A Review of Pharmacotherapy for Posttraumatic Stress Disorder (PTSD)

Objectives

1. Describe posttraumatic stress disorder (PTSD) and its associated symptoms according to DSM-5 diagnostic criteria
2. Review medications that may be used to treat PTSD based on NICE and VA/DoD treatment guidelines
3. Discuss the mechanism of action, dosing, and common side effects of various medications used in the treatment of PTSD in detail along with specific patient education counseling points
Abstract

Objective: After reading this article, the reader should be able to describe symptoms associated with PTSD, list medications used in treatment, and be able to educate patients on important counseling points with regard to these medications in the treatment of PTSD.

Summary: It is estimated that the lifetime prevalence of posttraumatic stress disorder (PTSD) among adult Americans is 6.8 percent. In veterans, this percentage increases up to 30 percent. The Diagnostic and Statistical Manual, 5th edition (DSM-5) discusses the symptom clusters of PTSD which can include intrusion symptoms, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. According to VA/DoD and NICE treatment guidelines, first-line treatment options may include sertraline, fluoxetine, paroxetine, venlafaxine, mirtazapine, prazosin for PTSD-related nightmares, and psychotherapy. Other pharmacologic options that have shown some benefit include phenelzine, nefazodone, and tricyclic antidepressants (TCAs). There is insufficient evidence to recommend use of other treatments such as anticonvulsants or antipsychotics for adjunctive therapy in PTSD. Finally, there is evidence against the use of benzodiazepines (BZDs) in the treatment of PTSD. With antidepressant medications, several side effects may occur such as anxiety, headache, nausea, diarrhea, antidepressant discontinuation syndrome, and sexual dysfunction. It is important that patients are educated on these side effects and the treatment strategies to alleviate them.

Conclusion: The treatment of PTSD can involve a variety of pharmacological and non-pharmacological approaches. In order for treatment to be most successful, patient education is key.
Key words: PTSD, antidepressant, prazosin, SSRI

Introduction

Posttraumatic stress disorder (PTSD) is one of the most common psychiatric disorders among national military personnel. Although 50 to 90 percent of the general population may be exposed to a traumatic event during his or her lifetime, most individuals do not develop PTSD.\textsuperscript{1,2} The National Comorbidity Survey Replication (NCS-R) estimated the lifetime prevalence of PTSD among adult Americans to be 6.8 percent.\textsuperscript{3} It is estimated that up to 20 percent of veterans of the Iraq and Afghanistan wars (Operations Iraqi and Enduring Freedom), 10 percent of Gulf War (Desert Storm) veterans, and 30 percent of Vietnam veterans have PTSD.\textsuperscript{1}

There are several factors that can increase the risk of developing PTSD. Some of these include if a person was directly exposed to the trauma as a victim or witness, if the trauma was very severe or long-lasting, or if a person had a severe reaction during the event, such as shaking or feeling apart from the surroundings.\textsuperscript{4,5} There are also several comorbidities associated with PTSD including generalized anxiety disorder (GAD), major depressive disorder (MDD), substance use disorder, and alcohol abuse or dependence.\textsuperscript{3} It has been shown that 60 to 80 percent of Vietnam veterans seeking PTSD treatment have an alcohol use problem.\textsuperscript{6} The reason for this high percentage is likely due to the depressant effects of alcohol. Although the pathophysiology of PTSD is not quite understood, there are several theories. Theories include: altered glutamatergic processes with respect to information processing, altered memory function, abnormal increases in sympathetic nervous system activity, dysregulation of the hypothalamic-pituitary-adrenal axis (HPA), and abnormal serotonin (5-HT) activity.\textsuperscript{7}
Symptoms of PTSD

In the United States, the Diagnostic and Statistical Manual (DSM) serves as a general guide for the diagnosis of psychiatric disorders. It has recently been updated and was released in May 2013.8 There were some major changes with regard to the diagnostic criteria for PTSD. First, PTSD is no longer considered an anxiety disorder. It is now listed under “Trauma and Stressor-Related Disorders.” Instead of PTSD consisting of three symptom clusters as it did in DSM-IV, the updated DSM-5 divides it into four symptom clusters. These include intrusion symptoms (e.g. distressing memories, dreams, or flashbacks), avoidance (e.g. avoiding places or people that remind the person of the traumatic event), negative alterations in cognitions and mood (e.g. inability to remember an important aspect of the event, feeling detached from others, or negative beliefs), and alterations in arousal and reactivity (e.g. irritable behavior, hypervigilance, problems with concentration, reckless behavior, or sleep disturbance). Symptoms in the last cluster may be similar to symptoms consistent with bipolar disorder or attention-deficit/hyperactivity disorder (ADHD). Therefore, it is important that these diagnoses be ruled out before a diagnosis of PTSD is made.

