Clinician's Guide to Medications for PTSD

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Overview

While each case of PTSD has unique biological, psychological, and social determinants with differing treatment implications, there are empirically supported treatments that can reduce or alleviate symptoms. Medications can be used to ameliorate the biological basis for PTSD symptoms along with co-occurring psychiatric diagnoses, and indirectly may benefit psychological and social symptoms as well. Studies suggest that cognitive behavioral therapies (CBT) such as Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), and Eye Movement Desensitization and Reprocessing (EMDR) have greater effects on relieving PTSD symptoms than medications (2), but there have been few head-to-head comparisons, and there remain many unanswered questions regarding the role of pharmacotherapy.

Clinicians must consider the level of evidence available supporting the specific medication interventions being considered. Randomized clinical trials (RCTs) which are placebo-controlled and double blinded are the gold standard for guiding pharmacotherapy decision making. More powerful conclusions can be drawn from systematic reviews and meta-analyses that look at all RCTs that have been done with a specific medication. Less strongly supported evidence includes open trials and case reports. It is vital to question the level of evidence supporting the medications being prescribed for PTSD when making treatment recommendations, because there are a variety of influences on prescribing, including marketing, patient preferences, and clinical custom, all of which can be inconsistent with the current scientific evidence.

Evidence for PTSD pharmacology is strongest for specific selective serotonin reuptake inhibitors (SSRIs) - sertraline (Zoloft), paroxetine (Paxil), and fluoxetine (Prozac) -- and a particular serotonin norepinephrine reuptake inhibitor (SNRI) - venlafaxine (Effexor) (1). Currently, only sertraline and paroxetine are approved by the Food and Drug Administration (FDA) for PTSD (3,4). From the FDA perspective, all other medication uses are off label, though there are differing levels of evidence supporting their use. The 2017 VA/DoD Clinical Practice Guideline for PTSD further offers weak recommendation for, or suggests, other antidepressants for PTSD treatment if the four strongly recommended medications are ineffective, unavailable, or not tolerated. They are: the serotonin potentiator, nefazodone (Serzone); the tricyclic antidepressant, imipramine (Tofranil); and the mono-amine oxidase

inhibitor, phenelzine (Nardil). Both nefazodone and phenelzine require careful management as they carry potentially serious toxicities (1).

Treatment planning is a collaborative effort between the clinician and the individual. Clinicians recognize the need to tailor pharmacotherapy to the needs of the individual patient. For example:

- PTSD carries high comorbidities with major depressive and substance use disorders. There are times when medications used for PTSD treatment may positively or negatively impact these co-occurring disorders.
- Highly resilient individuals have responded more quickly to medications than those who are less resilient (5).
- Veterans naïve to treatment recruited from the community respond as well as civilians in some studies (6) while Veterans with persistent PTSD symptoms (especially older Veterans who have received PTSD treatment for decades) may not respond as well to new treatments (7).
- Older individuals may have a less robust response to medications for PTSD than younger patients (8).
- Patients with personality disorders may be treated effectively, but medications alone are unlikely to address all the needs of those with more complicated trauma histories (9,10).

What Core PTSD Symptoms Are Medications Targeting?

The four main PTSD symptom clusters of the *DSM-5* criteria are listed below:

- **Intrusion.** Examples include nightmares, unwanted thoughts of the traumatic events, flashbacks, and reacting to traumatic reminders with emotional distress or physiological reactivity.
- **Avoidance.** Examples include avoiding triggers for traumatic memories including places, conversations, or other reminders.
- **Negative alterations in cognitions and mood.** Examples include distorted blame of self or others for the traumatic event, negative beliefs about oneself or the world, persistent negative emotions (e.g., fear, guilt, shame), feeling alienated, and constricted affect (e.g., inability to experience positive emotions).
- **Alterations in arousal and reactivity.** Examples include angry, reckless, or self-destructive behavior, sleep problems, concentration problems, increased startle response, and hypervigilance.

PTSD symptoms may improve at differing rates during pharmacotherapy. For example, a study of venlafaxine ER demonstrated early resolution in irritability (week 2), a later decrease in intrusive recollections (week 4), and no differences for sleep, dreams, and some avoidance symptoms at week 12 (11).

What Are Some of the Biological Disturbances Found in PTSD?

The biological disturbances in PTSD can be conceptualized as a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the balance between excitatory and inhibitory brain neurocircuitry. There is a resultant dysregulation of adrenergic mechanisms that mediate the classical fight, flight or freeze response.

