show irritability with outbursts of anger and may exhibit hypervigilance and an exaggerated startle response.

PTSD can be either acute or chronic. In those with acute PTSD, symptoms last for at least 1 month but less than 3 months after the traumatic event. In chronic PTSD, symptoms last for more than 3 months after exposure to trauma. The only FDA-approved drugs for the treatment of PTSD are the selective serotonin reuptake inhibitors (SSRIs) sertraline (Zoloft, Pfizer) and paroxetine HCl (Paxil, GlaxoSmithKline). All other agents are used off-label, including paroxetine mesylate (Pexeva, Noven), which is chemically similar to paroxetine but is not FDA-approved for PTSD. SSRIs affect the neurotransmitter serotonin primarily, which is important in regulating mood, anxiety, appetite, sleep, and other bodily functions.

Although SSRIs are associated with an overall response rate of approximately 60% in patients with PTSD, only 20% to 30% of patients achieve complete remission. In two clinical studies of PTSD, sertraline was significantly more effective than placebo, according to several efficacy measures, including the Clinician-Administered PTSD Scale, Part 2 (CAPS-2). In two additional studies, however, the difference in response to treatment between patients receiving sertraline and patients receiving placebo was not statistically significant.

### Introduction

The U.S. Department of Veterans Affairs defines post-traumatic stress disorder (PTSD) as “the development of characteristic and persistent symptoms along with difficulty functioning after exposure to a life-threatening experience or to an event that either involves a threat to life or serious injury.” Patients with PTSD usually present for primary care with unexplained somatic and/or psychological symptoms, including sleep disturbances, night sweats, fatigue, and difficulty with memory or concentration (Table 1). PTSD consists of three main symptom “clusters.”

1. **Re-experiencing.** The traumatic event is persistently re-experienced through recurrent and intrusive recollections of the trauma and through recurrent distressing dreams of the event. The patient may also act or feel as though the traumatic event were recurring and may experience intense psychological distress when exposed to reminders of the trauma.

2. **Avoidance.** The patient persistently attempts to avoid stimuli associated with the traumatic event. This can include avoiding thoughts, feelings, or conversations related to the trauma and avoiding people, activities, and places that arouse memories of the trauma.

3. **Increased arousal.** Patients may have difficulty falling or staying asleep and difficulty concentrating. They may also show irritability with outbursts of anger and may exhibit hypervigilance and an exaggerated startle response.

### Table 1  Common Signs and Symptoms After Exposure to a Traumatic Event

<table>
<thead>
<tr>
<th>Physical</th>
<th>Cognitive/Mental</th>
<th>Emotional</th>
<th>Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>Blaming others</td>
<td>Agitation</td>
<td>Increased alcohol consumption</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>Change in alertness</td>
<td>Anxiety</td>
<td>Antisocial acts</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Confusion</td>
<td>Apprehension</td>
<td>Change in activity</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Hypervigilance</td>
<td>Denial</td>
<td>Change in communication</td>
</tr>
<tr>
<td>Fainting</td>
<td>Increased or decreased awareness of surroundings</td>
<td>Depression</td>
<td>Change in sexual functioning</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Intrusive images</td>
<td>Emotional shock</td>
<td>Change in speech pattern</td>
</tr>
<tr>
<td>Grinding teeth</td>
<td>Memory problems</td>
<td>Fear</td>
<td>Emotional outbursts</td>
</tr>
<tr>
<td>Headaches</td>
<td>Nightmares</td>
<td>Feeling overwhelmed</td>
<td>Inability to rest</td>
</tr>
<tr>
<td>Muscle tremors</td>
<td>Poor abstract thinking</td>
<td>Grief</td>
<td>Change in appetite</td>
</tr>
<tr>
<td>Nausea</td>
<td>Poor attention</td>
<td>Guilt</td>
<td>Pacing</td>
</tr>
<tr>
<td>Pain</td>
<td>Poor concentration</td>
<td>Inappropriate emotional response</td>
<td>Startle reflex intensified</td>
</tr>
<tr>
<td>Profuse sweating</td>
<td>Poor decision making</td>
<td>Irritability</td>
<td>Suspiciousness</td>
</tr>
<tr>
<td>Rapid heart rate</td>
<td>Poor problem solving</td>
<td>Loss of emotional control</td>
<td>Social withdrawal</td>
</tr>
</tbody>
</table>

Modified from the Department of Veterans Affairs and the Department of Defense.

