



# PTSD *Research Quarterly*

ADVANCING SCIENCE AND PROMOTING UNDERSTANDING OF TRAUMATIC STRESS

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## Exciting New Developments in Pharmacotherapy for PTSD

There has been a recent surge in clinical studies testing novel medications for posttraumatic stress disorder (PTSD). This welcome advancement comes after almost 30 years in which PTSD pharmacotherapy trials mostly evaluated medications developed for other disorders, e.g., antidepressants, anti-adrenergic agents, antipsychotics and anticonvulsants. This issue of the *Research Quarterly* highlights these exciting new pharmacologic targets, including psychedelic-assisted psychotherapy, and briefly reviews studies of drugs that show a positive signal at 4 weeks but not endpoint, older compounds, head-to-head psychotherapy vs. pharmacotherapy studies, and prophylactic interventions aimed to prevent PTSD. The renewed interest in PTSD pharmacotherapy trials is encouraging given the urgent need for more effective treatments in a disorder that is prevalent, causes personal suffering to patients and their family, contributes a high societal economic burden, and has known serious complications if left untreated.

### Novel Pharmacotherapy for PTSD

Ketamine offers the most novel mechanism of action of any new compound for the treatment of PTSD in the past 20 years. Ketamine has been used for decades as an anesthetic-analgesic agent and is now US Food and Drug Administration- (FDA) approved as a rapid-onset intervention for treatment-resistant depression. Ketamine is a noncompetitive glutamate N-methyl-d-aspartate (NMDA) antagonist and is thought to modify the expression of fear by altering memory reconsolidation, enhancing fear extinction, and improving synaptic plasticity. It also has some

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activating effects on opioid mu receptors which contributes to its anti-suicidality effects (Williams et al., 2019). Feder and colleagues (2020) published a comprehensive review of the rational and emerging findings for the use of ketamine in the treatment of PTSD. The article discusses the mixed findings on ketamine administered prophylactically after a recent traumatic event. Next, Feder and colleagues (2021) published results from their randomized controlled trial (RCT) in which 30 individuals with chronic PTSD were randomly assigned to receive six infusions over 2 consecutive weeks of ketamine or midazolam, a psychoactive placebo control. The ketamine group showed significantly greater improvement at 2 weeks in PTSD (Cohen's  $d = 1.13$ ) and depression ( $d = 0.92$ ) outcomes compared to the midazolam group. Ketamine yielded more treatment responders (67%) than midazolam (20%) and was well tolerated overall, without serious adverse events. The ketamine response appeared to subside about a month following the 2-week course of infusions. Larger studies over a longer duration, with perhaps the intranasal spray formulation, are needed to confirm ketamine's potential as a treatment for chronic and treatment-resistant PTSD.

NYX-783 is a novel small molecule that was recently tested in a multisite placebo-controlled trial using a 2-stage sequential parallel comparison design (Davis et al., 2021). NYX-783 targets the glutamate NMDA receptor by acting as a positive allosteric modulator. Participants with PTSD were randomized to monotherapy with daily 10 mg NYX-783 or 50 mg NYX-783 or placebo for 4 weeks, then placebo non-responders were re-randomized to one of the three arms for 4 additional weeks. Although total

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Clinician Administered PTSD Scale (CAPS-5) improvement in the NYX-783 (50 mg/d) group was numerically observed with a non-significant trend difference from placebo, the 50 mg dose resulted in significant improvement in some PTSD symptom clusters compared to placebo at week 4, specifically Arousal-Reactivity (both doses) and Negative-Cognitions-Mood scores (50 mg/d). After correcting for baseline imbalances in time since trauma, improvement in the total CAPS-5 was significant for 50 mg/d NYX-783 compared to placebo. In addition, significantly more subjects on the 50 mg dose (74%) demonstrated a clinically reliable change ( $\geq 13$ -point CAPS-5 reduction) compared to the placebo group (43%). NYX-783 was observed to be well tolerated with a comparable safety profile to placebo.

One of most robust findings for the pharmacologic treatment of PTSD is from an RCT of methylphenidate, a dopaminergic-noradrenergic stimulant that is FDA-approved for the treatment of attention deficit disorder. In a sample of 32 adults with PTSD and/or history of mild traumatic brain injury, McAllister and colleagues (2016) found a clinically meaningful and statistically significant improvement for methylphenidate compared to placebo on the PTSD Checklist (PCL-5), including all PTSD symptom clusters. The effect size for the PTSD outcome was very large ( $d = 1.88$ ) over the 12-week follow-up period, as well as for post-concussive symptoms ( $d = 0.89$ ) and depressive symptoms ( $d = 0.5$ ). Methylphenidate also improved cognition ( $d = 0.34$ ) and was well tolerated. The cholinesterase inhibitor galantamine arm did not differ from placebo. A larger trial of methylphenidate is urgently needed to confirm these promising results.

Investigators have been testing the efficacy of a bedtime sublingual formulation of cyclobenzaprine, called TNX-102 SL, which has a tricyclic antidepressant-like mechanism of action. The first 12-week randomized multicenter trial of TNX-102 in Veterans and transitioning service members with military-related PTSD was recently published (Sullivan et al., 2021). Although the primary analysis comparing change from baseline in CAPS-5 score between 2.8 mg/d TNX-102 SL ( $n = 90$ ) and placebo ( $n = 92$ ) was not significant, the 5.6 mg/d dose was significantly better than placebo in reducing CAPS-5 (Cohen's  $d = 0.36$ ), as well as the Clinician Global Impression - Improvement responder rate and mean functional improvement in Sheehan Disability Scale social and work domains. Post-hoc analyses found that sleep improvement at week 4 predicted improvement in PTSD at 12 weeks for TNX-102 SL (pooled doses;  $p < .01$ ), but not for placebo. TNX-102 SL was well tolerated. This study provides preliminary evidence that 5.6 mg/d TNX-102 SL reduces PTSD symptoms, improves sleep and psychosocial function, and is well tolerated. A larger study has been conducted, but the results have not been published.

Giovanna et al. (2020) reviewed the rationale and emerging evidence from 14 studies on the therapeutic effects of intranasal oxytocin, a peptide involved in the modulation of social cognition, emotional skills, and the reward system. Results on PTSD outcomes from these small studies are mixed; however, larger studies are underway to study oxytocin as a strategy to augment prolonged exposure therapy.

## MDMA-assisted Psychotherapy

Several comprehensive reviews have been recently published on the rationale and emerging evidence of psychedelics, including lysergic

acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, and ayahuasca in the treatment of psychiatric conditions (Krediet et al., 2020; Reiff et al., 2020; Jerome et al., 2020; Hoskins et al., 2021). A lot of attention has been paid to the use of MDMA-assisted psychotherapy for the treatment of severe PTSD, especially since it was given Breakthrough Therapy designation by the FDA, which means it is designated as a drug that can be expedited in the FDA review process, not that it is actually a “breakthrough” or that there is sufficient evidence of treatment efficacy. Previously known as a party drug called “ecstasy,” MDMA binds primarily to presynaptic serotonin transporters and induces a robust serotonin release that has many downstream effects known to be involved in processing of fear-laden memories and regulation of emotional responses. Efficacy studies of psychedelic medication-assisted psychotherapy must all grapple with how to maintain the double-blinded conditions, since MDMA and other psychedelics are very psychoactive and thus the participant and/or therapists might become aware that the participant is under the influence of the study drug instead of placebo. Various approaches have been included in study designs to mitigate the chance of accidental unblinding.

Mitchell et al. (2021) recently published the results of their RCT in which 90 participants with a diagnosis of PTSD were randomized to MDMA-assisted psychotherapy or placebo-assisted psychotherapy. The manualized psychotherapy was provided by a specialty-trained two-person therapist team. Participants engaged in three unmedicated 90-minute preparatory sessions, followed by three 8-hour experimental sessions in which either MDMA or placebo was taken at the beginning of each session spaced 4 weeks apart, and then three unmedicated 90-minute integration sessions spaced 1 week apart. To mitigate the problem of accidental unblinding, the outcome measures were collected by a centralized, independent raters via live video interviews. The independent raters were kept blinded to the final study design, visit number, treatment assignment and all other data collected, and did not repeatedly evaluate the same participants over the course of the study. Adverse events were closely tracked throughout the study and the drug appeared to be well tolerated without cardiovascular side effects and did not increase suicidality. Compared with group who received placebo, MDMA-assisted psychotherapy led to a significant improvement in both CAPS-5 ( $P < 0.0001$ ,  $d = 0.91$ ) and Sheehan Disability Scale ( $P = 0.0116$ ,  $d = 0.43$ ) total score. For the participants completing treatment, the mean change in CAPS-5 was -24.4 (s.d. 11.6) in the MDMA group and -13.9 (s.d. 11.5) in the placebo group. These results are indeed notable for the large effect size demonstrated in a small sample of severely symptomatic and treatment-resistant patients. Confirmatory studies are underway.

## Drugs that Showed Early Signal but Lost Their Edge at Endpoint

Vortioxetine is a relatively new antidepressant that acts as a serotonin modulator through inhibition of the serotonin transporter and actions at multiple types of serotonin receptors. Dunlop et al. (2021) conducted a 12-week randomized double-blind, flexibly dosed, placebo-controlled trial of vortioxetine in 41 adults with PTSD (mostly women and predominantly sexual assault-related trauma). Although there were no between-group differences in the change from baseline in CAPS-5 at week 12, vortioxetine's effect size at week 12 was comparable to that reported with serotonin reuptake inhibitors (Cohen's  $d = 0.29$ ), which indicates that larger sample sizes

are needed to properly test vortioxetine's efficacy. When the investigators looked at week 8 differences, vortioxetine was significantly better than placebo in reducing CAPS-5 severity (week 8 Cohen's  $d = 0.78$ ;  $P = 0.014$ ) and had 2x higher rates of response compared to placebo. The investigators gave a compelling presentation of their trial results in comparison with the published literature (7 RCTs) to illustrate the issue of week 8 and 12 trajectories and the impact of late-phase improvement in placebo group and a plateau or diminishing effects in the drug-treated group between week 8 and 12.

Angiotensin type 1 receptor inhibition has been implicated as part of the mechanism of fear inhibition and extinction (Seligowski et al., 2021). A recent RCT found that the angiotensin-1 receptor antagonist, losartan, was significantly better than placebo in reducing CAPS-5 at week 4, but these differences were not sustained through the remainder of the 10-week trial in 149 subjects with PTSD (Stein et al., 2021). Unfortunately, this study failed to show an association between angiotensin-converting enzyme (ACE) genotype and CAPS-5 improvement on losartan. This study is yet another illustration of early signal detection that is diminished at the endpoint due to continued progression of placebo responders in small to medium sample sizes.

