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DISASTER PSYCHIATRY: TRAUMA, PTSD, AND RELATED DISORDERS (E FOA AND A ASNAANI, SECTION EDITORS)

Psychopharmacological Strategies in the Management of Posttraumatic Stress Disorder (PTSD): What Have We Learned?

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Abstract There have been significant advancements in the pharmacologic management of posttraumatic stress disorder (PTSD) in the past two decades. Multisite randomized clinical trials (RCTs) have noted the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNR Is) for PTSD treatment. Unfortunately, there have been no new medications approved to treat PTSD in the past 10 years. Although there have been exciting new findings in our knowledge of the neurobiology of PTSD, clinical trials testing new medications have lagged. This review summarizes recent research that builds on the unique pathophysiology of PTSD and suggests ways to move the field forward.

Keywords Posttraumatic stress disorder · Pharmacotherapy · Antidepressants · Depression · Substance use disorder · Insomnia · Clinical trial · Prazosin

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Introduction

Although research of randomized clinical trials of psychotherapy treatments for patients with a diagnosis of posttraumatic stress disorder (PTSD) have shown that they may be more effective than medications, pharmacologic strategies in the management of PTSD are still relevant. Patients may not be willing to revisit their trauma, an essential part of the most effective psychotherapies for PTSD and thus may not take part in psychotherapy. Among those patients who do initiate psychotherapy, dropouts from these treatments are not insignificant. Despite the considerable efforts to train clinicians in the effective psychotherapies for PTSD in the Department of Veterans Affairs (VA), there is still a limited pool of trained psychotherapy providers in our communities so many of our best therapies are not accessible. Finally, the stigma too often associated with mental health disorders may keep patients from seeking effective PTSD psychotherapies and drive them to seek treatment from a primary care provider. All of these reasons suggest that it is important for clinicians to know psychopharmacological strategies to best manage PTSD.

This review summarizes recent research on pharmacotherapy for PTSD in adults. In order to emphasize interesting new findings and bring readers up to date on the subject, we begin with a brief overview on the use of first-line recommended antidepressants in patients with PTSD and then answer the following questions: what is now known about predictors of response to antidepressants in patients with PTSD? Conversely, what is recognized about non-responders to pharmacological management? What is known about treatment augmentation in patients with PTSD? What is our current knowledge of how best to treat the common co-occurring disorders associated with PTSD? Finally, how has our improved understanding of the neurobiology of PTSD informed the field on potential novel alternative treatments to address the complicated symptoms often observed in individuals with PTSD?

Research on Antidepressant Use for PTSD Treatment

It has now been a decade and a half since the first randomized clinical trials (RCTs) testing effective medications for PTSD focused on new antidepressants, the selective serotonin reuptake inhibitors (SSRIs). Earlier small, single-site RCTs had indicated the effectiveness of the tricyclic antidepressants (TCAs) imipramine and amitriptyline and the monoamine oxidase inhibitor (MAOI) phenelzine [1]. These agents continue to be recommended as second-line treatments [2, 3] and used by clinicians for various reasons, particularly for those patients with a co-occurring major depressive disorder that does not respond to SSRIs, although they do have a more complicated side-effect profile and require closer monitoring than SSRIs. Multisite and primarily industry-sponsored RCTs have examined sertraline, paroxetine, and fluoxetine and found them effective in treating PTSD symptoms measured by the Clinician-Administered PTSD Scale (CAPS) or in the case of the Connor et al. fluoxetine trial [4], the Duke Global Rating for PTSD [1]. The between-group effect sizes for SSRIs varied substantially, ranging from significant effects for paroxetine (0.58–0.84), fluoxetine (0.49–0.90), and sertraline (0.28–0.30) [1]. Based on these trials [5–8], paroxetine and sertraline received U.S. Food and Drug Administration (FDA) approval for PTSD. These SSRIs are generally well tolerated and are recommended as first-line agents in several treatment guidelines [2]. Success with SSRIs was later followed by positive results with the serotonin-norepinephrine reuptake inhibitor (SNRI), venlafaxine. Two large multisite trials of venlafaxine-extended release (ER) showed PTSD symptom improvements using the baseline-to-end point change in total CAPS score compared to placebo, one that was maintained for 12 weeks [9] and the other for 6 months [10]. Secondary measures included CAPS symptom cluster scores, frequency of remission and changes in Davidson Trauma Scale total score and symptom cluster scores.