In addition to assessing for subjective symptoms as noted above, it can also be helpful to administer the PTSD Checklist (PCL).9,10 There are different versions of the PCL including a civilian and a military version (PCL-C or PCL-M). This scale is a 17-item, standardized self-report rating scale that takes only five to ten minutes to complete. It can be used to determine the severity of PTSD overall or to determine which symptom clusters are most bothersome. If desired, treatment can be guided by the patient’s PCL score. Overall, a ten to 20 point change from baseline is considered clinically significant. A clinically significant change means that the treatment being utilized is effective.
Treatment

There are several treatment guidelines for PTSD. These include the American Psychiatric Association (APA) (2004), the British Association for Psychopharmacology (2005), Canadian Psychiatry Association (2006), World Federation of Societies of Biological Psychiatry (WFSBP) (2008), Veterans Association Department of Defense (VA/DoD) (2010), and the National Institute for Health and Clinical Excellence (NICE) (2011) treatment guidelines. The remainder of the discussion will focus on treatments for PTSD according to both the VA/DoD and NICE guidelines as these are the most current.\textsuperscript{11,12}

Antidepressants

Most treatment guidelines list antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), as first-line treatment considering these agents are effective for all symptom clusters of PTSD. In the VA/DoD guidelines, fluoxetine, sertraline, and paroxetine have the largest collection of evidence demonstrating their efficacy.\textsuperscript{13} In addition, venlafaxine, a serotonin-norepinephrine reuptake inhibitor, is another first-line agent and can also treat all four symptom clusters.\textsuperscript{13,14} With regard to non-pharmacological treatment, psychotherapy is considered to be first-line alone or in conjunction with pharmacotherapy. The evidence-based psychotherapeutic options for PTSD that are most strongly supported by randomized controlled trials include prolonged exposure (PE), cognitive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR) or stress inoculation training.\textsuperscript{11} If patients do not respond to a specific SSRI or venlafaxine, the provider should switch to another agent (e.g., an alternative SSRI or venlafaxine) and/or add psychotherapy. If the patient fails to clinically respond, the provider can switch to mirtazapine and/or psychotherapy. Finally, if the patient is
still not responding to treatment, the last step is to switch the patient to phenelzine, nefazodone, or a tricyclic antidepressant (TCA) and add psychotherapy. Mirtazapine, phenelzine, nefazodone, and TCAs have been shown to be effective for all symptoms clusters with the exception of avoidance.\textsuperscript{11}

Interestingly, the NICE guidelines do not recommend pharmacological treatment as first-line therapy unless the individual refuses trauma-focused psychological treatment (e.g. trauma-focused cognitive behavioral therapy [CBT] or EMDR). If the individual decides to proceed with pharmacological treatment, paroxetine or mirtazapine are the preferred agents if prescribed by a general provider. Amitriptyline or phenelzine may also be an option, but these agents should only be prescribed by a mental health specialist.\textsuperscript{12} Initial and maximum doses of these agents along with their titration schedules are listed in Table 1. Patients should be educated on antidepressant therapy prior to initiation. Education should include potential side effects and strategies to alleviate these side effects, the delay in onset of action and the amount of time needed to achieve a response, and the risk of discontinuation/withdrawal syndrome.

**Mechanism of Action and Side Effects of Antidepressants SSRI/SSNRIs\textsuperscript{15,16}**

Selective serotonin reuptake inhibitors (SSRIs) act on the serotonin transporter (SERT) pump. Inhibition of the SERT results in an increase of serotonin in the body. Serotonin-norepinephrine reuptake inhibitors (SNRIs) act in a similar fashion, however they also inhibit the reuptake of norepinephrine in addition to serotonin.

The main side effects of SSRIs and SNRIs include nausea, diarrhea, headache, dizziness, sexual dysfunction, and/or what is known as “jitteriness syndrome.” Jitteriness syndrome may occur when initiating a SSRI/SNRi and includes shakiness or tremor, increased anxiety, and
insomnia. Some common treatment strategies for jitteriness syndrome include using a lower initial dose or slower titration.