Patients with PTSD have abnormal HPA function as compared to patients without PTSD and have a much greater variation in their levels of adrenocorticoids (12). A recent study measuring salivary cortisol levels found decreased cortisol variability for responders to PE with continued high variability in cortisol levels for non-responders (13). Further study of this complex interaction between cortisol levels and successful treatment is needed.

There are differences between individuals with PTSD and individuals without PTSD in both brain structures and brain circuits that process threatening input. It is not known for certain whether these changes were present before the traumatic event and predisposed the person to developing PTSD or if these changes were the result of the PTSD. The fear circuitry exhibits excessive activation in PTSD and is no longer integrated well with the executive planning and judgment centers in the prefrontal cortex (14). Even minor stresses may then trigger the "fight or flight" response, which leads to activation of the brain's adrenergic circuitry as well as increased heart rate, sweating, rapid breathing, tremors, and other symptoms of hyperarousal in patients with PTSD. The HPA system and other components of the human stress response are also mobilized in response to threat or other stressful stimuli (15). Conversely, overactivity of the prefrontal cortex could lead to a "freeze" response, emotional detachment, and dissociation (16).

How Do Medications Help Regulate Biological Responses in PTSD?

The medications prescribed for treating PTSD symptoms broadly act upon neurotransmitters affecting the fear and anxiety circuitry of the brain including serotonin, norepinephrine, gamma-aminobutyric acid (GABA), the excitatory amino acid glutamate, and dopamine, among many others. Note that there are a number of different glutamatergic receptors, including NMDA (n-methyl-d-aspartate), AMPA (Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), kainate and metabotropic, all of which are potential targets for different medications. There is great need to develop agents with novel and more specific mechanisms of action than are currently available to target the PTSD symptoms described earlier while also minimizing potential side effects.

Studies show that a number of medications are helpful in minimizing PTSD symptoms. Most of the time, medications do not entirely eliminate symptoms, but provide symptom reduction,

while trauma-focused psychotherapy such as CPT, PE, and EMDR are strongly recommended as the most effective treatments (17).

What Are Current Clinical Tools to Measure Treatment Outcomes?

Measurement based care has been shown to improve clinical outcomes for a variety of psychiatric conditions (18). There are self-rating scales and structured clinical interviews to monitor the effects of treatment recommended in the CPG (1). Two examples include the Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5) and the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5). The PCL-5 is an example of a patient self-rating scale, while the CAPS-5 is an example of a structured clinical interview including Criterion A stressor information recorded on the Life Events Checklist. The CAPS-5 provides a much richer dialogue between the clinician and the individual being treated regarding the severity and nature of the PTSD symptoms and is considered the gold standard for PTSD evaluation. For further information or to obtain these measures, see the Assessments Section.

While the CAPS-5 is preferred for initial evaluation, there is literature supportive of a strong correlation between the two measures, and the PCL-5 has the advantage of being quick and easy to administer as a follow up measure for PTSD symptom severity. The CPG suggests using a quantitative measure of PTSD severity, such as the PCL-5 in the initial treatment planning and to monitor treatment progress. Both the PCL-5 and the CAPS-5 provide a quantitative measure of the patient's PTSD symptoms and response to treatment over time. This information enhances the clinical assessment and interview with the patient, and is consistent with measurement based care strategies.

What is the Evidence for Specific Classes of Medications Used for PTSD Treatment?

Selective Serotonin Reuptake Inhibitors (SSRIs)
The neurotransmitter serotonin has a well-recognized role in the modulation of a number of mood and anxiety disorders. For example, a deficiency in amygdala serotonin transport has been identified in some individuals with PTSD (19). The level of this neurotransmitter in both the peripheral and central nervous systems can be modulated by the selective serotonin reuptake inhibitors (SSRIs). Whereas SSRIs as a class were included as first line medications in the 2010 VA/DoD CPG, such across-the-board endorsement is no longer recommended since some SSRIs have either not been tested or have not shown efficacy for treating PTSD. Therefore, the revised 2017 VA/DoD CPG only lists three SSRIs (sertraline, paroxetine and fluoxetine) along with the SNRI venlafaxine (see below) as strong recommendations for treatment of PTSD. These medications have the most robust empirical evidence for reducing PTSD symptoms in RCTs. They are the preferred medications to be used in PTSD treatment (1,3,4).

