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Treatment of posttraumatic stress disorder: Focus on pharmacotherapy

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Abstract

Current clinical practice guidelines for the treatment of posttraumatic stress disorder offer varying recommendations regarding the use of pharmacotherapy. Many direct head-to-head comparisons of pharmacotherapy are lacking, and recommendations are based on meta-analyses and small trials. While selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors are considered first-line pharmacotherapy, clear distinctions do not exist when considering other classes of psychotropic medications. Ultimately, when selecting an appropriate medication for a patient diagnosed with posttraumatic stress disorder, the clinician needs to consider the current symptomatology being experienced, comorbid conditions, and evidence for efficacy of specific treatments prior to initiating medications.

Keywords: posttraumatic stress disorder (PTSD), antidepressants, benzodiazepines, mood stabilizers, antipsychotics, prazosin, anxiety, nightmares

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Introduction

Posttraumatic stress disorder (PTSD) can be diagnosed when symptoms have persisted for more than 1 month after exposure to a traumatic event (ie, directly witnessing the traumatic event, witnessing in person the event(s) as it occurred to others, learning that the traumatic event(s) occurred to a close family member or close friend, or experiencing repeated or extreme exposure to aversive details of a traumatic event).[1] Of note, in cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.[1] The core symptoms of PTSD (ie, intrusion, avoidance, negative alterations in cognition and mood, and marked alterations in arousal and reactivity) also must cause significant distress or impairment in social, occupational, or other important areas of functioning.[1] Posttraumatic stress disorder can occur alone as the only diagnosis, or more commonly, with other co-occurring *Diagnostic and Statistical Manual*, 5th edition (DSM-5) disorders, such as substance use disorder, mood disorder, or anxiety disorder.[2,3] Additionally, PTSD is strongly associated with functional difficulties, reduced quality of life, and adverse physical health outcomes.[4]

The Wave 3 National Epidemiologic Survey on Alcohol and Related Conditions study,[5] using DSM-5 criteria, suggests comparable lifetime (6.1%) and current (4.7%) PTSD prevalence estimates. Estimates of PTSD in active duty US service members ranges from 4% to 17% in those

Take Home Points

1. Clinical controversy exists regarding the place of pharmacotherapy in the treatment of posttraumatic stress disorder (PTSD). While some guideline authors consider pharmacotherapy a first-line treatment option, others recommend psychotherapy prior to considering any pharmacotherapy. When pharmacotherapy is chosen, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors (specifically sertraline, fluoxetine, paroxetine, and venlafaxine) are considered first-line treatment options. Use of antipsychotics and mood stabilizers should be reserved as last-line options.
2. Current guidelines vary on recommendations regarding the role of prazosin for treatment of PTSD nightmares. While older guidelines recommended prazosin based on smaller positive trials, a recent large Veterans Affairs Cooperative Study with negative results had conflicting results regarding the efficacy of the medication. Prazosin continues to be used clinically in patients who experience a positive response from the medication.
3. Benzodiazepines continue to be contraindicated for the treatment of PTSD, even though up to 74% of patients with a diagnosis of PTSD continue to receive prescriptions for them. Benzodiazepines may actually interfere with the extinction of fear conditioning and/or potentiate the acquisition of fear response and worsen recovery from trauma. Careful consideration should be given prior to use of benzodiazepines for the treatment of PTSD or anxiety associated with PTSD.

serving during Operation Enduring Freedom and Operation Iraqi Freedom.[6]

Current first-line treatments for PTSD vary even with recent guideline updates. Contradictory recommendations exist between the use of pharmacotherapy or psychotherapy as first-line treatment options. The American Psychiatric Association[7,8] and British Association of Psychopharmacology[9] guidelines recommend pharmacotherapy and psychotherapy as first-line treatments (Table 1). Conversely, the updated Veterans Affairs/Department of Defense (VA/DoD)[12] and the National Institute for Clinical Excellence[13] assert trauma-focused psychotherapies (TFPs) as superior to pharmacotherapy. They further recommend TFPs as first-line treatment over pharmacotherapy when they are available and preferred by patients.[12,13]

