16 Pharmacologic Treatment of PTSD

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Contents

Abstract

There has been a welcome increase of pharmacologic randomized controlled trials (RCTs) for post-traumatic stress disorder (PTSD) during the past two decades. Progress clearly has been made toward a rational psychopharmacology of PTSD, but recommendations of authoritative practice guidelines as well as prescribing patterns, especially for military veterans with chronic PTSD, often appear disconnected from evidence obtained from these RCTs. Furthermore, an Institute of Medicine assessment found the existing evidence inadequate to determine efficacy of any drug or drug class for PTSD. This chapter reviews data from the more informative PTSD drug RCTs, the rationale for potential efficacy of the drug classes evaluated, and the implications of the evidence available for clinicians who must decide how to prescribe for the patients in their practices.

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HISTORICAL OVERVIEW: PROGRESS AND DISCONNECTS

Post-traumatic stress disorder (PTSD) was formally defined by the American Psychiatric Association (APA) as an anxiety disorder in 1980. The major impetus for this recognition came from the numerous Vietnam War veterans who continued to suffer distress and disability from this disorder for many years after returning home *(1,2)*. Epidemiologic studies subsequently demonstrated that PTSD caused by civilian trauma was highly prevalent in the general population *(3,4)*. For the first decade after its definition, PTSD pharmacologic treatment rationale was largely derivative. Drug selection relied on the substantial symptom overlap between some PTSD symptoms and those of other psychiatric disorders; the urgent need to relieve patients' and their significant others' distress from discrete PTSD symptoms such as severe sleep disruption and anger outbursts; and efforts to reduce comorbid anxiety and depression. Despite the lack of data from randomized controlled trials (RCTs), generically available antidepressant, antianxiety, and sedative hypnotic drugs demonstrated effective for other behavioral symptoms and disorders became widely prescribed "off label" to treat PTSD.

Since 1990, and particularly since 2000, there has been a welcome increase in data available from PTSD placebo-controlled trials. Although results of RCTs have been inconsistent, some progress has been made toward a rational PTSD psychopharmacology. Yet, prescribing practices for PTSD (particularly for American military veterans), and even the recommendations of authoritative practice guidelines *(5,6)*, sometimes appear disconnected from, or contrary to, evidence obtained from RCTs. Differential RCT results between studies performed in civilian trauma PTSD samples and American veteran PTSD samples have been particularly troublesome *(7)*. Another contributor to these disconnects may be that the outcome focus of most RCTs is improvement of PTSD as an overall disorder, whereas the outcome focus of individual prescribers often appears to be improvement in specific target symptoms *(8)*. Furthermore, the pharmacology of drugs chosen for evaluation in PTSD RCTs (with the exception of drugs that reduce central nervous system [CNS] adrenergic activity; see next section) has often lacked grounding in available knowledge about the neurobiology of PTSD. Confusion for practitioners has increased since the publication of a prestigious Institute of Medicine report commissioned by the Department of Veterans Affairs (VA) to assess the evidence on PTSD treatment modalities as of 2007 *(9)*. This report concluded that for all drug classes reviewed, the evidence is inadequate to determine efficacy in the treatment of PTSD.

This chapter discusses progress made in pharmacologic treatment of PTSD as well as the frequent disconnects between the data generated from clinical trials and prescribing practices. The available data from the most informative RCTs for each psychotropic drug class is reviewed in the order used in the Institute

of Medicine report with some modification of nomenclature. Discussion of each drug class will include the neurobiologic rationale (or lack thereof) for choosing the drug class for treatment of PTSD.

ANTIADRENERGICS

Neurobiologic and Phenomenologic Rationale

The central and peripheral adrenergic systems prominently contribute to mammalian adaptive responses to traumatic stress. Excess CNS adrenergic activity produces hyperarousal, anxiety, startle, sleep disruption, and other "fight-or-flight" responses *(10,11)*. The phenomenologic similarities between the behaviors elicited by increased CNS adrenergic activity and many symptoms of PTSD are clear. Studies performed largely (but not exclusively) in veterans with chronic PTSD consistently have demonstrated increased CNS adrenergic activity at both presynaptic and postsynaptic levels. For example, there are elevated concentrations of norepinephrine and its metabolites at rest and in response to stress in cerebrospinal fluid (CSF) *(12)* and in peripheral compartments coregulated with the CNS adrenergic system *(13)*. These results are consistent with increased CNS presynaptic adrenergic outflow from the locus ceruleus contributing to PTSD symptomatology, particularly at night *(14)*.

Increased behavioral and cardiovascular responses to psychologic and pharmacologic stimulation of adrenergic outflow are consistent with increased responsiveness of postsynaptic adrenoreceptors (the α1-adrenoreceptor or the β-adrenoreceptor) also contributing to clinical expression of PTSD *(15–17)*. In addition to its possible involvement in PTSD symptom expression, preclinical and clinical studies suggest the postsynaptic β-adrenoreceptor may be involved in PTSD pathogenesis by mediating consolidation of emotionally arousing memories *(18)*.

The postsynaptic α1-adrenergic receptor is a particularly attractive treatment target in PTSD. Several neurobiologic systems likely involved in PTSD pathophysiology are under stimulatory regulation by α1-adrenergic receptors. These include (1) components of sleep architecture relevant to emergence of trauma nightmares *(19,20)*; (2) CNS release of corticotropin-releasing factor *(21)*, a neuropeptide that generates anxiety and fear *(22)*; and *(3)* prefrontal neocortex systems that favor primitive fear and alarm cognitions *(23)*.

Lipid-soluble antiadrenergic drugs that are CNS active when administered peripherally are available to reduce CNS adrenergic activity by several mechanisms *(24)*. Presynaptic CNS norepinephrine outflow can be reduced with agonists for the inhibitory presynaptic α2-adrenoreceptor such as guanfacine and clonidine. The CNS postsynaptic β-adrenoreceptor is antagonized by propranolol. The CNS postsynaptic α1-adrenoreceptor is antagonized by prazosin. Originally introduced in the 1970s to treat hypertension, these inexpensive generic antiadrenergic drugs have been widely and safely used in general medicine *(25–27)*.