Exceptions may occur for patients based upon their individual histories of side effects, response, comorbidities, and personal preferences. An example of an exception would be a PTSD patient with co-occurring bipolar disorder where an antidepressant could cause mood instability which could be mitigated with a mood stabilizing medication (such as lithium or an anti-epileptic medication) before prescribing SSRIs. However, there is evidence that different antidepressants have varying effects on destabilizing mood in bipolar disorder (20). Another example would be intolerable sexual dysfunction or gastrointestinal side effects due to the effects of increased serotonin levels in the peripheral nervous system. Each patient varies in their response and ability to tolerate a specific medication and dosage, so medications must be tailored to individual needs.

Research indicates that maximum benefit from SSRI treatment depends upon adequate dosages and duration of treatment, and ensuring treatment adherence is key to successful pharmacotherapy for PTSD. Some typical dosage ranges for SSRIs, side effects, and initial mechanisms of action in the treatment of PTSD are listed below. It is not fully understood how medications affect different brain circuitry to improve symptoms. For example, it has been hypothesized that the long-term effect of antidepressants on mood and anxiety is related to the downregulation of the targeted serotonin synaptic receptors. In PTSD, one mechanism of action might be to stimulate neuronal connections through brain-derived neurotropic factor (BDNF) based upon animal and clinical studies (21,22). Dosage ranges for the strongly recommended SSRIs are:

- **sertraline (Zoloft)** 50 mg to 200 mg daily
- **paroxetine (Paxil)** 20 to 60 mg daily
- **fluoxetine (Prozac)** 20 mg to 60 mg daily

Note: Only sertraline and paroxetine have been approved for PTSD treatment by the FDA. All other medications described in this guide are being used "off label" and have empirical support and practice guideline support only.

Other antidepressants for PTSD

Antidepressants that affect the balance of serotonergic and noradrenergic neurotransmission or which alter serotonin neurotransmission through other mechanisms of action are also helpful in PTSD. Venlafaxine acts primarily as a serotonin reuptake inhibitor at lower dosages and as a combined serotonin and norepinephrine reuptake inhibitor at higher dosages. It is a strongly recommended treatment for PTSD in the 2017 VA/DoD Clinical Practice Guideline for PTSD based upon large multi-site RCTs (23).

Nefazodone is an effective medication. Unfortunately, because of liver toxicity it only received a weak recommendation for treatment of PTSD (1). It affects serotonin by blocking the post-synaptic 5-HT2 receptor as well as blocking pre-synaptic reuptake (like an SSRI). Nefazodone is only available in a generic form. Brand name nefazodone (Serzone) was removed from the

market because of its black box warning regarding liver failure (1 per 250,000 patient-years), so liver function tests need to be carefully monitored and appropriate precautions must be taken as recommended in the medication's prescribing information (24,25). Nefazodone causes less sexual dysfunction than the SSRIs and may have favorable effects on co-occurring sleep disturbance.

The tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) act on multiple neurotransmitters including serotonin and norepinephrine. The tertiary tricyclics such as imipramine and amitriptyline which are more serotonergic were thought to be more beneficial in PTSD treatment than the secondary amines such as nortriptyline and desipramine which are more adrenergic (26). However, one study demonstrated no difference between desipramine and paroxetine in reducing PTSD symptoms (27). While there are RCTs supporting their use, these medications are not considered strongly recommended agents due to their safety and side effect profiles. This is because tricyclics can cause ventricular arrhythmias through QT prolongation especially in overdose. On the other hand, they do not usually cause the sexual side effects seen with SSRIs. Since some SSRIs such as citalopram can prolong cardiac intraventricular conduction (e.g. longer PR, QRS and QT intervals), if patients fail to respond to the strongly recommended SSRIs or SNRI medication, then tricyclics used with these precautions in mind may be a viable alternative. There has been so little research with TCAs that there is little data on which to base any recommendations. At this time, imipramine is the only TCA to be classified as a suggested, or weak recommendation, for treatment of PTSD (1).

The MAOI phenelzine has been shown to be effective in PTSD (28). The MAOIs increase a number of neurotransmitters, such as serotonin, norepinephrine, and dopamine, through inhibition of their degradation by the enzyme monoamine oxidase (MAO). Careful management of the MAOIs and strict dietary controls are important because they can cause potentially fatal hypertensive reactions when taken with other medications or certain foods rich in tyramine. They are contraindicated for patients who take stimulants therapeutically (e.g., for ADHD) or illicitly. MAOIs can also provoke the potentially fatal serotonin syndrome when used concurrently with SSRIs. At this time, the only MAOI suggested as a second line treatment for PTSD is phenelzine (1).

