Pharmacotherapy of Post-Traumatic Stress Disorder

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Abstract Post-traumatic stress disorder (PTSD) is a prevalent psychiatric disorder that may result in significant social and occupational debilitation unless symptoms are recognized and treated appropriately. Considerable research effort has been devoted over the last 20 years to developing effective pharmacological treatments for this illness. At this time, the bulk of the agents investigated include antidepressants, anticonvulsants, atypical antipsychotics, benzodiazepines, and antiadrenergic agents. Herein, we review the existing evidence base for these different classes of psychotropics in PTSD. Emphasis is placed on discussion of

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evidence stemming from randomized placebo-controlled clinical trials wherever possible. A brief description of novel agents that have shown initial promise for PTSD treatment is also provided.

Keywords Pharmacotherapy · Post-traumatic stress disorder · PTSD · Treatment · Biological treatment · Medication

List of Abbreviations

BZD	Benzodiazepine
CAPS	Clinician Administered PTSD Scale
DCS	D-Cycloserine
DSM-III	Diagnostic and Statistical Manual, Third Edition
FDA	United States Food and Drug Administration
GABA	Gamma Aminobutyric Acid
GC	Glucocorticoid
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
MAOI	Monoamine oxidase inhibitor (irreversible)
PTSD	Post-traumatic stress disorder
RIMA	Reversible inhibitor of monoamine oxidase type A
RCT	Randomized clinical trial
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin norepinephrine reuptake inhibitor
TCA	Tricyclic antidepressant
VA	Veterans administration

1 Introduction

Descriptions of the adverse psychological consequences in soldiers following battle exposure can be found as far back as ancient Egypt and Greece. Not limited to military populations, accounts of similar symptoms in civilians can be found throughout history in reaction to natural disasters and other traumatic events. However, official recognition by the medical community of the collection of symptoms now known as post-traumatic stress disorder (PTSD) only occurred in 1980 with inclusion of the diagnosis in DSM-III. The current understanding of PTSD consists of direct or indirect exposure to a traumatic event resulting in an intense aversive reaction that is subsequently accompanied by social and

occupational dysfunction, and by a number of symptoms that can be characterized as belonging to one of three symptoms clusters: re-experiencing symptoms, avoidance/numbing behavior, or hyperarousal symptoms. Lifetime exposure to a traumatic event is not uncommon but only a relatively small proportion of those exposed will end up developing PTSD. In the US general population, lifetime prevalence of PTSD has been estimated at 6.8% (Kessler et al. 2005), but rates may be significantly higher in particular populations such as military veterans (Milliken et al. 2007), individuals with a prior history of trauma, or those with comorbid psychiatric disorders (Copeland et al. 2007). Rates may also be particularly elevated in inhabitants of areas where war and trauma exposure are common (de Jong et al. 2001).

PTSD is clearly not a rare or unimportant illness. Yet in spite of the research attention focused on finding effective treatments for it, the quest is not complete. For many years the mainstay of treatment was rest and use of sedative hypnotics – likely for treatment of hyperarousal symptoms, followed by psychotherapeutic intervention (Sargant and Slater 1940) – where even then it was recognized that early intervention was crucial. With the advent of antidepressant medications, and other more selective and better tolerated psychotropics, pharmacological approaches to PTSD treatment have been increasingly common. In this chapter, we review the evidence from randomized clinical trials (RCTs) of available psychotropic agents investigated for PTSD. Psychotherapeutic interventions in PTSD also have a considerable literature base, but discussion of these is beyond the scope of this chapter. Discussion of pharmacotherapy strategies when combined with psychotherapy are discussed elsewhere in this volume.

2 Antidepressants

2.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

Over the last 20 years, SSRIs have become the treatment of choice for both depressive and anxiety disorders, in large part due to the combination of their efficacy, tolerability, and safety profiles. This holds true for PTSD treatment as well where SSRIs are the first-line agents of choice in multiple treatment guidelines (Foa et al. 2000; Ursano et al. 2004; Bandelow et al. 2008). These drugs, which as a class work to enhance serotonergic neurotransmission by preventing reuptake at the presynaptic 5-HT transporter pump (Stahl 1998), are all commonly used in the clinical treatment of PTSD, although only two, sertraline and paroxetine, have official FDA indications for this purpose.

Fluoxetine was the first of the SSRIs to be investigated for efficacy in PTSD. A sample of subjects ($N = 64$) with either combat-related or civilian-related PTSD was randomized to receive treatment with fluoxetine (up to 60 mg daily) or placebo for 5 weeks (Van Der Kolk et al. 1994). Significant reduction in overall PTSD

symptoms, as measured by the Clinician Administered PTSD Scale (CAPS) was noted in this double-blind trial, with particular improvements in symptoms of numbing/avoidance and hyperarousal. The authors also made particular note of the fact that the degree of symptomatic improvement was perceptibly greater in the subpopulation with civilian-related PTSD in this sample relative to the subpopulation with combat-related PTSD (40% vs. 15%).