Some treatment guidelines have either failed to endorse SSRIs/SNRIs or have recommended them when psychotherapy is unavailable or ineffective; medication is also recommended for people with PTSD who have concurrent moderate to severe depression [11–13]. The latest Agency for Healthcare Research and Quality [14] report noted reasonably good efficacy for paroxetine and venlafaxine but weaker efficacy for other SSRIs. A recent investigation in a small sample noted paroxetine's efficacy for subthreshold PTSD [15], suggesting its promise as a treatment for those whose symptoms does not meet full PTSD diagnostic criteria.

There have been concerns about the generalizability of findings from the SSRI treatment trials since most participants were Caucasian women with chronic PTSD due to physical or sexual assault that occurred many years prior to the trials. A perplexing finding of the SSRI RCTs has been the strong placebo response that resulted in no statistically significant difference between groups seen in several large studies [9, 16–21]. Interestingly, these strong placebo responses appear to depend on a number of factors that include the complexity of the study population, previous treatment history, and chronicity [22]. The positive placebo responses point to the nonspecific benefit of observation, clinician contact, regular assessment, and the review of symptoms with an empathic clinician.

What Have We Learned About the Type of Patient who Benefits From the Use of Antidepressants in Treating PTSD?

Thus, there have been continued questions not just about the effectiveness but also the generalizability of SSRIs for treatment of PTSD, particularly for combat veteran populations treated in Department of Veterans Affairs (VA) clinical facilities. In this regard, results are mixed with positive results in SSRI trials for younger veteran cohorts than with veterans over 45 years of age [23]. It is possible that there could be age-related differences in treatment response. Investigators have noted that both medication and psychotherapy treatments for several anxiety disorders may not be as effective for older individuals as they are for younger people [24]; this may also account for poorer SSRI responses among older, as compared to younger, veterans with PTSD. Despite such considerations, meta-analyses have generally confirmed the efficacy of SSRI/SNRIs for PTSD [14, 25] and most clinical practice guidelines recommend these agents—as a first-line treatment option for patients with PTSD [2], particularly for those who do not want to engage in trauma-focused psychotherapy or have limited access to psychotherapy options.

A number of factors have been investigated to look at predictors of treatment response to antidepressants in the management of PTSD. One previous question that has been resolved is that we now know that both men and women can benefit from SSRIs for treatment of PTSD. In both the paroxetine studies [7, 8] and the fluoxetine trial [23], the concerns about effectiveness for male patients were put to rest. A second question concerns the responsiveness of military veterans relative to civilians. Male veterans recruited from the general population showed as much improvement from SSRI treatment as did civilian men and women [7, 18]. This finding was also confirmed in work confirming the efficacy of sertraline over placebo in military veterans recruited from the community who were not in treatment in the VA [26]. Fluoxetine treatment produced significantly greater results compared to placebo with male veterans of more recent deployments than those of less recent wars [23]. Effect sizes were particularly strong among those with combat exposure in this study (0.78), a factor once thought to predict non-response. Because of the work done by Martenyi et al. in veterans from United Nations

military missions as well as military deployments from several war-torn countries outside the United States, it is now noted that veterans with PTSD due to combat trauma are as likely to respond to an SSRI as civilians who have experienced other types of trauma. However, older Vietnam-era veterans who have long histories of treatment in the VA appear to remain a treatment-resistant cohort that is not representative of veterans with PTSD overall as noted in a null multisite sertraline randomized controlled trial [19]. There are a number of factors that may be related to the non-response in this group including chronicity of PTSD, type and length of previous treatments including exposure to numerous other medications and long-term supportive therapy, and age.

