

Long-Term Treatment and Prevention of Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is a disabling condition almost universally associated with psychiatric comorbidity, reduced quality of life, and a chronic, often lifelong, course. Although acute treatment with selective serotonin reuptake inhibitors (SSRIs) has been shown to be effective, successful strategies for preventing PTSD have not been established. In addition, studies of the long-term treatment of chronic PTSD are just beginning to emerge. This review considers available evidence for the secondary prevention of PTSD in the acute aftermath of trauma and the long-term treatment of established PTSD. Unanswered questions pertaining to duration of treatment, candidates for long-term treatment, and potentially harmful treatments will also be considered.

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Posttraumatic stress disorder (PTSD), which has long been known to be a negative consequence of war-time exposure, is becoming increasingly recognized as a psychiatric illness of significance in civilian populations around the world. This is particularly relevant for countries in which civilians of the general community are exposed to ongoing violence and unrest. Not surprisingly, the worldwide prevalence of PTSD in civilian populations varies widely, from 37.4% in Algeria to 1.3% in Germany.^{1–3} As predicted by the World Health Organization's Global Burden of Disease study,⁴ exposure to traumatic events, such as motor vehicle accidents, war, and violence, will be the 3rd, 8th, and 12th leading causes of disability worldwide by the year 2020, which suggests that rates of PTSD will continue to increase.

PTSD is a chronic, disabling, and generally life-long condition. Individuals with PTSD often suffer severe sleep disturbances, interpersonal isolation, and turbulent lives. The National Comorbidity Survey found that persons with

untreated PTSD had symptoms for a mean duration of 5 years.² Unfortunately, PTSD rarely exists as a pure disorder, and psychiatric comorbidities, such as depression, alcohol abuse, substance abuse, other anxiety disorders, and suicidality, add to the burden of this disorder. The net effect of PTSD and its associated comorbidities is significantly impaired quality of life, missed educational and occupational opportunities, and excessive hospitalization and use of health care resources. The social and economic burden of PTSD is heavy for patients, their friends and families, and society as a whole.^{5–7} Early diagnosis and prevention of PTSD and effective treatment of established PTSD appear to be key in breaking this vicious cycle.

During the past decade, the efficacy of acute treatment of PTSD with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and cognitive behavioral therapy (CBT) has been well established.^{8–17} Only recently have studies been undertaken to assess prevention and long-term treatment. The purpose of this review is to discuss the issues of and research findings in studies of treatment duration, relapse prevention, and early intervention of PTSD.

PREVENTION OF ACUTE STRESS DISORDER/PTSD

A seminal question in the field of PTSD involves secondary prevention. Can early intervention prevent the development of acute stress symptoms and the later-onset symptoms of established PTSD? Related issues include which interventions are most likely to work and which persons are best candidates for early intervention. There are relatively few studies of the secondary prevention of PTSD, particularly with regard to pharmacotherapy. The database for psychosocial intervention in acute trauma is substantially larger.

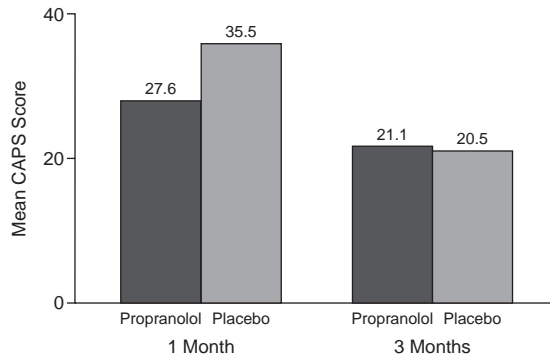
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Figure 1. Efficacy of Propranolol Treatment Within 6 Hours of Trauma Exposure in the Secondary Prevention of Acute Stress Disorder^{a,b}



^aReproduced with permission from Pitman et al.¹⁸

^bPropranolol, 160 mg per day for 10 days followed by a 9-day taper. Abbreviation: CAPS = Clinician-Administered PTSD (posttraumatic stress disorder) Scale.

Pharmacotherapy

Evidence supporting a role of pharmacotherapy in the secondary prevention of PTSD is scant and includes studies of a β -blocker,¹⁸ a corticosteroid,¹⁹ imipramine,²⁰ and high-potency benzodiazepines.^{21,22}

In a pilot study of 41 motor vehicle accident victims, patients were randomized to receive a 10-day course of propranolol, 160 mg/day or placebo within 6 hours of the accident.¹⁸ After 1 month, mean Clinician-Administered PTSD Scale (CAPS) scores were 27.6 for the propranolol group compared with 35.5 for the placebo group (Figure 1), but these differences did not achieve statistical significance. Although between-group differences in the CAPS scores were less apparent at 3 months, physiologic responses (e.g., heart rate, skin conductance) were significantly greater among placebo-treated patients during script-driven imagery ($p = .04$) at 3 months. In keeping with the expectations from a pilot study, these findings are inconclusive, but do suggest that acute treatment with a β -blocker may prevent or ameliorate the conditioned physiologic responses associated with PTSD.