Similar positive RCTs of acute treatment (<12 weeks) with fluoxetine for PTSD were subsequently published (Connor et al. 1999, Martenyi et al. 2002a) and support for the utility of fluoxetine as a relapse prevention agent has also been found. Martenyi et al. (2002b) rerandomized responders of an earlier 12-week placebo controlled trial of fluoxetine to either double-blind continuation treatment or placebo for a further 24 weeks. Continuation treatment with active medication was associated with a significantly longer time to relapse as well as additional improvement in not only PTSD but also in symptoms of comorbid disorders. Conversely, not all PTSD studies of fluoxetine report positive results. In a small sample ($N = 12$) of male veterans, Hertzberg et al. (2000) failed to detect benefit for fluoxetine following the 12-week trial, which they theorized could be related to factors including nature (civilian-related vs. combat-related), severity, or chronicity of trauma. A more recent three-arm study (Martenyi et al. 2007) compared treatment response after 12 weeks to two fixed doses of fluoxetine (20 and 40 mg) to placebo in a large sample ($N = 411$) of predominantly female subjects ($N = 294$) with PTSD. Treatment outcomes were not noticeably different between the three treatments. The authors speculated that the large proportion of females may have been a factor in these results or that, more likely, the doses of fluoxetine investigated in this study were lower than the mean doses used in similar positive trials.

The first SSRI to receive regulatory approval in the US was sertraline following the publication of two multicenter trials (Brady et al. 2000; Davidson et al. 2001a). Both trials were RCTs comparing placebo to flexibly dosed sertraline (50–200 mg daily) over a 12-week period in subjects with moderate to severe PTSD. In the first trial (Brady et al. 2000), active medication resulted in global improvement of post-traumatic symptoms with significant benefits noted for avoidance/numbing symptoms and hyperarousal. This study was also able to demonstrate that benefits of sertraline treatment were not limited to clinical symptoms, but also extended to improvements in quality of life and both social and occupational functioning. Finally, observing that the mean duration of illness in the study population was over 10 years, the authors felt that the clinical improvement with sertraline detected as early as 4 weeks into treatment was particularly noteworthy given the chronicity of illness in the studied population. Similar rates of response were observed in the subsequent study by Davidson et al. (2001a) which also confirmed that the majority of the clinical benefit derived from sertraline occurred in the first 4 weeks of the trial. As these studies used primarily civilian subjects, Zohar et al. (2002) conducted a small 10-week pilot RCT ($N = 42$) of sertraline in military veterans suffering from PTSD. In contrast to the findings of the earlier studies, improvement in post-traumatic symptoms with sertraline was associated with a numeric but not statistical advantage over placebo, with the range of improvement detected

proportionately less than that noted in the prior civilian studies (25–33% vs. 45–50%). The authors wondered if the relatively greater mean baseline severity in this military population might have played a role in the results. Friedman et al. (2007) attempted to explore this issue further in a larger 12-week RCT of subjects seen in a VA medical setting. In this population, of which 71% had combat-related PTSD, no statistical differences in outcome were detected between active drug and placebo, nor could any potential moderators of outcome, such as gender or substance abuse, be definitively identified.

In spite of these mixed results from acute phase trials, studies of continuation treatment are more supportive of sertraline use. Using a sample of patients ($N = 252$) who had previously participated in one of two acute phase RCTs of sertraline for PTSD, Londborg et al. (2001) followed these individuals in an open-label fashion during a 24-week continuation phase trial. One of the more noteworthy findings of the trial was the observation that 54% of nonresponders during the original 12-week trials subsequently converted to responders, underlining the importance of patience with extended pharmacotherapy treatment to obtain maximum clinical response. The other finding of note in this study was that 92% of the original acute phase responders maintained their recovery during this extension period. Subsequent analyses of investigational measures also showed that 20–25% of the overall improvement in PTSD symptoms during the combined 36 weeks of treatment occurred during the latter 24 weeks as did 31% of the improvement in quality of life (Rapaport et al. 2002). A subsample ($N = 96$) of the responders from this continuation-phase study was subsequently rerandomized to double-blind maintenance treatment with either sertraline or placebo for a further 28 weeks. In this instance, both relapse (sertraline 5.3% vs. placebo 26.1%) and discontinuation (sertraline 15.8% vs. placebo 45.7%) rates were significantly higher in the placebo group (Davidson et al. 2001b). These studies serve to underscore the importance of extended antidepressant treatment to elicit maximal improvement of symptoms, maintain recovery, and prevent relapse. At present, guidelines for duration of pharmacotherapy treatment recommend continuing medications for 6–12 months in cases of acute PTSD or 12–24 months for chronic PTSD; under certain circumstances, such as persistent residual symptoms or poor psychosocial functioning, an even longer treatment period may be of benefit (Foa et al. 1999; Stein et al. 2003).

Evidence from acute phase RCTs also supports the utility of paroxetine, fixed dose (20 or 40 mg) or flexibly dosed (20–50 mg), for PTSD (Marshall et al. 2001; Tucker et al. 2001). As with sertraline, the beneficial effects of paroxetine were noticeable at week 4 (Tucker et al. 2001) in one trial, and both trials showed evidence of significant improvement in measures of social and occupational function at endpoint. With the majority of previously published trials using primarily Caucasian populations, a more recent RCT by Marshall et al. (2007) was able to demonstrate that the positive effects of paroxetine (up to 60 mg) extended to a sample with a high proportion of ethnic minorities (75%). Further, benefits of the medication were seen not only for core PTSD symptoms but also for dissociative symptoms and interpersonal problems, psychopathology that often accompanies this illness.