Randomized Controlled Trials

α-2-Adrenoreceptor Agonists: Clonidine and Guanfacine

The α2-adrenoreceptor agonist clonidine was reported in open-label case series to reduce PTSD trauma nightmares and improve sleep in Cambodian refugees *(28)* and improve PTSD symptoms in veterans *(29)*. Improved sleep in one open-label study was accompanied by improved sleep physiology objectively demonstrated with polysomnography *(30)*. Despite these encouraging anecdotal reports from experienced PTSD clinicians, there have been no clonidine RCTs for PTSD.

Guanfacine is a well-tolerated α2-adrenoreceptor agonist pharmacologically similar to clonidine that has been evaluated in two recent multisite RCTs in American veterans with chronic PTSD. In the first study, 63 veterans were randomized to guanfacine (mean dose 2.4 mg/day) or placebo for 8 weeks *(31)*. Improvements in Clinician Administered PTSD Scale (CAPS) *(32)* total score (–4.4 vs. –6.1, $p = .8$), and other changes in the outcome measures were almost identical in the active medication and placebo groups. A second trial of guanfacine for PTSD in predominantly male combat veterans also was negative *(33)*. That reducing overall norepinephrine outflow with guanfacine has not been effective for PTSD suggests that adrenergic contributions to PTSD pathophysiology are complex and may involve differential responsiveness of postsynaptic adrenoreceptor subtypes.

β-Adrenergic Antagonist: Propranolol

Elevated heart rate following trauma predicts subsequent development of PTSD *(34)*, and persons with PTSD compared to controls have an enhanced heart rate response to adrenergic stimulation *(15,16)*. These findings are consistent with increased β-adrenoreceptor responsiveness in PTSD. Because propranolol is the most lipid soluble of available β-adrenoreceptor antagonists (and thus crosses easily from blood to brain) and is nonselective among β-adrenoreceptor subtypes *(24)*, it is a rational choice for evaluation in PTSD. Despite an early anecdotal report of beneficial propranolol effects on chronic PTSD symptoms in veterans *(29)*, there have been no RCTs of propranolol for chronic PTSD reported in the literature. This lack of propranolol RCTs may reflect the general problem of finding resources to support adequately powered RCTs of already clinically available generic drugs for a potential new behavioral indication. The absence of patent protection effectively eliminates the possibility of pharmaceutical industry support. That propranolol can produce vivid dreams as an adverse effect *(34)* may exacerbate trauma nightmares in PTSD (unpublished observations).

Propranolol has been evaluated as potential pharmacotherapy to prevent development of PTSD following a traumatic event. Forty-one traumatized persons recruited in a hospital emergency department were randomized to a 10-day course of propranolol 40 mg tid (three times a day) or placebo within 6 h of trauma *(35)*. At 1-month follow-up, CAPS total scores of the 11 propranolol completers (28 ± 16) did not differ significantly from the 20 placebo completers (36 ± 22). However, physiologic responses to script-driven imagery 3 months afterward suggested possible benefit of the propranolol treatment. In a subse-

quent study *(36)*, 48 persons recruited in a surgical trauma center were randomized to begin within 48 h of trauma a 14-day course of propranolol 40 mg tid, the anticonvulsant gabapentin 400 mg tid, or placebo. Neither propranolol nor gabapentin compared to placebo showed any effect on reducing PTSD symptoms or other psychopathology at follow-up.

α1-Adrenoreceptor Antagonist: Prazosin

Of the pharmacologic approaches to reducing CNS adrenergic activity in PTSD, only antagonizing the α1-adrenoreceptor with prazosin has been demonstrated clearly effective for reducing core PTSD symptoms. Prazosin is the most lipid soluble of available α1-adrenoreceptor antagonists *(24)*. Peripherally administered prazosin specifically blocks CNS α1-adrenoreceptors *(37)* and suppresses CNS α1-mediated hyperexcitability and stress-induced anxiety *(38)*.

In each of the three RCTs evaluating prazosin for PTSD, drug was administered as a single evening dose specifically to target persistent and distressing trauma-related nightmares and sleep disruption as primary outcome measures. These distressing nighttime symptoms are the most common chief complaint of combat veterans seeking treatment for PTSD (unpublished observation). Measures of global clinical change also were assessed to determine the impact of nightmare reduction and sleep improvement on sense of well-being and ability to function. Because prazosin duration of action is only 7 to 10 h *(24)*, the single evening dose regimen was not designed to test prazosin effects on the daytime PTSD symptoms that comprise the large majority of PTSD symptoms assessed by the CAPS. That said, each study also assessed prazosin effects on total PTSD symptomatology using either the CAPS (in the two veteran sample studies) or the PTSD Checklist Civilian version (PCL-C) *(39)* in the civilian sample study.

A double-blind, placebo-controlled crossover study was performed in ten Vietnam combat veterans *(40)*, all of whom were receiving disability compensation for PTSD. Because nightmares return within a few days of discontinuing prazosin, even after years of successful treatment (unpublished observations), the "carryover effect" that makes a crossover design inappropriate for many psychotropics is not an issue with prazosin. Because of the possibility of "first-dose" hypotension if α1-adrenoreceptor antagonists are initiated at a high dose *(34)*, prazosin was titrated to an apparently effective dose beginning at an initial dose of 1 mg 1 h before bedtime. Both active drug and placebo were then increased during a 3-week dose titration phase that was followed by a 6-week maintenance dose phase. At a mean achieved maintenance dose of 9.6 mg given an hour before bedtime, prazosin was significantly and substantially superior to placebo for reducing nightmares (CAPS "recurrent distressing dreams" item) and sleep disturbance (CAPS "sleep difficulty" item) and improving global clinical status (Clinical Global Impression of Change [CGIC]) *(41)*. All Cohen's d effect sizes were large, greater than 1.0. Change in total CAPS score and all three CAPS clusters (reexperiencing, avoidance, and hyperarousal) also significantly favored prazosin. The large beneficial effects of evening prazosin on trauma nightmares, sleep disturbance, and global clinical status were confirmed and extended in a parallel group placebo-controlled trial of 40 veterans with chronic PTSD, most of whom experienced combat

trauma in the Vietnam War *(42)*. A 4-week dose titration of prazosin or placebo was followed by 8 weeks of maintenance medication (13.3 mg mean maintenance evening prazosin dose). Prazosin again was significantly and substantially superior to placebo for reducing nightmares and sleep disturbance and improving global clinical status. Effect sizes again were large (Cohen's d all > 0.9). Ratings of dream characteristics demonstrated a change from trauma nightmares to normal dreaming during prazosin treatment. Adverse effects were minimal. Although there was a numerically greater reduction in total CAPS score with prazosin than placebo, differences in this trial did not reach statistical significance.