Examples of these antidepressant dosage ranges are listed below:
- **venlafaxine (Effexor)** 75 mg to 300 mg daily
- **nefazodone (Serzone)** 200 mg to 600 mg daily
- **imipramine (Tofranil)** 150 mg to 300 mg daily
- **phenelzine (Nardil)** 15 mg to 90 mg daily

All of the antidepressants described above are also effective in treating comorbid major depressive disorder (MDD) which, depending upon the study, accompanies PTSD about fifty percent of the time. While bupropion is useful in treating comorbid MDD, it has not been shown effective for PTSD in controlled trials (29) and there is insufficient evidence overall for its use in PTSD.

Mood stabilizers for PTSD

The revised 2017 VA/DoD CPG suggests against the use of lamotrigine and topiramate and recommends against the use of divalproex for the treatment of PTSD (1). These medications, also known as anticonvulsants or anti-epileptic drugs, affect the balance between the excitatory neurotransmitter glutamate the most common neurotransmitter in the central nervous system and the inhibitory neurotransmitter GABA by acting indirectly to affect these neurons when their neuronal receptor sites are activated.

Topiramate has demonstrated promising results in randomized controlled trials with civilians and Veterans with PTSD. But because of inconsistent results in clinical trials, topiramate is listed as having no demonstrated benefit in the 2017 VA/DoD Clinical Practice Guideline for PTSD. There are two double-blind, placebo-controlled trials evaluating topiramate as monotherapy in civilians with PTSD (30,31). The trial published in 2007 included 38 participants and found no significant difference in total CAPS scores between topiramate and placebo. The 2010 trial included 35 participants and demonstrated a significant decrease in total CAPS scores. There are also two published double-blind, placebo-controlled trials evaluating topiramate as adjunctive treatment for PTSD in Veterans (32,33). The trial published in 2004 included 67 participants and found a significant decrease in the total CAPS score. The 2007 trial included 40 participants and showed no significant decrease in total CAPS scores.

At this time, topiramate cannot be considered a useful evidence-based option for patients who do not respond favorably to strongly recommended pharmacotherapy options. Further studies are needed regarding the place of topiramate in PTSD treatment (34). Topiramate has been found helpful in reducing alcohol consumption in those with an alcohol use disorder and could prove beneficial in the PTSD patient dually diagnosed with an alcohol use disorder (35, 36).

Despite some promising open label data, there have been two negative RCTs for divalproex and one negative RCT for tiagabine in treating PTSD (37-39). A small trial of lamotrigine in 15 individuals with PTSD demonstrated possible benefit (40). In summary, the effectiveness of mood stabilizers, as a class, remains uncertain.

Some of these medications are definitely indicated for bipolar disorder whether or not it is comorbid with PTSD, and require close monitoring for side effects. Divalproex and carbamazepine require regular lab work to monitor side effects, but neither lamotrigine nor topiramate require lab work but must be titrated slowly according to package insert directions to avoid potentially serious side effects. Examples are given below:

- **carbamazepine (Tegretol).** Requires monitoring of white blood cell counts due to risk of agranulocytosis. Will self-induce its own metabolism and increase the metabolism of other medications including oral contraceptives.

- **divalproex (Depakote).** Requires monitoring of liver function tests due to risk of hepatotoxicity and platelet levels due to risk of thrombocytopenia. Target dosage is 10 times the patient's weight in pounds.
- **lamotrigine (Lamictal).** Requires slow titration according to the package insert due to risk of serious rash.
- **topiramate (Topimax).** Requires clinical monitoring for glaucoma, sedation, dizziness and ataxia.