## New Findings for Older Medications

Recently published studies of older medications that did not separate from placebo include the atypical antipsychotic ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRI; Hamner et al., 2019), the anticonvulsant zonisamide combined with cognitive processing therapy (Petraakis et al., 2020), the antidepressant mirtazapine as monotherapy (Davis et al., 2020), the non-benzodiazepine  $\gamma$ -aminobutyric acid-A receptor agonist eszopiclone (Dowd et al., 2020), and the glutamatergic modulator riluzole augmentation of SSRI or serotonin-norepinephrine reuptake inhibitors (SNRI; Spangler et al., 2020). However, several secondary analyses are worth mentioning. In the Davis et al. (2020) study, significant overall clinical global improvements were found for the mirtazapine group compared to the placebo group. In the Dowd et al. (2020) study, improvement in sleep was significantly correlated with overall improvement in PTSD for eszopiclone-treated subjects, but not for those treated with placebo. In the Spangler et al. (2020) study, although the change in overall PTSD symptoms showed a small effect size ( $d = 0.25$ ), riluzole treatment led to significantly greater improvement on self-reported hyperarousal symptoms (PCL-5 subscale D) compared to placebo ( $d = 0.48$ ) and near-significant findings on the CAPS-5 Subscale D.

Although not using an RCT design, two publications are worth mentioning. A retrospective chart review added support for low-dose clonidine in the treatment of PTSD in 79 Veterans (Burek et al., 2021). Clonidine is an alpha2-adrenergic agonist that reduces the release of norepinephrine and has been implicated in the treatment of hyperarousal and sleep disturbances in PTSD. The authors found that after treatment with low-dose clonidine, 72% of patients experienced improvement, and 49% scored "much improved" or "very much improved" based on chart reviews by three independent clinicians using the Clinical Global Impressions (CGI) scales for severity and improvement. Sogo and colleagues (2021) provided treatment with a central anticholinergic drug, trihexyphenidyl, to 34 patients with refractory PTSD-related nightmares and flashbacks (open-label

$n = 22$ ; single-blind  $n = 12$ ), and found that most patients reported absent or mild nightmares (88%) and flashbacks (79%) at follow-up.

## Recent Systematic Reviews, Meta-analyses, and Archival Record Analyses

Several analyses of pooled studies and large electronic medical record databases have recently been published. It is curious that depending on the methods of the selection of studies and analysis, investigators arrived at somewhat different conclusions as described below.

In a systematic review of RCTs published through August 2018, investigators compared efficacy and acceptability among drug treatment for PTSD in adults (de Moraes et al., 2020). The study included 58 studies comprising 6,766 patients randomized to 26 different interventions and used a random-effects pairwise and network meta-analyses approach to evaluate efficacy. Regarding efficacy, risperidone, quetiapine, topiramate, paroxetine, venlafaxine, fluoxetine, and sertraline outperformed placebo. The authors noted that quetiapine and topiramate relied on only a few small studies. In terms of acceptability, phenelzine, lamotrigine, and fluoxetine outperformed placebo, with fluoxetine ranking the most acceptable. Meanwhile, Huang and colleagues (2020) conducted a more expanded meta-analysis of RCTs published through June 2019 evaluating the efficacy and acceptability of pharmaceuticals for PTSD in adults (70 placebo-controlled RCTs involving 31 drugs and 8 active-comparator RCTs involving 12 active drugs; 8,083 subjects). In terms of efficacy, all active drugs when pooled demonstrated a more superior effect than placebo, and more specifically the following individual drug classes were more efficacious than placebo: atypical antipsychotics, SNRIs, SSRIs, and tetracyclic antidepressants. The following specific drugs presented more beneficial effects than placebo: quetiapine, risperidone, olanzapine, venlafaxine, fluoxetine, paroxetine, sertraline, hydroxyzine, and mirtazapine. For acceptability, pharmacologic interventions for PTSD showed no increase in all-cause discontinuation compared with placebo, although medications had a higher risk of adverse effect compared with placebo. Only atypical antipsychotics showed superior efficacy than placebo in Veterans, which was expanded upon by the same group of investigators in a subsequent manuscript (Zhao et al., 2020).

Zhang and colleagues (2020) conducted a systematic review and meta-analysis of prazosin for the treatment of nightmares, insomnia and overall PTSD symptoms. The analysis included data from 8 RCTs involving 575 participants with diagnosis of PTSD, including the large negative US Department of Veterans Affairs (VA) Cooperative Studies Program study (Raskind et al., 2018). According to this meta-analysis, prazosin significantly improved nightmares compared to placebo but did not separate from placebo for overall PTSD symptoms and sleep quality. There was no significant difference between the prazosin and the placebo groups with respect to discontinuation for all causes. Additional studies are needed before downgrading the use of prazosin in the treatment of nightmares in patients with PTSD, particularly for those patients with exaggerated sympathetic nervous system signs and symptoms, such as REM sleep without atonia and awakening from nightmares with profuse sweating and rapid heart rate.

In a novel approach, Zhao and colleagues (2020) pooled the results of pharmaceutical RCTs in which >95% participants were Veterans

with a diagnosis of combat-related PTSD (36 RCTs;  $n = 2,331$ ). In comparison with placebo, all drugs pooled showed an overall significant therapeutic effect in terms of PTSD severity and response rates. The pooled studies of atypical antipsychotics (included monotherapy and augmentation of antidepressants trials), which included risperidone, aripiprazole, olanzapine, and quetiapine studies, showed a significant improvement in PTSD for this class of drugs compared to placebo. This analysis included the large VA Cooperative Study Program (CSP) of risperidone, which did not separate drug from placebo on its own. In their stratified analysis of risperidone studies, the therapeutic effect of monotherapy was better than that of combined therapy. Other types and classes of drugs were not statistically significantly different from placebo or control, including alpha adrenergic blockers, anticonvulsants, corticosteroids, D-cycloserine,  $\gamma$ -aminobutyric acid (GABA) agonists, monoamine oxidase inhibitors, N-acetylcysteine, reversible cholinesterase inhibitor, serotonin antagonist and reuptake inhibitor (nefazodone), serotonin modulators and stimulators, SSRIs, tricyclic antidepressants, and adrenergic  $\alpha$ 2A receptor agonists. Reduction in PTSD symptom clusters were significant for drugs acting on 5-HT receptors (re-experiencing, avoidance, hyper-arousal), drugs acting on dopamine receptors (re-experiencing), and drugs acting on  $\alpha$ 2 receptor (total PTSD symptoms scale). Counter to recent Clinical Treatment Guidelines, this analysis, which is limited to studies conducted in predominantly Veteran samples, supports the use of atypical antipsychotics, particularly risperidone, as well as the SSRI antidepressants, especially sertraline as an effective treatment for PTSD.

Shiner and colleagues (2020) examined VA electronic medical records of 834 outpatients diagnosed with PTSD and compared PCL-5 scores before and after receiving an adequate trial of fluoxetine, paroxetine, sertraline, topiramate, or venlafaxine. Overall, patients' PCL-5 scores improved and up to 11% achieved remission of PTSD symptoms. Comparatively, those taking venlafaxine were significantly more likely to achieve remission. Although there were no differences in utilization of acute psychiatric care over 6 months between specific medications, those who continued their medication were significantly less likely to use acute psychiatric services, indicating that regardless of the agent chosen, medication discontinuation is associated with a higher risk of acute psychiatric care use.

## Pharmacotherapy versus Psychotherapy

Rauch and colleagues (2019) conducted the first ever adequately powered, rigorous RCT head-to-head comparison between psychotherapy and pharmacotherapy. Over 200 Iraq/Afghanistan War Veterans or service members were randomly assigned to one of three treatment conditions: prolonged exposure (PE) therapy plus placebo pill, PE plus sertraline, or sertraline plus enhanced medication management. The drug/placebo component was double-blinded and outcome evaluators were blinded to all treatment assignments. All treatment groups showed significant reduction in PTSD symptoms, but there were no between-group differences in the change of PTSD severity, response, or remission rates. The combination of PE and sertraline led to a greater number of early responders (19%) compared to PE plus placebo (9%) or sertraline (6%) groups. Sertraline plus enhanced medication management resulted in a much lower rate of early drop-out (27%) compared to PE plus placebo (48%) and PE plus sertraline (41%). Additionally,

there were no significant differences across the three treatment conditions in persistence of individual PTSD symptoms those with or without PTSD diagnosis at posttreatment (Tripp et al., 2020). However, among those who did not lose the PTSD diagnosis, sleeping difficulties (63%), hypervigilance (47%), and nightmares (45%) were most likely to persist indicating that additional medication or cognitive behavioral therapy may be warranted for these targeted symptoms.

Merz et al. (2019) compared outcomes of pharmacological to psychotherapeutic treatments or their combination in a network meta-analysis. Although no treatment approach was superior at the primary endpoint of treatment, psychotherapy showed significantly greater benefit compared to pharmacotherapy at the longer-term follow-up. All three treatment approaches had similar patterns of acceptability, i.e., no differences in dropout rate for pharmacological compared with psychotherapeutic treatments. Although acute phase outcomes which appear to be quite similar, these findings speak to the potential durability of psychotherapeutic interventions when compared to medication monotherapy. Sonis and Cook (2019) included the above described Rausch et al. (2019) study in their recent meta-analysis of head-to-head comparison studies and concluded that there is still insufficient evidence to definitively determine whether SSRI/SNRI antidepressants or trauma-focused psychotherapies are more effective for PTSD among adults with PTSD. These authors stress that until there is more definitive evidence, treatment guidelines should not favor trauma-focused psychotherapies over medications (or vice versa), but rather patient preferences and shared decision-making should be emphasized.

Patient choice is an important factor in terms of promoting adherence and improved outcomes as some patients may prefer psychotherapy options and others may not have the time, interest, or resources to attend psychotherapy sessions. In a doubly randomized preference trial of PE versus sertraline, patients who received their preferred treatment (PE or sertraline) were more likely to lose their diagnosis of PTSD, achieve responder status, adhere to treatment, and show an overall improvement in self-reported PTSD, depression and anxiety symptoms (Zoellner et al., 2019). Both prolonged exposure and sertraline showed large gains that were maintained over 24 months without differential effects on interviewer-rated PTSD severity. However, compared to sertraline, PE led to higher rates of remission (loss of diagnosis) and greater number of responders. Of note, more study participants expressed a preference for PE over sertraline at baseline, which may have contributed to some of the PE advantages. Clearly, accommodating patient preferences for treatment enhances the therapeutic benefits and treatment adherence.