The third prazosin study is unique among all PTSD RCTs in that it measured effects of drug on an objective measure of sleep physiology *(43)*. Thirteen civilian trauma PTSD participants with trauma nightmares and sleep disturbance were randomized to prazosin or placebo in a double-blind crossover trial. Prazosin or placebo was rapidly titrated to 3 mg in the evening during each 3-week treatment period. In the final three nights of each treatment condition, total sleep time, rapid eye movement (REM) sleep time, and sleep latency were recorded at home with the portable REMView device. Total sleep time was 94 min longer in the prazosin than in the placebo condition (374 ± 86 min vs. 280 ± 105 min, $p < .01$, Cohen's d = 0.98). Sleep latency was not significantly different in the prazosin and placebo conditions and actually was several minutes longer in the prazosin conditions. This is consistent with the nonsedating nature of prazosin, which normalizes and extends sleep once sleep is achieved but is not initially "hypnotic." Both REM time and mean REM period duration increased as well, suggesting reduced disruption of REM sleep. Such disruption of REM sleep by inappropriate bursts of CNS adrenergic activity may contribute to the genesis of trauma nightmares *(43,44)*. Clinical outcome measures also favored prazosin in this study, with significantly greater reductions during prazosin treatment of trauma nightmares and PCL-C quantification of total PTSD symptoms, as well as significantly greater improvement in global clinical status.

These studies suggest a specific role for increased α1-adrenoreceptor responsiveness in the pathophysiology of PTSD. A VA multisite cooperative study of prazosin for combat trauma PTSD began randomizing subjects in summer 2008. This study includes both morning and evening doses to enable evaluation of prazosin's effects on both daytime and sleep-associated symptoms.

Several types of psychotropic drugs used clinically in the treatment of PTSD also have substantial α1-adrenergic antagonist activities among their pharmacologic properties *(45,46)*. These drugs include all the atypical antipsychotic drugs (e.g., risperidone, olanzapine, and quetiapine) (discussed separately here), the original tricyclic antidepressants (e.g., imipramine and amitriptyline), and the novel antidepressants trazodone and nefazodone. It is possible that this α1-adrenoreceptor antagonist property contributes to the potential usefulness of these traditional psychotropic drugs in PTSD treatment.

In clinical practice, the beneficial effects of prazosin once achieved usually continue for years with little or no development of tolerance (unpublished observation). In addition, chronic prazosin treatment modifies blood lipids in

a beneficial direction by reducing harmful LDL cholesterol and triglycerides and increasing protective HDL cholesterol *(24)*. Beneficial effects of prazosin on blood lipids and absence of effects on weight and blood sugar are in marked contrast to the increased risk of weight gain, hyperglycemia, dyslipidemia, and metabolic syndrome development during chronic treatment with many of the atypical antipsychotic drugs *(47)*.

Prazosin also has reduced alcohol abuse and dependence, an important comorbidity of PTSD in veterans who "self-medicate" with alcohol to alleviate sleep disturbance and other hyperarousal PTSD symptoms (unpublished observations). Prazosin reduces alcohol consumption in animal models of alcohol dependence *(48,49)* and has reduced alcohol consumption in a recent RCT in alcohol-dependent persons *(50)*.

ANTICONVULSANTS

Phenomenological and Neurobiological Rationale

The stereotyped repetitive nature of reexperiencing symptoms in PTSD has suggested similarity to epileptic phenomena such as temporal lobe seizures. Reduced activity of the widely distributed inhibitory neurotransmitter γ-aminobutyric acid (GABA) has been proposed as a mechanism contributing to PTSD pathophysiology. Increasing CNS GABA activity is an important mechanism of action of anticonvulsant drugs such as divalproex, tiagabine, and topiramate *(51–53)*. Low plasma GABA concentrations following trauma have been associated with subsequent emergence of PTSD *(54)*. Several neuroimaging studies *(55,56)* (but not all; *57)* suggest decreased brain GABA receptor binding in PTSD. Some anticonvulsants also have antikindling effects. Such "kindling" has been postulated to cause limbic brain regions involved in emotional memory to become hypersensitive after traumatic events and reexperiencing phenomena, possibly by repetitive noradrenergic stimulation from the locus ceruleus *(58)*.

Unfortunately, recent well-designed, industry-supported RCTs have failed to confirm efficacy of anticonvulsants in chronic PTSD. Divalproex is an effective anticonvulsant and antimanic drug that increases brain GABA levels *(51)*. Eighty-five American veterans were randomized to divalproex (mean dose 2,309 mg/day) or placebo for 8 weeks *(59)*. Reductions in CAPS total scores did not differ between divalproex and placebo (15.1 vs. 16.5 points, nonsignificant p value not reported). Reductions on the primary outcomes measure, the CAPS hyperarousal symptom cluster, did not differ between divalproex and placebo (5.9 vs. 4.8 points).

Tiagabine is an anticonvulsant that selectively inhibits GABA reuptake and may have antianxiety activity *(52)*. Two hundred thirty-two people with chronic PTSD (including 9% with combat trauma PTSD) were randomized to tiagabine (mean dose 11.2 mg/day) or placebo for 12 weeks *(60)*. Reduction in total CAPS score did not differ between tiagabine and placebo groups (30.7 vs. 30.2 points, $p = .85$).

Topiramate is an effective anticonvulsant that may have antikindling effects and enhances inhibitory effects of GABA *(52)*. Thirty-eight civilian trauma

patients (30 women) with chronic PTSD were randomized to topiramate (mean dose 150 mg/day) or placebo for 12 weeks *(61)*. There were large reductions of CAPS total scores in both treatment groups, but these reductions did not differ between topiramate and placebo (52.7 vs. 42.0 points, $p = .23$).