The efficacy of other SSRIs has also been investigated, albeit to a lesser extent, for treatment of PTSD. A single double-blind trial of citalopram (20–50 mg) exists in which it is compared to sertraline (50–200 mg) and placebo. While sertraline appeared to demonstrate an advantage over the other arms on avoidance/numbing symptoms (as measured by the CAPS) following the 10 weeks of treatment, no other statistical differences in efficacy could be detected between the three groups. No other placebo-controlled RCTs have been published investigating citalopram, escitalopram, or fluvoxamine. Nevertheless, evidence from a number of open trials supports the use of these three agents in PTSD subpopulations that include military veterans, civilians, and even children and adolescents (Davidson et al. 1998; English et al. 2006; Escalona et al. 2002; Marmar et al. 1996; Robert et al. 2006; Seedat et al. 2002).

The SSRIs currently represent the mainstay of pharmacological intervention in PTSD, primarily because of their extensive evidence base relative to other pharmacological agents which is reflected in the widespread clinical use of these drugs. However, a recent report by the Institute of Medicine, published in 2007, found the evidence base for the use of pharmacotherapy, including the SSRIs was insufficient to confirm their efficacy in PTSD – a conclusion based in part on the modest effect sizes (≈0.5) seen in SSRI pharmacotherapy trials. Recommendations by the committee that larger independent trials with these drugs, in a greater variety of clinical settings, and over a greater duration are certainly valid and would no doubt enrich the literature. Nor is there any doubt that the degree of SSRI efficacy is highly variable between individuals and may be dependent on other factors which include chronicity, severity of illness, and comorbidity. Nevertheless, the prevalent use of SSRIs is unlikely to change in the near future, particularly given their relative safety and tolerability. While certain antidepressants within the SSRIs have been investigated more than others, clinicians are inclined to treat their efficacy as equal across the class. As such, choice of a particular agent tends to be based on side-effect profile and prior response. Prospective trials that investigate the use of systematic augmentation, combination, and switching strategies which include both psychotherapeutic and psychopharmacologic options specifically targeting residual symptoms will be a crucial area of future research.

2.2 Serotonin Norephinephrine Reuptake Inhibitors (SNRIs)

There are four SNRIs currently available on the market – venlafaxine XR, duloxetine, milnacipran, and desvenlafaxine. Although trials of duloxetine for PTSD are currently in progress, to date the only published PTSD RCTs involving SNRIs have focused on venlafaxine XR. This drug, whose mechanism is thought to involve differential reuptake of serotonin and norepinephrine at either end of the dosing spectrum, has demonstrated efficacy for both acute-phase and continuation treatment of PTSD, with comparable benefits to SSRIs. In their 12-week trial, Davidson et al. (2006a) compared flexibly dosed venlafaxine XR (37.5–300 mg)

to sertraline (25–200 mg) or placebo in subjects with moderate to severe PTSD ($N = 538$). Remission rates following venlafaxine treatment (mean maximum dose 224.6 mg) were significantly better than placebo (30.2% vs. 19.6%, $p < 0.05$), with particular efficacy noted for symptoms of avoidance/numbing and hyperarousal. Differentiation in outcomes between venlafaxine XR and placebo were seen as early as week 2 and overall efficacy and tolerability between venlafaxine and sertraline were similar. Davidson et al. (2006b) also subsequently published the results of a 24-week double-blind RCT comparing venlafaxine (37.5–300 mg) to placebo. In this sample ($N = 329$), venlafaxine was once again superior to placebo with respect to improvement in overall PTSD symptoms and the individual symptom clusters with the exception of hyperarousal symptoms, although there was a trend toward significance ($p = 0.06$). Changes in measures of resilience, stress vulnerability, and quality of life similarly favored venlafaxine. Although the number of trials is few, the efficacy and tolerability reports from these large RCTs support the notion that venlafaxine represents a reasonable alternative to SSRIs for pharmacologic treatment of PTSD.

2.3 Tricyclic Antidepressants (TCAs)

With the advent of newer, more tolerable antidepressants, TCAs have largely fallen out of favor as first-line pharmacological agents for anxiety disorders. Nevertheless, published RCTs investigating TCAs do exist. Desipramine, a TCA thought to work primarily by inhibiting norepinephrine reuptake into the presynaptic neuron, was investigated in an 8-week double-blind cross-over trial (Reist et al. 1989). During each of the 4-week active treatment period, hospitalized male veterans with PTSD ($N = 18$) received either desipramine (50–200 mg) or placebo with an intervening 4-day switchover. In this trial, desipramine was not associated with significant changes in PTSD symptoms. However, it should be noted that no validated observer-rated scale of PTSD was used; rather items from the Hamilton Rating Scale for Depression (HAM-D) thought to be relevant to PTSD were selected post-hoc. Similarly, the active treatment period was quite short (only 4 weeks) and it may very well have been insufficient to see a therapeutic effect.