## Cannabinoids

Cannabis plant (*Cannabis sativa*) derivatives include the psychoactive delta-9-tetrahydrocannabinol (THC) and non-intoxicating cannabidiol (CBD). Studies are being conducted on the effects of THC and CBD on affective disorders, anxiety disorders, and PTSD. Stanciu and colleagues (2021) reviewed the 8 small studies of CBD or THC for anxiety, depression and PTSD. Open label studies had mixed results of THC for anxiety and modest improvements with CBD on anxiety in individuals with social anxiety disorder. One small crossover trial showed that THC added to standard pharmacotherapy reduced self-reported PTSD-related

nightmares. Two small studies of THC found no improvement in depression; instead, anxiety and psychotic symptoms emerged in over half of the hospitalized patients with unipolar or bipolar depression. LaFrance et al. (2020) reported on data from 404 medical cannabis users who self-identified as having PTSD were obtained from Strainprint®, a medical cannabis app that tracks changes in symptoms as a function of different strains and doses of cannabis across time. The investigators examined PTSD-related symptoms (intrusive thoughts, flashbacks, irritability, and/or anxiety) immediately before and after inhaling cannabis over 31 months and found that all symptoms were temporarily reduced by more than 50% immediately after cannabis use and time and dose predicted larger decreases in intrusions, irritability and anxiety. Cannabis was not effective over the long-term, as baseline symptom severity was maintained over time and the dose increased over time, which is indicative of development of tolerance. The authors point out the limitation of a self-selected, self-identified sample of patients with no placebo control group. Given the lack of placebo-controlled evidence of efficacy combined with the risk of adverse events including cognitive complaints, THC is not considered at this time to be an effective treatment for PTSD. The evidence for CBD is also lacking but the risk level is much lower than THC. Studies of cannabinoid compounds in the treatment of PTSD, such as an oromucosal spray of cannabis extracts called nabiximols and a synthetic analog of THC called nabilone, are planned and/or underway.

## An Early Intervention to Consider and One to Avoid

Given the role of the hypothalamic-pituitary (HPA) axis in the stress response and pathophysiology of PTSD, Kothgassner and colleagues (2021) conducted a meta-analysis focused on the RCTs of hydrocortisone (8 studies, 362 participants) in the prevention, treatment, and cure for PTSD. Hydrocortisone significantly reduced PTSD symptoms and PTSD incidence as compared to placebo, especially when administered in a preventative context, but not when it was administered in a curative context. This study was consistent with a previous systematic review and meta-analysis of 19 RCTs (Astill et al., 2019), which concluded that hydrocortisone administered within three months of a traumatic event in adults with severe physical illness/injury was superior to placebo in preventing PTSD, whereas there were no significant preventative effects for propranolol, oxytocin, gabapentin, fish oil, dexamethasone, escitalopram, imipramine or chloral hydrate. Hydrocortisone possibly represents a low cost and effective prophylactic intervention for people who have experienced recent severe physical illness or injury, but more methodologically rigorous studies are warranted.

A very recent publication adds to the growing evidence that benzodiazepines are not only ineffective at preventing PTSD but can in fact increase the risk of developing PTSD when administered during or immediately after a trauma (von Känel et al., 2021). The investigators examined the severity and incidence of PTSD symptoms after exposure to benzodiazepines, morphine,  $\beta$ -blockers, or antidepressants used to alleviate anxiety and/or pain during acute coronary syndromes. Three months following a verified acute coronary syndrome in 154 patients, in which 38% were exposed to benzodiazepines, 72% to morphine, 88% to  $\beta$ -blockers, and 7% to antidepressants, the severity of PTSD was assessed with the CAPS. Benzodiazepine use was significantly associated with increased PTSD severity, particularly the reexperiencing symptoms. While morphine,  $\beta$ -blockers, and antidepressants showed no protective

value, benzodiazepines were associated with an almost 4-fold increased relative risk of developing clinical PTSD following acute coronary syndrome. Benzodiazepines interact with the GABAergic systems to short-circuit glutamatergic availability that is otherwise necessary for new learning to extinguish fear-mediated behaviors.

## Featured Articles

Davis, L., Stein, M., Arnold, L., King, K., Young, K., & Gutierrez-Esteinou, R. (2021) **A randomized, placebo-controlled, double-blind study of NYX-783 in patients with post-traumatic stress disorder.** [Poster abstract] *Biological Psychiatry*, 89, S109–S388 doi:10.1016/j.biopsych.2021.02.500 *Background:* PTSD is a complex and difficult-to-treat psychiatric condition with high unmet need. NYX-783 is a small molecule that modulates the N-methyl-D-aspartate receptor. *Methods:* This was a double-blind, randomized, placebo-controlled study using a 2-stage sequential parallel comparison design in participants with diagnosis of PTSD, PTSD Checklist for the fifth edition, *Diagnostic and Statistical Manual of Mental Disorders* (PCL-5 for DSM-5) score 38, and Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total score 30. Participants were randomized to NYX783 10mg or 50mg or placebo for 4 weeks, then placebo participants were rerandomized (stratified by response) to continue placebo or NYX-783 for 4 weeks. The primary endpoints were LS mean change from baseline for CAPS-5-Total and CAPS-5 cluster scores during Stage 1 and Stage 2 combined, with prespecified significance P0.1. Analyses for LS mean change in PCL-5 and responder-analyses were predetermined. *Results:* CAPS-5-Total improvement was observed with NYX-783 50mg with strong trend difference from placebo (-15.7 [1.79 SEM] p¼0.12 vs. placebo Stage 1; p¼0.16 vs. placebo Stages 1+2 [n¼153]). PCL-5 improvement was significant for NYX-783 50mg vs. placebo in Stage 1 (p¼0.099). CAPS-5 Arousal-Reactivity score improvement was significant for Stages 1+2 with NYX-783 50mg and 10mg vs. placebo (p¼0.04 and p¼0.049, respectively). For CAPS-5 Negative-Cognitions-Mood score, improvement was significant in Stage 1 with 50mg vs. placebo (p¼0.049). Among patients who completed Stage 1, 30% and 50% improvement from baseline in CAPS-5-Total was 78% and 50% with NYX-783 50mg vs. 44% (p¼0.008) and 26% with placebo (p¼0.044), respectively. NYX-783 was well tolerated and comparable to placebo. *Conclusions:* NYX-783 demonstrated promising results for the treatment of PTSD.

de Moraes Costa, G., Zanatta, F. B., Ziegelmann, P. K., Soares Barros, A. J., & Mello, C. F. (2020). **Pharmacological treatments for adults with post-traumatic stress disorder: A network meta-analysis of comparative efficacy and acceptability.**

*Journal of Psychiatric Research*, 130, 412–420. doi:10.1016/j.jpsychires.2020.07.046 *Background:* The purpose of this study was to compare efficacy and acceptability among drug treatments for adults with PTSD through a systematic review, random-effects pairwise and network meta-analyses. *Methods:* Double-blind randomized controlled trials comparing pharmacological interventions for adults with PTSD were searched from database inception through Aug. 28, 2018, on Cochrane (Central), Embase, LILACS, PILOTS, PsycINFO, PubMed, and Web of Science. Clinical trial registries and the websites of pharmaceutical companies were also searched. The GRADE system was used to assess the quality of the evidence.

**Results:** The systematic review included 58 studies comprising 6766 patients randomized to 26 different interventions. Regarding efficacy, topiramate (SMD = -0.57; 95%CrI: -1.07,-0.10), risperidone (SMD = -0.53; 95%CrI: -0.93,-0.15), quetiapine (SMD = -0.59; 95%CrI: -1.06,-0.11), paroxetine (SMD = -0.35; 95%CrI: -0.48,-0.21), venlafaxine (SMD = -0.25; 95%CrI: -0.44,-0.05), fluoxetine (SMD = -0.28; 95%CrI: -0.46,-0.08), and sertraline (SMD = -0.21; 95%CrI: -0.33,-0.09) outperformed placebo.

Moreover, phenelzine (RR = 3.39; 95%CrI: 1.43,11.09), lamotrigine (RR = 4.39; 95%CrI: 1.18,26.38), and fluoxetine (RR = 1.28%CrI: 1.01,1.59) outperformed placebo in terms of acceptability.

**Conclusions:** The NMA supports topiramate, risperidone, quetiapine, paroxetine, venlafaxine, fluoxetine and sertraline as effective pharmacological choices for the treatment of PTSD. Quetiapine and topiramate have the shortcoming of relying on a few small studies, but the clinically meaningful change in symptoms is noteworthy and merits further investigation. Among the pharmacological treatments with evidence of efficacy compared to placebo, fluoxetine achieved a relatively high rank regarding acceptability. To the best of our knowledge, this is the largest contemporary NMA on the subject and the addition of new medications is an important extension of previous meta-analyses, enabling a larger number of drug comparisons.

Dowd, S. M., Zalta, A. K., Burgess, H. J., Adkins, E. C., Valdespino-Hayden, Z., & Pollack, M. H. (2020). **Double-blind randomized controlled study of the efficacy, safety and tolerability of eszopiclone vs placebo for the treatment of patients with post-traumatic stress disorder and insomnia.** *World Journal of Psychiatry, 10*(3), 21–28. doi:10.5498/wjp.v10.i3.21

**Background:** Sleep disturbance is a core feature of PTSD. Given the relationship between sleep disturbance and PTSD, there has been a relative paucity of studies examining the potential therapeutic impact of using pharmacotherapy to target sleep disturbance in patients with PTSD. Eszopiclone (ESZ) is a non-benzodiazepine  $\gamma$ -aminobutyric acid-A receptor agonist indicated for the treatment of sleep and may affect sleep in patients with PTSD. **Aim:** To evaluate the efficacy of ESZ vs placebo (PBO) for patients with PTSD and insomnia. **Methods:** The study was a 12-wk, double blind, randomized controlled trial with 3 mg of ESZ ( $n = 13$ ) or PBO ( $n = 12$ ). **Results:** Patients in both arms experienced significant improvement in PTSD symptoms as assessed by the Clinician-Administered PTSD Scale for the fourth edition, *Diagnostic and Statistical Manual of Mental Disorders* (CAPS for DSM-IV): ESZ ( $t_{11} = -3.12, P = 0.005$ ) and PBO ( $t_{11} = -3.5, P = 0.002$ ) and by self-report with the Short PTSD Rating Interview (ESZ  $t_{11} = -3.38, P = 0.003$  and PBO  $t_{11} = -4.48, P = 0.0005$ ). There were no significant differences between treatments on the CAPS ( $t_{22} = -0.13, P = 0.70$ ) or the Short PTSD Rating Interview ( $t_{22} = -0.58, P = 0.56$ ). Similarly, both treated groups improved on sleep measures as assessed by the Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI) and on total sleep time (TST) and sleep latency assessed by actigraphy with no significant differences between groups (PSQI  $t_{22} = -0.24, P = 0.81$ ; total sleep time  $t_{10} = 0.13, P = 0.90$  and sleep latency  $t_{10} = 0.68, P = 0.50$ ). There was a significant correlation between improvement in sleep and overall improvement in PTSD as measured by change scores on the PSQI and CAPS,  $r(8) = 0.79, P = 0.01$  for ESZ treated subjects, but

not for those treated with PBO ( $r(9) = 0.16, P = 0.69$ ). Adverse events of ESZ were consistent with the known profile of the medication including dysgeusia (30%, mild), sedation (20%, mild) and headache (20%, moderate to severe). **Conclusion:** Results do not support the hypothesis of a specific positive effect of ESZ compared to PBO for measures of PTSD and associated sleep disturbance.