These negative RCTs make it unlikely that anticonvulsants are effective for core symptoms of PTSD. Together with absence of benzodiazepine effects on core PTSD symptoms (see below Benzodiazepine), these results argue against an important role for GABA in PTSD pathophysiology. The nonspecific sedative effect of many of the anticonvulsant drugs may be subjectively helpful for some PTSD patients but deleterious for others (unpublished observations).

ATYPICAL ANTIPSYCHOTICS

Phenomenological and Neurobiological Rationale

The presence of positive psychotic symptoms is associated with more severe PTSD symptomatology and decreased responsiveness to conventional treatments *(62)*. Flashbacks, a core reexperiencing symptom of PTSD in which the patient transiently but vividly perceives himself or herself experiencing the traumatic event, can mimic psychosis and be difficult to distinguish from complex hallucinations. The presence of comorbid psychotic-like symptoms, the phenomenologic resemblance of intense "flashback" reexperiencing symptoms to psychosis, the sedating property of several atypical antipsychotics, and their ability to reduce cognitive and perceptual distortions in psychosis have been cited as rationale for evaluating atypical antipsychotic drugs as treatment for PTSD. Pseudoparkinsonian adverse effects of first-generation antipsychotics such as haloperidol are much less prevalent with the atypical antipsychotics (risperidone, olanzapine, and quetiapine) that have been used to treat PTSD *(46)*.

The neurobiologic basis of the effects of atypical antipsychotics in psychotic disorders such as schizophrenia is believed to involve antagonism of the dopamine type 2 (D2) and the serotonin type 2 ($5HT_2$) receptors *(46)*. There is no clear evidence implicating abnormal responsiveness of these receptors in the pathophysiology of PTSD. Less widely appreciated is that the atypical antipsychotics all are α1-adrenoreceptor antagonists. Their binding affinities for the α1-adrenoreceptor are equivalent to (and for quetiapine substantially exceed) their binding affinities for the D2 and $5HT_2$ receptors *(46)*. Risperidone has the strongest affinity for the α1-adrenoreceptor among the atypical anticonvulsants that have been evaluated for PTSD *(46)*. This high affinity of atypical antipsychotics for the α1-adrenoreceptor has generally been considered a nuisance cause of orthostatic hypotension as an adverse effect in the treatment of psychotic illnesses. However, this α1-adrenoreceptor antagonist property increases the likelihood that atypical antipsychotics could reduce PTSD reexperiencing and hyperarousal symptoms (see antiadrenergic drugs discussion). Some atypical antipsychotics (e.g., olanzapine and quetiapine) also strongly antagonize the histamine type 1 (H1) receptor *(46)*, a property that likely contributes to their

sedative effects. H1 histamine receptor antagonism and α1-adrenoreceptor antagonism are particularly prominent for quetiapine *(46)*, an atypical antipsychotic that is widely used for the sleep disturbance of PTSD in veterans and active duty military personnel (unpublished observation).

A Note of Caution

Although the atypical antipsychotics are much less likely than first-generation antipsychotics to produce extrapyramidal adverse effects, their ability to induce substantial weight gain, dyslipidemia, elevated blood glucose, and the metabolic syndrome is increasingly recognized as a major public health problem *(47)*. Increased risk for the metabolic syndrome must be taken into account in deciding if and when atypical antipsychotics are appropriate for the long-term treatment that often is necessary for chronic PTSD. The atypical antipsychotics aripiprazole and ziprasadone that do not induce the metabolic syndrome unfortunately have not been evaluated for treatment of PTSD.

Randomized Controlled Trials

Two trials have evaluated olanzapine for PTSD. Fifteen subjects (14 women) with PTSD caused predominantly by military sexual trauma and civilian sexual abuse or other violence were randomized to olanzapine (14 mg/day) or placebo for 10 weeks *(63)*. Reduction in PTSD symptoms measured by the Structured Interview for PTSD did not differ significantly between olanzapine (−20.5) and placebo (−28.9). A troublesome adverse effect was an 11.5-lb weight gain over the 10-week trial in the olanzapine group versus only a 0.9-lb weight gain in the placebo group. In another olanzapine PTSD study, 19 male veterans with combat-related PTSD and pronounced sleep problems but no psychotic symptoms were randomized to 8 weeks augmentation with olanzapine (15 mg/day) or placebo *(64)*. All subjects had been only minimally responsive to 12 weeks of selective serotonin reuptake inhibitor (SSRI) treatment that was continued unaltered during the trial. Reduction of PTSD symptoms by total CAPS score was significantly greater with olanzapine (−14.8) than with placebo (−2.2). The investigators suggested that enhanced sleep accounted for much of the reported improvement. Again, weight gain was a prominent adverse effect. Olanzapine subjects gained 13.2 lb over the 8-week trial compared to a loss of 3.0 lb in the placebo subjects.

Risperidone has received the greatest research attention among the atypical antipsychotics. There have been three adjunctive risperidone RCTs in American veterans with combat trauma PTSD and two adjunctive and one monotherapy risperidone studies in civilian trauma PTSD. Forty combat veterans with chronic PTSD who reported psychotic symptoms (hallucinations, delusions, thought disorder) but did not meet criteria for a primary psychotic disorder (e.g., schizophrenia) were randomized to risperidone (mean dose 2.5 mg/day) or placebo for 5 weeks *(65)*. The risperidone group compared to the placebo group showed a modest but significantly greater reduction in psychotic symptoms but not in PTSD symptoms by the total CAPS or CAPS subscales. However, there was a trend-level effect on the CAPS

reexperiencing subscale (which includes flashbacks among its symptoms). Weight change was not reported. That psychotic symptoms included phenomena that were referable to the original combat trauma (e.g., hearing gunfire or soldiers screaming, visual hallucinations of enemy soldiers) raises the possibility that some of these drug-responsive psychotic symptoms may have been intense flashbacks.