There are specific side effects associated with each antidepressant mentioned previously. Fluoxetine is considered to be the most stimulating SSRI. Therefore, for some patients, this agent can potentially worsen anxiety or irritability. It is important that fluoxetine is administered in the morning as it can cause insomnia if dosed at bedtime. In addition, fluoxetine and its metabolite have long half-lives and therefore, tapering is not necessary when discontinuation of this agent occurs. Sertraline has been shown to have a higher risk of gastrointestinal discomfort (e.g., diarrhea/nausea) in comparison to other SSRIs. Taking sertraline with food may help alleviate this side effect. Paroxetine has the highest risk of sexual dysfunction, weight gain, and anticholinergic side effects such as dry mouth and constipation. It also has the shortest half-life and can lead to more pronounced withdrawal symptoms if the patient misses a dose. The SNRI, venlafaxine, may also be stimulating for patients receiving higher doses resulting in anxiety or irritability. Venlafaxine may lead to elevated blood pressure due to an increase in norepinephrine. At lower doses (e.g. 75 mg/day), venlafaxine acts mostly on serotonergic receptors versus adrenergic receptors and may not affect blood pressure as compared to higher doses (e.g. 150 to 225 mg/day). It is important to monitor blood pressure at each visit if a patient is on venlafaxine. Similar to paroxetine, venlafaxine has a short half-life which can lead to withdrawal symptoms upon abrupt discontinuation. Therefore, this antidepressant should be tapered upon discontinuation.

Sexual dysfunction is a particularly concerning side effect that can occur in up to 70 percent of patients taking an SSRI. However, it is important to note that depression or anxiety itself can cause sexual dysfunction along with a variety of other health conditions
including smoking, alcohol use, cardiovascular disease, and diabetes. To help guide treatment, a provider should ask the patient to describe their sexual dysfunction in more detail. For example, if a patient is having difficulty with ejaculation, phosphodiesterase-5 (PDE-5) inhibitors will not be beneficial as these agents are primarily effective for erectile dysfunction (ED). The sexual side effects that can occur with antidepressant therapy include delayed orgasm, anorgasmia, problems with ejaculation (e.g., delayed ejaculation), and erectile dysfunction. There are several approaches to the treatment of sexual dysfunction.\textsuperscript{18,19} One approach to treatment is the ‘watch and wait’ strategy. Within six months, it has been shown that roughly ten percent of patients report remission of sexual dysfunction and improvement may be noted in up to 15 to 20 percent of patients. Lowering the dose of the antidepressant may be considered, although there is a risk of worsening PTSD and/or depressive symptoms. Studies on PDE-5 inhibitors and bupropion are conflicting, however, a provider may add either as an adjunctive therapeutic option. Another strategy to consider is switching the antidepressant to one with a lower risk of sexual dysfunction (e.g., bupropion, mirtazapine, or nefazodone). Of note, bupropion is a stimulating antidepressant that may lead to worsening of PTSD symptoms. In addition, there is an insufficient amount of literature supporting its use in PTSD. Finally, since there is a risk of seizures with bupropion, it is not recommended in patients with a history of seizure disorder. A summary of antidepressant side effects and treatment approaches can be found in Table 2.

**Other Antidepressant Agents**\textsuperscript{15,16}

Other antidepressants that can be used in the treatment of PTSD include mirtazapine, phenelzine, nefazodone, or tricyclic antidepressants (TCAs). Through negative feedback, mirtazapine increases the levels of serotonin and norepinephrine by blocking pre-synaptic alpha-
2 receptors. Mirtazapine also acts as an antagonist at serotonin-2A and 2C (5-HT$_{2A}$ and 5-HT$_{2C}$), serotonin-3 (5-HT$_3$), and histamine-1 (H$_1$) receptors. Due to the blockade of 5-HT$_2$ and 5-HT$_3$ receptors, 5-HT$_1$ mediated transmission is enhanced. Mirtazapine has a lower risk for sexual dysfunction as compared to SSRIs and SNRIs which is believed to be attributed to its effects on 5-HT$_1$ and 5-HT$_2$ receptors. In addition, due to the potent blockade of the H$_1$ and 5-HT$_{2C}$ receptors, mirtazapine can be quite sedating, may increase appetite, and cause weight gain. This agent should be dosed at bedtime. Interestingly, when mirtazapine is used at lower doses (e.g., 7.5 mg/day), it is more likely to cause sedation and weight gain compared to higher doses (e.g., 15-30 mg/day). The higher doses of mirtazapine tend to be less sedating, less likely to cause weight gain, and more likely to be efficacious for mood.

Phenelzine is a monoamine oxidase inhibitor (MAO-I). This agent inhibits the activity of the MAO enzyme, which breaks down monoamine neurotransmitters including norepinephrine, dopamine, and serotonin. If a patient is initiated on a MAO-I, a strict diet must be followed in which foods high in tyramine content must be limited or avoided altogether (e.g., aged cheese, processed meats). Tyramine can trigger a cascade which may cause a rise in norepinephrine in the body. Therefore, if a patient does not adhere to this diet, then a hypertensive crisis can result. In addition, prior to starting an MAO-I, a wash-out period of 14 days is usually recommended if a patient is being switched from another antidepressant. Since fluoxetine has a longer half-life, it is recommended to wait at least five weeks after stopping this agent prior to initiating a MAO-I. Other side effects of MAO-I's include dry mouth, constipation, orthostatic hypotension, and insomnia.