Atypical antipsychotics for PTSD

The 2017 VA/DoD CPG recommends against the use of risperidone in PTSD and suggests against the use of other atypical antipsychotics in the treatment of PTSD (1). These medications were originally developed for patients with a psychotic disorder, there has been an interest in these medications as treatment for many other psychiatric disorders including PTSD. This would seem reasonable given their effects on the balance between dopaminergic and serotonergic neurotransmitter systems. The dopaminergic system has well established effects on reward and gratification and the serotonin system on mood and anxiety. Also, the antipsychotics can reduce psychotic symptoms in PTSD patients. The real question is whether these medications are useful for core PTSD symptoms when psychotic symptoms are not present.
Previously, a number of small single-site studies suggested that atypical antipsychotic agents were effective adjunctive treatment for PTSD patients who had poor responses to first-line SSRIs or SNRIs (41). A subsequent large-scale multi-site trial of risperidone as an adjunctive agent for SSRI poor/partial responders showed that there was no benefit (in comparison with a placebo group) for adjunctive use of this agent (42). It should be noted that the patients receiving adjunctive risperidone had failed 2 SSRI trials and adjusting for combat era did not change the results, though the study was not specifically designed to address differing responses to treatment based upon combat era.

A study published outside the 2017 VA/DoD CPG search timeline and apart from the evidence upon which the CPG recommendations regarding the use of atypical antipsychotics were based, assessed the efficacy of quetiapine as monotherapy for the treatment of PTSD (43). Despite the moderate effect size demonstrated in the quetiapine RCT, the study had a high risk of bias including a lack of information regarding amount of missing data, analytic method of handling missing data, high attrition, and differential dropout; coupled with quetiapine's known adverse effect profile, these factors necessitated a recommendation suggesting against the use of quetiapine as monotherapy for the treatment of PTSD.

At this time, the evidence indicates that harms clearly outweigh benefits for all atypical antipsychotics, with the strongest evidence showing that risperidone is contraindicated for PTSD treatment. Thus, the 2017 VA/DoD Clinical Practice Guideline for PTSDmakes the following recommendations regarding the use of atypical antipsychotics:

- Atypical antipsychotics are not recommended as monotherapy for PTSD.

- Risperidone (Risperdal) is contraindicated for use as an adjunctive agent - potential harm (side effects) exceeds benefits.
- There is a specific suggestion against the use of olanzapine and quetiapine.
- There is insufficient evidence to recommend any other atypical antipsychotic as an adjunctive agent for PTSD.

Thus, atypical antipsychotics are recommended as treatment for co-occurring psychotic symptoms and mood disorders in PTSD, but not for treatment of core PTSD symptoms.

Prazosin

The most notable change between the 2010 and 2017 editions of the VA/DoD CPG concerns prazosin (Minipress). The 2017 VA/DoD Clinical Practice Guideline for PTSD recommendations concerning prazosin are:

1. For global symptoms of PTSD, suggest against the use of prazosin as either mono- or augmentation therapy.
2. For traumatic nightmares, there is insufficient evidence to recommend for or against the use of prazosin.

Several studies have found prazosin to be effective in decreasing nightmares in PTSD (44-46), presumably because of its blockade of norepinephrine at the post-synaptic alpha-1 receptor. However, the 2017 VA/DoD CPG suggests against the use of prazosin for treatment of global symptoms of PTSD and concludes there is insufficient evidence to recommend for or against the use of it for nightmares based upon a large multicenter trial which found no difference between prazosin and placebo (47).

Since some patients may have already benefited from prazosin treatment, clinicians are invited to use their own clinical judgment about whether or not to keep their patients on prazosin. Because of prazosin's short half-life, divided dosage schedules may be necessary. Additionally, prazosin demonstrated a significant beneficial effect on alcohol cravings and sobriety in two small pilot studies of newly abstinent individuals with alcohol dependence (48,49). The first study did not address PTSD symptoms specifically, and the second study did not demonstrate an improvement in PTSD symptoms including nightmares. The author hypothesized it may have been due to the bedtime prazosin dosage being relatively low at 8 mg.

Buspirone

Buspirone and beta blockers are sometimes used adjunctively in treatment of hyperarousal symptoms, though there is little empirical evidence in support of their use. Buspirone is an agonist at the pre-synaptic serotonin 5-HT(1A) receptor and a partial agonist at the post-synaptic serotonin 5-HT(1A) receptor and might reduce anxiety in PTSD without sedation or addiction. There are some case reports but no randomized trials supporting its use.

Beta Blockers

Beta blockers provide post-synaptic blockade of norepinephrine at synapses and blockade of adrenalin (epinephrine) at the organs such as the heart, sweat glands, and muscles. There has been long-standing interest in using beta blockers to prevent PTSD. Unfortunately, the evidence at the current time does not support this (50). Beta blockers reduce both central and peripheral manifestations of hyperarousal and may reduce aggression as well. They may be used for comorbid conditions such as performance anxiety in the context of social anxiety disorder.