Recommendations for TFPs (eg, prolonged exposure, narrative exposure therapy, and cognitive processing therapy) mirror the current state of research into PTSD treatment.[12,13] Two meta-analyses[16,17] compared the treatment effects of psychotherapies and pharmacotherapies, and the results strongly demonstrate that TFPs have greater change with regard to core PTSD symptoms over pharmacotherapies. Additionally, improvements from TFPs persist longer with fewer negative effects associated with TFPs compared with pharmacotherapy. The positive effects of pharmacotherapy treatments can diminish over time and could be lost when medications are stopped.[12]

Despite current treatment guideline recommendations for psychotherapy as first-line, pharmacotherapies are still used frequently as first-line in the treatment of PTSD. Currently only 2 medications are approved by the US Food and Drug Administration for the treatment of PTSD: paroxetine and sertraline.[12] Polypharmacy and off-label use of medications are extremely common and likely to be driven by the suboptimal response and high prevalence of psychiatric comorbidities.[18] In this article, 3 cases will explore the impact of psychotropic medications on the treatment of PTSD, specifically reviewing the role of antidepressant, mood stabilizer, and antipsychotic medications, the use of prazosin for nightmares associated with PTSD, and the use of benzodiazepines for comorbid anxiety with PTSD.

Case 1

A 52-year-old patient presents to the behavioral health clinic complaining of symptoms of anxiety about Veterans Day activities. The patient is a teacher and becomes anxious and easily startled while walking down the hallway at the school. Its crowded space brings back memories of work in the military and having to inform families of service member's deaths. The patient detailed one experience of providing the news to a young woman when the woman's husband had died and the faces of the widow's children when they learned of the death. A diagnosis of PTSD is made and a referral for trauma-focused therapy is provided. Because of increased trouble sleeping and recurrent nightmares, the patient is unable to go to work every day.

The patient returns after 2 sessions of TFP and states an inability to tolerate the therapy and would prefer to trial a medication for PTSD instead. Current medications include lisinopril, atorvastatin, metformin, and levothyroxine.

While TFPs should be recommended first-line for the treatment of PTSD, patients may not be able to tolerate the therapy, may be unable to access the level of therapy required, or may request pharmacotherapy instead. In these cases, current treatment guidelines recommend pharmacotherapy as a treatment option. However,

TABLE 1: Current PTSD guidelines[7-15]

Guideline	Intervention Level			
	Process	First Line	Second Line	Third Line
APA (2004)[7] Guideline Watch (2009)[8]	Systematic review and clinical consensus	Psy SSRI: fluoxetine, paroxetine, sertraline SNRI: venlafaxine Prazosin (combat-related PTSD)	TCA: amitriptyline, imipramine, desipramine Nefazodone Mirtazapine	SGA: risperidone, olanzapine
BAP[9] (2014)	Systematic review and expert opinion/clinical experience	TF: CBT and EMDR SSRI: paroxetine, sertraline SNRI: venlafaxine	Augmentation with: olanzapine, risperidone, prazosin	. . .
ACPMH[10] (2014)	Systematic review	TF: CBT or EMDR SSRI: clinician choice	Other antidepressants Risperidone Olanzapine Prazosin	. . .
ADAC[11] (2014)	Systematic review and consensus process	CBT SSRI: fluoxetine, paroxetine, sertraline SNRI: venlafaxine XR Trauma nightmares and improving sleep quality: prazosin	Fluvoxamine, mirtazapine, phenelzine Adjunctive SGA: risperidone, olanzapine Adjunctive: eszopiclone	Amitriptyline, aripiprazole, bupropion SR, buspirone, carbamazepine, desipramine, duloxetine, escitalopram, imipramine, lamotrigine, memantine, quetiapine, risperidone, topiramate, trazodone Adjunctive: clonidine, gabapentin, levetiracetam, pregabalin, quetiapine, tiagabine
VA/DoD[12] (2017)	Systematic review and weighted recommendations	TF: Psy or SM	Non-TF Psy SSRI: paroxetine, sertraline, fluoxetine SNRI: venlafaxine	Imipramine Nefazodone Phenelzine
NICE[13] (2018)	Systematic review and expert testimony, including costs	TF: CBT EMDR: non-combat trauma if a preference for EMDR TF: computerized CBT: preference versus face-to-face CBT for specific symptoms: sleep disturbance or anger	Medication treatments: venlafaxine, SSRI, antipsychotics	. . .
AHRQ[14] (2018)	Systematic review and weighted recommendations with peer review and public commentary	CBT (exposure and mixed therapies) SSRI: fluoxetine, paroxetine SNRI: venlafaxine	CPT, CT, EMDR, and NET	BE Psy, imagery rehearsal therapy, trauma affect regulation Prazosin Topiramate Olanzapine Risperidone Sertraline
APA[15] (2017)	Systematic review; compared to previous recommendations	Strongly recommends: TF: Psy interventions: CBT, CPT, CT, PET Suggests or conditionally recommends: BE Psy, EMDR, NET Supports: fluoxetine, paroxetine, sertraline, venlafaxine	. . .	. . .