An alternate TCA, amitriptyline, was used in an 8-week RCT of 46 veterans with combat-related PTSD (Davidson et al. 1990). Amitriptyline, a mixed norepinephrine/serotonin reuptake blocker, did demonstrate superiority over placebo on several outcome measures (including both the HAM-D and the Hamilton Rating Scale for Anxiety (HAM-A)), but not the structured interview of PTSD symptoms. Of note, the rates of response in this trial were quite low with 64% of subjects receiving amitriptyline and 72% of those receiving placebo still meeting criteria for PTSD at endpoint. Two other controlled trials investigating TCAs for PTSD have also been reported. These are discussed below in the section below entitled: "Monoamine oxidase inhibitors."

The underwhelming results from the above trials in the context of both the drug–drug interactions and the adverse event/toxicity profiles of the TCAs (which include both anticholinergic and antiadrenergic effects) have largely relegated these drugs to third or fourth line options. Nevertheless, TCAs may still have a place in PTSD treatment in special cases such as comorbid depression or intolerance to other agents.

2.4 Monoamine Oxidase Inhibitors

The mechanism of action of monoamine oxidase inhibitors involves enhancing availability of monoamines via inhibition of the enzyme monoamine oxidase responsible for their breakdown. The conventional monoamine oxidase inhibitors, referred to as MAOIs, work by irreversible inhibition of the enzyme; in contrast, a newer more selective subgroup of MAOIs work via *reversible* inhibition of monoamine oxidase type A and are thus termed RIMAs. As with TCAs, the use of conventional MAOIs is increasingly rare as a result of both their side-effect profile and the necessity of a low-tyramine diet to decrease risk of hypertensive crises. In one early report, the MAOI phenelzine was used in a double-blind cross-over trial in 13 subjects with PTSD. Outcomes following use of phenelzine (30–75 mg) during the 5-week treatment periods were not significantly different from placebo (Shestatzky et al. 1988). In contrast, two positive RCTs have been reported in which phenelzine was compared to imipramine and placebo. In the first of these 8-week double-blind studies, Frank et al. (1988) found active treatment with phenelzine (15–75 mg) and imipramine (50–300 mg) to both be effective in reducing post-traumatic symptoms in the sample of 34 veterans with PTSD. Kosten et al. (1991) similarly found both medications to be effective in their larger sample of male veterans ($N = 60$). However, with a 44% symptom improvement in the phenelzine-treated group compared to 25% improvement in the imipramine group, use of an MAOI seemed to be associated with added benefit. In spite of these mixed findings, no larger definitive placebo-controlled trials have since been conducted nor, to our knowledge, have any investigations compared more novel agents (e.g., SSRIs) to MAOIs for this purpose. Results from such trials would be helpful in more clearly delineating a role for MAOIs in current pharmacotherapy strategies for PTSD.

As noted earlier, reversible inhibitors of monoamine oxidase A (RIMAs) are a more selective subtype of MAOIs. These drugs, which include brofaromine and moclobemide, do not require the same dietary restrictions as the MAOIs and are generally more tolerable. Although RIMAs are not available in the US, they are available in other parts of the world such as Europe and Canada. Studies of brofaromine, a mixed RIMA/serotonin reuptake inhibitor, in PTSD have resulted in inconsistent findings. While Katz et al. (1994) found an advantage for brofaromine over placebo in the treatment of individuals with PTSD of greater than 1 year duration, these findings were not replicated in the subsequent multicenter trial reported by Baker et al. (1995). Moclobemide has not been investigated in any placebo controlled trials, but in an open label comparison to fluoxetine and

tianeptine all three drugs were found to be similarly effective (Onder et al. 2006). Nevertheless, these results have not been replicated in a double-blind trial nor are there any other RCTs of moclobemide for PTSD.

2.5 Other Antidepressants

Nefazodone is an older antidepressant thought to work by a dual mechanism of action: potent postsynaptic antagonism of serotonin 5-HT2A receptors as well as modest inhibition of presynaptic serotonin/norepinephrine reuptake (Davis et al. 1997). A 12-week RCT of nefazodone found it to be superior to placebo for improvement in both PTSD and depressive symptoms (Davis et al. 2004); however, the sample size ($N = 41$) was limited. McRae et al. (2004) published results of a head-to-head comparison with sertraline. In this study, nefazodone (up to 600 mg) and sertraline (up to 200 mg) were both similarly effective treatments for PTSD with comparable tolerability. Once again, however, sample size was small ($N = 37$). Amid concerns of liver toxicity, nefazodone was recently withdrawn from the market in Europe, Canada, Australia, and New Zealand. While it is still available in the US, these concerns have noticeably curtailed its use and may prevent further investigation of this drug in clinical trials.

A small 8-week placebo-controlled trial ($N = 30$) of bupropion SR, a combined norepinephrine/dopamine reuptake inhibitor, failed to distinguish active medication from placebo on PTSD outcomes (Becker et al. 2007). Similarly, an earlier RCT that investigated bupropion SR as a smoking cessation aid in veterans with chronic PTSD did not find it efficacious on the secondary measure of PTSD improvement (Hertzberg et al. 2001).

