drug metabolism require attention to dosing issues and side effects when treating trauma. In some Asian populations, for example, higher plasma drug levels occur with tricyclic antidepressants, lithium, and haloperidol, leading to a greater incidence of side effects.[48]

There is currently a lack of studies assessing the efficacy and safety of pharmacotherapy in children with PTSD. SSRIs are effective in other anxiety disorders such as obsessive-compulsive disorder, social phobia, and generalized anxiety disorder in children, and although these findings may be reasonably extrapolated to PTSD for the purposes of routine clinical practice, PTSD-specific trials are needed. It is also unclear for how long children should receive medication. If the response is good after 9 months, discontinuation may be considered, although this should depend on the stability of the individual's life and circumstances.

ALGORITHM FOR PHARMACOTHERAPY OF PTSD

The International Psychopharmacology Algorithm Project (accessible at http://www.ipap.org) has completed the development of psychopharmacology algorithms for the management of PTSD. These algorithms, which are reflections of consensus opinions from experts throughout the world, are intended to provide helpful guidance for all professionals engaged in the treatment of PTSD, particularly with respect to clinical decision making during the various stages of the management of PTSD.

SUMMARY

SSRIs and SNRIs are recommended as first-line therapy for PTSD. They are effective across all symptom clusters, demonstrate no firmly established gender differences in efficacy, and appear to be useful in treating PTSD following all types of trauma. They are also effective in treating PTSD with comorbid disorders, such as depression and anxiety disorders. While further information is required on the role of SSRIs and SNRIs in the treatment of survivors of mass trauma and disaster, many people believe that effective pharmacotherapy of PTSD in survivors of the 2004 Asian tsunami can contribute in important ways toward both the recovery process for individuals and public health and economic recovery in the region.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), mirtazapine (Remeron), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), prazosin (Minipress and others), propranolol (Inderal and others), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, carbamazepine, divalproex sodium, fluoxetine, imipramine, lamotrigine, mirtazapine, nefazodone, olanzapine, prazosin, propranolol, risperidone, topiramate, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of posttraumatic stress disorder.

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