In an interesting study extending anecdotal observations that atypicals may reduce irritability/anger outbursts in PTSD, 16 combat veterans were administered low-dose risperidone (mean dose 0.57 mg/day) or placebo for 6 weeks as adjunctive therapy. Specifically targeted as outcome measures were irritability and aggressive behavior *(66)*. These behaviors were measured with the Overt Aggression Scale–Modified for Outpatients (OAS-M). Active drug was significantly more effective for irritability (but not for aggression) than placebo. Low-dose risperidone also was effective for intrusive PTSD symptoms. Weight change was not reported. The majority of veterans in both treatment groups were receiving maintenance trazodone or nefazodone, two novel antidepressants with substantial α1-adrenoreceptor antagonist activity *(45)*. A possible explanation for the observed therapeutic effect of low-dose risperidone augmentation in this study is that the atypical antipsychotics added enough α1-adrenoreceptor antagonist activity to that of the novel antidepressants to achieve beneficial effects on intrusive and hyperarousal symptoms.

In a larger 16-week study, 65 veterans with severe PTSD despite maintenance psychotropic medication regimens were randomized to adjunctive risperidone (mean CAPS total at baseline = 102 ± 12) or placebo (mean CAPS total at baseline = 99 ± 16) *(67)*. Risperidone was initiated at 1 mg at bedtime and increased to 3 mg at bedtime while subjects were receiving inpatient psychiatric care. Reduction in total CAPS score (−14.3 vs. −4.6) and CAPS hyperarousal cluster score (−5.5 vs. −1.1) were significantly greater in risperidone versus placebo groups. This study is one of the few to have reported change scores in the 17 individual CAPS items. These results demonstrated greater reduction in risperidone than placebo for psychological distress to trauma reminders, detachment, and restricted affect. There were significant changes over time within the risperidone group for physiologic reaction to trauma reminders, thought avoidance, disturbed sleep, irritability/anger outburst, and hypervigilance. End study weight (214 vs. 213 lb) did not differ between groups, but change in weight from baseline was not reported.

Risperidone has been evaluated in three studies in women with civilian trauma PTSD. Twenty women with PTSD related to sexual assault and domestic abuse were randomized to risperidone monotherapy (mean dose 2.6 mg) or placebo for 10 weeks *(68)*. There was a modest numeric advantage of risperidone compared to placebo on the reduction in CAPS total score, but this did not approach statistical significance. Twenty-one women with PTSD related to childhood abuse were randomized to risperidone (mean dose 1–4 mg/day) or placebo for 8 weeks with other psychotropics held constant during the study *(69)*. CAPS total score reduction at end of study was greater in the risperidone group (−30 ± 32) than placebo group (±19 ± 12). Weight gain did not differ between risperidone and placebo groups (2.5 ± 4.1 lb vs. 3.0 ± 6.2 lb). In a third study, 25 civilian trauma PTSD subjects,

predominantly women, who had an incomplete response to an 8-week open-label trial of sertraline were randomized for an additional 8 weeks to risperidone (2.1 mg/day) or placebo *(70)*. There was no difference in total CAPS score reduction (23 ± 13 vs. 24 ± 20 points) among the 21 completers between risperidone and placebo groups. However, there was a greater reduction in CAPS sleep difficulty item favoring risperidone at a trend significance ($p = .09$) level. Trend significance differences favoring risperidone for reductions on the positive symptoms and paranoia scales of the positive and negative syndrome scale (PANSS) were interpreted as consistent with beneficial effects of risperidone on anger and hypervigilance symptoms in these nonpsychotic patients. There also was a trend for more participants in the risperidone group to terminate study participation ($p = .10$). Weight changes were not reported.

Quetiapine

Among the atypical antipsychotics, quetiapine has particularly strong H1 antihistaminic and substantial α1-adrenergic receptor antagonist effects *(46)*. Because sedating antihistaminics (e.g., diphenhydramine) induce sleep and the CNS-active α1-adrenoreceptor antagonist prazosin reduces sleep disruption and distressing trauma nightmares (see prazosin section), there is rationale for evaluation of quetiapine for the sleep difficulty that is so troublesome for many persons with PTSD. To date, there are no reported quetiapine RCTs for PTSD. An open-label trial in combat veterans with PTSD suggested subjective benefit of quetiapine for sleep latency and duration *(71)*. An RCT of quetiapine for PTSD is under way currently, and results soon will be available (M. Hamner, March 2008, personal communication). The increased risk for weight gain and metabolic syndrome with quetiapine may limit its utility for long-term treatment of chronic PTSD. Although the prominent sedating quality of quetiapine taken at bedtime can be useful for difficulty falling asleep, "hangover" into the subsequent day can interfere with daytime activities that require alertness and vigilance (unpublished observation). This daytime sedation can be troublesome for active duty soldiers and others who need a high level of alertness to perform their jobs successfully.

Taken together, these atypical antipsychotic PTSD trials suggest potential benefits of this drug class for PTSD sleep difficulty, irritability/anger outburst, intense flashbacks, and comorbid psychotic symptoms in both veterans and civilian trauma patients. The consistent very large weight gain in the two olanzapine trials likely will limit the potential usefulness of this drug. Results of ongoing multicenter risperidone and quetiapine PTSD trials will help clarify the efficacy and safety of these atypical antipsychotics in PTSD.

BENZODIAZEPINES

Phenomenological and Neurobiological Rationale

Phenomenological similarities between symptoms of several anxiety disorders and several symptoms of PTSD are clear. There is also some neurobiologic

rationale for potential benzodiazepine efficacy in PTSD *(72)*. The antianxiety mechanism of benzodiazepines likely is enhancement of $GABA_A$ receptor function *(73)*. As reviewed in the anticonvulsant section (and benzodiazepines also are effective anticonvulsants; *73)*, reduced GABA concentrations and reduced $GABA_A$ benzodiazepine-binding activity have been demonstrated in PTSD in some studies *(54–56)*. Arguing against major benzodiazepine/$GABA_A$ receptor involvement in PTSD pathophysiology is a study in which the benzodiazepine receptor antagonist flumazanil did not increase anxiety or other PTSD symptoms in Vietnam combat veterans *(74)*.