Dunlop, B. W., Rakofsky, J. J., Newport, D. J., Mletzko-Crowe, T., Barone, K., Nemeroff, C. B., & Harvey, P. D. (2021). **Efficacy of vortioxetine monotherapy for posttraumatic stress disorder: A randomized, placebo-controlled trial.**

*Journal of Clinical Psychopharmacology, 41*(2),172–179.

doi:10.1097/JCP.0000000000001363 **Purpose/background:** There are few efficacious pharmacological treatments for PTSD and many patients fail to benefit from existing treatments. Vortioxetine, a recently developed antidepressant, acts as a serotonin modulator through inhibition of the serotonin transporter and actions at multiple types of serotonin receptors. Its unique pharmacodynamic profile suggests it may have efficacy for the treatment of PTSD. **Methods/procedures:** We conducted a 12-week placebo-controlled, randomized clinical trial of vortioxetine (flexibly dosed from 10 to 20 mg/d) versus placebo in adults with PTSD. The primary outcome was change from baseline in the past-month version of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), analyzed using a mixed-model repeated-measures analysis of variance. **Findings/results:** Forty-one patients were randomized, and 32 (78%) completed the 12 weeks of treatment. The mean reduction in CAPS-5 scores at week 12 did not significantly differ between the 2 arms; the effect size for the difference in changes between vortioxetine and placebo on CAPS-5 total scores at week 12 was Cohen  $d = 0.29$ . However, at week 8, the drug-placebo difference was  $d = 0.78$ , which met the multivariate criteria for statistical significance,  $P = 0.014$ . **Implications/conclusions:** In this study of 41 patients, vortioxetine did not demonstrate superiority over placebo for adults with PTSD. Future PTSD trials may benefit from stratifying the randomization based on number of years since the index traumatic event and a history of failure to respond to treatment.

Feder, A., Costi, S., Rutter, S. B., Collins, A. B., Govindarajulu, U., Jha, M. K., Horn, S. R., Kautz, M., Corniquel, M., Collins, K. A., Bevilacqua, L., Glasgow, A. M., Brallier, J., Pietrzak, R. H., Murrrough, J. W., & Charney, D. S. (2021). **A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder.** *American Journal of Psychiatry, 178*(2),193–202.

doi:10.1176/appi.ajp.2020.20050596 **Objective:** PTSD is a chronic and disabling disorder, for which available pharmacotherapies have limited efficacy. The authors' previous proof-of-concept randomized controlled trial of single-dose intravenous ketamine infusion in individuals with PTSD showed significant and rapid PTSD symptom reduction 24 hours postinfusion. The present study is the first randomized controlled trial to test the efficacy and safety of repeated intravenous ketamine infusions for the treatment of chronic PTSD. **Methods:** Individuals with chronic PTSD ( $N = 30$ ) were randomly assigned (1:1) to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) (psychoactive placebo control) over 2 consecutive weeks. Clinician-rated and self-report assessments were administered 24 hours after the first infusion and at weekly visits. The primary outcome measure was change in PTSD symptom

severity, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), from baseline to 2 weeks (after completion of all infusions). Secondary outcome measures included the Impact of Event Scale-Revised, the Montgomery-Åsberg Depression Rating Scale (MADRS), and side effect measures. *Results:* The ketamine group showed a significantly greater improvement in CAPS-5 and MADRS total scores than the midazolam group from baseline to week 2. At week 2, the mean CAPS-5 total score was 11.88 points ( $SE = 3.96$ ) lower in the ketamine group than in the midazolam group ( $d = 1.13$ , 95% CI = 0.36, 1.91). Sixty-seven percent of participants in the ketamine group were treatment responders, compared with 20% in the midazolam group. Among ketamine responders, the median time to loss of response was 27.5 days following the 2-week course of infusions. Ketamine infusions were well tolerated overall, without serious adverse events. *Conclusions:* This randomized controlled trial provides the first evidence of efficacy of repeated ketamine infusions in reducing symptom severity in individuals with chronic PTSD. Further studies are warranted to understand ketamine's full potential as a treatment for chronic PTSD.

Feder, A., Rutter, S. B., Schiller, D., & Charney, D. S. (2020). **The emergence of ketamine as a novel treatment for posttraumatic stress disorder.** *Advances in Pharmacology*, 89, 261–286. doi:10.1016/bs.apha.2020.05.004 A serious lack of effective pharmacotherapeutic interventions for PTSD raises the urgent need for the development of novel treatments. Ketamine—a noncompetitive glutamate NMDA receptor antagonist in use for decades as an anesthetic and analgesic agent—has more recently been demonstrated to have rapid-onset antidepressant effects in patients with treatment-resistant depression (TRD). In the present review of ketamine as an emerging novel pharmacotherapeutic intervention for chronic PTSD, we discuss findings from the first proof-of-concept, randomized clinical trial (RCT) of single-dose intravenous ketamine in patients with chronic PTSD, as well as open-label studies and current practice. We introduce ongoing RCTs investigating the efficacy of repeated ketamine infusions in rapidly reducing symptoms and maintaining improvement in samples of individuals with PTSD stemming from civilian and military traumas. Additionally, we discuss mixed findings from published reports on ketamine administration in the acute aftermath of trauma. Studies in animal models of chronic stress have investigated molecular mechanisms underlying ketamine's effects, generating a shift in the conceptualization of PTSD as a disorder of impaired neural connectivity. We review animal studies examining the potential of ketamine to modify the expression of fear by altering memory reconsolidation or enhancing fear extinction, as well as others investigating ketamine administration prophylactically prior to stress exposure. We introduce the need for additional study in humans to evaluate whether ketamine might enhance the efficacy of psychotherapeutic interventions in individuals with chronic PTSD, harnessing a window of ketamine-induced neuroplasticity. While research on ketamine for PTSD is still in its early stages, it brings about the promise of novel and more effective treatments for this disabling condition.

Hoskins, M. D., Sinnerton, R., Nakamura, A., Underwood, J. F. G., Slater, A., Lewis, C., Roberts, N. P., Bisson, J. I., Lee, M., & Clarke, L. (2021). **Pharmacological-assisted psychotherapy for post-traumatic stress disorder: A systematic review and meta-analysis.**

*European Journal of Psychotraumatology*, 12, 1853379. doi:10.1080/20008198.2020.1853379 *Background:* Pharmacological-assisted psychotherapies, using conventional and novel drug agents, are increasingly being used both in clinical and experimental research settings, respectively. *Objective:* To determine the efficacy of conventional and novel pharmacological-assisted psychotherapies in reducing PTSD symptom severity. *Method:* A systematic review and meta-analysis of randomised-controlled trials were undertaken; 21 studies were included. *Results:* MDMA-assisted therapy was found to be statistically superior to active and inactive placebo-assisted therapy in reduction of PTSD symptoms (standardised mean difference -1.09, 95% CI -1.60 to -0.58). There was no evidence of superiority over placebo for any other intervention. *Conclusions:* MDMA-assisted therapy demonstrated an impressive effect size; however, it is difficult to have confidence at this stage in this intervention due to the small numbers of participants included, and more research in this area is needed. There was no evidence to support the efficacy of any other drug-assisted interventions.

Huang, Z.-D., Zhao, Y.-F., Li, S., Gu, H.-Y., Lin, L.-L., Yang, Z.-Y., Niu, Y.-M., Zhang, C., & Luo, J. (2020). **Comparative efficacy and acceptability of pharmaceutical management for adults with post-traumatic stress disorder: A systematic review and meta-analysis.** *Frontiers in Pharmacology*, 11, 559. doi:10.3389/fphar.2020.00559 The current clinical guidelines on PTSD recommend selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) of drugs. However, there is uncertainty about the efficacy of other drugs and selecting which treatments work best for which patients. This meta-analysis evaluated efficacy and acceptability of pharmaceutical management for adults with PTSD. Randomized-controlled trials, which reported active comparators and placebo-controlled trials of pharmaceutical management for adults with PTSD, from the Ovid Medline, EMBase, CENTRAL, PsycINFO, Ovid Health and Psychosocial Instruments, and ISIWeb of Science, were searched until June 21, 2019. In terms of efficacy, all active drugs demonstrated superior effect than placebo (SMD = -0.33; 95% CI, -0.43 to -0.23). The medications were superior to placebo in reducing the symptom of re-experiencing, avoidance, hyperarousal, depression, and anxiety. For acceptability, medicine interventions for PTSD showed no increase in all-cause discontinuation compared with placebo. Nevertheless, in terms of safety, medicine interventions indicated a higher risk of adverse effect compared with placebo (RR = 1.47, 95% CI: 1.24 to 1.75). Compared with placebo, the SSRIs and atypical antipsychotics drugs had significant efficacy whether in patients with severe or extremely severe PTSD status. However, only atypical antipsychotics (SMD = -0.29, 95% CI: -0.48 to -0.10) showed superior efficacy than placebo in Veterans. Medication management could be effective in intervention of PTSD, which demonstrated a sufficient improvement in the core symptoms. This meta-analysis supports the status of SSRIs and SNRIs as recommended pharmacotherapy. However, patients with different clinical characteristics of PTSD should consider individualized drug management.