A finding that has come up often is that chronicity of PTSD predicts a negative response to an SSRI. Military veterans from the Vietnam era treated in VA hospital settings appear to be a particularly chronic and treatment refractory group who are less likely to show positive response to either pharmacological or psychological PTSD treatments [27, 28]. However, this speculation is complicated by questions regarding service disability for the disorder. Contrary to the expectation that veterans seeking disability compensation for PTSD would exhibit poorer motivation to participate in treatment, review of relevant research findings indicates the opposite; veterans who are seeking or have been awarded compensation participate in treatment at similar or higher rates than do their non-compensation-seeking counterparts [29]. More recently, it was noted that evidence-based PTSD treatments, even when they result in substantial symptom improvements, may not be adequate to achieve full symptom remission or eliminate disability among veterans with severe PTSD [30]. It is difficult to know how much of this failure to reach full recovery is due to chronicity, symptom severity, previous treatments, service disability, or other factors. The data indicate that veterans seeking care in the VA are interested in recovery [29]. Until evidence is shown that disability policies impact treatment motivation or response, such veterans should continue to be offered quality care.

Another consideration is the recency of the traumatic event since women who had positive responses in the early large-scale multisite SSRI trials had experienced their trauma, on average, approximately 12 years earlier than less responsive male Vietnam veterans, whose combat trauma had occurred 25–35 years before the trial. So, it is possible that in addition to chronicity, other factors such as time since trauma and receipt of previous treatment including exposure to previous antidepressants and other medications may influence treatment outcomes.

Additionally, the chronicity finding has been complicated by more recent work that has examined the impact of co-morbid depression on response to SSRIs in PTSD patients. Over half of the patients participating in the large-scale SSRI RCTs (that led to FDA approval for sertraline and paroxetine) had co-occurring depression. Analyses of treatment outcome data, however, found no difference between those with high vs. low depression scores [7]. A recent large single-blind randomized trial, however, reported different results as higher levels of baseline depression in PTSD patients predicted less improvement from SSRI treatment [31•]. Other studies report greater improvement among PTSD patients with moderate-severe depression than those with mild suggesting that more complicated patients may benefit further from the treatment [32]. To summarize, at this point, results are mixed regarding the impact of co-morbid depression on treatment response to SSRIs by patients with PTSD. Friedman's work [31•] and that of others now suggest that it is actually childhood maltreatment (physical, emotional, or sexual abuse), co-morbid depression and suicidality, or the presence of "complex PTSD" that predict a negative response to medications for PTSD [33–35]. Clearly, more work is needed in this emerging area of research that explores the role of childhood abuse and its impact on treatment response in patients with PTSD.

We also now recognize that if patients are maintained on SSRIs, they are likely to benefit from continued treatment. A significant open-label study showed that when sertraline treatment was extended for a longer period of time, from 12 to 36 weeks, remission rates increased from 30 to 55 % [36]. As with medications for other psychiatric disorders, however, it appears that PTSD patients need to continue SSRIs in order to maintain their recovery. Research has examined relapse and has found that discontinuation of sertraline and fluoxetine is associated with clinical relapse and a return of PTSD symptoms [6, 10, 23, 37, 38]. This relapse on discontinuation of SSRIs is no different than that observed in other psychiatric disorders as positive responders to pharmacotherapy generally need to continue medication to maintain clinical improvement. Work that has been done with psychotherapy augmentation of SSRI partial responders suggests that this might be a treatment approach that would help promote recovery [29, 39].

Resilience may be an important predictor of treatment response. Patients with higher baseline resilience had a greater chance of achieving remission using the SNRI venlafaxine ER, as did those with lower PTSD symptoms [40]. Intuitively, this finding makes sense and if examined, would be expected to be the case with SSRIs and other medications, as well. Furthermore, Camardese et al. [41] have found that patients with major depressive disorder who had higher degrees of resilience were more likely to achieve remission from active drug therapy. Other interesting results observed in the venlafaxine trials include significant medication-related improvements in one's ability to deal with daily stress, anger, and aggression [40, 42]. These findings all suggest that inclusion of resilience-promoting approaches may enhance treatment response and reduce further episodes of PTSD [40]. It also suggests that SNRIs may be safer agents for treating

anger and aggression than off-label use of atypical antipsychotics or benzodiazepines which are not only ineffective for reducing treatment-resistant anger and aggression, but carry their own drug-related risks [43].

