Clinician's Guide to Medications for PTSD

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Overview

Posttraumatic Stress Disorder (PTSD) has biological, psychological, and social components. Medications can be used in treatment to address the biological basis for PTSD symptoms and co-morbid Axis I diagnoses. Medications may benefit psychological and social symptoms as well. While studies suggest that cognitive behavioral therapies such as prolonged exposure (PE) and cognitive processing therapy (CPT) have greater effects in improving PTSD symptoms than medications, some people may prefer medications or may benefit from receiving a medication in addition to psychotherapy.

Placebo-controlled double-blind randomized controlled trials are the gold standard for pharmacotherapy. Less strongly supported evidence includes open trials and case reports. It is important for the clinician to question the level of evidence supporting the medications prescribed in PTSD treatment. There are a variety of factors influencing prescribing, including marketing, patient preferences, and clinical custom, all of which can be inconsistent with the evidence base.

Currently, the evidence base is strongest for the selective serotonin reuptake inhibitors (SSRIs). The only two FDA approved medications for the treatment of PTSD are sertraline (Zoloft) and paroxetine (Paxil) (1, 2). All other medication uses are off label, though there are differing levels of evidence supporting their use. In addition to sertraline and paroxetine, there is strong evidence for the SSRI fluoxetine (Prozac) and for the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor) which are considered first-line treatments in the VA/DoD Clinical Practice Guideline for PTSD. There are a number of biological changes which have been associated with PTSD, and medications can be used to modify the resultant PTSD symptoms. Veterans whose PTSD symptoms have been present for many years pose a special challenge. Studies indicate they are more refractory to the beneficial effects of medications for PTSD symptoms (3).

What core PTSD symptoms are we trying to treat?

The three main PTSD symptom clusters are listed below:

- Re-experiencing. Examples include nightmares, unwanted thoughts of the traumatic events, and flashbacks.
- Avoidance. Examples include avoiding triggers for traumatic memories including places, conversations, or other reminders. The avoidance may generalize to other previously enjoyable activities.
- Hyperarousal. Examples include sleep problems, concentration problems, irritability, increased startle response, and hypervigilance.

What are some of the biological disturbances found in PTSD?

Some of the main biological disturbances in PTSD can be conceptualized as dysregulation of the naturally occurring stress hormones in the body and increased sensitivity of the stress and anxiety circuits in the brain. There is dysregulation of adrenergic mechanisms that mediate the classical fight-flight or freeze response. Yehuda and others have found that patients with PTSD have hypersensitivity of the hypothalamic-pituitary-adrenal axis (HPA) as compared to patients without PTSD (4). Patients have a much greater variation in their levels of adrenocorticooids than patients without PTSD. Other researchers have found differences in both brain structures and brain circuits that process threatening input between patients with PTSD and those without.

It is not known for certain whether these changes were present before the traumatic event and predisposed the person to developing PTSD or whether these changes were the result of the PTSD. One way to think of this is the fear circuitry no longer being integrated with the executive centers of the brain located in the prefrontal cortex (5). Even minor stresses may then set off the "fight or flight" response in patients with PTSD which leads to increased heart rate, sweating, rapid
breathing, tremors, and other symptoms of hyperarousal listed above.

How do medications help regulate these responses?

The medications prescribed for treating PTSD symptoms act upon neurotransmitters related to the fear and anxiety circuitry of the brain including serotonin, norepinephrine, GABA, and dopamine among many others. There is great interest in developing newer, more specific agents than are currently available to target the PTSD symptoms described earlier while also minimizing potential side effects of medications.

Studies show that a number of medications are helpful in minimizing the three symptom clusters of PTSD. Most of the time, medications do not entirely eliminate symptoms but provide a symptom reduction and are best used in conjunction with an ongoing program of trauma specific psychotherapy for patients such as PE or CPT.

How do we measure the effects of treatment?

There are a number of self-rating scales and structured clinical interviews to monitor the effects of treatment. Two examples include the Post-Traumatic Stress Disorder Checklist (PCL) and the Clinician Administered PTSD Scale (CAPS). The PCL military or civilian version is an example of a patient self-rating form without stressor information, while the CAPS is an example of a structured clinical interview including stressor information.

There is literature supportive of a strong correlation between the two measures, and the PCL has the advantage of being quick and easy to administer. Both the PCL and the CAPS 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.

What is the evidence base for the specific groups of medications used for PTSD treatment?

Selective Serotonin Reuptake Inhibitors (SSRIs)

These medications are the only FDA approved medications for PTSD. SSRIs primarily affect the neurotransmitter serotonin which is important in regulating mood, anxiety, appetite, and sleep and other bodily functions. This class of medication has the strongest empirical evidence with well designed randomized controlled trials (RCTs) and is the preferred initial class of medications used in PTSD treatment (1, 2). Exceptions may occur for patients based upon their individual histories of side effects, response, and comorbidities.