Kothgassner, O. D., Pellegrini, M., Goreis, A., Giordano, V., Edobor, J., Fischer, S., Plener, P. L., & Huscsava, M. M. (2021). **Hydrocortisone administration for reducing post-traumatic stress symptoms: A**

**systematic review and meta-analysis.** *Psychoneuroendocrinology*, 126.105168. doi:10.1016/j.psyneuen.2021.105168 **Background:** PTSD is a debilitating disorder that is often accompanied by alterations in the HPA axis. While there is abundant evidence for the efficacy of psychological therapies in reducing post-traumatic stress symptoms, barely anything is known about pharmacological interventions. Given the role of the HPA axis in the pathophysiology of PTSD, the aim of this study was to provide the first meta-analysis of Hydrocortisone as a potential treatment for this condition. **Method:** A systematic review of randomized-controlled trials (RCTs) was conducted to investigate the efficacy of hydrocortisone in the prevention and curative treatment of post-traumatic stress symptoms. This study was pre-registered with the OSF (doi:10.17605/OSF.IO/GJAZF). **Findings:** Eight studies (9 effect sizes) covering 362 participants met our inclusion criteria. We found that Hydrocortisone as compared to placebo significantly reduced PTSD symptoms ( $d = 0.96$ , 95% CI 0.22–1.69  $p = 0.011$ ) and PTSD incidence (logRR = 0.85, 95% CI 1.12–1.59,  $p = 0.023$ ). Subgroup analyses revealed a significant effect of Hydrocortisone when it was administered in a preventative context ( $d = 1.50$ ; 95%CI 0.30–2.69,  $p = 0.014$ ), but not when it was administered in a curative context ( $d = 0.28$ ; 95%CI -0.11 to 0.66,  $p = 0.161$ ). **Conclusion:** Hydrocortisone appears to be a promising and efficient low-cost medication for the prevention of PTSD. However, the small number of included studies and their limited methodological quality emphasize the need for further rigorous studies in this field.

McAllister, T. W., Zafonte, R., Jain, S., Flashman, L. A., George, M. S., Grant, G. A., He, F., Lohr, J. B., Andaluz, N., Summerall, L., Paulus, M. P., Raman, R., & Stein, M. B. (2016). **Randomized placebo-controlled trial of methylphenidate or galantamine for persistent emotional and cognitive symptoms associated with PTSD and/or traumatic brain injury.** *Neuropsychopharmacology*, 41(5), 1191–1198. doi:10.1038/npp.2015.282 We report findings from a 12-week randomized double-blinded placebo-controlled trial of methylphenidate or galantamine to treat emotional and cognitive complaints in individuals ( $n = 32$ ) with a history of PTSD, TBI, or both conditions. In this small pilot study, methylphenidate treatment was associated with clinically meaningful and statistically significant improvement compared with placebo on the primary outcome, a measure of cognitive complaints (Ruff Neurobehavioral Inventory-Postmorbidity Cognitive Scale), as well as on the secondary outcomes reflecting post-concussive (Rivermead Post Concussive Symptom Questionnaire) and post-traumatic stress symptoms (Posttraumatic Stress Disorder Checklist). Treatment was well tolerated. These results suggest the need for a larger RCT to replicate and confirm these findings. Design considerations for such a trial should include the need for multiple sites to facilitate adequate recruitment and extension of the treatment and follow-up periods.

Merz, J., Schwarzer, G., & Gerger, H. (2019). **Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: A network meta-analysis.** *JAMA Psychiatry*, 76(9), 904–913. doi:10.1001/jamapsychiatry.2019.0951 **Importance:** PTSD is a prevalent mental disorder, with a high risk of chronicity, comorbidity, and functional impairment; PTSD is complicated to treat, and the debate on the best treatment approach is ongoing.

**Objective:** To examine comparative outcomes and acceptability of psychotherapeutic and pharmacological treatments and their combinations in adults with PTSD. **Data Sources:** Embase, MEDLINE, PsycINFO, Cochrane Controlled Trials Register, and PSYINDEX were searched for studies published from January 1, 1980, to February 28, 2018. Reference lists of included studies and of previously published guidelines and systematic reviews were also searched. **Study Selection:** Of 11 417 records identified, 12 published randomized clinical trials (RCTs) comprising 922 participants, contributing 23 direct comparisons between psychotherapeutic and pharmacological treatments or their combinations were included. **Data Extraction and Synthesis:** Standardized mean differences (SMDs) and odds ratios were aggregated using random-effects network and pairwise meta-analyses. Risk of bias and indirectness was rated for each study, and network confidence was rated using the Confidence in Network Meta-Analysis framework. **Main Outcomes and Measures:** The primary outcome was the comparative benefit between 2 treatment approaches to PTSD symptom improvement, and secondary outcome was the comparative acceptability of the treatment approaches, as indicated by patient dropout rates before treatment termination. **Results:** No treatment approach was found to be superior at the end of treatment (for all, 95% CI included 0). At the last follow-up, psychotherapeutic treatments showed greater benefit than pharmacological treatments in both network (SMD, -0.83; 95% CI, -1.59 to -0.07) and pairwise (SMD, -0.63; 95% CI, -1.18 to -0.09, 3 RCTs) meta-analyses. No difference was found between combined treatments and psychotherapeutic treatments at long-term follow-up, and combined treatments were associated with better outcomes than pharmacological treatments in the network meta-analysis (SMD, -0.96; 95% CI, -1.87 to -0.04), but not in the pairwise meta-analysis, which included 2 RCTs (SMD, -1.02; 95% CI, -2.77 to 0.72). No evidence was found for differential acceptability of the 3 treatment approaches. **Conclusions and Relevance:** These results suggest superiority of psychotherapeutic treatments over pharmacological treatments; network, but not pairwise, meta-analyses suggest superiority of combined treatments over pharmacological treatments in improving PTSD symptom severity in the long term. The scarcity of reported long-term findings hampers definite conclusions and demonstrates the need for robust evidence from large-scaled comparative trials providing long-term follow-up data.

Mitchell, J.M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G, M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mithoefer, A., Quevedo, S., Wells, G., Claire, S. S., van der Kolk, B., Tzarfaty, K., ... Doblin, R. (2021). **MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study.** *Natural Medicine* 27, 1025–1033. doi:10.1038/s41591-021-01336-3 PTSD presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of MDMA-assisted therapy for the treatment of patients with severe PTSD, including those with common comorbidities such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma. After



psychiatric medication washout, participants ( $n = 90$ ) were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5, the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint) were assessed at baseline and at 2 months after the last experimental session. Adverse events and suicidality were tracked throughout the study. MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ( $P < 0.0001$ ,  $d = 0.91$ ) and to significantly decrease the SDS total score ( $P = 0.0116$ ,  $d = 0.43$ ). The mean change in CAPS-5 scores in participants completing treatment was  $-24.4$  (s.d. 11.6) in the MDMA group and  $-13.9$  (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. These data indicate that, compared with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.

Rauch, S. A. M., Kim, H. M., Powell, C., Tuerk, P. W., Simon, N. M., Acierno, R., Allard, C. B., Norman, S. B., Venners, M. R., Rothbaum, B. O., Stein, M. B., Porter, K., Martis, B., King, A. P., Liberzon, I., Phan, K. L., & Hoge, C. W. (2019). **Efficacy of prolonged exposure therapy, sertraline hydrochloride, and their combination among combat Veterans with posttraumatic stress disorder: A randomized clinical trial.** *JAMA Psychiatry*, *76*(2), 17–126. doi:10.1001/jamapsychiatry.2018.3412

**Importance:** Meta-analyses of treatments for PTSD suggest that trauma-focused psychotherapies produce greater benefits than antidepressant medications alone. **Objective:** To determine the relative efficacy of prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline hydrochloride, and sertraline plus enhanced medication management in the treatment of PTSD. **Design, setting, and participants:** The Prolonged Exposure and Sertraline Trial was a randomized, multisite, 24-week clinical trial conducted at the Veterans Affairs Ann Arbor Healthcare System, Veterans Affairs San Diego Healthcare System, Ralph H. Johnson Veterans Affairs Medical Center, and Massachusetts General Hospital Home Base Veterans Program between January 26, 2012, and May 9, 2016. Participants and clinicians were blinded to pill condition, and outcome evaluators were blinded to assignment. Participants completed assessments at weeks 0 (intake), 6, 12, 24, and 52 (follow-up). Participants ( $n = 223$ ) were service members or Veterans of the Iraq and/or Afghanistan wars with combat-related PTSD and significant impairment (Clinician-Administered PTSD Scale score,  $\geq 50$ ) of at least 3 months' duration. Analyses were on an intent-to-treat basis. **Intervention:** Participants completed up to thirteen 90-minute sessions of prolonged exposure therapy by week 24. Sertraline dosage was titrated during a 10-week period and continued until week 24; medication management was manualized. **Main outcomes and measures:** The primary outcome was symptom severity of PTSD in the past month as assessed by the Clinician-Administered PTSD Scale score at week 24. **Results:** Of 223 randomized participants, 149 completed the study at 24 weeks, and 207 (180 men and 27 women; mean [SD] age, 34.5 [8.3 years]) were

included in the intent-to-treat analysis. Modified intent-to-treat analysis using a mixed model of repeated measures showed that PTSD symptoms decreased significantly during the 24 weeks (sertraline plus enhanced medication management, 33.8 points; prolonged exposure therapy plus sertraline, 32.7 points; and prolonged exposure therapy plus placebo, 29.4 points;  $\beta$ ,  $-9.39$ ; 95% CI,  $-11.62$  to  $-7.16$ ;  $P < .001$ ); however, slopes did not differ by treatment group (prolonged exposure therapy plus placebo group,  $-9.39$ ; sertraline plus enhanced medication management group,  $-10.37$ ; and prolonged exposure therapy plus sertraline group,  $-9.99$ ;  $P = .81$ ). **Conclusions and relevance:** No difference in change in PTSD symptoms or symptom severity at 24 weeks was found between sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline.