Despite the conflicting recommendations from clinical practice guidelines for PTSD, the use of SSRIs as a first-line treatment for PTSD has increased. Research that examined prescribing patterns in veterans with a diagnosis of PTSD receiving treatment in VA facilities found that over a 10-year period of time, from 1999 to 2009, prescribing frequency of SSRIs increased from 49.7 to 59 % [44]. Overall, this widespread increase in SSRI use among military veterans is consistent with guideline-concordant care. Clearly, prescribing clinicians believe that veterans benefit from these medications and that they offer an important treatment option. From a stepped-care perspective, the ability of primary care and other physicians to provide optimal pharmacotherapy to patients with PTSD allows the preservation of psychotherapy time for those who most clearly need or want to pursue that approach.

What Have We Learned About Non-Responders to Antidepressants in the Treatment of PTSD?

Despite the advances in pharmacotherapy for PTSD, monotherapy with the currently available antidepressants does not always work. Combined pharmacotherapy and psychotherapy approaches are often suggested for partial responders to either treatment alone. Relatively few RCTs have examined the additive benefits of combination treatments in this regard, thus the best approach is not yet clear. Rothbaum et al. [39] added prolonged exposure (PE) psychotherapy to a 10-week open-label sertraline trial. Overall, participants receiving sertraline showed significant reductions in PTSD severity on the Structured Interview for PTSD, on depression, and general anxiety. Augmentation with 10 sessions of twice-weekly PE for partial responders to sertraline resulted in further reductions in PTSD symptom severity but not in depression or general anxiety. Clinically, this finding is very relevant as it helps inform real-world treatment recommendations. Simon et al. [45] tested the opposite approach, adding medication (e.g., paroxetine versus placebo) to PE partial responders. They found that adding medication to continued PE did not improve outcomes. In contrast, more recent work by Schneier and colleagues [46] working with patients exposed to the World Trade Center attacks, initially administered PE to patients and then randomized them to 12-week paroxetine or placebo, and found those who received paroxetine showed significantly greater improvement in PTSD.

Similar to this line of work, researchers have examined the effects of a medication called d-cycloserine (DCS) augmentation of exposure therapy for PTSD by accelerating the pace of treatment through facilitatory action at n-methyl-d-aspartate (NMDA) receptors. After initial excitement surrounding early studies of DCS augmentation of CBT for anxiety disorders, the use of DCS to extinction learning in humans with PTSD has provided a mixed picture of success [47]. One trial found that patients who received DCS reported less improvement than those who received placebo [48]. As Hofmann notes, this trial is interesting because it suggests that DCS only augments exposures that lead to a clear reduction of fear but might impair improvement when administered with unsuccessful exposure sessions. A larger augmentation trial of 156 war veterans combined virtual reality exposure sessions with DCS, alprazolam, or placebo [49]. Although no difference was noted between the DCS and placebo groups, the study showed that between-session extinction learning was only a treatment-specific enhancer of outcome in the DCS group. Importantly, alprazolam, the benzodiazepine Xanax, commonly used clinically for anxiety, impaired recovery whereas DCS enhanced outcomes in patients who showed within-session learning. A recent study explored the use of DCS augmentation on PE in non-combat PTSD [50]. While the study did not find a significant effect of DCS on PTSD symptoms, DCS did lead to greater symptom improvement for patients who had more severe pre-treatment PTSD and required longer treatment. Finally, in pilot work, [51] DCS was used to augment virtual reality exposure therapy for PTSD related to the World Trade Center attacks. Although the study did not show differences at immediate post-treatment, those in the DCS group did show reduced PTSD symptoms at 6-month follow-up. These studies have all helped provide critically important information that informs DCS augmentation strategies. As characterized by Hofmann [47], DCS may make not only "good" exposure better but also "bad" exposure worse. Clinically, this suggests that patients receiving DCS may show greater improvement when they report low fear at the end of the exposure session as compared to patients who remain high in their reported fear. The reason for this is suggested to be due to the fact that DCS enhances cognitive processes not only during extinction learning but also during reconsolidation of fear memories [47]. These findings point towards new ways to enhance current practices by improving response rates. Combined treatment of medication and psychotherapy deserves further study in larger samples of PTSD patients due to varied types of traumas and over longer follow-up periods to determine the best outcomes.