Nefazodone is an antidepressant that is similar to trazodone in terms of its mechanism of action, however it also acts upon noradrenergic receptors, has a lower affinity for alpha-1
receptors, and lacks histamine activity. Nefazodone increases levels of serotonin and norepinephrine, antagonizes 5-HT\(_2\) and slightly antagonizes alpha-1 receptors. As a result, there is a lower risk for both sexual dysfunction and postural hypotension. There is a black box warning for hepatotoxicity which warrants the monitoring of liver function periodically throughout treatment. Nefazodone is also a potent inhibitor of CYP3A4, therefore, potential drug/drug interactions should be monitored.

Tricyclic antidepressants (TCAs) include agents such as amitriptyline, imipramine, nortriptyline, and desipramine. With regard to their mechanism of action, these agents are very similar to SNRIs as they can increase both serotonin and norepinephrine levels. The TCAs are metabolized to secondary and tertiary amines. The secondary amines (desipramine and nortriptyline) are more potent at noradrenergic receptors and are thought to have a lower incidence of side effects as compared to tertiary amines. TCAs also act on several other receptors including H\(_1\), alpha-1, and acetylcholine receptors. Several side effects can result from this receptor binding profile including sedation, orthostatic hypotension, blurred vision, dry mouth, and constipation. In addition, there is a warning for potential cardiac side effects such as ventricular arrhythmias and tachycardia. Due to these various reasons, TCAs have the potential to be toxic in overdose and are usually not recommended in patients with suicidal ideation.

**Time to Effect for Antidepressants**

It is important that patients are educated on the length of time it can take for an antidepressant to be effective. Contrary to the belief that these agents work immediately, it may take up to four to six weeks at an adequate dose to see mood improvement.\(^{15,16}\) An adequate antidepressant dose can be loosely defined as the minimally effective tolerated dose that has been
shown to improve symptoms in clinical trials. Therefore, an adequate dose of an antidepressant may be different for each individual. The initial dose of an antidepressant is not likely to be an adequate dose and should be increased if needed/tolerated.

Almost immediately however, patients may notice side effects such as diarrhea, nausea, or anxiety. These side effects usually dissipate within a few days to a week. This is an important counseling point since patients who start an antidepressant may develop side effects early on, but show no improvement. Patients may discontinue their medication because they believe it is not effective. Withdrawal symptoms may occur and may also lead to poor control of PTSD.

Antidepressant Discontinuation Syndrome

Patients should be counseled to avoid abrupt discontinuation of an antidepressant medication as it can lead to what is known as antidepressant discontinuation or withdrawal syndrome. Symptoms of this syndrome include nausea, flu-like symptoms, tremor, anxiety, and/or “electric shock” sensations throughout the body and head. This syndrome is most common with antidepressants that have a shorter half-life such as paroxetine and venlafaxine and least likely to occur with fluoxetine therapy.

Other Medications Used in the Treatment of PTSD

Other classes of medications that are commonly used in the treatment of PTSD include antipsychotics and anticonvulsants. Of note, none of the agents in these classes are FDA approved for the treatment of PTSD.
Second Generation Antipsychotics (SGAs)

In the VA/DoD treatment guidelines, second generation antipsychotics (SGAs) as adjunct therapies are listed as “unknown benefit.” The NICE guidelines list risperidone and olanzapine as having “limited evidence” as adjunct therapy. There have been ten published randomized controlled trials examining olanzapine and risperidone and two trials examining quetiapine as adjunct therapy in PTSD.\textsuperscript{21-32} One of the main drawbacks of these trials is the small number of patients studied (n = 15 to 48). In addition, not all of the trials involve the combat veteran population. In summary, the results of these studies are variable and the details can be viewed elsewhere.\textsuperscript{11, 21-32}

One randomized, multicenter double-blind, placebo-controlled VA study involving nearly 300 patients was performed in 2011.\textsuperscript{27} This was the largest controlled trial to date examining a SGA as adjunctive therapy in PTSD. Veterans received risperidone up to 4 mg per day as adjunctive therapy versus placebo for chronic military service-related PTSD. The primary endpoint was a change in Clinician-Administered PTSD Scale (CAPS) score from baseline to 24 weeks. A change of 15 points in the CAPS score was considered to be clinically significant. The results of this study found that risperidone was no better than placebo in reducing PTSD symptoms. After this study, an update was made to the VA/DoD treatment guidelines which now specifically list risperidone as “no benefit” versus other SGAs which still are listed as “unknown benefit.” Both VA/DoD and NICE treatment guidelines conclude that there is insufficient evidence to recommend the use of any SGA as adjunct therapy in the treatment of PTSD. It should also be noted that patients with PTSD may have psychotic features as a part of this syndrome. There is a lack of sufficient data in this area. Psychotic symptoms must first be differentiated as part of PTSD or due to a comorbid psychotic disorder. If the symptoms are
thought to be part of PSTD, the treatment of choice is a SSRI. If a patient fails to respond to SSRI therapy, a SGA may be used to augment therapy.\textsuperscript{11} No data are available on the use of first generation antipsychotics (FGAs) in the treatment of PTSD. If PTSD is thought to be a comorbid condition with a psychotic disorder, an antipsychotic (either SGA or FGA) should be initiated.\textsuperscript{11}