Results of RCTs

Only one benzodiazepine RCT has directly addressed PTSD core symptom reduction. In a placebo-controlled crossover study in 16 subjects, including 6 with combat trauma *(75)*, the antianxiety benzodiazepine alprazolam failed to demonstrate efficacy for core PTSD reexperiencing and avoidance symptoms. There was some improvement in anxiety and sleep, but rebound anxiety also was observed. Other benzodiazepine trials either have addressed post-trauma PTSD prevention or have specifically targeted PTSD sleep disturbance and nightmares. Although low post-trauma GABA plasma levels were associated with subsequent development of PTSD *(52)*, treatment with alprazolam or clonazepam started within 1 week of trauma in persons selected for substantial post-trauma distress had no effect on development of PTSD symptoms, anxiety, or depression *(76)*. In other small trials targeting sleep disturbance, benzodiazepines were ineffective in improving sleep disturbance, particularly nightmares, in combat veterans *(77,78)*.

Despite these negative benzodiazepine studies and guideline recommendations against using benzodiazepines to treat PTSD *(6)*, benzodiazepines are widely prescribed to veterans with PTSD. Of the more than 220,000 veterans with a PTSD diagnosis prescribed any psychotropic in 2004 in the VA, 24% were prescribed a benzodiazepine *(8)*. The percentage increased to 31% in veterans seen in mental health clinics. Clinical experience suggests that benzodiazepines are prescribed to veterans with PTSD for comorbid anxiety symptoms and for sleep initiation.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

Phenomenological and Neurobiological Rationale

The phenomenologic similarity of many PTSD core and comorbid symptoms to those of depression and the anxiety disorders for which SSRIs and serotonin norepinehprine reuptake inhibitors (SNRIs) have been demonstrated effective are the major cited rationale for their evaluation in PTSD. This rationale together with patent protection for then newly approved compounds generated large-scale pharmaceutical industry support for multicenter PTSD trials of these drugs.

A few neurobiologic studies suggested possible involvement of serotonergic systems in PTSD pathophysiology. An H^3 paroxetine-binding study in platelets revealed decreased receptor number and increased receptor affinity in Vietnam combat veterans with PTSD *(79)*. In a clinical study, the mixed serotonergic agonist/antagonist meta-chlorophenylpiperazine (m-CPP) provoked PTSD symptoms in some veterans with PTSD *(80)*. Whether and how CNS serotonergic systems neurobiologically contribute to PTSD remains unclear.

Results of RCTs

The SSRIs were first evaluated for PTSD in multicenter trials of sertraline and paroxetine in samples predominantly of women with civilian trauma PTSD. In each of two sertraline studies *(81,82)*, total CAPS scores decreased significantly more in sertraline than placebo groups (–33 vs. –26 points and –33 vs. –23 points, respectively), but effect sizes were modest. Sertraline-versus-placebo differences reached statistical significance for the CAPS avoidance/numbing symptom cluster and the CAPS hyperarousal symptom cluster but not for the CAPS reexperiencing/intrusion cluster. Also, insomnia was a common sertraline adverse effect in both studies. In the two paroxetine studies *(83,84)*, significantly greater CAPS-2 decreases with drug versus placebo were similar in magnitude to those in the sertraline studies (–38 vs. –23 points and –36 vs. –26 points, respectively). In contrast to the sertraline studies *(81,82)* (and perhaps suggesting potential advantage for paroxetine), paroxetine-versus-placebo differences were significant for all three CAPS clusters, and insomnia was not a common adverse effect.

These positive results, albeit with modest effect sizes, from the SSRI studies performed in civilian trauma PTSD samples led to Food and Drug Administration (FDA) approval for the then-proprietary SSRIs sertraline (Zoloft) and paroxetine (Paxil) in 2002. SSRIs soon were recommended as the "first-line" drugs for PTSD. The American Psychiatric Association practice guidelines recommended the SSRIs for PTSD with "substantial clinical confidence" *(5)*. Although SSRI RCTs in American veterans consistently have been negative (see Interventions: PTSD Pharmacotherapy), the VA/Department of Defense (DoD) *Clinical Practice Guideline(6)* classified the SSRIs as being "of significant benefit" for PTSD and "strongly recommended" them as monotherapy. As of 2004, SSRIs were prescribed to 85% of the more than 220,000 veterans with a PTSD diagnosis given any psychotropic drug prescription by the VA *(8)*. It is likely that these drugs are widely prescribed for PTSD in the general population as well.

Overall, this progression from results of earlier SSRI RCTs to widespread SSRI use in clinical practice, at least in nonveterans, is consistent with principles of evidence-based medicine. But, there remain questions about the role of SSRIs and SNRIs in PTSD psychopharmacology. The first question is whether SSRIs are as effective (or effective at all) for combat trauma-induced PTSD in military veterans. Ironically, although PTSD was first delineated as a clinical disorder in military veterans, the large majority of multicenter PTSD RCTs have recruited predominantly women with PTSD caused by civilian trauma. In contrast to the mostly positive results of RCTs in civilian trauma PTSD, four of five SSRI RCTs in combat trauma PTSD have been negative. All three

performed in American veterans, including the only large multicenter SSRI trial in this population *(7)*, have been negative.

In a pioneering and still instructive study, 31 veteran outpatients with chronic PTSD were randomized to fluoxetine (average dose 40 mg/day) for 5 weeks *(85)*. Change in total PTSD scores as measured by the CAPS did not differ between fluoxetine and placebo. The authors concluded: "Most VA patients on fluoxetine treatment showed little change: only 1 of the VA patients on fluoxetine had a robust change in his CAPS score, while 2 on placebo did." Fluoxetine was significantly superior to placebo for their comorbid depression symptoms. In contrast to the clear absence of fluoxetine benefit for PTSD symptoms in these veterans, fluoxetine was effective for PTSD symptoms in a sample of predominantly women with civilian trauma PTSD studied concurrently and reported in the same publication *(85)*. In a second single-site SSRI study in veterans, 12 Vietnam War veterans were randomized to fluoxetine (mean dose 48 mg/day) or placebo for 12 weeks *(86)*. Mean improvement on the Davidson Trauma Scale *(87)* actually favored placebo (9 points) compared to fluoxetine (3 points), but differences were not significant. Only one of the fluoxetine subjects as compared to two of the placebo subjects was rated as globally "very much improved."