### Disclosure:
The author reports no commercial or financial relationships in regard to this article.

Mr. Alexander, a freelance medical writer, covers Meeting Highlights. He lives in New York City.
Post-traumatic Stress Disorder in Combat Veterans

Moreover, few published trials have demonstrated the superiority of paroxetine over placebo in managing the three symptom clusters of PTSD. A comparison of paroxetine with placebo in patients with PTSD demonstrated that sertraline was significantly superior to placebo for the change from baseline in the CAPS-2 total score but not for the proportion of responders on the Clinical Global Impression–Improvement (CGI–I) scale.

The SSRI fluoxetine (Prozac, Eli Lilly) was evaluated in a placebo-controlled study of combat veterans with severe, chronic PTSD. Veterans treated with fluoxetine failed to show a greater clinical response compared with placebo-treated veterans, even though fluoxetine was effective in patients with less severe PTSD in previous studies. Fluoxetine has been on the market since 1987 and is indicated for the treatment of major depressive disorder, obsessive compulsive disorder, bulimia nervosa, and panic disorder.

In a study of extended-release (ER) venlafaxine (Effexor XR, Pfizer), a serotonin–norepinephrine reuptake inhibitor (SNRI), the response rate was 78% and the remission rate was 40% (both assessed with an abbreviated version of CAPS) in patients with PTSD. Hyperarousal, however, did not show significant improvement. The extended-release formulation of venlafaxine is approved for patients with major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder.

The variable efficacy results reported with SSRIs and SNRIs in patients with PTSD led investigators to a search for alternative therapies. Second-generation (atypical) antipsychotic drugs have been used to treat PTSD based on limited data and theoretical mechanisms of action involving the serotonergic and dopaminergic systems, alpha-adrenergic receptors, and antihistaminic effects.

This article reviews the use of SSRIs, SNRIs, and atypical antipsychotic agents in patients with combat-related PTSD.

Combat-Related Post-traumatic Stress Disorder

In a recent article, Dr. Charles W. Hoge described the conundrum of PTSD in war veterans.

The paradox of war-related PTSD is that reactions labeled ‘symptoms’ upon return home can be highly adaptive in combat, fostered through rigorous training and experience. For example, hyperarousal, hypervigilance, and the ability to channel anger, shut down (numb) other emotions even in the face of casualties, replay or rehearse responses to dangerous scenarios, and function on limited sleep are adaptive in war.

Among veterans with PTSD, as diagnosed by the Department of Veterans Affairs, 89% are treated with SSRIs. Reductions in PTSD scores in clinical trials of SSRIs have been similar to those observed in studies of psychotherapy for PTSD. Regardless of the treatment modality used, a high percentage of veterans who begin PTSD treatment eventually drop out. It has been estimated that no more than 20% of veterans with PTSD are effectively treated, possibly because SSRIs are more effective in women than in men and because they are more effective in acute PTSD than in chronic disease.

In an assessment of mental health problems among soldiers returning from the Iraq War, Milliken et al. screened the veterans immediately after deployment and again a few months later. Upon rescreening, a large cohort of soldiers with PTSD who were missed on the initial screening were identified; it was also noted that most soldiers with significant PTSD symptoms at the initial screening subsequently improved without treatment. Of the 88,235 soldiers involved in the assessment, 14,213 (16%) were referred for mental health care. The authors noted that combat-related PTSD might represent a more refractory form of PTSD than that resulting from other types of traumatic events, perhaps because of later-emerging comorbidities.