There are some studies examining the use of SGAs for the treatment of insomnia or nightmares in PTSD. However, data supporting the use of SGAs for the treatment of nightmares in PTSD is sparse compared to prazosin. One study examined prazosin versus quetiapine.\textsuperscript{33} This cohort study involving 237 veterans found that the two drugs had similar efficacy which was defined as symptomatic improvement over the course of six months (61% versus 62%, \(p=0.54\)). However, a higher percentage of patients continued on prazosin long-term (three to six years) versus those taking quetiapine (48% versus 24%, \(p<0.001\)). Patients were more likely to discontinue quetiapine due to lack of efficacy (13% versus 3%, \(p=0.03\)) and adverse effects (35% versus 18%, \(p=0.008\)) compared to prazosin.

Overall, there are several risks associated with SGAs, including weight gain, elevations in lipid and blood glucose levels, hypotension, cardiac effects, and movement disorders.\textsuperscript{15,16} Therefore, SGAs are reserved as a last-line treatment option for PTSD that has not responded to first line therapies or to treat comorbid psychotic symptoms in PTSD.

**Anticonvulsants**

The VA/DoD and NICE treatment guidelines state there is insufficient evidence to recommend an anticonvulsant as adjunctive therapy for the treatment of PTSD. However, mood stabilizers may have a possible role in PTSD for patients who have specific intrusion symptoms,
such as re-experiencing and hyperarousal, and may even help treat affective instability.\textsuperscript{11,12} There have been several open-label and randomized controlled trials examining divalproex, carbamazepine, lamotrigine, topiramate, lithium, and phenytoin which have demonstrated mixed or limited efficacy. It appears that divalproex has the most literature, although results are varied.\textsuperscript{34,35} A meta-analysis was performed in 2007 which examined divalproex as adjunct therapy for the treatment of PTSD. It involved one single-blinded study, four open-label studies, and three case reports. The analysis demonstrated that divalproex could be beneficial in reducing hyperarousal, improving irritability, anger outbursts and mood.\textsuperscript{36} Unfortunately, these studies were small in number and did not include any double-blind trials. The dose ranged from 1250 – 1400 mg per day, but the dose is typically based on weight (target 10-15 mg/kg/day). Adverse effects may include sedation, nausea, weight gain, thrombocytopenia, alopecia, and pancreatitis.\textsuperscript{16}

**Benzodiazepines**

All guidelines recommend against the use of benzodiazepines (BZDs) in PTSD. There is no evidence that BZDs reduce core symptoms of PTSD. The use of these agents can interfere with the extinction of fear conditioning and worsen recovery from trauma.\textsuperscript{11} Fear conditioning is a behavioral model in which people learn to predict hostile events. Patients who have PTSD often have alterations in arousal and reactivity. Therefore, they may misinterpret their surroundings as a hostile environment. Benzodiazepines can interrupt restructuring of this thought process.\textsuperscript{11} In addition, there is a high percentage of patients with PTSD who also have a substance use disorder and/or history of a traumatic brain injury (TBI).\textsuperscript{3,6} This is concerning because an increased risk of respiratory depression may occur when combining BZDs with alcohol or
opioids. In patients who have a history of TBI, BZDs can cause paradoxical agitation/aggression.\textsuperscript{37} In the VA/DoD treatment guidelines, BZDs are listed as “no benefit/harm.” Unfortunately, if a patient is already on a BZD, it can be difficult to withdraw the agent. The discontinuation of a BZD can result in anxiety, sleep disturbances, rage, hyperalertness, increased nightmares, and intrusive thoughts. These withdrawal symptoms have been reported after as little as five weeks of therapy.\textsuperscript{16} A BZD should never be discontinued abruptly. When discontinuing a BZD, the taper schedule depends on the length of time the patient was on the BZD. For example, if a patient was previously on a BZD for greater than one year, the taper can occur over two to four months. A general rule of thumb for discontinuation to avoid withdrawal is to reduce the dose by 50 percent the first two to four weeks and maintain that dose for one to two months. Then, reduce the dose by 25 percent every two weeks.\textsuperscript{38}