Mirtazapine is a newer antidepressant with a novel mechanism of action resulting in increased overall norepinephrine and serotonin neurotransmission. It works presynaptically to inhibit the α_2 heteroreceptors on serotonergic neurons and the α_2 adrenergic autoreceptors. It also works to selectively block serotonergic 5-HT_2 and 5-HT_3 receptors on the postsynaptic neuron, as well as having potent antagonist effects at histaminic H1 receptors which may contribute to its sedative effects. Evidence from open trials (Bahk et al. 2002; Chung et al. 2004; Kim et al. 2005) suggest that mirtazapine may be a useful agent in both short-term and long-term treatment of PTSD, with comparable efficacy to sertraline. Only a single placebo-controlled trial of mirtazapine has been reported in the literature (Davidson et al. 2003). In this 8-week pilot study ($N = 29$), mirtazapine (up to 45 mg) showed benefit over placebo on a global improvement measure of PTSD, but failed to show any significant advantage on other outcome variables (e.g., Davidson Trauma Scale). Based on the measures, effect sizes for mirtazapine ranged from moderate to strong, but no subsequent placebo-controlled trials have been performed to validate these findings.

3 Anticonvulsants

Kindling, a phenomenon by which repeated subthreshold electrical stimulation progressively acts to produce profound brain changes such that eventually spontaneous events occur with minimal or no stimulation, is one mechanism proposed to explain PTSD symptom development. For instance, the repeated recall of conditioned fear memories that may eventually result in spontaneous flashbacks or intrusive memories is a process that resembles kindling (Post et al. 1997). Based on their putative antikindling effects, the effects of several anticonvulsant agents (as either monotherapy or adjunctive treatment) for PTSD have been reported in the literature; these include divalproex, lamotrigine, tiagabine, topiramate, carbamazepine, levetiracetam, phenytoin, gabapentin, and vigabatrin. Though the case studies and open trials provide some preliminary evidence of support, results from the few controlled trials are more mixed.

The first RCT of an anticonvulsant in PTSD involved lamotrigine, which is thought to work by inhibition of glutamate transmission (Hertzberg et al. 1999). In this 12-week pilot trial ($N = 15$), lamotrigine (50–500 mg) appeared to be superior to placebo for re-experiencing and avoidance/numbing symptoms, but the small sample size and lack of subsequent replication preclude more definitive conclusions. In another trial, responders ($N = 18$) following 12 weeks of open-label tiagabine treatment (up to 16 mg) were randomized to an additional 12 weeks of double-blind continuation with either active drug or placebo (Connor et al. 2006). Although there were no differences in rates of relapse between the two groups during this period, a trend towards significance ($p = 0.08$) was observed for subjects who received ongoing tiagabine to achieve remission. Unfortunately, a subsequent, larger multicenter RCT ($N = 232$) comparing 12 weeks of double-blind tiagabine (up to 16 mg) to placebo failed to show group differences on any of the primary or secondary efficacy measures (Davidson et al. 2007). Similarly, an 8-week placebo-controlled trial of divalproex monotherapy (1000–3000 mg), specifically for treatment of PTSD hyperarousal symptoms, in military veterans ($N = 85$) failed to show benefit over placebo for any of the PTSD symptom clusters, nor for any other symptoms of depression and anxiety (Davis et al. 2008a). Topiramate is an anticonvulsant thought to promote GABA-ergic but inhibit glutamatergic transmission. In their 7-week double-blind trial ($N = 40$), Lindley et al. (2007) compared topiramate augmentation (50–200 mg) to placebo. Although no benefit was noted for this treatment regimen, it should be noted that the dropout rate for topiramate-treated subjects was noticeably higher than for the placebo-treated group (55% vs. 25%), and mainly related to adverse events. Topiramate monotherapy (25–400 mg) was also investigated in a 12-week double-blind RCT ($N = 38$) of civilians with non-combat related PTSD (Tucker et al. 2007). In this case, topiramate did show benefit over placebo for the re-experiencing cluster of symptoms, but statistical differences between groups was not seen in overall CAPS scores.

Based on the results of above studies, the use of anticonvulsants in PTSD has only very limited support. The evidence, which mainly suggests a role for either

topiramate or lamotrigine monotherapy, is based on single trials of each medication, each with an underpowered sample size. As such, treatment recommendations that involve these medications must be interpreted with caution. Nevertheless, a role for anticonvulsant agents in PTSD may exist particularly in specific subpopulations; for instance, lamotrigine in subjects with comorbid PTSD and bipolar disorder or topiramate for individuals with an underlying seizure disorder. Treatment studies that examine anticonvulsant use in these specific clinical populations would be helpful.