Mortality rates in septic shock are high, and survivors often develop PTSD. Schelling and associates¹⁹ studied whether high doses of hydrocortisone administered during the course of septic shock reduced the rate of PTSD upon recovery and discharge from the hospital. The primary phase of this study was a prospective, placebo-controlled, randomized trial of the hemodynamic effects of high doses of hydrocortisone administered while in the intensive care unit.²³ Twenty patients who survived their illness were enrolled in the postseptic shock study 31 months after discharge from the intensive care unit.¹⁹ Patients underwent diagnostic assessment for PTSD, and traumatic memories of their hospital stay were recorded. Despite

no differences in traumatic memories between treatment groups, the rates of PTSD among patients who received hydrocortisone (11%; 1 of 9 patients) were significantly lower than in the placebo group (64%; 7 of 11 patients; $p = .02$). Given the limitations of this retrospective design, the finding of lower rates of PTSD in patients whose steroid levels were therapeutically manipulated during the period of trauma warrant further study.

A small pilot study of 25 children and adolescents aged 2 to 19 years with burn injury (mean 45% burn surface area) were randomized to a 7-day course of double-blind imipramine, 1 mg/kg or chloral hydrate. Severity of acute stress disorder was measured at baseline and again at 6-week follow-up using a structured interview. Rates of improvement in symptoms of acute stress were higher in the imipramine group (83%) than in the chloral hydrate group (38%; $p < .02$), suggesting a possible role for antidepressants in the prophylaxis of PTSD in pediatric patients with burn injury.²⁰ Future studies would ideally assess the optimal antidepressant dose and consider drug-drug interactions and pharmacokinetic alterations associated with thermal injury.

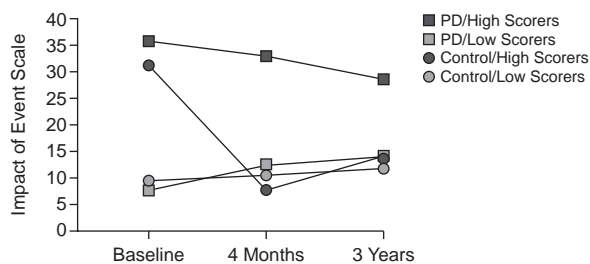
Although benzodiazepines have not been shown to effectively treat established PTSD,²⁴ they might have value in the prevention of PTSD in patients with symptoms of acute stress. In one study, a 1-month course of clonazepam or alprazolam was administered within 1 week of trauma exposure to 13 trauma victims. A group of 13 matched, but untreated, trauma victims comprised the control group. At 6-month follow-up, 69% of patients in the benzodiazepine group versus 15% of control subjects fulfilled criteria for a diagnosis of PTSD. It is noteworthy that 7 of the 13 patients treated with benzodiazepines, but none of the control subjects, had major depression at 6-month follow-up.²¹ Similar findings were observed by Mellman and associates²² in their study of 21 trauma victims who received either temazepam or placebo. At 6-week follow-up, rates of PTSD were 55% in the benzodiazepine group and 27% in the placebo group.²²

Psychotherapeutic Interventions

The use of single-session psychological debriefing and brief cognitive behavioral therapy has been studied in the treatment of acute stress disorder and prevention of PTSD.

Single-session psychological debriefing is an intervention that has been employed in both military and civilian populations in the immediate aftermath of exposure to a traumatic event. The goal of psychological debriefing is to manage distress in the acute posttrauma period and prevent the development of PTSD. The role of psychological debriefing is controversial, and the findings of some,²⁵⁻²⁷ but not all^{28,29} randomized, controlled trials question the efficacy of this intervention in preventing PTSD. Psychological debriefing of motor vehicle accident victims was

Figure 2. Psychological Debriefing (PD) Hinders Recovery After Motor Vehicle Accidents in Symptomatic Patients With High Impact of Event Scale (IES) Scores (i.e., > 23)^a



^aReproduced with permission from Mayou et al.²⁶

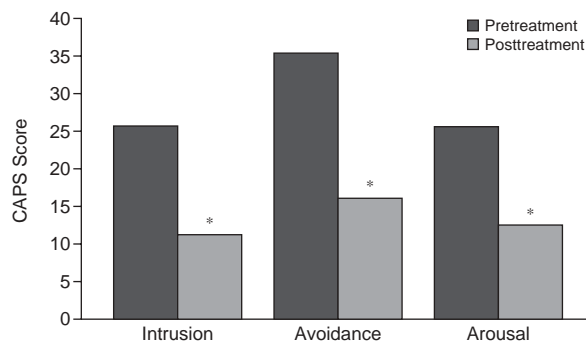
found in 1 series of randomized, controlled studies to be ineffective 4 months after the trauma³⁰ and again at 3-year follow-up.²⁶ In fact, psychological debriefing resulted in markedly worse outcomes for patients who were experiencing intrusive and avoidance symptoms in the immediate posttrauma period than for control patients (Figure 2), and the investigators concluded that psychological debriefing was harmful and should not be used to prevent PTSD.