Benzodiazepines and PTSD

Benzodiazepines enhance activity of GABA at the GABA-A receptor which produces CNS depression. **This is the only potentially addictive group of medications discussed.** Limited studies have not shown them to be useful in treating the core PTSD symptoms (51,52). There are several other concerns about the use of benzodiazepines including potential disinhibition, difficulty integrating the traumatic experience, interfering with the mental processes needed to benefit from psychotherapy, increased falls and mental clouding in the elderly, addiction, and increases in overall mortality. In a recent study combining PE and alprazolam, the group receiving alprazolam had a poorer outcome in PTSD symptom reduction than the group receiving PE alone (53). Furthermore, a recent meta-analysis found benzodiazepines to worsen symptom outcome for patients with PTSD (54). Because of these potentially negative effects, it is recommended that benzodiazepines not be used in PTSD. Any acute use should be short term (e.g., no more than five days) with frequent re-evaluation for side effects. Examples of commonly used benzodiazepines are listed below:

- **lorazepam (Ativan)**
- **clonazepam (Klonopin)**
- **alprazolam (Xanax)**
- **diazepam (Valium)**

What Are Future Research Directions for PTSD Pharmacotherapy?

The pathophysiological mechanisms for PTSD in the brain are unknown, but there are several interesting neurotransmitters and pathways that could lead to new drug development for the treatment or the prevention of PTSD. There are competing hypotheses about the role of glucocorticoids following trauma and their effects on the brain. It might be possible to intervene at some level in the HPA axis or at the level of the glucocorticoid receptors in the brain to modulate the effects of stress and the development of PTSD. Some research suggests the potential ability of supplemental cortisol in reducing PTSD symptoms (55). Furthermore, in

one small study, cortisol administered prior to PE demonstrated significantly better retention in treatment especially among those patients with increased sensitivity to glucocorticoids. The authors cite several actions of glucocorticoids including: potentiating glutamate at NMDA receptors, decreased retrieval of fear memories, and interactions with noradrenergic systems, as potential mechanisms of action on brain pathways affecting PTSD (56).

In addition to corticotropin releasing factor (CRF) and adrenocorticotropin hormone (ACTH), other neuropeptides such as Substance P and Neuropeptide-Y (NPY) appear to play a role in PTSD (57). Combat troops exposed to stress have been found to have lower levels of NPY while resilient Special Forces troops exhibit elevated NPY levels (58). Perhaps potentiation of this neuromodulator could improve the resiliency of the brain's capacity to cope with trauma. One challenge with this new focus of research is dealing with the blood-brain barrier for introducing neuropeptides into the brain, but researchers have delivered the neuropeptide oxytocin intranasally through the olfactory pathway in veterans with PTSD and have demonstrated a decrease in hyperarousal symptoms (59).

D-cycloserine (DCS) has been used in panic disorder, specific phobia, obsessive-compulsive disorder, and social anxiety disorder, to enhance the effects of exposure therapy (60). It is a partial agonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor. Based upon animal research supporting the use of DCS to facilitate extinction of conditioned fear, it is hypothesized that use of DCS in conjunction with exposure therapy may reduce the number of psychotherapy sessions required (61). A recent study of DCS did not demonstrate a significant treatment benefit by adding the drug to PE. However, there were some interesting findings in this study; DCS reduced cortisol and startle reactivity more than placebo when combined with PE (62). Clearly further research is needed; at this time, however, DCS is not recommended for pharmacotherapy as adjunctive treatment used to facilitate trauma-focused psychotherapy.

A recent study compared methylphenidate and the acetylcholinesterase inhibitor galantamine to placebo and found that methylphenidate, but not galantamine, improved cognitive complaints as well as PTSD symptom severity in patients with mild traumatic brain injury (mTBI) and/or PTSD. The authors propose larger randomized controlled trials to further evaluate improving cognition in those with PTSD and co-occurring mTBI (63).

Ketamine is an anesthetic agent which modulates the balance between glutaminergic activity at the NMDA receptor and serotonergic activity at the 5-HT receptors. This agent is showing promise for treatment of refractory depression in research studies (64) and a recent study showed beneficial effects in PTSD as well (65). The limitations so far include a short-term benefit of a few weeks and the anesthetic nature of the drug and potential for addiction. However, this could lead to a new line of medication research and to newer agents with distinct mechanisms of action for treatment of PTSD.