A new pilot study published by Yehuda and colleagues examined the use of hydrocortisone as a strategy to enhance PE by helping patients manage the initial stress of the treatment, resulting in reduced drop-out rates [52•]. They found that hydrocortisone augmentation of PE indicated that the veterans in the treatment group were more likely to benefit from PE than those randomized to the placebo group. In their study design, the significant effect of hydrocortisone cannot be

separated from its effect to increase treatment retention. Thus, the current study cannot fully distinguish clinical improvement due to the effect of hydrocortisone augmentation from its utility in reducing treatment drop-out. It does point, however, to potential new directions in pharmacological augmentation.

There have been several studies that examined SSRI pharmacotherapy augmentation by atypical antipsychotics. Risperidone and olanzapine are the only atypical antipsychotics to date with RCTs investigating their efficacy as adjunctive treatment for PTSD. Risperidone has been evaluated as adjunctive PTSD treatment in five RCTs, three noting positive effects and two showing no benefit. The positive studies showed effects on aggression, hyperarousal, and re-experiencing symptoms [53–57]. One of the null trials did show an improvement in sleep disturbance [58], and this finding is consistent with the use of these agents at lower doses for PTSD-related sleep problems. Indeed, survey work conducted in 2013 noted that "sleep/sedation" was the reason VA providers gave for their use of atypical antipsychotics in individuals with PTSD [59].

Based on the aforementioned small single-site studies, atypical antipsychotics were recommended as adjunctive agents in several PTSD clinical practice guidelines until the large, multicenter trial conducted by Krystal et al. [60]. Two hundred and forty-seven veterans with PTSD participated in this RCT in which antidepressant non-responders were randomized to adjunctive risperidone or placebo; there was no significant difference in treatment response between the two groups [60]. These findings led to a change in the VA/DoD treatment guideline, which now recommends against the use of risperidone for SSRI non-responders. It is important to remember that the use of atypical antipsychotics for PTSD is an off-label treatment that is only recommended for those PTSD patients who exhibit psychotic features. There is currently not enough evidence to support their use as monotherapy or adjunctive therapy, and concerns about their costs and harmful side effects remain an important consideration [3].

Overall, the SSRI and SNRI antidepressants have been found to decrease core PTSD symptoms but too often, there is little improvement noted in sleep-related disturbances and it is thought that this contributes to the use of medications such as benzodiazepines and the atypical antipsychotics [44, 61]. The use of the alpha-adrenergic antagonist, prazosin, has proven to be an effective treatment for PTSD-related nightmares [62, 63]. Work by Byers et al. [64] demonstrated that patients may benefit more from the use of prazosin to address PTSD-related insomnia rather than from atypical antipsychotics. A recent RCT with military personnel had positive results on both daytime and sleep-associated PTSD symptoms in which prazosin was administered twice daily, in morning and evening doses, rather than just at bedtime, as in previous studies [65]. Indeed, improvements occurred in total PTSD symptom severity, especially with respect to arousal symptoms, as well as in trauma-related nightmares, sleep quality, and global functioning. Overall, prazosin has consistently shown the greatest efficacy in relieving PTSD-related insomnia whereas results are mixed regarding its impact on other core PTSD symptoms.

An area of augmentation research that also addresses PTSD-related sleep disorders is the use of eszopiclone [66]. A small cohort of patients was randomized to either 3 weeks of eszopiclone or placebo at bedtime; the eszopiclone patients exhibited significantly greater improvement on PTSD measures and sleep. This study provided initial evidence that pharmacotherapy with eszopiclone may be associated with short-term improvement in overall PTSD severity as well as associated sleep disturbances. Another medication used for insomnia, trazodone, has limited efficacy as monotherapy for PTSD but does have effective sedating actions and is recommended and often used at low doses adjunctively with SSRIs to address PTSD-related sleep disorders [3].