ACPMH = Australian Centre for Posttraumatic Mental Health; ADAC = Anxiety Disorders Association of Canada; AHRQ = Agency for Healthcare Research and Quality; APA = American Psychiatric Association; BAP = British Association of Psychopharmacology; BE Psy = brief eclectic psychotherapy; CBT = cognitive behavioral therapy; CPT = cognitive processing therapy; CT = cognitive therapy; EMDR = eye movement desensitization and reprocessing; NET = narrative exposure therapy; NICE = National Institute for Clinical Excellence; PET = prolonged exposure therapy; Psy = psychotherapy; PTSD = posttraumatic stress disorder; SGA = second generation antipsychotic; SM = stress management; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin norepinephrine reuptake inhibitors; TCA = tri-cyclic antidepressant; TF = trauma-focused; VA/DoD = Veterans Association/Department of Defense.

TABLE 2: Range of effect sizes using CAPS/SPRINT/PSS-I for monoagent pharmacotherapy[14,17,19,20]

Drug	Point Estimate Range	No. of Meta-Analyses With Significant Differences
Fluoxetine	0.23-0.43	4
Paroxetine	0.36-0.74	4
Venlafaxine	0.20-1.78	4
Sertraline	0.15-0.51	3
Risperidone	0.27-0.48	2
Olanzapine	−0.10-0.72	1

CAPS = Clinician-Administered PTSD Scale; SPRINT = Short PTSD Rating Interview; PSS-I = PTSD Symptom Scale-Interview.

medication recommendations differ across the various guidelines. The majority conclude that selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are first-line treatments due to their positive effects on re-experiencing, avoidance, and hyperarousal symptoms.[8-11,14,15] Several guidelines[8-12,14,15] recommend specific antidepressants (ie, fluoxetine, paroxetine, sertraline, and venlafaxine) over others in the same or similar classes. Results of 4 systematic reviews and meta-analyses[16,17,19,20] are fairly consistent demonstrating greater efficacy of paroxetine, fluoxetine, and venlafaxine compared to placebo as monotherapy for the treatment of PTSD, while 3 studies[16,17,20] of the 4 find significance with sertraline as well (Table 2).

Specific antidepressants are recommended in particular guidelines, but whether or not there are meaningful differences in efficacy between SSRIs and SNRIs can be debated. The lack of recommendation for or against a medication in several guidelines was based on available efficacy data and known adverse effects of the medication, while other guidelines include expert opinion as evidence for recommending a medication (Table 1).[7-15] The lack of robust studies to warrant a recommendation for or against several antidepressants (ie, escitalopram, duloxetine, levomilnacipran, vilazodone, bupropion, mirtazapine, and vortioxetine) leaves the clinician with questions regarding their place in therapy. While a paucity of data for these particular antidepressants exists, clinicians should consider their use after weighing any known adverse effects, comorbid conditions, potential interactions, warnings, and risks when selecting an appropriate antidepressant medication, as one would do in the treatment of major depressive disorder.

The use of citalopram as a first-line agent should be avoided as one meta-analysis found insufficient evidence of efficacy and a lack of separation from placebo in addition to the known QTc prolongation warning.[16] While this recommendation is not a contraindication to the use of citalopram, clinicians are advised to evaluate the patient's medication regimen and preexisting medical issues prior to selecting citalopram.[21]