4 Atypical Antipsychotics

In clinical practice, atypical antipsychotics, with their dual dopaminergic and serotonergic mechanisms, are frequently used as adjunctive treatment to standard antidepressant treatment for both mood and anxiety disorders. Since up to 40% of individuals with PTSD may experience concurrent psychotic symptoms, the use of an antipsychotic certainly has a rational basis. However, the increased popularity of these medications may also stem from their relatively lower risk of unpleasant side-effects such as tardive dyskinesia and Parkinsonism commonly seen with more traditional antipsychotics. Further, the sedating qualities (thought to be due to histaminic H_1 receptor blockade) seen with a number of atypicals have also been used to target the sleep disturbances common to many psychiatric disorders including PTSD. Interestingly, in spite of their relative common usage, the evidence base for using atypicals in PTSD is still quite limited. Currently, seven atypical antipsychotics have FDA approval in the United States; these include olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, clozapine, and most recently paliperidone. Of these agents, only case-reports or open trials exist for clozapine, ziprasidone, quetiapine, and aripiprazole in PTSD. The only published RCTs of atypicals in PTSD involve either risperidone or olanzapine.

Five double-blind placebo-controlled trials of adjunctive risperidone (0.5–8 mg) in PTSD have been reported (Bartzokis et al. 2005; Hamner et al. 2003; Monnelly et al. 2003; Reich et al. 2004; Rothbaum et al. 2008). Of these, three (Bartzokis et al. 2005; Monnelly et al. 2003; Reich et al. 2004) reported improvement in PTSD symptoms within the re-experiencing or hyperarousal clusters but no improvements were seen in the avoidance/numbing cluster. In contrast, Hamner et al. (2003) found in their sample of 40 combat veterans diagnosed with chronic PTSD and associated psychotic symptoms, adjunctive risperidone improved the psychotic but not overall post-traumatic symptoms. In the most recent study (Rothbaum et al. 2008), subjects who did not remit following 8 weeks of open label sertraline were randomized to a further 8 weeks of placebo or risperidone augmentation. At the end of the study, no differences were found between groups on CAPS overall score or individual clusters. However, post-hoc analyses did reveal an advantage for risperidone in terms of improved sleep. Only a single RCT of risperidone monotherapy in PTSD has been published (Padala et al. 2006). In this 12-week study of women ($N = 20$)

with PTSD stemming from sexual assault or domestic abuse, flexibly dosed risperidone (mean dose of 2.62 mg) was well-tolerated and superior to placebo on the primary outcome measure – score on the 8-item Treatment Outcomes PTSD Scale, but not on secondary outcomes (CAPS, HAM-D, or HAM-A).

The utility of olanzapine as an adjunctive agent has been investigated in a single RCT. Stein et al. (2002) randomized male veterans ($N = 19$) with combat-related PTSD but minimally responsive to an adequate trial of SSRIs to double-blind augmentation with olanzapine (10–20 mg) or placebo for 8 weeks. Olanzapine was associated with a significantly greater reduction in overall CAPS scores, relative to placebo, as well as greater improvements in sleep and depressive symptoms, although clinician ratings of global improvement did not differ statistically between groups. Of concern, however, was the mean 13 lb weight gain following olanzapine treatment which may be a significant issue impacting compliance and general health. As with risperidone, only a single RCT of olanzapine as monotherapy in PTSD has been reported (Butterfield et al. 2001). In contrast to the results of the risperidone study, the results of this 10-week double-blind placebo-controlled pilot study ($N = 15$) did not show differences in PTSD outcomes between olanzapine (5–20 mg) and placebo. Once again treatment with olanzapine resulted in significant weight gain (mean weight gain with olanzapine: 11.5 ± 4.4 lb vs. mean weight gain with placebo: 0.9 ± 0.06 lb) highlighting the need to weigh the benefits of olanzapine use against the potential health risks. The mixed results of RCTs involving these two medications in PTSD underscore the need for larger, more definitive clinical trials investigating these agents to justify their increasingly common use in the psychopharmacological management of PTSD.

5 Benzodiazepines and Other Hypnotics

Benzodiazepines (BZDs) have long played an important role in the management of anxiety disorders. Efficacy, rapid onset of action, and tolerability are all key factors in their popularity. However, with growing concerns about possible development of tolerance with long-term use and potential for abuse, and the development of newer, more tolerable antidepressants, the use of BZDs has declined considerably. Currently, BZD use in PTSD is largely directed towards symptomatic management of hyperarousal symptoms such as sleep disturbance. However, despite the long history of BZD use for anxiety, very few RCTs exist investigating their efficacy in PTSD.

In a 12-week cross-over trial (5-week treatment periods) of 10 subjects, alprazolam monotherapy showed some benefit for nonspecific anxiety, but not for specific PTSD symptoms (Braun et al. 1990). Cates et al. (2004) attempted to validate the common practice of providing BZDs for PTSD-related sleep disturbances with their 5-week, randomized, single-blind cross-over trial (2-week treatment periods) of clonazepam (1–2 mg). In their very small sample ($N = 6$),

clonazepam showed modest numerical but no statistical superiority over placebo on any of the sleep-related measures.