The muscle relaxant, baclofen, was tested as an adjunctive treatment for PTSD in a double-blind clinical trial with 40 Iranian combat veterans [67]. Recent work has suggested that activation of GABA receptors could be helpful in reducing PTSD severity by inhibiting the overstimulation of the sympathetic nervous system. Significantly positive findings in PTSD symptoms as measured by the CAPS, depression, anxiety, and functioning were observed after 8 weeks of baclofen augmented citalopram treatment. Baclofen has been used in the treatment of alcohol dependence and has been shown to be beneficial in the treatment of PTSD [68]. The mechanism here is interesting in that baclofen acts on the GABA B receptor which has noted agonists effective in treating mood and anxiety disorders rather than the GABA A receptor where benzodiazepines act, thereby offering a new line of investigation for novel pharmacotherapeutic agents.

Even when complete remission from PTSD is not achieved, significant improvement is often observed with SSRIs and venlafaxine, both of which had medium effects in meta-analysis and were superior compared to placebo [25]. Recommended first-line pharmacotherapies often reduce irritability, low anger threshold, and depression; such a clinical response can have a large impact on quality of life, even if PTSD persists [69]. What we know is that it is critical that both clinicians and patients be cognizant of the time required to observe a positive response to medications, to follow recommended dosing guidance, and to determine that medication is taken as prescribed. It is also important to appropriately evaluate and monitor symptoms to determine the need for a change in treatment recommendations. Clinicians should determine if patients who have "failed" previous pharmacological treatments were compliant with treatment recommendations or if they received an adequate trial. Based on stepped-care recommendations in the PTSD guideline [3], it may be

the case that another antidepressant should be prescribed to insure that the patient has had an adequate therapeutic trial before concluding that a patient is unresponsive to medication.

What Have We Learned About Treating Common Co-Occurring Disorders Associated With PTSD?

We have already touched upon two of the most common co-occurring disorders, depression and insomnia, noted in PTSD patients. In those instances, first-line recommendations for core PTSD symptoms are SSRIs, SNRIs, or cognitive-behavioral psychotherapies with the addition of prazosin for PTSD-related nightmares [3]. One of the other most common and serious challenge for clinicians is co-morbid PTSD and substance use disorder (SUD) [70]. The evidence base, unfortunately, is still too sparse to support evidence-based treatment recommendations for patients with both PTSD and SUD. It can also be complicated by the fact that several PTSD symptoms overlap greatly with common alcohol withdrawal symptoms, so it is important to take this into consideration when confirming diagnoses [71]. Perhaps, the most important point we can emphasize is that pharmacological treatments for SUD are vastly underutilized and that treatment of SUD saves lives [71]. For cannabis and stimulant use disorder, no Food and Drug Administration (FDA) pharmacotherapies exist. For alcohol use disorder (AUD), the FDA has approved three medications—disulfiram, naltrexone, and acamprosate. Topiramate, an anticonvulsant agent, has some newly demonstrated efficacy in reducing alcohol consumption and craving as well as reduced PTSD symptom severity, particularly hyperarousal symptoms [72], although it has not been approved for treatment of alcohol use disorder. Interestingly, the recent meta-analysis by the AHRQ [14] concluded that topiramate was at least as effective as first-line recommended agents for PTSD, paroxetine, and venlafaxine. Exceptional benefit was noted using topiramate in a group of antidepressant treatment-resistant patients [73]. Other studies have been mixed or suffer from small numbers but topiramate does show encouraging evidence of efficacy and may be particularly helpful for patients with co-occurring PTSD and SUD. As with baclofen, some of the excitement about topiramate is that it works through a different mechanism than antidepressants.