Clinical Practice Guidelines

In 2010, the Department of Veterans Affairs and the Department of Defense (VA/DoD) updated their clinical practice guidelines for the management of post-traumatic stress. These guidelines were originally issued in 2004 in an effort to bring evidence-based practice to clinicians who were treating trauma survivors and patients with stress disorders in the VA/DoD. In these guidelines, the term post-traumatic stress covers a spectrum of disorders, including acute stress reaction, acute stress disorder, and acute and chronic PTSD.

Although PTSD can occur alone, it usually accompanies other conditions, including persistent difficulties in interpersonal relations, mood disturbances, chronic pain, sleep disturbances, and psychiatric disorders. The guidelines’ Working Group recognized the importance of comorbidities in patients with PTSD and pointed out that few clinical trials have provided guidance on how to manage PTSD accompanied by comorbid conditions, such as substance abuse.

The guidelines state that veterans who have sustained a concussion or mild traumatic brain injury in combat are at significantly greater risk for developing PTSD, which may be associated with neurocognitive impairment and other post-concussion symptoms. Not surprisingly, the frequency and intensity of combat are the strongest predictors for the development of PTSD.

The guidelines’ Working Group noted that all current therapies of post-traumatic stress have limitations and urge the “creative integration of combined treatments that are driven by sound evidence-based principles.” Interestingly, of the more than 100 pages that address the treatment of post-traumatic stress, fewer than 20 pages discuss pharmacotherapies.

According to the VA/DoD guidelines, there is growing evidence that PTSD is characterized by specific “psychobiologic dysfunctions,” and this has contributed to an increased interest in the use of medications to treat trauma-related biologic effects. Importantly, only SSRIs and SNRIs have provided significant benefit in PTSD, according to the guidelines. The guidelines give the use of SSRIs and SNRIs in patients with PTSD an “A” recommendation, defined as follows: “A strong recommendation that clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.”

The same level of evidence supports the guidelines’ recommendation for monotherapy with the SSRIs sertraline, paroxetine, and fluoxetine, and with the SNRI venlafaxine in patients.
with PTSD. As noted previously, only sertraline and paroxetine HCI have received FDA approval for the treatment of PTSD.

In 2004, the American Psychiatric Association (APA) published practice guidelines for patients with acute stress disorder and PTSD. These guidelines identify SSRIs (sertraline, paroxetine, and off-label fluoxetine) as the medications of choice for patients with PTSD, for several reasons:

- They ameliorate all three PTSD symptom clusters (i.e., re-experiencing, avoidance, and hyperarousal).
- They are effective for psychiatric disorders that frequently occur with PTSD (e.g., depression, panic disorder, social phobia, and obsessive–compulsive disorder).
- They may reduce clinical symptoms (such as suicidal, impulsive, and aggressive behaviors) that often complicate the management of PTSD.
- They are associated with relatively few side effects.

The APA guidelines note that because no psychotropic medications have been developed specifically for use in PTSD, drugs have been used in doses similar to those recommended or approved for other psychiatric illnesses, both in clinical practice and in pharmacotherapy research.

Although the APA guidelines have not been formally updated, a “Guideline Watch,” published in March 2009, provided additional information that became available after the guidelines were first published. The authors reported that newer studies in patients with non–combat-related PTSD augment the evidence base for SSRI efficacy previously established in patients (predominantly women) with PTSD resulting from civilian trauma, including childhood and adult sexual assault, other interpersonal traumas, and motor vehicle accidents. Studies in combat veterans with PTSD, however, have reported variable responses to SSRI therapy. These findings suggest that SSRIs might not be as useful in veterans with combat-related PTSD as they are in civilian patients with PTSD.

**Selective Serotonin Reuptake Inhibitors**

**Sertraline (Zoloft)**

In early studies, sertraline demonstrated clinical efficacy in patients with PTSD and comorbid alcohol dependence, in rape victims with PTSD, and in patients with obsessive–compulsive disorder. Based on these findings, Brady and colleagues conducted a randomized, double-blind study of sertraline in patients with chronic PTSD with a minimum duration of symptoms of 6 months. A total of 187 patients were randomly assigned to receive 12 weeks of treatment with sertraline (20 to 50 mg/day) or matched placebo. CAPS-2 and CGI–I scores were used to assess efficacy. Therapy with sertraline resulted in numeric, but not statistically significant, improvements in CAPS-2 total severity and symptom-cluster scores versus placebo. CGI–I responder rates were 53% for sertraline and 20% for placebo (P = 0.057). Thirteen percent of the sertraline group discontinued treatment because of adverse events.