Two additional studies have investigated the effects of BZD administration in the acute aftermath of trauma. Gelpin et al. (1996) prospectively compared 13 trauma survivors who received either clonazepam or alprazolam in the days following the trauma (range 2–18 days) to 13 controls matched for symptom severity. At 6-month follow-up, 69% of the BZD-treated group but only 23% of controls had developed PTSD. In their single-blind trial, Mellman et al. (2002) randomized 21 subjects recently admitted to a trauma center to treatment with temazepam (15–30 mg) or placebo for 1 week. At 6-week follow-up, 50% of the temazepam-treated group but only 27% of the placebo-treated group had developed PTSD. Although both studies are limited by small samples, they suggest that early BZD administration following trauma is not helpful in the prevention of PTSD. There is also a commonly held clinical misconception that, because of the high rates of substance abuse among those with PTSD, it is necessary to exclude BZDs from the pharmacological management of these patients despite a lack of evidence to support this belief. It is possible that this faulty idea and the negative results of the studies above have contributed to the lack of recent research investigating BZDs in PTSD. Nevertheless, a review of medications prescribed for PTSD within the VA system revealed that BZDs are among the commonest class of medications used in its management (Mohamed and Rosenheck, 2008). Since BZDs are cost-effective, useful, and commonly prescribed anxiolytics, but have only been investigated in two very small trials, there is evidently an urgent need for larger clinical trials to either validate the earlier results or to re-explore potential utility of BZDs in the prevention or treatment of PTSD.

6 Antiadrenergic Agents

Dysregulation of the noradrenergic system is one of the proposed mechanisms involved in the pathophysiology of PTSD. The presence of the hyperarousal symptoms, such as hypervigilance and sleep disturbance, as well as abnormalities in different biological measures of norepinephrine suggested to researchers that a hyperadrenergic state was at play in PTSD. Based on this hypothesis, a number of investigators proposed a role for antiadrenergic medications in its treatment. Prazosin, a centrally acting selective α_1 adrenergic antagonist, is one agent that has received considerable interest lately for its effects on PTSD-related sleep disturbance. A double-blind, 20-week, cross-over trial in combat veterans with PTSD ($N = 10$) found prazosin (up to 10 mg) significantly more effective than placebo for improving sleep quality and decreasing distressing dreams (Raskind et al. 2003). Further, on the secondary measure of changes in CAPS scores, prazosin was associated with significant improvement across all symptom clusters. Extending these findings to a larger sample of combat veterans ($N = 40$) in an 8-week parallel-group study, prazosin (up to 15 mg) was again associated with improvements in overall sleep

quality and frequency of trauma-related nightmares (Raskind et al. 2007). Similarly, positive findings were seen in a 7-week placebo-controlled cross-over trial (3-week treatment periods) of civilians with PTSD ($N = 13$) (Taylor et al. 2008). Along with improvements in sleep quality and a shift in dream content from nightmares to more "normal" subject matter, prazosin was also associated with a substantial increase in total sleep time (94 min).

Two RCTs of guanfacine, a centrally acting α_2 adrenergic agonist, in PTSD have been reported. In the first, an 8-week, double-blind trial of veterans with PTSD ($N = 63$) guanfacine failed to demonstrate superiority over placebo on measures of post-traumatic symptoms, sleep, or depression (Neylan et al. 2006). Similarly, negative results were also found in a more recent 8-week RCT (Davis et al. 2008b). Clonidine, commonly used as an antihypertensive agent because of its effects on decreasing sympathetic outflow, has a similar mechanism to guanfacine. Although a single paper reported that a combination of clonidine and imipramine was helpful in the symptomatic improvement of Cambodian refugees suffering from chronic PTSD and major depression (Kinzie and Leung, 1989), no RCTs have been published to confirm this.

Although no RCTs have reported on the use of β-blockers to treat post-traumatic symptoms once they have developed, three controlled studies have examined their utility in the secondary prevention of PTSD following trauma exposure. Based on literature that propranolol appears to impair recall of emotionally arousing material (Cahill et al. 1994), investigators argued that β-blockers administered in the peri-traumatic period might inhibit the consolidation and subsequent ability to retrieve and replay traumatic memories. However, findings from these studies are inconsistent. Pitman et al. (2002) randomized 41 patients in the emergency department who had just experienced a traumatic event and had physiological signs of arousal (thought to predict those at risk of PTSD development) to treatment with either placebo or propranolol (160 mg in four divided doses) for 10 days, with the first dose of study medication administered within 6 h of the traumatic event. While no differences were found between groups on CAPS scores at either 1- or 3-month follow-up, the authors contended that propranolol-treated subjects had reduced physiologic responsiveness to trauma-related cues. The results must also be interpreted with caution because of the elevated attrition rate in the propranolol group. Later, Vaiva et al. (2003) prospectively followed 11 emergency department trauma patients who agreed to an open trial of propranolol (40 mg TID) for 7 days followed by a taper period comparing them to a group of 8 similar patients who refused propranolol but agreed to be assessed in follow-up by a psychiatrist blinded to the subject's treatment status. At 2-month follow-up, fewer propranolol-treated subjects met criteria for PTSD (9% vs. 37.5%, $p = 0.012$).

A more recent double-blind, 3-arm trial randomized 48 physically injured patients admitted to a surgical trauma center to 14 days of propranolol (up to 40 mg TID), gabapentin (up to 400 mg TID), or placebo (Stein et al. 2007), with the first dose of medication administered within 48 h of injury. In contrast to the earlier results, neither of the study drugs was significantly better than placebo in preventing acute stress disorder at 1-month follow-up nor PTSD at 4-month follow-up.

