Antidepressant Treatment of Posttraumatic Stress Disorder

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Recent large double-blind, placebo-controlled trials have indicated that sertraline is an effective and well-tolerated treatment for posttraumatic stress disorder (PTSD). The avoidance/numbing symptom cluster improved the most significantly with sertraline, but significant improvements were also noted for the intrusive/reexperiencing and arousal symptom clusters. Smaller double-blind, placebo-controlled trials have also indicated that fluoxetine is an effective treatment for PTSD. Multiple small, open studies with other selective serotonin reuptake inhibitors and newer antidepressants indicate that these medications show some promise. Older studies indicate some efficacy for tricyclic antidepressants, and monoamine oxidase inhibitors are a reasonable choice, particularly for intrusive/reexperiencing symptoms.

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Given the prevalence and morbidity of posttraumatic stress disorder (PTSD) in the community, it is surprising that fewer than a dozen double-blind, placebo-controlled pharmacotherapy trials in PTSD have been published in the treatment literature. The pathophysiology of PTSD is considered to be multifactorial, and treatments have historically been targeted toward regulation of a possible pathophysiologic abnormality or toward relief of specific symptomatology. Recent evidence suggests that the serotonergic system[1,2] as well as the noradrenergic system may be dysregulated in PTSD, and the efficacy of antidepressants is likely to involve enhancement of one or both of these neurotransmitters. Results of several multicenter controlled antidepressant trials should be available in the near future. Advantages of the newer studies include large sample sizes, the use of PTSD rating scales as outcome measures, and the assessment of functioning and quality of life in some of the studies. Outcome measures commonly used in treatment studies have included clinician-rated scales such as the Clinical Global Impressions scale (CGI), the Clinician-Administered PTSD Scale (CAPS), and the Treatment Outcome PTSD Scale (TOP-8) and self-rating scales such as the Davidson Trauma Scale (DTS) and the Impact of Event Scale (IES).[3]

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TRICYCLIC ANTIDEPRESSANTS AND MONOAMINE OXIDASE INHIBITORS

The oldest medication studies have involved tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Several open studies of TCAs and MAOIs have suggested modest efficacy for these medications, and these studies have been reviewed.[4] Controlled studies have compared TCAs to placebo with mixed results. Desipramine (200 mg/day) was reported to be superior to placebo for improving depression but not IES scores in 18 veterans.[5] However, this trial was only 4 weeks in duration, and the TCA might have been effective after more time. Amitriptyline (mean dose = 169 mg/day) was superior to placebo in 26 veterans by IES, CGI, depression, and anxiety scores.[6] Phenelzine (mean dose = 66 mg/day) was not superior to placebo in 10 subjects at 4 weeks, but again, the short duration, small number of subjects, and lack of specific PTSD assessments may have obscured efficacy.[7] Imipramine (mean dose = 225 mg/day) and phenelzine (mean dose = 68 mg/day) were both compared with placebo in an 8-week trial in 60 veterans.[8,9] Both imipramine and phenelzine were superior to placebo, and phenelzine was superior to imipramine for decreasing intrusive PTSD symptoms on the IES. A quantitative review of the open and controlled trials of TCAs and MAOIs suggested that the global efficacy of phenelzine (82%) exceeded the global efficacy of TCAs (45%), owing in part to the specific MAOI benefit for intrusive symptoms.[4]

Reversible inhibitors of monoamine oxidase A (RIMAs), such as brofaromine and moclobemide, which are not available in the United States, have also been studied in PTSD. Brofaromine (150 mg/day) was not superior to placebo after 12 weeks on the CAPS, IES, or DTS in

113 subjects with PTSD.[10] This same dose of brofaromine was minimally more effective than placebo after 14 weeks in another study of 45 subjects, with more efficacy noted in subjects with PTSD of longer duration.[11] Both of these studies noted a 30% placebo response rate. An open trial of 12 weeks of moclobemide (600 mg/day) indicated improvement of PTSD symptoms in 20 subjects who were also taking other medications.[12]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Four open trials of fluoxetine with flexible dosing (20–80 mg/day) over at least 8 weeks have suggested that fluoxetine improves many of the symptoms of PTSD.[13–16] Two controlled trials[17,18] of fluoxetine have also indicated that this selective serotonin reuptake inhibitor (SSRI) is helpful for decreasing PTSD symptoms. Van der Kolk and colleagues[17] reported that fluoxetine up to 60 mg/day (mean dose = 40 mg/day) for 5 weeks was superior to placebo in decreasing CAPS scores, particularly the avoidance and arousal clusters, in 64 female and male subjects. Civilian subjects displayed a more robust response than did the veteran subjects in this study sample. Connor and colleagues[18] reported that fluoxetine up to 60 mg/day (median dose = 30 mg/day) was superior to placebo at 12 weeks as measured by the Duke Global Rating for PTSD, Structured Interview for PTSD, DTS, and disability scales in 53 subjects with civilian trauma. In this study, subjects with a more chronic course of PTSD showed a lower response rate with fluoxetine and a higher placebo response rate. A pilot study suggested that responders from this trial maintained their improvement better with fluoxetine than placebo after 6 months of double-blind treatment.[19]