Other second- and third-line antidepressants with strong efficacy include nefazodone, imipramine, and phenelzine.[12,20] Recent research on these agents is lacking, however older placebo-controlled studies demonstrated modest therapeutic effects. Although the confidence in this data can be low, it does demonstrate that nefazodone significantly improves PTSD symptoms in a veteran population.[22] Additionally, when compared to sertraline in two studies,[23,24] nefazodone demonstrated no difference on outcome measures such as the Clinician Administered PTSD Scale (CAPS). Larger nefazodone trials for the treatment of PTSD were planned, but when the medication received its black box warning for severe and possibly irreversible liver failure in 2002, the trials were canceled. One small study[25] has also demonstrated measurable therapeutic effects of imipramine and phenelzine in combat veterans. In the most recent meta-analysis,[20] phenelzine was considered better than many of the other active treatments (ie, imipramine, sertraline, guanfacine, tiagabine, bupropion, prazosin, divalproex, and citalopram) and was the only medication that was significantly better than placebo in terms of dropout rate (odds ratio 7.50, 95% CI 1.72-32.80). Even with positive efficacy data, these medications have fallen out of favor because of their adverse effects. With careful implementation and proper monitoring, the adverse effects (ie, sleep enhancing effects of imipramine or reduced sexual dysfunction from nefazodone) could be used favorably.[12]

The use of antipsychotics for general PTSD symptomatology is controversial and confusing regarding differences in monotherapy versus augmentation strategies, and when comparing results from meta-analyses or recommendations from guidelines. Some authors[7-15] recommend them as second-line as monotherapy or third-line as augmentation strategies, and others recommend against their use altogether (Table 1). Risperidone has mixed results from meta-analyses with authors reporting benefit in 2 of the 4 applicable publications.[17,20] Olanzapine showed statistically significant benefit in 1 out of the 4 meta-analyses reported (Table 2).[16] A recent study[26] using quetiapine as monotherapy demonstrated a small to moderate effect size comparing endpoint CAPS total scores between quetiapine and placebo (Cohen d = 0.49), but the study had a high risk of bias including a lack of information regarding the amount of missing data, method of how the missing data was handled, high attrition, and differential dropout (53% dropout for placebo vs 31% dropout for quetiapine).

Risperidone and olanzapine are the only atypical antipsychotics with data on their use as augmenting agents. Meta-analyses[16,17] concluded small effect sizes and lack of

clinical significance for both medications. In a VA Cooperative Study (N = 247),[27] risperidone augmentation was compared to placebo for treatment of PTSD resistant to SSRIs. After 6 months, no difference in change from baseline CAPS scores was seen. In a subscale analysis, differences in symptoms of reexperiencing and hyperarousal were found to be statistically, but not clinically, significant.

Clinicians need to weigh the small benefit with the risk when considering the use of antipsychotics for the treatment of PTSD and limit them to last-line for general PTSD symptomatology. Risks include adverse effects that may exacerbate a patient's comorbidities or result in new medical problems such as metabolic syndrome, hyperprolactinemia, or potential extrapyramidal effects.[28,29]

Mood stabilizers, including topiramate, lamotrigine, and divalproex have contradictory recommendations within the various guidelines. A recent meta-analysis[16] did not find a significant effect size for topiramate or lamotrigine, and in a single study[30] divalproex monotherapy did not demonstrate efficacy in a small sample of veterans over 8 to 12 weeks of treatment. Adverse effects associated with mood stabilizers could also hinder use. Topiramate is known to cause paresthesia, metabolic acidosis, kidney stones, and cognitive adverse effects, while lamotrigine's risk of Stevens-Johnson syndrome limits its rapid titration.[31,32] Divalproex requires monitoring of liver enzymes and platelets. Additionally, it has significant risks of weight gain, hyperammonemia, polycystic ovarian syndrome, and teratogenicity.[33] Similar to antipsychotics, the use of mood stabilizers should be limited to the treatment of other comorbid psychiatric illnesses.

When selecting a pharmacotherapy treatment option for the patient in case 1, the clinician should identify the specific symptoms the patient is experiencing. One should use potential adverse effects (eg, sedation) to benefit target symptoms (eg, insomnia). Additionally, one must recognize potential adverse effects the patient may not be able to tolerate. In the current case, the patient is experiencing anxiety, trouble sleeping, guilt, and distress. Antidepressant medications, in particular SSRIs and SNRIs, would be effective for most of these symptoms. While paroxetine is the most sedating of consistently recommended antidepressants and may be beneficial to the patient, risks of sexual dysfunction and withdrawal should also be discussed. If the patient is able to tolerate the adverse effects and demonstrate adherence, paroxetine would be an ideal recommendation. Other SSRIs including sertraline and fluoxetine could be considered as potential treatment options. SNRIs and fluoxetine may alleviate the anxiety, but they may also contribute to increased insomnia if dosed late in the day. Proper education on adverse effects and proper titration is essential for continued benefit of the medication.