\textbf{Prazosin for the Treatment of Nightmares}

Patients who experience the intrusion symptom of nightmares with PTSD should be tried on prazosin therapy. This agent is considered to be the first-line option for PTSD-related nightmares and has been shown to be more effective versus quetiapine as noted above.\textsuperscript{33} In combat, a rush of adrenaline or norepinephrine can occur and help soldiers stay alert. Unfortunately, this may become persistent and maladaptive in normal situations in which this rush of adrenaline is not needed. Prazosin can normalize the arousal response to norepinephrine in low threat environments.\textsuperscript{39} It is a centrally active alpha-1 adrenergic antagonist that is FDA approved for the treatment of hypertension.\textsuperscript{16} Prazosin is thought to be the most effective alpha antagonist due to its high lipophilicity. It has the ability to penetrate the blood brain barrier to a greater extent than doxazosin and terazosin which cross the blood brain barrier poorly.\textsuperscript{40}
However, prazosin has a short half-life (two to three hours) and its duration of action ranges from six to twelve hours.\textsuperscript{16} As a result, more frequent dosing may be needed to manage hyperarousal symptoms during the day.

Prazosin was originally examined by Dr. Raskind in 1995. It was first thought that PTSD-related nightmares were the result of a general adrenergic effect. However, it was noted that when propranolol was administered, a beta-adrenergic antagonist, nightmares became worse. In contrast, when prazosin was administered, it was quite effective.\textsuperscript{41} In the open-label case study that was performed, four combat veterans with PTSD were treated for 8 weeks with prazosin.\textsuperscript{42} Nightmare severity was measured using the nightmare item from the CAPS and Clinical Global Impression of change (CGI) scale. Two patients achieved a daily dose of 5 mg per day of prazosin. These patients markedly improved and had complete resolution of nightmares. The other two patients received 2 mg daily due to having low blood pressure at baseline. The patients that received the lower dose of prazosin moderately improved and had at least a 50 percent reduction in nightmare severity. There have been several studies since involving prazosin that have demonstrated both safety and efficacy in trauma-related nightmares, sleep disturbances, and overall PTSD severity and function.\textsuperscript{43-45} Despite the fact that prazosin has been shown to be helpful for global PTSD symptoms, the goal of the studies was to evaluate the targeted symptoms of nightmares and sleep disturbances. Therefore, the VA/DoD treatment guidelines currently list prazosin as “unknown” for the treatment of global PTSD symptoms.

Based on the studies from Raskind et al., the initial dose of prazosin should be 1 mg at bedtime, and the average dose ranges from 9 to 13 mg per day. Although the maximum dose is listed as 20 mg per day for hypertension, some patients may require a higher dose if needed and tolerated. Divided dosing of prazosin to manage daytime hyperarousal symptoms is currently
being studied. Side effects of prazosin include hypotension, dizziness, and headache.\textsuperscript{16} A slow titration can help to reduce these adverse effects. Once the dose is increased up to 6 mg at bedtime, patients are usually able to tolerate higher doses when titrated (see Table 1). An important counseling point for patients is to take prazosin on a daily basis, not as needed. If patients discontinue prazosin, the nightmares and hyperarousal symptoms usually return. Finally, in order for prazosin to be most effective, the dreams should be trauma nightmares that reenact the event and include sympathetic arousal (e.g., sweating, racing heart) versus normal bizarre dreams. Prazosin will not eliminate dreams altogether, but changes traumatic nightmares to normal dreams.\textsuperscript{41}

One major drug interaction to be aware of is the combination of prazosin and another alpha antagonist such as terazosin or doxazosin often used for benign prostatic hypertrophy (BPH).\textsuperscript{16,46} This combination is considered to be a duplication in therapy. To manage this drug/drug interaction, it is recommended to switch from terazosin or doxazosin to prazosin monotherapy. The conversion is 1:1 for terazosin to prazosin, and 1:1 for doxazosin to prazosin (except 4 mg doxazosin = 5 mg prazosin). However, for doses greater than 4 or 5 mg/day for doxazosin and terazosin, one should start with prazosin 5 mg at bedtime and titrate up if needed.\textsuperscript{16}

\textbf{Other Medications for the Treatment of PTSD-Related Nightmares}

There are several other medications that may be used in the treatment of PTSD-related nightmares, but the data are low grade and sparse. Potential treatments include trazodone, SGAs, topiramate, fluvoxamine, phenelzine, gabapentin, cyproheptadine, clonidine, and TCAs (Level C evidence – assessment is supported by low grade data without the volume to recommend more
highly and likely subject to revision with further studies). With regard to cyproheptadine, a few open-label trials suggest that this antihistamine may be a potential option for nightmares. Cyproheptadine acts as a H₁ and 5-HT₂ receptor antagonist. It has been shown that 5-HT₂ antagonists increase stages of slow-wave sleep without altering total sleep time and can improve sleep outcomes. Most of the other trials examining cyproheptadine are small and open-label. The dose can range from 4 mg to 24 mg at bedtime and results are usually seen within a few days of treatment. Side effects include dizziness, increased appetite, and sedation. In theory, there is some concern that cyproheptadine can reverse the effects of a SSRI, although this has not been clinically demonstrated in studies.