Reiff, C. M., Richman, E. E., Nemeroff, C. B., Carpenter, L. L., Widge, A. S., Rodriguez, C. I., Kalin, N. H., McDonald, W. M. & the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. (2020). **Psychedelics and psychedelic-assisted psychotherapy.** *American Journal of Psychiatry*, *177*(5), 391–410. doi:10.1176/appi.ajp.2019.19010035

**Objective:** The authors provide an evidenced-based summary of the literature on the clinical application of psychedelic drugs in psychiatric disorders. **Methods:** Searches of PubMed and PsycINFO via Ovid were conducted for articles in English, in peer-reviewed journals, reporting on "psilocybin," "lysergic acid diethylamide," "LSD," "ayahuasca," "3,4-methylenedioxymethamphetamine," and "MDMA," in human subjects, published between 2007 and July 1, 2019. A total of 1,603 articles were identified and screened. Articles that did not contain the terms "clinical trial," "therapy," or "imaging" in the title or abstract were filtered out. The 161 remaining articles were reviewed by two or more authors. The authors identified 14 articles reporting on well-designed clinical trials investigating the efficacy of LSD, MDMA, psilocybin, and ayahuasca for the treatment of mood and anxiety disorders, trauma and stress-related disorders, and substance-related and addictive disorders as well as in end-of-life care. **Results:** The most significant database exists for MDMA and psilocybin, which have been designated by the U.S. Food and Drug Administration (FDA) as "breakthrough therapies" for PTSD and treatment-resistant depression, respectively. The research on LSD and ayahuasca is observational, but available evidence suggests that these agents may have therapeutic effects in specific psychiatric disorders. **Conclusions:** Randomized clinical trials support the efficacy of MDMA in the treatment of PTSD and psilocybin in the treatment of depression and cancer-related anxiety. The research to support the use of LSD and ayahuasca in the treatment of psychiatric disorders is preliminary, although promising. Overall, the database is insufficient for FDA approval of any psychedelic compound for routine clinical use in psychiatric disorders at this time, but continued research on the efficacy of psychedelics for the treatment of psychiatric disorders is warranted.

Shiner, B., Leonard, C. E., Gui, J., Cornelius, S. L., Schnurr, P. P., Hoyt, J. E., Young-Xu, Y., & Watts, B. V. (2020). **Comparing medications for DSM-5 PTSD in routine VA practice.** *Journal of*

*Clinical Psychiatry*, 81(6), 20m13244. doi:10.4088/JCP.20m13244

**Objective:** Fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine have previously shown efficacy for PTSD. One prior study using US Department of Veterans Affairs (VA) medical records data to compare these agents found no differences in symptom reduction in clinical practice. The current study addresses several weaknesses in that study, including limited standardization of treatment duration, inability to account for prior treatment receipt, use of an outdated symptomatic assessment for PTSD, and lack of functional outcome. **Methods:** A total of 834 VA outpatients were identified with DSM-5 clinical diagnoses of PTSD between October 2016 and March 2018 who initiated one of the medications and met prespecified criteria for treatment duration and dose, combined with baseline and endpoint DSM-5 PTSD Checklist (PCL-5) measurements. Twelve-week acute-phase changes in PCL-5 score and remission of PTSD symptoms were compared among patients receiving the different medications, as was use of acute psychiatric services in the subsequent 6-month continuation phase. **Results:** In the acute phase, patients improved by a mean of 6.8-10.1 points on the PCL-5 and 0.0%-10.9% achieved remission of PTSD symptoms. Those taking venlafaxine were significantly more likely to achieve remission ( $P = .008$  vs fluoxetine and  $P < .0001$  vs paroxetine, sertraline, and topiramate). In the continuation phase, there were no differences in acute psychiatric care use between medications. Those who continued their medication were less likely to use acute psychiatric services (HR = 0.55;  $P = .03$ ). **Conclusions:** There may be an advantage to venlafaxine over other agents in achieving acute-phase remission for DSM-5 PTSD in routine clinical practice, but this finding requires further study. Regardless of the agent chosen, medication cessation during the continuation phase is associated with a higher risk of acute psychiatric care use.

Spangler, P. T., West, J. C., Dempsey, C. L., Possemato, K., Bartolanzo, D., Aliaga, P., Zarate, C., Vythilingam, M., & Benedek, D. M. (2020). **Randomized controlled trial of riluzole augmentation for posttraumatic stress disorder: Efficacy of a glutamatergic modulator for antidepressant-resistant symptoms.** *Journal of Clinical Psychiatry*, 81(6), 20m13233. doi:10.4088/JCP.20m13233

**Objective:** Current pharmacologic treatments for PTSD have shown limited efficacy, prompting a call to investigate new classes of medications. The current study investigated the efficacy of glutamate modulation with riluzole augmentation for combat-related PTSD symptoms resistant to treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). **Methods:** A randomized, double-blind, placebo-controlled, parallel trial was conducted at Walter Reed National Military Medical Center and Syracuse VA Medical Center between December 2013 and November 2017. Veterans and active duty service members with combat-related PTSD (per the Clinician Administered PTSD Scale [CAPS]) who were not responsive to SSRI or SNRI pharmacotherapy were randomized to 8-week augmentation with a starting dose of 100 mg/d of riluzole ( $n = 36$ ) or placebo ( $n = 38$ ) and assessed weekly for PTSD symptoms, anxiety, depression, disability, and side effects. **RESULTS:** Intent-to-treat analyses ( $n = 74$ ) of the primary outcome (CAPS for DSM-IV) showed no significant between-group difference in change in overall PTSD symptoms ( $F = 0.64$ ,  $P = .422$ ), with a small effect size ( $d = 0.25$ ). There was clinically significant within-group improvement in overall PTSD symptoms in both

groups, with a greater mean (SD) decrease in CAPS score in the riluzole group (-21.1 [18.9]) than in the placebo group (-16.7 [17.2]). Exploratory analyses of PTSD symptom clusters showed significantly greater improvement on hyperarousal symptoms in the riluzole group as measured by the PTSD Checklist-Specific-Subscale D ( $d = 0.48$ ) and near-significant findings on the CAPS Subscale D. Riluzole augmentation was not superior to placebo on change in depression, anxiety, or disability severity. **Conclusions:** Although preliminary, the exploratory findings of this study offer some evidence that riluzole augmentation of an SSRI or SNRI may selectively improve PTSD hyperarousal symptoms without changes in overall PTSD symptoms, depression, anxiety, or disability. Additional investigation of the mechanism of the efficacy of riluzole for hyperarousal symptoms is warranted.

Stanciuc, C. N., Brunette, M. F., Teja, N., & Budney, A. J. (2021). **Evidence for use of cannabinoids in mood disorders, anxiety disorders, and PTSD: A systematic review.** *Psychiatric Services*, 72(4), 429-436. doi:10.1176/appi.ps.202000189 **Objective:** Two primary compounds of the cannabis plant (*Cannabis sativa*), THC and CBD, differentially and dose-dependently affect mood and anxiety. In this systematic review, the authors summarize the design and results of controlled trials assessing the effects of THC and CBD on affective disorders, anxiety disorders, and PTSD. **Methods:** A keyword search of eight online literature databases identified eight randomized controlled trials of defined CBD or THC doses for the target populations. **Results:** A 1-month trial of daily THC (up to 3 mg per day) for the second edition, *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* anxiety disorder reduced anxiety symptoms, but symptoms were very low throughout the study. Another trial of sequential, single-day, low-dose THC in social anxiety disorder found no symptom changes. Two studies reported that single-dose CBD pretreatment reduced anxiety in laboratory paradigms among individuals with social anxiety disorder. A study of daily CBD for 4 weeks among adolescents with social anxiety disorder indicated modest symptom improvements. One crossover trial involving 10 patients with PTSD showed that THC added to standard pharmacotherapy reduced self-reported nightmares. Two small studies of THC for hospitalized patients with unipolar or bipolar depression found no improvement of depression; instead, anxiety and psychotic symptoms emerged in >50% of patients. **Conclusions:** With only eight very small studies, insufficient evidence was found for efficacy of CBD and THC to manage affective disorders, anxiety disorders, or PTSD. Therefore, medical cannabis should not be recommended for treating patients with these disorders. Further research should investigate the safety and efficacy of managing psychiatric disorders with cannabinoids.

Stein, M., Jain, S., Simon, N., West, J., Marvar, P., Bui, E., Ressler, K., & on behalf of LOSe-PTSD Investigators. (2021). **Randomized placebo-controlled trial of the angiotensin receptor antagonist lasartan for posttraumatic stress disorder.** [Symposium abstract]. *Biological Psychiatry*, 89(9), S50. **Background:** A large body of preclinical research and observational studies suggests that angiotensin type 1 receptor (AT1R) inhibition facilitates fear inhibition and extinction, a mechanism thought to be important for recovery from PTSD. This proposal is designed to test the efficacy of the AT1R antagonist losartan, repurposed for the treatment of PTSD.

**Methods:** RCT of 10 weeks duration in 149 individuals with DSM-5 PTSD. Losartan (or placebo) was started at 25 mg/d and increased to 100 mg/d by Week 6 and then held to Week 10. Primary outcome was change in CAPS-5 from baseline to 10 weeks in the losartan vs. placebo arm. Key secondary outcome was change in CAPS-5 associated with the rs4311 SNP in the angiotensin converting enzyme gene (ACE). Another secondary outcome was the proportion of responders based on CGI-I of “much” or “very much” improved. **Results:** Both groups had robust improvement in PTSD symptoms but change from baseline in CAPS-5 on Losartan was not significantly greater than on placebo (-16.0 [95% CI -18.9 e -13.1] vs. -16.9 [95% CI -19.8 e -14.0]) at 10 weeks. There was no significant difference in the proportion of responders on losartan (58.6%) vs. placebo (57.9%), and no association between rs4311 genotype and CAPS-5 outcome. **Conclusions:** At these doses and durations, there was no significant benefit of losartan compared to placebo for the treatment of PTSD. Implications for the failure to determine benefit of a repurposed drug with strong a priori expectations of success based on preclinical and epidemiological data are discussed.