**Paroxetine (Paxil)**

Paroxetine, the other SSRI approved for the treatment of PTSD, was evaluated in 551 patients with chronic PTSD. The patients were randomly assigned to receive 12 weeks of treatment with paroxetine (20 mg/day), paroxetine (40 mg/day), or placebo. CAPS-2 and CGI–I scores were used to assess efficacy. Both dosages of paroxetine achieved significant improvements in the primary outcome measures compared with placebo. The mean changes from baseline in CAPS-2 were –39.6 and –37.9 for paroxetine (20 mg/day and 40 mg/day, respectively), compared with a mean change of –25.3 for placebo (P = 0.001). In addition, all three symptom clusters of PTSD were significantly improved with paroxetine compared with placebo (P = 0.0001). Significantly more paroxetine-treated patients at both doses were rated as responders compared with the placebo-treated group (65% and 55% vs. 35%, respectively; P < 0.001).

Paroxetine was well tolerated. The most commonly reported adverse events associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence.

Tucker et al. compared flexible dosages of paroxetine (20 to 50 mg/day) with placebo in 307 outpatients with PTSD.
After 12 weeks of treatment, the paroxetine group showed significantly greater improvements in PTSD symptoms, compared with the placebo group, on all primary and secondary outcome measures. In addition, more patients who were treated with paroxetine achieved a response (60% vs. 40%, respectively; \( P < 0.05 \)) and remission (30% vs. 20%, respectively; \( P = 0.008 \)).

Fluoxetine (Prozac)

Although fluoxetine is recommended as a first-line (off-label) therapy in PTSD, efficacy results from clinical trials have been variable. For example, Connor et al. reported a superior response with fluoxetine in civilian patients with PTSD, and Meltzer-Brody et al. observed that fluoxetine reduced all symptom clusters of the disorder in civilians. Martenyi et al., however, found that fluoxetine did not differ significantly from placebo in civilian patients with PTSD. Similarly, Hertzberg et al. reported that fluoxetine lacked efficacy, compared with placebo, in combat veterans with PTSD, whereas Martenyi et al. noted that fluoxetine was significantly superior to placebo in veterans.

Serotonin–Norepinephrine Reuptake Inhibitors

Venlafaxine

Like fluoxetine, the SNRI venlafaxine is not approved for the treatment of PTSD, but it is often used off label as first-line monotherapy in these patients. Venlafaxine acts primarily as a serotonin reuptake inhibitor (SRI) at lower dosages and as a combined serotonin–norepinephrine reuptake inhibitor (SNRI) at higher dosages. Extended-release (ER) venlafaxine was shown to be effective in two trials involving more than 800 patients with non–combat-related PTSD. In a long-term double-blind study, 329 adult outpatients with PTSD were randomly assigned to receive venlafaxine ER (37.5–100 mg/day) or placebo for 6 months. Venlafaxine ER provided a significant change in CAPS total scores when compared with placebo (51.7 vs. 43.9, respectively; \( P = 0.006 \)). Remission rates were 50.9% for venlafaxine ER and 37.5% for placebo (\( P = 0.01 \)). Venlafaxine ER also significantly improved cluster scores for re-experiencing (\( P = 0.008 \)) and for avoidance (\( P = 0.006 \)) but not for hyperarousal. The authors theorized that drugs with noradrenergic-enhancing effects might promote arousal.

In another double-blind study, venlafaxine ER performed as well as sertraline in adult outpatients with PTSD. A total of 538 patients were randomly assigned to receive venlafaxine ER (37.5–100 mg/day), sertraline (25–200 mg/day), or placebo for 12 weeks. Mean changes in CAPS symptom-cluster scores were –41.8, –39.4, and –33.9 for venlafaxine ER, sertraline, and placebo, respectively.