Case 2

A 37-year-old Navy officer presents to the behavioral health clinic complaining of inability to sleep. The psychologist completing the intake discovers a recent event in which the officer was called to help find a fellow officer who did not show up for a class and discovered that the other officer had died by suicide. The Navy officer tried to perform life saving measures but was unsuccessful. When questioned further regarding the inability to sleep, the patient reports frequent awakenings after nightmares of seeing the scene of the suicide. Other symptoms include being on edge at home, feeling trapped and hopeless, and being unable to help with simple tasks at home such as taking care of the children. Driving home each night takes longer due to avoiding the street where the fellow officer lived. When the patient's phone rings during the intake, the psychologist notes that the officer jumps. The officer explains constant jumping when the phone rings, anticipating a similar call as the one received about the suicide. The psychologist diagnoses the patient with PTSD and brings the case to the team for discussion of treatment options.

The PTSD-associated nightmares are frequently studied because of the high rate of patient reports (up to 80%).[34] The presence of nightmares following a traumatic event predicts subsequent onset of PTSD.[35] Unfortunately, PTSD-associated nightmares can persist throughout life even if core PTSD symptoms resolve.[36] Currently, treatment of nightmares associated with PTSD is a controversial topic. Pharmacotherapy is frequently used without recommendation for the treatment of nightmares associated with PTSD.[12]

Prazosin is a widely studied and used medication for PTSD-related nightmares. However, debate has recently arisen regarding its continued use for this purpose. Multiple studies[7-11,14] have demonstrated the efficacy of prazosin for the treatment of PTSD-associated nightmares, and many guidelines recommend its use. Contradicting most guidelines, the most recent revision of the VA/DoD PTSD Guidelines[12] changed its recommendation for PTSD-related nightmares to state that there is insufficient evidence to recommend for or against the use of prazosin as monotherapy or augmentation therapy. Disagreements between guidelines stem partly from the criteria according to which studies were included in the assessment.[37] The VA/DoD recommendations were based on 4 small, published trials[38-41] of variable quality. While most of these trials had promising results for nightmares, in a much larger, well-designed VA Cooperative multi-site trial[42] (N = 304), prazosin (mean maintenance dose = 14.8

mg + 6.1 mg) failed to separate from placebo in the treatment of both global symptoms of PTSD and nightmares. At the time of the writing of the VA/DoD guidelines, the VA Cooperative multi-site trial had not been published for the Work Group to review. The Work Group felt it was essential to include the study in the updated recommendations despite its predefined study inclusion criteria because of their knowledge of the study's data in the public domain.[43] The Work Group had in-depth conversations and debates regarding this recommendation because of: (1) the positive results in nearly all of the small studies, (2) the results of a recent meta-analysis that concluded that prazosin was beneficial at 14 to 27 weeks as an augmentation medication for the global symptoms of PTSD, and (3) the contradictory negative results in the much larger and stronger VA Cooperative Study.[12,16] In 3 trials[38-40] (of the 4 smaller trials[38-41]), prazosin demonstrated a significant decrease in recurrent distressing dreams and improvement in sleep quality, while the VA Cooperative Study[42] demonstrated no difference between prazosin and placebo on recurrent distressing dreams or sleep quality. The Work Group ultimately agreed on not recommending for or against the continuation of prazosin in patients who believe it to be beneficial.[12]

The Work Group concluded that the decision to stop, initiate, or continue prazosin should be individualized based on the history of response and adverse effects experienced. If patients and/or providers decide to discontinue prazosin, a slow taper should be used with monitoring for symptom worsening or reappearance. The Work Group suggests that prazosin may need to be restarted or continued in some patients where response is demonstrated.[12]

While the VA/DoD Work Group did not have the published VA Cooperative Study, the American Academy of Sleep Medicine (AASM) recently released a position paper for the treatment of nightmare disorder in adults, which included a review of the complete, published paper.[35] The position paper recommends image rehearsal therapy for the treatment of PTSD-associated nightmares and nightmare disorder. Additionally, it suggests a host of other options with varied evidence levels, including various psychotherapies and numerous medications, many with very little evidence (eg, nabilone, clonidine, gabapentin).[35]