Sullivan, G. M., Gendreau, R. M., Gendreau, J., Peters, P., Peters, A., Engels, J., Daugherty, B. L., Vaughn, B., Weathers, F. W., & Lederman, S. (2021). **Randomized clinical trial of bedtime sublingual cyclobenzaprine (TNX-102 SL) in military-related PTSD and the role of sleep quality in treatment response.** *Psychiatry Research*, 307, 113974. doi:10.1016/j.psychres.2021.113974 Effective PTSD pharmacotherapy is needed. This 12-week randomized multicenter trial evaluated efficacy and safety of TNX-102 SL, a bedtime sublingual formulation of cyclobenzaprine, in patients with military-related PTSD randomized to TNX-102 SL 2.8 mg or 5.6 mg, or placebo. Primary analysis comparing change from baseline in Clinician-Administered PTSD Scale-5 score between 2.8 mg ( $n = 90$ ) and placebo ( $n = 92$ ) was not significant. Secondary analysis of 5.6 mg ( $n = 49$ ) vs placebo demonstrated a mean difference of -4.5 units,  $p = .05$ , or, accounting for missing data by multiple imputation, -5.0 units,  $p = .03$ . Clinician Global Impression - Improvement responder rate was greater in 5.6 mg than placebo ( $p = 0.04$ ), as was mean functional improvement in Sheehan Disability Scale social domain ( $p = .03$ ) and trended in work domain ( $p = .05$ ). Post-hoc analyses showed early sleep improvement predicted improvement in PTSD after 12 weeks for TNX-102 SL ( $p < .01$ ), not for placebo. Most common administration site reaction in TNX-102 SL groups was oral hypoaesthesia (5.6 mg, 36%; 2.8 mg, 39%; placebo, 2%), while most common systemic adverse event was somnolence (5.6 mg, 16%; 2.8 mg, 12%; placebo, 6%). This provides preliminary evidence that TNX-102 SL 5.6 mg reduces PTSD symptoms, improves sleep and psychosocial function, and is well tolerated. Clinicaltrials.gov Identifier: [NCT02277704](https://clinicaltrials.gov/ct2/show/study/NCT02277704).

von Känel, R., Schmid, J.-P., Meister-Langraf, R. E., Barth, J., Znoj, H., Schnyder, U., Princip, M., & Pazhenkottil, A. P. (2021). **Pharmacotherapy in the management of anxiety and pain during acute coronary syndromes and the risk of developing symptoms of posttraumatic stress disorder.** *Journal of the American Heart Association*, 10(2), e018762. doi:10.1161/JAHA.120.018762 **Background:** Benzodiazepines and morphine are given during acute coronary syndromes (ACSs) to alleviate anxiety and pain, and

$\beta$ -blockers may also reduce pain. ACS may induce PTSD symptoms (PTSS). When taken during trauma other than ACS, benzodiazepines increase the risk of PTSS, but it is unknown if benzodiazepines increase the risk of PTSS in ACS. We examined the effects of drug exposure during ACS on the development of PTSS. **Methods and Results:** Study participants were 154 patients with a verified ACS. Baseline demographics, clinical variables, and psychological measures were obtained through a medical history, through a psychometric assessment, and from patient records, and used as covariates in linear regression analysis. Three months after ACS, the severity of PTSS was assessed with the Clinician-Administered PTSD Scale. During ACS, 37.7% of patients were exposed to benzodiazepines, whereas 72.1% were exposed to morphine and 88.3% were exposed to  $\beta$ -blockers, but only 7.1% were exposed to antidepressants. Eighteen (11.7%) patients developed clinical PTSD. Adjusting for all covariates, benzodiazepine use was significantly associated with the Clinician-Administered PTSD Scale total severity score (unstandardized coefficient B [SE], 0.589 [0.274]; partial  $r = 0.18$ ;  $P = 0.032$ ) and the reexperiencing subscore (B [SE], 0.433 [0.217]; partial  $r = 0.17$ ;  $P = 0.047$ ). Patients exposed to benzodiazepines had an almost 4-fold increased relative risk of developing clinical PTSD, adjusting for acute stress disorder symptoms (odds ratio, 3.75; 95% CI, 1.31-10.77). Morphine,  $\beta$ -blockers, and antidepressants showed no predictive value. **Conclusions:** Notwithstanding short-term antianxiety effects during ACS, benzodiazepine use might increase the risk of ACS-induced PTSS with clinical significance, thereby compromising patients' quality of life and prognosis. Registration URL: <https://www.clinicaltrials.gov>; Unique identifier: [NCT01781247](https://clinicaltrials.gov/ct2/show/study/NCT01781247).

Zhang, Y., Ren, R., Sanford, L. D., Yang, L., Ni, Y., Zhou, J., Zhang, J., Wing, Y.-K., Shi, J., Lu, L., & Tang, X. (2020). **The effects of prazosin on sleep disturbances in post-traumatic stress disorder: A systematic review and meta-analysis.** *Sleep Medicine*, 67, 225-231. doi:10.1016/j.sleep.2019.06.010 **Background:** Nightmares are a highly prevalent and distressing feature of PTSD. Previous studies have reached mixed conclusions regarding the effects of prazosin on nightmares, sleep quality, and overall PTSD symptoms in patients with PTSD. **Methods:** MEDLINE, EMBASE, all EBM databases, PsycINFO, and CINAHL were systematically searched from inception date to October 2018 for randomized clinical trials that included reporting of nightmares, sleep quality or overall PTSD symptoms. The analysis included data from eight trials involving 286 PTSD patients in the prazosin group and 289 PTSD patients in the placebo group. **Results:** In our meta-analysis, prazosin resulted in a statistically significant improvement in nightmares (standardized mean difference (SMD) = -1.13, 95% confidence interval (CI) = -1.91 to -0.36), but was not more beneficial than placebo for overall PTSD symptoms (SMD = -0.45, 95% CI = -0.95 to 0.05) and sleep quality (SMD = -0.44, 95% CI = -1.44 to 0.55). In terms of acceptability, there was no significant difference between the prazosin group and the placebo group with respect to discontinuation for all causes (odds ratio (OR) = 1.00, 95% CI = 0.62-1.62). In conclusion, the use of prazosin was associated with an improvement of nightmare symptoms. **Conclusion:** Our findings indicate that additional studies are needed before considering downgrading the use of prazosin in the treatment of nightmares in patients with PTSD.

Zhao, Y.-F., Huang, Z.-D., Gu, H.-Y., Guo, G.-L., Yuan, R.-X., & Zhang, C. (2020). **Key clinical interest outcomes of pharmaceutical administration for Veterans with post-traumatic stress disorder based on pooled evidences of 36 randomised controlled trials with 2,331 adults.** *Frontiers in Pharmacology*, *11*, 602447. doi:10.3389/fphar.2020.602447 *Background:* The effects of drug treatment on Veterans, who have a high risk of PTSD, are not clear, and the guidelines are different from the recommendations of the recent meta-analysis. Our goal was to find the efficacy and frequencies of complications of drugs that can treat PTSD in Veterans. *Method:* We searched Ovid MEDLINE, Ovid Embase, The Cochrane Library and Web of Science until January 1, 2020. The outcomes were designed as the change of PTSD total scale, subsymptom score, response rate, frequencies of complications outcomes, and acceptability. *Results:* We included a total of 36 randomised controlled trials with a total of 2,331 adults. In terms of overall effect, drug treatment is more effective than placebo in change in total PTSD symptoms scale (SMD = -0.24, 95% CI [-0.42, -0.06]) and response (RR = 1.66, 95% CI [1.01, 2.72]). However, in terms of frequencies of complications, drugs generally had a higher withdrawal rate (RR = 1.02, 95% CI [0.86, 1.20]) and a higher frequencies of complications (RR = 1.72, 95% CI [1.20, 2.47]) than placebo. Risperidone showed a good curative effect in change in total PTSD symptoms scale (SMD = -0.22, 95% CI [-0.43, 0.00]) and acceptability (RR = 1.31, 95% CI [0.82, 2.59]). The drugs acting on 5-HT receptors, our results showed that symptoms of hyper-arousal (SMD = -0.54, 95% CI [-0.86, -0.21]), symptoms of re-experiencing (SMD = -0.62, 95% CI [-0.86, -0.39]) and symptoms of avoidance (SMD = -0.53, 95% CI [-0.77, -0.3]), The drugs acting on dopamine receptors, our results showed that symptoms of re-experiencing (SMD = -0.35, 95% CI [-0.55, -0.16]) and the drugs acting on  $\alpha_2$  receptor has a significant effect on reducing total PTSD symptoms scale (SMD = -0.34, 95% CI [-0.62, -0.06]). *Conclusion:* Drug therapy can effectively treat PTSD, but its frequencies of complications should be considered. Different from the guidelines for adult PTSD, this study supports atypical antipsychotics, selective serotonin reuptake inhibitors and receptors that act on 5-HT and dopamine for the treatment of PTSD in Veterans. Based on evidence among these drugs, the risperidone is the most effective for Veterans, otherwise, sertraline is used as an alternative.

Zoellner, L. A., Roy-Byrne, P. P., Mavissakalian, M., & Feeny, N. C. (2019). **Doubly randomized preference trial of prolonged exposure versus sertraline for treatment of PTSD.** *The American Journal of Psychiatry*, *176*(4), 287–296. doi:10.1176/appi.ajp.2018.17090995 *Objective:* The authors examined the effect of patient treatment preference on the differential effectiveness of prolonged exposure and sertraline for the treatment of PTSD. *Method:* In a doubly randomized preference trial, 200 patients with PTSD viewed standardized treatment rationales prior to randomization. Patients were first randomized to choice of treatment or no choice. Those assigned to no choice were then randomized to prolonged exposure or sertraline. Acute treatment was 10 weeks, with 24-month follow-up. Interviewer-rated PTSD symptom severity was the main outcome measure, and depression, anxiety, and functioning were assessed as additional outcomes. *Results:* Patients preferred prolonged exposure over sertraline (number needed to benefit [NNTB]=4.5). Using intent-to-treat

analyses ( $N=200$ ), both prolonged exposure and sertraline showed large gains that were maintained over 24 months. Although no differential effect was observed on interviewer-rated PTSD severity, there was a significant benefit of prolonged exposure over sertraline on interview-rated loss of PTSD diagnosis (NNTB=7.0), responder status (NNTB=5.7), and self-reported PTSD, depression, and anxiety symptoms and functioning (effect sizes, 0.35-0.44). Patients who received their preferred treatment were more likely to be adherent, lose their PTSD diagnosis (NNTB=3.4), achieve responder status (NNTB=3.4), and have lower self-reported PTSD, depression, and anxiety symptoms (effect sizes, 0.40-0.72). *Conclusions:* Prolonged exposure and sertraline confer significant benefits for PTSD, with some evidence of an advantage for prolonged exposure. Giving patients with PTSD their preferred treatment also confers important benefits, including enhancing adherence.

### Additional Citations

Astell Wright, L., Sijbrandij, M., Sinnerton, R., Lewis, C., Roberts, N. P., & Bisson, J. I. (2019). **Pharmacological prevention and early treatment of post-traumatic stress disorder and acute stress disorder: A systematic review and meta-analysis.** *Translational Psychiatry*, *9*(1), 334. doi:10.1038/s41398-019-0673-5 A meta-analysis was conducted to evaluate randomized controlled trials (RCT) of pharmacotherapeutic interventions within three months of a traumatic event used to prevent and treat PTSD and acute stress disorder. Only hydrocortisone was found to be superior to placebo in preventing PTSD in adults with severe physical illness (3 studies,  $n = 88$ , RR: 0.21 (CI 0.05 to 0.89)). No significant effects were found for propranolol, oxytocin, gabapentin, two types of fish oil, dexamethasone, escitalopram, imipramine and chloral hydrate. More research is needed to establish the most efficacious use of hydrocortisone in the prevention of PTSD.