The difference between venlafaxine ER and placebo was statistically significant (\( P < 0.05 \)). Both active treatments provided significant improvements in avoidance compared with placebo, but only venlafaxine ER differed significantly from placebo in improving hyperarousal. The two active treatments were no better than placebo in improving re-experiencing. Remission rates were 30.2% for venlafaxine ER (\( P < 0.05 \) vs. placebo), 24.3% for sertraline, and 19.6% for placebo.

Atypical Antipsychotic Agents

Although second-generation (atypical) antipsychotic agents were originally developed to treat psychotic disorders, they are also used in patients with other psychiatric disorders, including PTSD. These drugs act primarily on the dopaminergic and serotonergic systems. Clinical studies have indicated that they are useful in ameliorating psychotic symptoms in patients with PTSD.

A review of the use of off-label antipsychotic medications in the VA health care system found that 60.2% of patients who received an antipsychotic drug had no record of a diagnosis for which these drugs are approved. Prescriptions for off-label antipsychotic agents were most often written for PTSD (41.8% of patients). Quetiapine (Seroquel, AstraZeneca) had the greatest off-label use (42.9%), followed by risperidone (Risperdal, Janssen) (21.2%). Recently few patients received off-label olanzapine (Zyprexa, Eli Lilly) (7.5%).

Quetiapine (Seroquel)

Quetiapine, a dibenzothiazepine derivative, is indicated for the treatment of schizophrenia and bipolar disorder. Its precise mechanism of action is unknown. However, the drug’s clinical activity is believed to be mediated through a combination of dopamine type-2 (D2) and serotonin type-2 (5-HT2) antagonism. Quetiapine monotherapy was evaluated in an open-label study of veterans with combat-related PTSD with psychotic features. A total of 53 veterans were treated with quetiapine (25–400 mg/day) for 8 weeks. A reduction in total and subscale scores on CAPS was a primary outcome measure, and CGI–S scores were used to assess global clinical improvement. Quetiapine reduced the majority of the psychotic and PTSD symptoms in these patients, as indicated by significant reductions in CAPS scores and CGI–S ratings.

In another open-label study, Alhearn et al. added quetiapine to sertraline in 15 patients with severe PTSD; 10 patients had combat-related PTSD, and the remaining five patients had non–combat-related PTSD. The patients received quetiapine (mean dosage, 216 mg/day) for 8 weeks. The addition of quetiapine to SSRI therapy resulted in a 42% overall improvement in PTSD symptoms, based on CAPS scores, and significant improvements in re-experiencing (\( P = 0.0012 \)), avoidance (\( P = 0.03 \)), and hyperarousal (\( P = 0.001 \)).

In a prospective study, Sokolski et al. reviewed medical charts to evaluate the effects of adjunctive quetiapine therapy in 68 Vietnam War veterans with treatment-resistant, combat-induced PTSD. The investigators found that the addition of quetiapine to ongoing therapy had resulted in further symptomatic improvements in re-experiencing, avoidance, and hyperarousal in 35%, 28%, and 65% of the veterans, respectively. Low doses of quetiapine (mean dose, 155 mg) were associated with minimal adverse effects.

Hamner et al. enrolled 18 veterans with combat-related PTSD who had shown an inadequate response to other medications in an open-label study of adjunctive quetiapine. Treatment at 25 to 300 mg/day for 6 weeks resulted in a significant improvement in CAPS scores, from 89.8 to 67.5 (\( P < 0.005 \)). General psychopathology and depressive symptoms were also reduced.
Post-traumatic Stress Disorder in Combat Veterans

Risperidone (Risperdal)

Risperidone, a benzisoxazole derivative, is used primarily to treat schizophrenia. Its precise mechanism of action is unknown. However, its therapeutic activity in schizophrenia is believed to be mediated through a combination of D₂ and 5-HT₂ antagonism. A prospective, randomized, double-blind, placebo-controlled study was conducted to investigate the potential efficacy of risperidone in treating the psychotic symptoms of chronic PTSD in 40 combat veterans. Thirty-seven veterans completed at least 1 week of treatment with risperidone or placebo during the 5-week follow-up period. The investigators assessed symptoms according to CAPS and the Positive and Negative Syndrome Scale (PANSS) scores.