Clonidine is an alpha-2 agonist that is thought to work by decreasing centrally mediated adrenergic activity which may help alleviate PTSD arousal symptoms (Level C evidence). In an open-label trial performed in 2007, the dose of 0.2 to 0.6 mg daily improved intrusive symptoms, startle, anger, vigilance, and nightmares. Common side effects of clonidine include low blood pressure, rebound hypertension, dry mouth, and sedation.

**Conclusion**

In summary, although there is clear evidence for the use of certain antidepressants and prazosin in the treatment of PTSD and PTSD-related nightmares, respectively, there is limited evidence with regard to other agents including antipsychotics and anticonvulsants. Prazosin may not only be helpful in treating PTSD-related nightmares but also for hypervigilance during the day and improving overall global PTSD symptoms. The routine use of prazosin for the latter indications will depend on future studies. There are several important counseling points with each medication that patients should be made aware of if any of these agents are prescribed. If
patients know what to expect with various treatments, they are more likely to be adherent with their medications and ultimately improve their health-related outcomes for PTSD.
References


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25


Table 1: Doses of Medications Commonly Used in the Treatment of PTSD\textsuperscript{11,12,16}

<table>
<thead>
<tr>
<th>Antidepressant Generic (Brand)</th>
<th>Initial dose (mg/day)</th>
<th>Titration</th>
<th>Maximum dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10</td>
<td>10 – 20 mg every 2 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25</td>
<td>Increase by 50 mg within 1 week, then by 25 – 50 mg every 1 – 2 weeks</td>
<td>200</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10</td>
<td>10 mg every 2 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Venlafaxine (Effexor or Effexor XR)</td>
<td>37.5</td>
<td>Increase to 75 mg within the first week, then by 37.5 – 75 mg every 2 weeks</td>
<td>375 (IR) 225 (XR)</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>15</td>
<td>15 mg every 2 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Phenelzine (Nardil)</td>
<td>15</td>
<td>15 mg every 4 days as tolerated</td>
<td>75</td>
</tr>
<tr>
<td>Nefazodone (Serzone)</td>
<td>200</td>
<td>100 – 200 mg (in 2 divided doses) every week</td>
<td>600</td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>25 – 100</td>
<td>25 – 50 mg every week</td>
<td>300</td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td>100 – 200</td>
<td>100 mg every week</td>
<td>300</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>50</td>
<td>25 – 50 mg every week</td>
<td>150</td>
</tr>
<tr>
<td>Prazosin (Minipress)</td>
<td>1</td>
<td>Days 1 – 3: 1 mg Days 4 – 7: 2 mg Week 2: 4 mg Week 3: 6 mg Week 4: 10 mg *After week 4, the dose can be increased by 5 mg increments until symptoms are resolved *If therapy is interrupted for 3 or more days, then reinitiate at the lowest dose and re-titrate according to schedule</td>
<td>20 (or higher if needed/tolerated)</td>
</tr>
</tbody>
</table>

*IR = immediate release; XR = extended release
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>• Start with a lower dose and titrate slowly</td>
</tr>
<tr>
<td>Insomnia or sedation</td>
<td>• Adjust time of day that patient takes the medication</td>
</tr>
<tr>
<td>Headache</td>
<td>• Take at bedtime. Of note, antidepressants may cause insomnia if dosed at bedtime.</td>
</tr>
<tr>
<td>Nausea</td>
<td>• Take with food</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>• May go away with continued treatment; however, may need to switch to another antidepressant</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>• “Watch and wait”</td>
</tr>
<tr>
<td></td>
<td>• Reduce the dose of the antidepressant</td>
</tr>
<tr>
<td></td>
<td>• Switch to another antidepressant that has lower risk of sexual dysfunction (e.g., mirtazapine, bupropion, or nefazodone)</td>
</tr>
<tr>
<td></td>
<td>• Adjunctive therapy with a PDE-5 inhibitor if the issue is erectile dysfunction; adjunctive therapy with bupropion</td>
</tr>
</tbody>
</table>
Self-assessment questions

1. Which of the following is NOT a symptom cluster of PTSD?
   a. Intrusion symptoms
   b. Avoidance
   c. Psychosis
   d. Negative alterations in cognitions and mood