The third study in American veterans, a large multicenter RCT of the subsequently FDA approved (for PTSD) SSRI sertraline, was performed in 169 outpatients recruited from 10 VA medical centers between May 1994 and September 1996 *(7)*. Results unfortunately confirmed and extended the negative results of the two smaller fluoxetine trials in American veterans. Following a 1-week placebo run-in period, veterans were randomized to 12 weeks of flexibly dosed sertraline (mean dose 156 mg/day among completers) or placebo. PTSD symptom reduction as measured by the CAPS total score did not differ between sertraline (-13.1 ± 3.0) and placebo (-15.4 ± 3.1) groups. Although sertraline was fairly well tolerated, discontinuation rate due to adverse effects tended to be greater in the sertraline group than in the placebo group. For both sertraline and placebo groups, combat-related PTSD was associated with relatively poorer outcome than non-combat-related PTSD. In contrast to the first fluoxetine study in American veterans *(85)*, this multicenter trial failed even to show significant beneficial sertraline effects for comorbid depressive symptoms. In another sertraline RCT, 42 Israeli male combat veterans with chronic PTSD were randomized to sertraline (mean achieved dose 120 ± 60 mg/day) or placebo *(88)*. There were no significant differences in change in CAPS total PTSD symptom scores or any of the three CAPS cluster scores between sertraline and placebo groups. However, there were trends for greater benefit of sertraline for global clinical status and depression symptoms. Also, a post hoc analysis among completers demonstrated a significant effect of sertraline on the CAPS "irritability/anger outburst" item.

Taken together, these four SSRI RCTs in American and Israeli veterans with chronic PTSD provide little rationale for their use for PTSD per se in this population *(8)*, and they do not justify VA/DoD practice guidelines recommending SSRIs as the first-line monotherapy for PTSD. Their widespread use in the VA, however, suggests that clinicians detect symptomatic benefit from SSRIs in their chronic PTSD patients. Clinical observations supported by some

study results suggest that PTSD "irritability/low anger threshold" and comorbid depression and anxiety symptoms are among the symptoms that appear most likely to benefit.

The sole positive SSRI study in combat-related PTSD evaluated fluoxetine in 143 men (and 1 woman) recruited at eight sites in Bosnia-Herzegovina, Croatia, and Yugoslavia *(89)*. Subjects were randomized to fluoxetine (n = 110) or placebo (n = 34) for 12 weeks. The mean dose of 65 ± 18 mg achieved at week 12 was relatively high but was well tolerated in this sample. Fluoxetine was significantly superior to placebo for PTSD as measured by reductions in total CAPS and CAPS cluster scores. Fluoxetine was also effective for depression symptoms as measured by the Montgomery Asberg Depression Rating Scale *(90)*, for anxiety symptoms, and for global clinical status. Several factors may have contributed to the positive findings in this study compared to the other negative SSRI studies in Vietnam and Israeli veterans. These Balkan war veterans were somewhat younger (mean age 36 years) and somewhat more recently traumatized (although PTSD was still chronic with mean time since traumatic event 6 to 7 years) than veterans in the other studies. They also likely had received less treatment of any type for their chronic PTSD. Given the phenotypic similarity between some symptoms of depression and PTSD, the similar reductions with fluoxetine treatment in Montgomery Asberg Depression Rating Scale (MADRS) total score (35%) and CAPS total score (39%), and the similarity of a number of items between these depression and PTSD rating scales raises the possibility that antidepressant effects of fluoxetine contributed in part to the reduction in total CAPS score. An analysis of the 17 individual CAPS symptom items could clarify this possibility. Finally, nonobvious differences between study populations or methods may have contributed importantly to this unique positive finding among RCTs for combat trauma PTSD.

The second question is whether the effect sizes of SSRIs and SNRIs in RCTs in the general population warrant the enthusiasm with which they are recommended in clinical guidelines. Recently published SSRI and SNRI multicenter PTSD trials have shown smaller effect sizes than earlier trials or lack of efficacy altogether. A recent large (n = 411) multicenter RCT of fluoxetine for predominantly civilian trauma PTSD failed to demonstrate separation of the SSRI from placebo *(91)*. Mean total PTSD symptoms (measured by the CAPS) decreased 43, 43, and 37 points in the 20 mg fluoxetine, 40 mg fluoxetine, and placebo groups, respectively. A large multicenter PTSD RCT of the SNRI venlafaxine that included a sertraline group showed a disappointingly small effect size for both medications *(92)*. Five hundred thirty-eight PTSD outpatients at 59 U.S. sites were randomized to venlafaxine (mean dose 64 mg/day), sertraline (mean dose 110 mg/day), or placebo for 12 weeks. CAPS total scores decreased 42, 39, and 34 points in the venlafaxine, sertraline, and placebo groups, respectively. Although venlafaxine was significantly superior to placebo (p = .015), effect size was small (0.26). Sertraline difference from placebo did not reach statistical significance (p = .08) and effect size was only 0.19.

The trials in which specific PTSD symptom responses to SSRIs or the SNRI venlafaxine have been examined individually *(93–95)* suggest some benefit for the majority of daytime PTSD symptoms, but they demonstrate little or no

benefit for trauma-related nightmares and sleep disturbance. This lack of SSRI and SNRI benefits for sleep disturbance are consistent with unpublished results from the original large multicenter sertraline trials that were positive for total PTSD symptoms *(81,82)*. Unpublished analyses of the individual CAPS items measuring trauma nightmares (item 2, "recurrent distressing dreams") and disturbed sleep (item 13, "difficulty falling or staying asleep") demonstrated no significant separation of sertraline from placebo (personal communication). The overall lack of benefit of SSRIs (and the SNRI venlafaxine) for PTSD nightmares and sleep disturbance is consistent with their disrupting REM sleep and intensifying dreaming when administered to normal persons *(96,97)*.

The preponderance of SSRI RCTs support small-to-moderate efficacy with variable response rate for daytime PTSD symptoms in civilian trauma victims. However, SSRIs are not effective for most core PTSD symptoms in veterans, at least not in older Vietnam War veterans, despite being widely prescribed to this population. SSRIs also do not appear to prevent PTSD when administered soon after trauma *(98)*. Whether SSRIs will be effective for core PTSD symptoms in more recently traumatized veterans returning from conflicts in Iraq and Afghanistan is a question deserving careful study. I agree with the thoughtful minority opinion to the Institute of Medicine report by committee member Thomas Mellman: "The evidence is suggestive but not sufficient to conclude efficacy of SSRIs in the general population. The available evidence is further suggestive that SSRIs are not effective in populations consisting of predominantly male veterans with chronic PTSD" *(9*, p. 210).