Veterans receiving risperidone showed a significantly greater decrease in psychotic symptoms, as indicated by PANSS scores, compared with placebo-treated veterans (P < 0.05). Both groups experienced declines in CAPS scores, but these differences were not statistically significant. The risperidone-treated veterans, however, had significantly greater improvements in re-experiencing at week 5 compared with the placebo-treated group (P < 0.05).

In a recent VA study, risperidone was no more effective than placebo in 296 veterans with treatment-resistant, combat-related PTSD. The CAPS score was the primary outcome measure. Changes in CAPS score from baseline to 6 months were −16.3 in the risperidone group compared with −12.5 in the placebo group (P = 0.11). Moreover, risperidone did not reduce symptoms of depression or anxiety compared with placebo.

Adverse events were more common with risperidone, including weight gain, fatigue, somnolence, and hypersalivation.

Olanzapine (Zyprexa)

Olanzapine, a member of the thienobenzodiazepine class, is approved for the treatment of schizophrenia and bipolar I disorder. With other drugs used to treat schizophrenia, its precise mechanism of action is unknown. However, as with risperidone, its efficacy in schizophrenia is believed to be mediated through the combination of dopamine and serotonin antagonism.

In a double-blind, placebo-controlled pilot study, olanzapine was no more effective than placebo in patients with PTSD. Fifteen patients received olanzapine (5–20 mg/day) or placebo for 10 weeks. Both treatment groups showed improvement in PTSD symptoms, but there were no between-group differences in treatment response.

In an open-label study, Petty et al. administered olanzapine for 8 weeks to 48 veterans with combat-induced PTSD. Thirty veterans completed the study. All primary and secondary outcomes measures, including CAPS and CGI-I scores, improved significantly during treatment, indicating that olanzapine was useful for treating the symptoms of combat-related PTSD.

In another open-label trial, olanzapine was compared with fluphenazine (Prolixin, Apothecon), a first-generation antipsychotic drug, in combat veterans with PTSD. Fifteen patients were initially assessed the results of 8 weeks of treatment with olanzapine and placebo, and the CAPS score served as the primary efficacy measure. Mark Hamner, MD, Professor of Psychiatry at the Medical University of South Carolina, Charleston, was the principal investigator.

In another open-label trial, olanzapine was compared with fluphenazine in a range of 5 to 10 mg/day, once or twice daily, for 6 weeks. Olanzapine was more effective than fluphenazine in reducing most psychotic and PTSD symptoms and was better tolerated. Prolonging treatment for an additional 3 weeks did not affect the efficacy of either drug.

Other studies have looked at olanzapine as adjunctive therapy for combat veterans with PTSD. In one report, olanzapine alleviated nightmares and insomnia when it was added to current therapies in veterans with treatment-resistant, combat-induced PTSD. In another study, olanzapine provided significant reductions in measures of post-traumatic stress, depression, and sleep disorder versus placebo in patients with SSRI-resistant, combat-related PTSD.

Adjunctive olanzapine has also improved chronic sleep disruption and the re-experiencing cluster of symptoms in civilian patients with PTSD presenting for primary care.

Veterans Affairs and Defense Department Guidelines Updated

The VA/DoD clinical practice guidelines originally recommended off-label risperidone, olanzapine, or quetiapine for the adjunctive treatment of patients with PTSD. However, in view of the disappointing results from the recent VA-sanctioned study of risperidone in PTSD, the guidelines have been revised to recommend against the use of risperidone as adjunctive therapy.

The revised guidelines further state that “there is insufficient evidence to recommend for or against the use of any other atypical antipsychotic as an adjunctive therapy for the treatment of PTSD.”

Table 2 depicts the VA/DoD’s current assessment of the drugs used to treat PTSD (see page 37).