These earlier studies have focused on using β-blockers to inhibit retrieval of fear memories. More recently, Kindt et al. (2009) used a fear-conditioning paradigm to demonstrate that β-adrenergic receptors were also involved in the reconsolidation of fear memory. But more importantly, they showed that following acquisition of a fear response, the administration of propranolol given prior to reactivating the fear memory resulted in rapid elimination of the behavioral response to the fear – in this case, measured by eyeblink startle reflex. Of note, declarative memory remained unaffected. These findings have interesting clinical implications for PTSD. For instance, the use of a β-blocker prior to undergoing prolonged exposure therapy sessions (which is based on recalling aspects of the traumatic memory) may facilitate extinction of behavioral fear responses and accelerate recovery.

7 Other Agents

Even with multiple pharmacological options, rates of response to standard treatments in PTSD are often lower than clinicians would like. When the usual augmentation and combination strategies fail, novel treatments may be of use. Preliminary results from case series and open trials have been published for multiple agents including, among others, memantine (Battista et al. 2007), baclofen (Drake et al. 2003), dehyroepiandosterone (Sageman and Brown 2006), and cyproheptadine (Clark et al. 1999), not to mention other members of the medication classes discussed above. However, two novel agents that have been investigated in a controlled fashion are cortisol and D-cycloserine (DCS).

Hypothalamic-pituitary-adrenal axis dysfunction has been implicated in PTSD. Studies of glucocorticoids (GCs) and memory have found that elevated GC levels, as seen during acute stress, may enhance consolidation of emotional, or traumatic, memories (Roozendaal et al. 2006). One model of PTSD suggests that these memories get retrieved, replayed, and reconsolidated thereby strengthening the traumatic memory – this may potentially contribute to the frequency of intrusive memories and other re-experiencing type symptoms (Pitman 1989). However, elevated GC levels have also been found to impair memory retrieval, particularly for emotionally arousing material (Buchanan et al. 2006). Aerni et al. (2004) suggested that the administration of exogenous GCs (e.g., cortisol) may be useful in impeding the recall of traumatic memories thus allowing newer nontraumatic memories to be encoded and resulting in eventual fear extinction. Three patients were randomized to 1 month of daily cortisol (10 mg) and placebo for 2 months in this randomized, double-blind, cross-over trial. While the results must be very cautiously interpreted, the authors found that cortisol treatment was associated with modest improvement of both re-experiencing and avoidance-numbing type symptoms.

Based on literature supporting a role for glutamatergic dysfunction in PTSD (Nair and Singh 2008), DCS, a partial agonist of the *N*-methyl-D-aspartate (NMDA)

receptor, has been investigated as a treatment. Results from a 12-week, double-blind, cross-over trial (4-week treatment periods) of 11 subjects suggest that DCS (50 mg) may be effective for numbing/avoidance symptoms of PTSD, although subjects also demonstrated a degree of improvement during placebo treatment (Heresco-Levy et al. 2002). Both of the agents discussed here would be served by replication with larger samples to clarify their utility for PTSD, particularly given their unique mechanisms of action.

8 Conclusions

Several classes of psychotropic medications have been investigated for efficacy in PTSD. Of the effective medications, the largest evidence base exists for antidepressants and particularly for the SSRIs. In spite of the conclusion of the Institute of Medicine that there was insufficient evidence to support their use in PTSD, most clinicians continue to use these drugs as first line agents. Their general tolerability, benefits across the multiple symptom clusters of PTSD, and efficacy for the comorbid psychiatric disorders that commonly occur with PTSD (e.g., depression) ensure that SSRIs will remain a favored treatment option for now. Although SNRIs represent a viable first line alternative to SSRIs, management strategies beyond this are less clear. Based on the available evidence, reasonable next steps might include augmentation with an atypical antipsychotic, anticonvulsant (e.g., lamotrigine), or even the antiadrenergic agent prazosin. The use of concurrent psychotherapy, such as prolonged exposure, might also be helpful. This lack of clarity regarding optimal treatment strategies in the face of partial or nonresponse to standard first-line medications highlights the need for larger, definitive trials that address these questions. A trial, similar to the Sequenced Treatment Alternatives to Depression ("STAR*D") study (Rush 2007) might be helpful in clarifying guidelines regarding these issues in PTSD.

Future research should also focus on the development of novel pharmacological agents that specifically target PTSD. The medications that are currently in use for PTSD have, in large part, been developed for other disorders before being investigated for post-traumatic symptoms. A better understanding of the underlying pathophysiology and neural circuitry affected in PTSD will be helpful in detecting unique pharmacologic targets or mechanisms which can in turn be used to develop specific compounds of use for this illness. As with other psychiatric disorders, an additional goal of future research should be identifying predictors of response to specific interventions to allow for individualized treatment; hopefully, the fields of genetics and neuroimaging will be useful for this purpose. Regardless of what type of treatment is provided, be it psychotherapeutic or pharmacologic in nature, ensuring effective delivery and compliance will be crucial in achieving the ultimate goal of treatment: remission of symptoms and optimal psychosocial function.

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