OTHER ANTIDEPRESSANTS

Almost a decade after the formal recognition of PTSD as a disorder, results from a few small-to-moderate-size single-site RCTs of generically available antidepressants performed in American military veterans began to appear in the literature. A small RCT demonstrated modest efficacy for the tricyclic antidepressant (TCA) amitriptyline *(99)*. A larger RCT demonstrated modest efficacy for the TCA imipramine and more robust efficacy for the monoamine oxidase inhibitor (MAOI) phenelzine *(100)*. Perhaps because of concerns about potential (albeit rare; *101)* adverse effects of MAOIs and dietary restrictions recommended with their use *(45)* or because these generic antidepressant drugs were without industry marketing support, the generally positive studies of TCAs and MAOIs for PTSD in veterans failed to generate either clinical enthusiasm or research support for large RCTs. For whatever reason, MAOIs and TCAs are infrequently prescribed to treat PTSD, at least among American veterans *(8)*.

The sedating generically available antidepressants trazodone and nefazodone are commonly prescribed to veterans with PTSD (e.g., *66)*, particularly for sleep difficulty (unpublished observation). There have been anecdotal reports *(102)* but no RCTs of trazodone for PTSD, perhaps because it has long been generic. An RCT of nefazodone in veterans showed modest but statistically superior reduction of CAPS total score for nefazodone versus placebo

(19.1 vs. 13.5 points) *(103)*. That these related compounds both have substantial α1-adrenoreceptor antagonist activity and are sedating may be relevant to their frequent prescription for nighttime PTSD symptoms. Mirtazapine is a very sedating antidepressant that has shown some benefit in one PTSD trial *(104)* but can produce troublesome daytime sedation and weight gain *(45)*.

MAOIs and TCAs remain rational options for PTSD patients, particularly those with prominent depression and panic symptoms. Given that some RCTs of amitriptyline, imipramine, and phenelzine have been positive for PTSD in American veterans whereas SSRI RCTs in this population have been consistently negative, it remains unclear why SSRIs are far more frequently prescribed to veterans within VA than are these other antidepressants *(8)*.

MISCELLANEOUS DRUGS

Several molecules with neurobiologic roles in memory have been proposed as possible therapeutic agents in PTSD. D-Cycloserine is a partial agonist of the *N*-methyl D-aspartate (NMDA) receptor associated glycine site *(105)* that has been proposed to facilitate psychotherapeutic reduction of the deleterious effects of trauma memories. D-Cycloserine has adjunctive benefit in psychotherapy of several anxiety disorders *(106)*. In a small RCT for PTSD, 11 persons with chronic civilian trauma PTSD received D-cycloserine (50 mg/day) and placebo in a double-blind, random-order crossover design study *(107)*. Small reductions in CAPS total score in both groups did not differ significantly ($p = .5$). However, D-cycloserine continues under active investigation as a potential adjunct to exposure-based psychotherapy. Oxytocin is a hypothalamic neuropeptide demonstrated in rodents to impair consolidation and retrieval of aversive memory *(108)*. Although oxytocin has not been evaluated therapeutically in PTSD, an elegant study demonstrated that single-dose oxytocin administered intranasally to Vietnam veterans reduced physiologic responding to personal combat imagery *(109)*. If memory-active neuropeptides or antagonists to the α1-adrenoreceptor-mediated anxiogenic neuropeptide corticotrophin-releasing factor *(110)* could be administered safely in preparations reliably able to cross from blood into brain, they would be interesting candidates for evaluation in PTSD trials. Cyproheptadine, a sedating antihistamine with complex pharmacologic properties, was demonstrated not more effective than placebo for trauma nightmares and sleep difficulty in veterans *(111)*.

CONCLUSION

Resolving the logical and practical discrepancies among the current evidence from available RCTs, the discouraging interpretation of this evidence by the Institute of Medicine committee that no drug has established efficacy for PTSD and clinicians' widespread prescription of pharmacologic treatment for their distressed patients suffering from PTSD is a challenging task. The high prevalence of PTSD among the millions of men and women who have participated in the war on terrorism in Iraq and Afghanistan (not to mention that of the many

severely traumatized civilians) makes resolving these discrepancies even more pressing. This task requires both short- and long-term approaches.

One potentially helpful approach is to reconceptualize what is meant by "effective treatment" of PTSD. If the "gold standard" efficacy outcome measure is disorder focused and limited to the sum score of all 17 PTSD symptoms listed in the CAPS, and these items are assumed to be equally weighted regarding impact on patients' lives, then clinically important therapeutic drug effects on particularly distressing individual symptoms may be obscured. Commenting on their finding a disconnect between the widespread prescription of multiple psychotropic drug classes for PTSD in American veterans and the RCT-derived data base *(8)*, Mohamed and Rosenheck stated: "A new type of efficacy research may be needed to determine symptom responses to psychotropic medications as well as disorder responses." Such target symptoms in PTSD research ideally would focus on those symptoms most distressing to patients and to their families.

A related issue is the failure of most drug RCTs to report active treatment-versus-placebo effects on individual PTSD symptoms. Such reporting of effects on all 17 CAPS items by Bartzokis, Lu, Turner, Mintz, and Saunders *(67)* is unique among published RCTs and enhanced the clinical value of their risperidone augmentation trial. Even relying on the three CAPS symptom clusters is not adequate to avoid potentially obscuring valuable information about individual symptom responses to treatment.

A powerful long-term approach to developing additional effective drug treatments for PTSD is an enhanced research effort to unravel the complex neurobiology of PTSD. Studies in animal models can help. Clinicians and patients need studies to determine efficacy of generic drugs widely prescribed for PTSD (e.g., trazodone and benzodiazepines) that will not be supported by pharmaceutical company funds. And, the likely complex interactions between pharmacotherapy and psychotherapy need to be addressed in carefully designed trials.

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