Burek, G. A., Waite, M. R., Heslin, K., Liewen, A. K., Yaqub, T. M., & Larsen, S. E. (2021). **Low-dose clonidine in Veterans with posttraumatic stress disorder.** *Journal of Psychiatric Research*, *137*, 480–485. doi:10.1016/j.jpsychires.2021.03.008 Clonidine, an alpha2-adrenergic agonist, reduces the release of norepinephrine which may dampen hyper-noradrenergic states underlying PTSD. In this retrospective analysis of 79 Veterans prescribed clonidine for PTSD, three independent clinicians rated clinical global improvement and results suggested improvement in PTSD symptoms (72% of patients experienced improvement, and 49% scored "much improved" or "very much improved") and minimal side effects (23% reported adverse events) following treatment with clonidine.

Davis, L. L., Pilkinton, P., Lin, C., Parker, P., Estes, S., & Bartolucci, A. (2020). **A randomized, placebo-controlled trial of mirtazapine for the treatment of posttraumatic stress disorder in Veterans.** *Journal of Clinical Psychiatry*, *81*(6), 20m13267. doi:10.4088/JCP.20m13267 This multisite, randomized, double-blind, placebo-controlled trial of mirtazapine monotherapy in US military Veterans with PTSD found no significant differences between groups in the 8-week acute placebo-controlled phase, but showed significant improvement in 8-week open label maintenance phase. There were no significant differences in the occurrence of adverse events between groups.

Giovanna, G., Damiani, S., Fusar-Poli, L., Rocchetti, M., Brondino, N., de Cagna, F., Mori, A., & Politi, P. (2020). **Intranasal oxytocin as a potential therapeutic strategy in post-traumatic stress disorder: A systematic review.** *Psychoneuroendocrinology*, *115*, 104605. doi:10.1016/j.psyneuen.2020.104605 Oxytocin (OT) is a peptide involved in the modulation of social cognition, emotional skills and the reward system, which are theorized to all be deficient in PTSD. The fourteen studies in this systemic review provide evidence that intranasal OT (INOT) could be a safe pharmacological intervention for PTSD patients to promote a better therapeutic alliance and treatment outcome; however, the studies' sample sizes were mostly small and the primary outcome measures differed. Further research is needed to support INOT's effects on core symptoms in PTSD patients.

Hamner, M. B., Hernandez-Tejada, M. A., Zuschlag, Z. D., Agbor-Tabi, D., Huber, M., & Wang, Z. (2019). **Ziprasidone augmentation of SSRI antidepressants in posttraumatic stress disorder: A randomized, placebo-controlled pilot study of augmentation therapy.** *Journal of Clinical Psychopharmacology*, *39*(2), 153–157. doi:10.1097/JCP.0000000000001000 This 2-phase, randomized, double-blind, placebo-controlled pilot study of ziprasidone augmentation of SSRI treatment of refractory PTSD found no significant differences in outcomes or safety measures between groups in the 8-week placebo-controlled treatment phase. The small sample size of this pilot, however, makes the results inconclusive.

Jerome, L., Feduccia, A. A., Wang, J. B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2020). **Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: A longitudinal pooled analysis of six phase 2 trials.** *Psychopharmacology*, *237*(8):2485–2497. doi:10.1007/s00213-020-05548-2 This longitudinal pooled analysis of six trials examined long-term effects of 3,4-methylenedioxyamphetamine (MDMA)-assisted psychotherapy for treatment of PTSD. PTSD symptoms were significantly reduced from baseline to 1-2 months post-treatment and continued to improve at least 12 months post-treatment with 67% no longer meeting PTSD criteria at the 12-month long-term follow-up endpoint.

Krediet, E., Bostoen, T., Breeksema, J., van Schagen, A., Passie, T., & Vermetten, E. (2020). **Reviewing the potential of psychedelics for the treatment of PTSD.** *International Journal of Neuropsychopharmacology*, *23*(6), 385–400. doi:10.1093/ijnp/pyaa018 Psychotherapy is typically a first line treatment for PTSD; however, PTSD is often a chronic illness, and few medications are efficacious for the treatment of PTSD. This review discusses the therapeutic rationale, administration setting, and current treatment evidence of 4 types of psychedelic compounds in the treatment of PTSD: 3,4-methylenedioxyamphetamine, ketamine, classical psychedelics (e.g., psilocybin and lysergic acid diethylamide), and cannabinoids. Future directions for research is discussed.

LaFrance, E. M., Glodosky, N. C., Bonn-Miller, M., & Cuttler, C. (2020). **Short and long-term effects of cannabis on symptoms of post-traumatic stress disorder.** *Journal of Affective Disorders*, *274*, 298–304. doi:10.1016/j.jad.2020.05.132 This study examined the

efficacy of cannabis for symptom management of PTSD in 404 medical cannabis users who self-identified as having PTSD and used a medical cannabis symptom tracking app over 31 months. Immediately following cannabis use, more than 50% of symptoms were reduced; however, baseline symptoms were maintained over time and the dose needed to treat anxiety increased over time. Therefore, cannabis may only provide temporary relief and not be an effective long-term treatment.

Petrakis, I., Ralevski, E., Arias, A. J., DeNegre, D., Newcomb, J., Gianoli, M., McCarthy, E., Meshberg-Cohen, S., Yoon, G. (2020). **Zonisamide as an adjunctive treatment to cognitive processing therapy for Veterans with posttraumatic stress disorder and comorbid alcohol use disorder: A pilot study.** *American Journal of Addiction*, *29*(6), 515–524. doi:10.1111/ajad.13061 This randomized (3:1), double-blind, placebo-controlled 12-week trial of zonisamide augmentation of cognitive processing therapy (CPT) in 24 US Veterans with PTSD and current alcohol dependence found a significant decrease in drinking, craving, and PTSD symptoms in all subjects; however, zonisamide did not separate from placebo group in alcohol use or PTSD outcomes. A larger study is needed to isolate the contributions of medication vs psychotherapy.

Raskind, M. A., Peskind, E. R., Chow B., Harris, C., Davis-Karim, A., Holmes, H. A., Hart, K. L., McFall, T. A., Mellman, C. R., Romesser, J., Rosenheck, M.-C., Stein, M. B., Swift, R., Gleason, Y. L., & Huang, G. D. (2018). **Trial of prazosin for post-traumatic stress disorder in military Veterans.** *New England Journal of Medicine*, *378*(6), 507–517. doi:10.1056/NEJMoa1507598 The VA Cooperative Studies Program (CSP) conducted a multisite, randomized, double-blind, placebo-controlled 26-week trial of prazosin, an  $\alpha$ 1-adrenoreceptor antagonist, in 304 US military Veterans with chronic PTSD and frequent nightmares. The main analyses found no significant differences between groups after 10 weeks or 26 weeks. Sleep quality was not improved, and distressing dreams were not alleviated by prazosin.

Seligowskic, A. V., Duffy, L. A., Merker, J. B., Michopoulos, V., Gillespie, C. F., Marvar, P. J., Stein, M. B., & Ressler, K. J. (2021). **The renin-angiotensin system in PTSD: A replication and extension.** *Neuropsychopharmacology*, *46*(4), 750–755. doi:10.1038/s41386-020-00923-1 The renin-angiotensin system may be targeted by medications that act as angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), may be associated with PTSD symptoms. This study examined whether the effects of ACE-I/ARB status on PTSD differ by sex in 840 trauma-exposed individuals recruited as part of the Grady Trauma Project with replication analyses conducted using a large biorepository database (Partners Healthcare Biobank). Results replicate and add on to prior observations that the renin-angiotensin system is associated with PTSD symptoms, women have higher PTSD symptoms compared to men, and presence of ACE-I/ARB medication (especially the ARB Losartan) was associated with lower rate of PTSD diagnosis. Future treatment research should consider the effects of sex and race.

Sogo, K., Sogo, M., & Okawa, Y. (2021). **Centrally acting anticholinergic drug trihexyphenidyl is highly effective in reducing nightmares associated with post-traumatic stress**

**disorder.** *Brain Behavior*, 11(6), e02147. doi:10.1002/brb3.2147 This open-label and single-blind trial of trihexyphenidyl (TP) in 34 patients with refractory PTSD-related nightmares and flashbacks who had received 2-15 years of psychiatric treatment without therapeutic benefits found that patients reported mild or no nightmares and flashbacks after receiving TP. The efficacy of TP in the treatment of refractory PTSD-related nightmares and flashbacks requires further double-blind, randomized control trials but shows potential as a treatment option.

Sonis, J., & Cook, J. M. (2019). **Medication versus trauma-focused psychotherapy for adults with posttraumatic stress disorder: A systematic review and meta-analysis.** *Psychiatry Research*, 282. doi:10.1016/j.psychres.2019.112637 This systemic review and meta-analysis reviewed trials for PTSD treatment in adults comparing trauma-focused psychotherapies (cognitive behavioral therapy, prolonged exposure, cognitive therapy, cognitive processing therapy or eye movement desensitization and reprocessing) to an selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs) and. Four trials met inclusion criteria—they showed no difference in PTSD symptom reduction (but with a wide confidence interval) and high heterogeneity. Insufficient evidence was found to determine whether SSRIs/SNRIs or trauma-focused psychotherapy were more effective in treating PTSD symptoms in adults.

Tripp, J. C., Norman, S. B., Kim, H. M., Venners, M. R., Martis, B., Simon, N. M., Stein, M. B., Allard, C. B., Rauch, S. A. M. on behalf of the PROGrESS Study Team. (2020). **Residual symptoms of PTSD following Sertraline plus enhanced medication management, Sertraline plus PE, and PE plus placebo.** *Psychiatry Research*, 297, 113279. doi:10.1016/j.psychres.2020.113279 study found no significant differences between treatment with sertraline plus enhanced medication management (EMM), PE plus placebo, or PE plus sertraline in terms of residual PTSD symptom in Veterans with a PTSD diagnosis compared to those without a PTSD diagnosis at posttreatment. Among those without a PTSD diagnosis at posttreatment, sleeping difficulties (63.0%), hypervigilance (47.3%), and nightmares (45.0%) were most likely to persist, suggesting that other treatments may be warranted for residual symptoms like insomnia, nightmares, and hypervigilance.

Williams, N. R., Heifets, B. D., Bentzley, B. S., Blasey, C., Sudheimer, K. D., Hawkins, J., Lyons, D. M., & Schatzberg, A. F. (2019). **Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism.** *Molecular Psychiatry*, 24(12), 1779–1786. doi:10.1038/s41380-019-0503-4 In a secondary analysis of a clinical trial, the authors found that, compared to placebo, naltrexone attenuated the anti-suicidality effects of ketamine. These results suggest that the opioid receptor activation plays a role in the effects of ketamine to reduce suicidality.