In contrast to single-session psychological debriefing, the literature supports the efficacy of brief courses of cognitive-behavioral interventions for emergent acute stress disorder and prevention of PTSD. Foa and colleagues³¹ compared the outcome in 20 female assault victims who received 4 sessions of CBT or repeated assessment of trauma-related symptoms (control group) shortly after the trauma. At 2-month follow-up, 10% of patients in the cognitive-behavioral group met criteria for PTSD compared with 70% of control patients, and the level of PTSD symptoms remained significantly lower at 6-month follow-up. In another series of studies, Bryant and co-workers enrolled civilian trauma victims with acute stress disorder within 2 weeks of the trauma and administered 5 sessions of either cognitive behavioral therapy or supportive counseling.^{32,33} At 6-month follow-up, rates of PTSD were significantly lower in the CBT groups ($\leq 23\%$) than in the supportive counseling groups (67%). A pilot study also showed that victims of motor vehicle accidents with signs of physiological arousal (i.e., heart rate > 94 bpm) who received 2 brief sessions of memory structuring intervention were significantly less likely than patients who received supportive counseling to exhibit PTSD symptoms at 3-month follow-up.³⁴

LONG-TERM TREATMENT OF PTSD

Relevant findings from long-term treatment studies of SSRIs or CBT in PTSD are reviewed here. SSRIs have been shown to effectively improve core symptoms of

Figure 3. Changes in Clinician-Administered PTSD Scale (CAPS) Score After 1 Year of Open-Label Treatment With Paroxetine, 20 to 50 mg, in 23 Men and Women With Posttraumatic Stress Disorder^a



^aReproduced with permission from Vermetten et al.³⁵

* $p < .001$.

Abbreviation: PTSD = posttraumatic stress disorder.

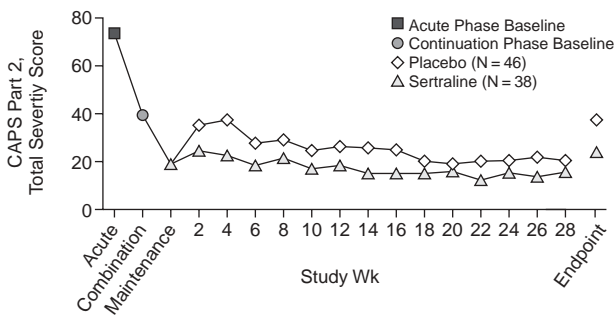
PTSD when administered for 9 months up to more than 1 year. Similarly, CBT has been found to maintain short-term treatment response for up to 12 months in some cases.

Long-Term Treatment With SSRIs

The efficacy of a 1-year course of paroxetine was studied as part of a neuroimaging trial designed to measure the effects of long-term SSRI treatment on memory and hippocampal volume.³⁵ This was an open-label, flexible-dose study of paroxetine (20–50 mg) in 28 men and women. Efficacy was measured with the CAPS. A placebo arm was not included in this study because of concerns about leaving symptomatic patients untreated for 12 months. Compared with mean baseline CAPS scores, paroxetine treatment for 1 year resulted in a 54% improvement in end point scores ($p < .0001$). End point scores on each of the symptom clusters (e.g., reexperiencing, avoidance/numbing, hyperarousal) also were significantly improved compared with baseline (Figure 3). Long-term SSRI treatment, in this case with paroxetine, also significantly improved verbal declarative memory and percent retention compared with baseline levels and was associated with a 4.6% increase in baseline hippocampal volume ($p = .005$).

Another study was designed to measure rates of relapse in patients with PTSD. In this study,³⁶ 131 patients with PTSD were administered open-label fluoxetine for 3 months, after which responders were randomized to receive continued fluoxetine treatment or placebo for another 6 months. Statistically significant differences were noted on the primary Treatment Outcome PTSD scale (TOP-8) at 3, 4, and 5 months, respectively, following discontinuation of fluoxetine. Relapse rates were 6% for patients in the fluoxetine group and 16% for patients in the placebo group ($p = .027$).³⁶

Figure 4. Mean Clinician-Administered PTSD Scale (CAPS) Score at Baseline in Studies of Acute and Continuation Sertraline Treatment for Posttraumatic Stress Disorder and During Double-Blind, Placebo-Controlled, Maintenance Treatment With Sertraline^a



^aAdapted with permission from Davidson et al.³⁷
Abbreviation: PTSD = posttraumatic stress disorder.