Small open trials with sertraline have suggested improvement in PTSD symptoms in male veterans,[20] rape victims,[21] and subjects with comorbid alcoholism.[22] Two large multicenter studies have now been conducted comparing sertraline at a flexible dose up to 200 mg/day with placebo for 12 weeks. The first trial included 208 subjects,[23] and the second trial included 187 subjects.[24] Subjects in both trials had to (1) be 18 years of age or older, (2) have met the criteria for PTSD for at least 6 months, and (3) have a baseline CAPS-2 score of 50 or greater after 1 week of single-blind placebo. Subjects could not have a primary mood or anxiety disorder, have psychosis, be taking psychotropic medication, or be receiving behavioral therapy. In both studies, the sample was approximately 75% women and 80% white, with a mean age of 37 to 40 years and a mean duration of illness of 11 to 13 years. More than 60% of the 2 samples identified a physical or sexual assault as the primary trauma. The mean dose for completers from both studies at endpoint was approximately 150 mg/day.[25]

The primary efficacy measures in both studies were the total CAPS-2, IES, and CGI scores. Response was defined as improvement on the CAPS-2 of greater than or equal to 30% compared with baseline and a CGI-Improvement score of 1 or 2 at endpoint. Both studies demonstrated a significantly greater response rate with sertraline than placebo. Sertraline was superior to placebo in reducing the total CAPS-2 and DTS scores in both studies, and the IES scores in the first study. Sertraline was superior to placebo in improving CGI scores in both studies. Further analysis of the effect on the PTSD symptom clusters indicated that sertraline was most effective for improving symptoms in the avoidance/numbing cluster, with less robust yet significant efficacy for the arousal and reexperiencing/intrusion clusters. A pooled analysis indicated that sertraline was significantly more effective than placebo by week 2 of the trials, and the significance was sustained from week 6 onward.[25] The second trial indicated superiority of sertraline over placebo in improving several quality of life measures.[24]

Five open trials with fluvoxamine have been published[26–28] or presented at national meetings.[29,30] Each study involved relatively small samples, was at least 8 weeks in duration, and involved flexible dosing. The studies each suggested efficacy of fluvoxamine for several PTSD symptoms. A 12-week open trial of paroxetine (mean dose = 42.5 mg/day) in 17 subjects indicated improvement on several PTSD measures as well as depression, anxiety, and functioning scales.[31]

OTHER ANTIDEPRESSANTS

Six open studies with nefazodone that have been published[32–35] or presented at national meetings[36,37] have indicated that nefazodone shows promise in reducing PTSD symptoms. A pooled analysis of the 92 subjects in these 6 trials indicated that nefazodone was helpful for the 3 PTSD symptom clusters and that response was associated with younger age, being female, and surviving civilian rather than combat trauma.[38] Small open trials suggested that trazodone reduced CAPS and DTS scores[39] and clomipramine improved obsessive intrusion symptoms.[40] Venlafaxine, which has both serotonergic and noradrenergic actions, was reported to improve both PTSD and major depression symptoms in 1 subject who had not responded to a TCA or SSRIs.[41] Open trials of mirtazapine (30–40 mg/day) have reported improvement of CGI ratings as a single medication after 8 weeks[42] and as a single or adjunctive medication with SSRIs after 4 weeks.[43]

MOOD STABILIZERS

Mood stabilizers and antiepileptic medications have also been examined for the treatment of PTSD. A recent double-blind, placebo-controlled trial of lamotrigine (up

to 500 mg/day) in 15 subjects indicated superior efficacy over placebo for the intrusion and avoidance/numbing symptom clusters.[44] Older small open trials and case reports with lithium, carbamazepine, and valproate have been reviewed, and they have suggested efficacy for some symptoms of PTSD.[45,46] Three recent open trials have also suggested efficacy with valproate for one or more of the symptom clusters.[47–49] Vigabatrin has been reported to decrease the startle response and improve sleep,[50] and topiramate has been reported to decrease nightmares and flashbacks.[51] Mood stabilizers may be particularly effective as single or adjunctive medications for the anger and explosive behavior common in PTSD.[52]

CONCLUSION

Two large double-blind, placebo-controlled trials involving approximately 400 subjects[23,24] have suggested that sertraline is an effective treatment for the 3 symptom clusters of PTSD, particularly the avoidance/numbing cluster. Two smaller double-blind, placebo-controlled trials,[17,18] each involving approximately 60 subjects, also have suggested that fluoxetine is effective in treating PTSD. The mean SSRI dose at endpoint in each of these 4 controlled studies was similar to doses used to treat major depression. Several small, open studies indicate possible efficacy for paroxetine, fluvoxamine, nefazodone, trazodone, and mirtazapine, and these medications deserve further study. Older studies indicate some efficacy for TCAs and MAOIs, and MAOIs may be particularly useful for the intrusive PTSD symptoms. Mood stabilizers also deserve further study. Although future treatments of PTSD should target the several possible etiologic factors in PTSD,[53,54] the SSRIs and other antidepressants are a promising first-line treatment.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), lamotrigine (Lamictal), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of her knowledge, the following agents are not approved by the U.S. Food and Drug Administration for the treatment of PTSD: amitriptyline, brofaromine, carbamazepine, clomipramine, desipramine, fluoxetine, fluvoxamine, imipramine, lamotrigine, lithium, mirtazapine, moclobemide, nefazodone, paroxetine, phenelzine, topiramate, trazodone, valproate, venlafaxine, vigabatrin. Brofaromine and moclobemide are not approved for use in the United States.

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