The endocannabinoid system is another potential area of interest in moderating depressive, anxiety, and PTSD symptoms. Abnormalities at cannabinoid (CB-1) receptors coupled with reduced levels of anandamide (an endogenous cannabinoid) have been found in PTSD patients

(66,67). While direct stimulation of the cannabinoid type 1 receptor (e.g. with marijuana) would likely lead to addiction and adverse side effects, indirect influences on this pathway, theoretically might prove beneficial. Studies of direct stimulation of the system through cannabis have demonstrated negative effects on PTSD outcomes (68,69). The revised CPG recommends against treating PTSD with cannabis or cannabis derivatives due to the lack of evidence for their efficacy, known adverse effects, and associated risks (1).

Baclofen is used clinically as a muscle relaxant and has GABA-B receptor agonist activity. A small randomized study of 23 Iranian combat Veterans with PTSD randomized to citalopram and baclofen (n=13) or citalopram and placebo (n=10) found that those on the combination of citalopram and baclofen had significantly more reduction in PTSD symptoms than the citalopram and placebo group (70). This is an area for potential future research.

There is ongoing interest in the possibility of early intervention and promoting resiliency following trauma with psychotherapy, pharmacotherapy, or some combination that would prevent the development of PTSD. There are no currently recognized medications which prevent the development of PTSD after trauma.

What Are Common Clinical Barriers to Successful Medication Treatment?

There are several common barriers to effective medication treatment for PTSD which are listed below.
- Fear of possible medication side effects including sexual side effects
- Psychological stigma that the medication is a "crutch" and that taking it is a weakness
- Fear of becoming addicted to medications
- Taking the medication inconsistently
- "Self-medicating" with alcohol or drugs along with prescribed medications

These need to be addressed with individuals receiving treatment in an ongoing dialogue with their prescribing clinician. Side effects need to be examined and discussed, weighing the risks and the benefits of continued medication treatment. Patient education about the side effects, necessary dosages, duration of treatment, and adherence can improve outcomes to medications. Simple interventions, such as enlisting family/caregiver support, can go a long way to improve adherence.

Other important considerations

- Patients with PTSD or anxiety disorders may be very aware of their somatic reactions, and it is important to start low and go slow on dosage adjustments to improve patient adherence.

- Be sure to ask female patients of childbearing age about contraception and pregnancy when prescribing medication. And be aware of medications that are contraindicated during pregnancy because of teratogenic effects.
- Be sure to ask all patients about substance abuse.
- Be sure to document all other medications that the patient is taking for other medical or psychiatric problems in order to avoid any drug-drug interactions that may interfere with therapeutic efficacy and which may also produce serious side effects.
- Once medications are started, it is crucial that the provider remember to discontinue medications which are not proving efficacious and to simplify the number and types of medications used whenever possible.

Final thoughts about medications for treatment of PTSD

A more comprehensive discussion of pharmacotherapy can be found online in the [2017 VA/DoD PTSD Clinical Practice Guideline](#).

Trauma-focused psychotherapies are more efficacious than pharmacotherapy and are strongly recommended treatments for PTSD. While there are few direct comparisons of pharmacotherapy and psychotherapy, the greatest benefits of treatment appear to come from evidence-based therapies such as CPT, PE, and EMDR based upon the effect sizes in the literature. However, the role of pharmacotherapy in combination with trauma-focused psychotherapy is unknown at this time (2). Some patients prefer medication to psychotherapy, although when given the choice, the majority choose psychotherapy (71). Based upon current knowledge, most prescribing clinicians view pharmacotherapy as an important adjunct to the evidenced-based psychotherapies for PTSD. Patients need to be informed of the risks and benefits of the differing treatment options along with the risks of no treatment.

When using a combined approach of medication and therapy, it is important to keep several practices in mind. If treatment is being provided by a therapist and a prescriber, it is important for the clinicians to discuss treatment response and to coordinate efforts. It is important for the prescribing clinician to have an ongoing dialogue with the patient about their medications and side effects. It is important for the patient to take an active role in his or her treatment rather than feeling they are a passive recipient of medications to alleviate their symptoms. There is emerging evidence that when given a choice, most patients will select psychotherapy treatment for their PTSD symptoms rather than medications.

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Last updated: November 17, 2017