Despite the lack of a clear benefit with risperidone in the VA-supported study and the lack of sufficient evidence supporting the use of any other atypical antipsychotic drug in PTSD, it is too soon to close the door on these agents in patients with PTSD. Some studies have suggested differential effects between atypical antipsychotic medications, and head-to-head comparative trials have not been conducted. Further, the unmet clinical need in PTSD, based on the partial remission rates with other classes of agents, remains substantial.

Ongoing Studies of Atypical Antipsychotic Agents

Additional information on the use of atypical antipsychotic drugs in patients with PTSD is forthcoming. Two studies with quetiapine have been completed, and manuscripts are in preparation.

The first investigation evaluated adjunctive treatment with quetiapine in 80 patients (mostly combat veterans) with treatment-resistant, chronic PTSD. The patients received 12 weeks of therapy with quetiapine or placebo, and the CAPS score served as the primary efficacy measure. Mark Hamner, MD, Professor of Psychiatry at the Medical University of South Carolina, Charleston, was the principal investigator.

The second study, in which Dr. Hamner also participated, initially assessed the results of 8 weeks of treatment with paroxetine in combat veterans with PTSD. A total of 102 non-responders were then assigned to receive 8 weeks of additional therapy with quetiapine. The CAPS score again served as the primary endpoint.
Table 2  Assessment of Pharmacotherapeutic Interventions for Post-traumatic Stress Disorder in War Veterans

<table>
<thead>
<tr>
<th>Significant Benefit</th>
<th>Some Benefit</th>
<th>Unknown Benefit</th>
<th>No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SSRIs</td>
<td>• MAO inhibitors (phenelzine) [caution*]</td>
<td>• Atypical antipsychotics (monotherapy)</td>
<td>• Benzodiazepines [harmful]</td>
</tr>
<tr>
<td>• SNRIs</td>
<td>• Mirtazapine</td>
<td>• Atypical antipsychotics (adjunctive)</td>
<td>• Guanfacine</td>
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<tr>
<td></td>
<td>• Nefazodone [caution*]</td>
<td>• Bupropion</td>
<td>• Risperidone</td>
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<tr>
<td></td>
<td>• Prazosin (for sleep/nightmares)</td>
<td>• Buspirone</td>
<td>• Tiagabine</td>
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<td>• TCAs</td>
<td>• Clonidine</td>
<td>• Topiramate</td>
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<tr>
<td></td>
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<td>• Conventional antipsychotics</td>
<td>• Valproate</td>
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<td>• Gabapentin</td>
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<td>• Lamotrigine</td>
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<td>• Non-benzodiazepine hypnotics</td>
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<td></td>
<td></td>
<td>• Prazosin (for global PTSD)</td>
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<td>• Propranolol</td>
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<tr>
<td></td>
<td></td>
<td>• Trazodone (adjunctive)</td>
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</tr>
</tbody>
</table>

*Attention to drug-drug and dietary interactions.

MAO = monoamine oxidase; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Adapted from the Department of Veterans Affairs and the Department of Defense.52

Conclusion

PTSD is a severe and chronic anxiety disorder, with impairment in daily functioning, frequent suicidal behavior, and high rates of comorbidity. SSRIs are considered first-line therapy for PTSD, in view of treatment guideline recommendations and the results of numerous clinical trials. Sertraline and paroxetine are the only antidepressants approved by the FDA for the treatment of PTSD and are the most extensively studied SSRIs for this indication. All other agents are used in an off-label fashion. In addition to sertraline and paroxetine, the SSRI fluoxetine has been recommended as first-line treatment (off label) for patients with PTSD.

If SSRIs are not tolerated or are ineffective, SNRIs should be considered as a second-line treatment. The SNRI venlafaxine has been shown to be beneficial in the treatment of PTSD.

Although atypical antipsychotics are not FDA-approved for the treatment of PTSD, they may have a role in severe cases of the disorder or when psychotic symptoms are prominent.

References

Post-traumatic Stress Disorder in Combat Veterans


55. Hamner MB. Personal communication; October 7, 2011.