The ability of an SSRI to protect against relapse of PTSD during maintenance treatment was demonstrated by Davidson and colleagues.³⁷ In this study, 275 patients with PTSD who completed a 3-month, double-blind, placebo-controlled, acute-treatment phase were entered into a 6-month, continuation-treatment phase of open-label sertraline. Following continuation treatment, responders were randomized to receive either sertraline or placebo for a 7-month maintenance/relapse prevention phase. A total of 84 patients completed the maintenance phase of sertraline (N = 38) and placebo (N = 46). The mean daily dose of sertraline during the maintenance phase was 137 mg. Sustained symptom improvement, which was achieved during continuation treatment, was greater during maintenance therapy with sertraline than with placebo (Figure 4). The risk of relapse was 6.4-fold greater among patients in the placebo maintenance group as compared with patients who were maintained on sertraline for the entire 13-month treatment period. Regression analysis revealed that patients who were early responders to either treatment (i.e., drug or placebo) had a greater than 16-fold lower likelihood of relapse when switched to placebo,³⁷ which may have implications for identifying patients who are more likely to achieve full resolution of the underlying pathophysiology associated with PTSD.

Long-Term Cognitive Behavioral Therapy

CBT, including stress-inoculation, prolonged exposure therapy, and cognitive therapy, is the most well-studied psychosocial intervention to date for PTSD.^{38,39} Although generally administered during a short-term course of roughly 3 months, follow-up studies of CBT have demonstrated the sustained benefit of short-term CBT over the long-term in studies of 3 to 12 months' follow-up.³⁸

CONCLUSIONS

Short of avoiding exposure to traumatic events altogether, early and appropriate intervention in the immediate aftermath of trauma is considered a rational method for preventing the development of PTSD. Unfortunately, the secondary prevention of PTSD is not well studied. Although the prophylactic studies reviewed here of early propranolol, hydrocortisone, or imipramine administration are small and often not well controlled, their findings suggest that some sort of pharmacotherapeutic intervention could interrupt the natural course of PTSD. Further studies are clearly warranted. In sharp contrast, the results of 2 benzodiazepine studies in patients with symptoms of acute stress warn against extended use of these agents, at least as monotherapy, in the acute posttrauma period.

Psychotherapy is another component of treatment for symptoms of acute stress in trauma victims. Single-session psychological debriefing remains a controversial intervention that has been shown in well-designed trials to be ineffective and even deleterious relative to the development of chronic PTSD, although it may possibly be of benefit in other ways.²⁸ However, brief courses of CBT shortly after exposure to trauma have been shown to prevent the development of PTSD 6 months later.³²⁻³⁴

Once PTSD is established, patients should be treated to full remission, which also should be the goal of long-term treatment strategies. Short-term courses of cognitive behavioral therapy for patients with PTSD appear to offer long-term benefit. The SSRIs are an effective and well-tolerated acute treatment for chronic PTSD, and an emerging database also suggests their role as first-line treatment for long-term therapy. As in major depression, social anxiety disorder, and panic disorder, long-term maintenance treatment of PTSD appears to tip the scale toward a positive prognosis and reduced risk of relapse.

Many unanswered questions remain, including optimal dose and duration of maintenance therapy, and the optimal type and duration of psychotherapy. It appears that once patients achieve full remission, treatment with SSRIs should be continued for at least another 9 months to 1 year. Some patients may require years of continued treatment to prevent relapse. The findings of one study suggest that patients who responded to treatment early in the course of therapy were less likely to relapse after switching to placebo.³⁷ Another study showed that treatment was associated with reversal of hippocampal volume reductions and improvement of memory deficits.³⁵ The population of patients with PTSD is extremely diverse, and many tend to drop out of treatment before achieving full therapeutic benefit. There is therefore a real need to maximize retention of patients so that optimal outcomes can be achieved.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), imipramine (Tofranil and

others), paroxetine (Paxil), propranolol (Inderal and others), sertraline (Zoloft), temazepam (Restoril and others).

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Question and Answer

Question: The data on benzodiazepines are interesting. Clearly, the short-term use of hypnotics, such as the benzodiazepines, is useful for patients who are experiencing sleep disturbances. Can you comment on this?

Dr. Davidson: I agree that sedative-hypnotics do serve a purpose for patients with insomnia. However, the evidence that they do not prevent development of PTSD suggests that they should be used with great caution. It may well be that other GABAergic agents that promote sleep (e.g., selective GABA reuptake inhibitors) are preferable to benzodiazepines. At this point, we do not have adequate information. □