2. All of the following medications are considered to be reasonable options as monotherapy for the treatment of PTSD according to NICE and VA/DoD treatment guidelines EXCEPT:
   a. Sertraline
   b. Bupropion
   c. Venlafaxine
   d. Mirtazapine

3. You are a pharmacist reviewing orders and realize that a provider entered an order for prazosin 1 mg QHS for nightmares, but the patient is already taking terazosin 2 mg QHS for BPH. What do you recommend?
   a. Discontinue prazosin as this is duplicate therapy and it cannot be used
   b. Start prazosin in combination with terazosin but monitor blood pressure closely
   c. Discontinue prazosin and increase terazosin slowly until effective for nightmares
   d. Switch terazosin to prazosin as a 1:1 conversion and titrate prazosin as needed/tolerated

4. A provider comes to you and says, “I really would like to try an antipsychotic for my patient who has PTSD and is having a lot of difficulty with irritability and re-experiencing. Which one is the best?” Although there is limited evidence for the use of antipsychotics for the treatment of PTSD, which agent should NOT be recommended per the VA/DoD treatment guidelines due to a large study published in 2011?
   a. Risperidone
   b. Quetiapine
   c. Olanzapine
   d. Aripiprazole

5. A patient is taking sertraline 200 mg/day and is experiencing sexual dysfunction. The provider calls you and asks what the best option would be. You respond:
   a. I first need to know what the patient is actually experiencing as this will guide the treatment
   b. Increase the dose to 250 mg/day as lower doses can cause more sexual dysfunction
   c. Add on sildenafil 50 mg/day if needed for sexual dysfunction
   d. Switch the patient to paroxetine 40 mg/day
6. A patient calls you and explains that she missed two doses of her antidepressant that she takes for PTSD because she went away for the weekend. She describes that she feels shock-like sensations all over her body, is very anxious, and is tremulous. What do you think she is experiencing and which antidepressant is the patient most likely taking?
   a. Allergic reaction, fluoxetine
   b. Allergic reaction, paroxetine
   c. Antidepressant discontinuation syndrome, fluoxetine
   d. Antidepressant discontinuation syndrome, paroxetine

7. A doctor calls you after reading a summary of the VA/DoD treatment guidelines and is concerned about his patient who has PTSD and has been taking alprazolam 1 mg BID for about 2 years. He would like to discontinue this medication and asks you how to do so. How would you reply?
   a. Decrease the dose of alprazolam by 1 mg every day and then discontinue
   b. Decrease the dose to 1 mg QHS for 4 – 8 weeks; decrease again 0.25 mg TID for 2 weeks, then 0.25 mg BID for 2 weeks, then 0.25 mg QHS for 2 weeks, then stop
   c. Switch alprazolam to clonazepam as this agent is more effective in PTSD
   d. Continue alprazolam 1 mg BID. The NICE guidelines state that benzodiazepines may be effective in PTSD.
**Answer Key**

1. **C**
   Although psychosis can be a symptom of PTSD, it is not considered to be a symptom cluster. All of the other answers are correct.

2. **B**
   Bupropion is not listed as a first-line option in either the VA/DoD or NICE treatment guidelines. SSRIs and venlafaxine are first-line options in the VA/DoD guidelines. Mirtazapine and paroxetine are first-line agents after psychotherapy according to the NICE guidelines (amitriptyline and phenelzine may be tried as well, but should only be prescribed by a mental health specialist).

3. **D**
   The combination of terazosin and prazosin is considered to be duplication of therapy, but it does not mean that prazosin cannot be used to manage both nightmares and BPH. Answer C is incorrect as terazosin poorly penetrates the blood brain barriers as compared to prazosin and has not been shown to be effective for nightmares. The conversion is usually 1:1 if a patient is taking 2 mg of terazosin. Prazosin 2 mg QHS can then be titrated as needed/tolerated.

4. **A**
   The study performed in 2011 showed that risperidone is no more effective versus placebo for adjunct therapy in PTSD. All of the other antipsychotics have insufficient data to support their use in PTSD, but may be tried for refractory symptoms.

5. **A**
   The best option is to first obtain more information regarding the sexual dysfunction he or she is experiencing. Answer C would not be the best choice as we do not know if the problem is erectile dysfunction. Answer B is incorrect as higher doses of antidepressants may worsen sexual dysfunction. Finally, answer D is incorrect as paroxetine usually has the highest risk of sexual dysfunction.

6. **D**
   These symptoms are most consistent with antidepressant discontinuation syndrome. The patient is likely taking paroxetine as it has a short half-life and is more likely to cause this syndrome versus fluoxetine which has a longer half-life.

7. **B**
   All treatment guidelines recommend against the use of benzodiazepines in the treatment of PTSD. Choice A is incorrect as this taper schedule is too rapid and will likely result in withdrawal symptoms.