Research conducted by Petrakis et al., 2006 [74], noted both naltrexone and disulfiram reduced alcohol use compared with placebo in veterans with the co-occurring disorder but had little impact on PTSD. Acamprosate has not yet been studied in this co-morbid population. Recent work by Foa et al. [75] examining PE therapy and naltrexone showed all participants had large decreases in number of days using alcohol as well as decreases in PTSD symptoms and supported the proposition that treatments for PTSD and SUD can be delivered in an integrated model. The important point is that these medications are safe to use in patients with co-occurring PTSD and SUD.

Promising work using prazosin has been noted in treating alcohol use disorder (AUD). In a small, double-blind, placebo-controlled trial, prazosin significantly reduced alcohol use in men with a diagnosis of alcohol dependence but without PTSD, indicating that it may have independent efficacy for alcohol use disorder [76]. More recent work has shown that prazosin has beneficial effects on stress and alcohol craving in those with AUD, suggesting that it could play a role in normalizing the stress dysregulation associated with early recovery from alcoholism [77]. RCTs are now underway to examine the use of prazosin for patients with co-occurring PTSD and AUD. Another approach, combining sertraline and naltrexone, has been successful for co-occurring depression and AUD [78].

A recent study, indicated that the TCA, desipramine, (which has equal efficacy and fewer side effects than amitriptyline and imipramine), significantly reduced PTSD symptoms among veterans with co-occurring AUD [79]. The study compared paroxetine to desipramine and also evaluated naltrexone relative to placebo. Paroxetine did not show statistical superiority to desipramine for the treatment of PTSD symptoms. However, desipramine was superior to paroxetine with respect to study retention and alcohol use outcomes. Naltrexone reduced alcohol craving compared to placebo but did not improve alcohol use outcomes. Overall, the study provided support for further research of desipramine treatment for patients with co-occurring PTSD and AUD.

A potential candidate for treating co-occurring PTSD and SUD is the alpha-2 agonist, guanfacine, which has recently been shown to reduce substance-related anxiety, craving, and arousal in cocaine-dependent patients [80•]. So, even though guanfacine has proven ineffective for PTSD alone, based on two negative RCTs [69], it may have a beneficial role for patients with co-morbid PTSD/SUD.

The question of how best to integrate interventions for SUD-specific medications for co-occurring PTSD and SUD requires further research. There is growing evidence that addressing both conditions concurrently is the most effective approach [81]. A landmark RCT demonstrated that prolonged abstinence rates from tobacco could be doubled by integrating PTSD and SUD treatments so that both PTSD and smoking cessation were delivered by the same provider [82]. Varenicline is noted as the most efficacious approved smoking cessation pharmacotherapy currently available. Since it is known that varenicline may produce sleep disturbance and abnormal dreaming, it should be monitored carefully when it is used for PTSD patients.

An area where work is still in its infancy and without clear guidance is in the treatment of co-occurring traumatic brain injury (TBI) and PTSD. The complexity of the two conditions makes pharmacotherapy treatment recommendations

challenging. Findings from a recent study with 207 surgically hospitalized injury survivors showing significant benefit from a stepped-care protocol suggest that further research is needed to test this approach for individuals with TBI and PTSD [83•]. Still many questions regarding optimal treatment options for other psychiatric disorders often associated with PTSD remain, including those for patients with chronic pain. It is noteworthy that, providing evidence-based psychotherapy treatments for PTSD patients with co-occurring disorders has led to concurrent improvements in personality disorders [84], in dementia [85], in obsessive-compulsive disorder (OCD) [86], and in other serious mental illness [87].

Suffice it to say, there is still a great deal of work to be done in the area of treatment of PTSD and common co-occurring disorders. The brief review above highlights some of the more promising areas of research; some of which have combined pharmacotherapy and psychotherapy. At this point, we do not have enough information to know which patients are most likely to benefit from pharmacotherapy for the various SUDs. It is recommended, however, that patients with the co-occurring disorder receive first-line psychotherapy or pharmacotherapy for PTSD as well as available recommended medications for SUD [3].

How Has Our Knowledge of the Neurobiology of PTSD Informed the Field on Novel Alternative Treatment Recommendations to Address the Complicated Symptoms Often Seen in Those Who Have a PTSD Diagnosis?