In addition to the studies reviewed by the VA/DoD Work Group, the AASM reviewed 10 studies (including a retrospective chart review and 4 small, uncontrolled trials)[38-42,44-50] that demonstrated the efficacy of prazosin for the treatment of PTSD-associated nightmares. The Academy notes that it is appropriate to downgrade the recommendation regarding prazosin for this use because of the VA Cooperative Study, but patients may respond well to prazosin and they continue to recommend it as a first-line option.[35]

While much larger than the previous studies, the VA Cooperative Study[42] described several limitations in the full paper. The study enrolled stable patients for treatment, which the principal investigators explained could have resulted in selection bias. Excluding those with psychosocial instability from recruitment because of the concern of suicide and violent behavior resulted in a different population than that previously studied. Similarly, the investigators had concern that enrolling patients who would deteriorate clinically during the 6 months of receiving placebo could have motivated providers to use available open-label prazosin rather than refer patients to this study. The study also did not allow continued use of trazodone, which could have limited those who may have had a response to prazosin. A further limitation is that participants were not screened for sleep apnea or sleep-breathing except by patient history or chart review. This may have interfered with the mechanism of prazosin or masked its possible beneficial effects.[42] With so many different limiting factors and variations from previous studies, many clinicians are uncertain whether prazosin provides efficacy for PTSD-associated nightmares. Given that many clinicians have seen clinical efficacy with the use of prazosin, continuing to use prazosin in patients with no contraindications is appropriate. Patients should be provided proper education regarding the mixed data regarding its efficacy, potential adverse effects, and continued monitoring regarding efficacy and risk of hypotension should be completed.

Risperidone, aripiprazole, and olanzapine are recommended by AASM specifically for PTSD-related nightmares, not general PTSD symptomatology, based on several very small and weak studies. Olanzapine is recommended based on a single case series comparing olanzapine augmentation to different psychotropic treatment regimens in 5 combat veterans. Subjects self-reported the frequency of nightmares.[51] Risperidone is recommended based on 2 studies[52,53] with self-reported outcomes, a 12-week open label trial evaluating the effects in veterans with chronic PTSD and a retrospective chart review of 10 civilian patients at a regional burn center. A single case series[54] ($N = 5$) found self-reported substantial improvement but not in total resolution of nightmares with aripiprazole in 4 of the 5 cases. In the recent, placebo-controlled quetiapine study[26] ($N = 60$), improved sleep was suggested by week 4 of the study ($F = 6.22$, $df = 1,77$, $P < .05$) but the effect was lost over time ($F = 1.49$, $df = 3,1175$, $P = 0.20$). These studies have many limitations, and the risks associated with the use of atypical antipsychotics outweigh their potential benefit. Atypical antipsychotics should be reserved as a last-line treatment

option for PTSD-related nightmares after TFP, antidepressants, and prazosin, but avoided as monotherapy for general PTSD symptomatology because of weak evidence for efficacy.

While benzodiazepines are commonly prescribed for the treatment of PTSD-related insomnia, there is a paucity of evidence to support this practice.[55] Two small trials[56,57] evaluating the efficacy of alprazolam and clonazepam in reducing symptoms of PTSD, including insomnia and nightmares, via sleep diaries, found no advantage over placebo. Additionally, benzodiazepines and nonbenzodiazepines can increase excitement, irritability, aggression, hostility, and impulsivity. These symptoms can result in attacks of rage or violence.[58] See case below for additional details regarding the safety of benzodiazepines in the treatment of anxiety associated with PTSD.

Nonbenzodiazepines are also frequently used for the treatment of PTSD-related insomnia. They are thought to offer a better side effect profile and not to disrupt the natural sleep architecture.[59] While a recent placebo-controlled, cross-over, randomized, controlled trial[60] with eszopiclone demonstrated improved sleep quality and decreased sleep latency, the small sample size (N = 24) and 3-week observation period make applying the results very difficult. Additionally, recent warnings regarding these medications causing abnormal thinking and behavior changes, decreased inhibitions, and potential visual and auditory hallucinations suggest that these medications should be used as last-line treatment options for PTSD-related insomnia based on the small amount of data available.

Other options for sleep could include trazodone or mirtazapine. Although trazodone does provide a safer alternative to the use of benzodiazepines and nonbenzodiazepines, only very low-level evidence in survey, open-label, and clinical observation data support its use in PTSD-related insomnia.[61] In a recent randomized controlled trial[62] evaluating augmentation of sertraline with mirtazapine versus sertraline monotherapy, the combination offered no advantage in self-reported sleep disruption.

Severe sleep deprivation warrants the immediate use of medication to prevent harm, while other sleep disorders would benefit from psychotherapy first.[12] The patient in case 2 would benefit from cognitive behavioral therapy for insomnia. The use of sleep medications should be limited to a short duration, although at times, longer medication use may be warranted in PTSD. This patient may benefit from a trial of prazosin as other sleep medications (ie, nonbenzodiazepine hypnotics and benzodiazepines) can intensify nightmares.[63] Prior to initiation of prazosin, clinical judgement must be used as some patients may respond while others may demonstrate no benefit. Adverse effects (eg, hypotension) and additive drug-drug interactions should be considered prior to initiating prazosin. When initiating prazosin, the patient should be started on 1 to 2 mg/d at bedtime with an increase of 1 mg every 2 weeks. Mean doses in clinical trials ranged from 2 to 13 mg/d. While once daily dosing at bedtime is frequently used, several trials used twice daily dosing due to the short half-life of prazosin. Other sleep medications, including atypical antipsychotics, benzodiazepines, and nonbenzodiazepines should be avoided and only used as last-line treatment options.

Case 3

A 25-year-old patient being treated for PTSD from a previous sexual assault describes severe anxiety prior to TFP appointments and at bedtime. The patient notes being very anxious and endorses symptoms of a panic attack including shortness of breath, sweating, and feelings of impeding death. These attacks typically last 10 to 15 minutes and the patient has only found relief from clonazepam prescribed by an emergency department physician. The patient asks for a continued prescription as it is the only thing that helps. Current medications include fluoxetine 20 mg daily for the past 6 weeks. Past medications include sertraline 150 mg (discontinued because of nausea) and trazodone 150 mg for sleep (did not find this effective).

All treatment guidelines currently recommend against the use of benzodiazepines in the treatment of PTSD because of the lack of evidence for effectiveness and the risks associated with their use; nevertheless, 30% to 74% of patients with PTSD still receive prescriptions for them.[18,64] Benzodiazepines have been used as a primary or "as needed" agent for the treatment of PTSD anxiety despite the lack of efficacy in randomized controlled trials. There was no significant differences between placebo and alprazolam on the Hamilton Rating Scale for Anxiety, or placebo and clonazepam using sleep diaries in 2 small studies.[56,57] Use of alprazolam 30 minutes prior to virtual reality exposure sessions demonstrated a reduction in the efficacy of exposure therapy and was associated with more severe PTSD symptoms at 3-month follow-up.[65]

Withdrawal symptoms, tolerance, and dependence can make it difficult to discontinue benzodiazepines.[66] Benzodiazepines are also relatively contraindicated in patients with a history of traumatic brain injury, sleep apnea, chronic obstructive pulmonary disease, or high rates of comorbid alcohol misuse and substance use disorder.[67] Additionally, preclinical data concluded that benzodiazepines could interfere with the extinction of fear conditioning and/or potentiate the acquisition of fear response and worsen recovery from trauma.[68,69]

The patient in case 3 should be educated about the risks of continued use of benzodiazepines and alternative recommendations should be made regarding other options to help control the anxiety the patient is experiencing. Additional psychotherapy should be offered to the patient as well as maximizing the dose of the antidepressant. As needed medications, such as hydroxyzine, may be beneficial for as needed treatment of anxiety.

Conclusion

There are numerous studies with varying degrees of rigor evaluating pharmacotherapy options for PTSD. While guideline authors provide many differing options, SSRIs and SNRIs remain first-line pharmacotherapeutic treatment options for PTSD. Although specific antidepressants may demonstrate greater published efficacy, any antidepressant could be considered with proper monitoring. Atypical antipsychotics lack robust studies demonstrating evidence and have more potentially severe adverse effects, making them last-line treatment options. Mood stabilizers are limited to treatment of comorbid illness because of their lack of data. While many patients continue to receive benzodiazepines for both PTSD-related anxiety and sleep disorders associated with PTSD, they should be avoided. Prazosin can be recommended for those with PTSD-associated nightmares, with proper education regarding its efficacy and blood pressure monitoring. Trauma-focused therapies and other psychotherapies should continue to be recommended first-line in all patients with a diagnosis of PTSD; medications should be used in cases when TFPs are unavailable or unsuccessful, a patient requests medication, or a specific indication compels a medication.

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