With greater understanding of the psychobiology of PTSD, recent work has shifted its focus from serotonergic agents. In contrast to the exciting findings regarding prazosin, early reports of beneficial effects of a *B*-adrenergic antagonist, propranolol, have not shown it to be an effective prophylactic agent compared to placebo so it is not recommended as an acute intervention in the guidelines [3]. Recent research with propranolol has tested the possibility that it might ameliorate chronic PTSD by disrupting the reconsolidation of traumatic memories [88]. This theoretically driven approach is exciting and awaits the necessary RCT evaluation.

Similarly, alpha-2 adrenergic agonists would be expected to be effective in treating PTSD, given antagonism of presynaptic norepinephrine release. Results from small open trials with clonidine are generally favorable whereas two RCTs with guanfacine have had negative results (possibly because of the chronicity of PTSD in the older Vietnam veteran participants) [69].

New research is now being conducted with medications that target the specific pathophysiology of PTSD. Such medications might act on the adrenergic, hypothalamic-pituitary-adrenocortical (HPA), glutamatergic, GABA-ergic, inflammatory, or other mechanisms that mediate the human stress response and which are altered among patients with PTSD, particularly those pathways involved in fear learning and extinction. Other work involves the use of agents that act on endocannabinoids, oxytocin, neurokinin/substance P and dopamine [89••]. Recently, a study of the efficacy of ketamine for PTSD [90•] noted evidence for rapid reduction in symptom severity and if replicated, may lead to novel approaches to the pharmacologic treatment of patients with this disabling condition. Groundbreaking work using positron emission tomography (PET) suggests that PTSD may be associated with a deficiency in the endocannabinoid system [91••]. Such findings suggest new targets for pharmacological interventions that may result in novel effective treatment approaches. Finally, a recent review noted the efficacy of anti-inflammatory treatment on depression compared to placebo [92]. Given the overlap of depression and PTSD and the growing knowledge of the neuroimmunology of PTSD [93], non-steroidal anti-inflammatory drugs (NSAIDs) may represent another class of pharmacologic treatment that offers promise with limited adverse side effects.

Perhaps, one of the most useful findings over the past recent years has been in the area of what NOT to recommend for treatment of PTSD. In short, there is no evidence for the efficacy of benzodiazepines in the management of PTSD and growing evidence that they pose significant clinical risks [94, 95]. Given such an unfavorable risk-benefit ratio, they are not recommended for treatment of PTSD. Further, it is interesting that work with zolpidem, a similar agent to eszopiclone, discussed previously, has not shown efficacy in the management of PTSD [96] and that new concerns about safety issues with this non-benzodiazepine hypnotic class of medications continue to be noted [97]. Similarly, atypical antipsychotic agents are not recommended in the management of PTSD. Neither conventional nor atypical antipsychotics are recommended as monotherapy or as adjunctive agents for PTSD.

Conclusions

In summary, investigators are making considerable progress in moving forward with recommended interventions for PTSD. With the new DSM-5 criteria [98] now in place, it appears possible that novel pharmacotherapies might target the different phenotypes of PTSD (e.g., anxious, depressive, externalizing, and dissociative). We anticipate the future development of effective medications that have been designed specifically to treat the unique pathophysiology of PTSD. The work by Neumeister et al. [91••] and by Kohler et al. [92] suggests that further development of biomarkers may serve as critical predictors of intervention response and can point to new directions in treatment. However, it is critical that patients and their treating clinicians recognize that, at this time, trauma-focused

psychotherapies are the first-line recommended treatments to address PTSD. Pharmacotherapy may play an important role, but there are unanswered questions about how long patients may need to remain on medications, withdrawal syndromes associated with any of the agents, and their efficacy for treating the overall disorder. There is a current debate about the effectiveness of psychiatric treatments and whether pharmacotherapy, psychotherapy, or some combination of the two, would be the best approach. Importantly, although we now can point to numerous effective interventions, there is still room for improvement. We await further results from clinical trials to address these questions in order to identify the best treatments for PTSD.

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Compliance with Ethics Guidelines

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