- An example of an exception would be a PTSD patient with comorbid Bipolar Disorder. In this patient, there is a risk of precipitating a manic episode with the SSRIs. Each patient varies in their response and ability to tolerate a specific medication and dosage, so medications must be tailored to individual needs.

Research has suggested that maximum benefit from SSRI treatment depends upon adequate dosages and duration of treatment. Treatment adherence is key to successful pharmacotherapy treatment for PTSD. Examples of the SSRIs and some typical dosage ranges are listed below:

- 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 may have empirical support but have not been through the FDA approval process for PTSD.

Other newer antidepressants for PTSD

Antidepressants that work through other neurotransmitter combinations or through different mechanisms for altering serotonin neurotransmission 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 now a recommended first-line treatment for PTSD in the revised VA/DoD Clinical Practice Guideline for PTSD based upon large multi-site RCTs (6).
There have been smaller RCTs with mirtazapine as well as open trials (7). Mirtazapine may be particularly helpful for treatment of insomnia in PTSD. Trazodone is also commonly used for insomnia in PTSD even though there is little empirical evidence available for its use. Nefazodone is still available in a generic form but carries a black box warning regarding liver failure, so liver function tests need to be monitored and precautions taken as recommended in the medication’s prescribing information (8, 9).

Examples of the newer antidepressants for PTSD and some typical dosage ranges are listed below:

- Mirtazapine (Remeron) 7.5 mg to 45 mg daily
- Venlafaxine (Effexor) 75 mg to 300 mg daily
- Nefazodone (Serzone) 200 mg to 600 mg daily

All of the antidepressants described above are also effective in treating comorbid Major Depressive Disorder (MDD) which often accompanies PTSD. While bupropion is useful in treating comorbid MDD, it has not been shown effective for PTSD in controlled trials (10). A recent trial showed superior outcomes on MDD when mirtazapine was combined initially with antidepressants versus patients being randomized to monotherapy with fluoxetine (11). This raises important questions regarding costs, side effects, and patient preferences which merit further study.

Mood stabilizers for PTSD

These medications, also known as anticonvulsants or anti-epileptic drugs, either block glutamate or potentiate GABA or do both. Topiramate has demonstrated promising results in randomized controlled trials with civilians and Veterans with PTSD, but currently is listed as having no demonstrated benefit in the VA/DoD Clinical Practice Guideline for PTSD.

There are two double-blind, placebo-controlled trials evaluating topiramate as monotherapy in civilians with PTSD (12,13). 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 38 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 (14,15). 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.

Based upon the current studies, topiramate could provide a useful option for clinicians in treatment of PTSD symptoms in patients who fail first line pharmacotherapy. Further studies and meta-analyses are needed regarding the place of topiramate in PTSD treatment (16).

Otherwise, despite some promising open label studies, other RCTs have been negative for this group of medications in treating PTSD (17). As a group, this class of medications is helpful in the treatment of comorbid Bipolar Disorder and PTSD. Patients who have Bipolar Disorder and PTSD often benefit from these medications since SSRIs and other antidepressants sometimes precipitate a manic episode. Most require some regular lab work to monitor side effects. 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

While originally developed for patients with a psychotic disorder, this class of medications is being applied to patients with many other
psychiatric disorders including PTSD. They act primarily on the dopaminergic and serotonergic systems. They can be used when a person with PTSD has a psychotic disorder. There is some evidence that they are useful in ameliorating psychotic symptoms in PTSD patients. The real question is whether these medications are useful in PTSD when psychotic disorder or 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 (18). A recent 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. As a result the recent VA/DoD PTSD Clinical Practice Guideline has been revised as follows:

- Atypical antipsychotics are not recommended as mono-therapy for PTSD.
- Risperidone (Risperdal) is contraindicated for use as an adjunctive agent - potential harm (side effects) exceeds benefits.
- There is insufficient evidence to recommend any other atypical antipsychotic as an adjunctive agent for PTSD.

Other medications for PTSD

There are a number of other medications that can be helpful for specific PTSD symptoms or that have been used as second line agents including the following:

- Prazosin (Minipress)
- Tricyclic Antidepressants (such as Imipramine)
- Monoamine Oxidase Inhibitors (MAOIs) (such as Phenelzine)

Prazosin has been found to be effective in RCTs in decreasing nightmares in PTSD. It blocks the noradrenergic stimulation of the alpha 1 receptor. Its effectiveness for PTSD symptoms other than nightmares has not been determined at this time (19, 20).

The tricyclic antidepressants and MAOIs act on a number of neurotransmitters. While there are RCTs supporting their use, these medications are not used as first line agents due to their safety and side effect profiles (21, 22). The tricyclics have quinidine like effects on the heart and can cause ventricular arrhythmias especially in overdose.

The MAOI phenezine has been shown to be effective in PTSD. 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. MAOIs can also provoke the potentially fatal serotonin syndrome when used concurrently with SSRIs.

Buspirone and beta blockers are sometimes used adjunctively in treatment of hyperarousal symptoms, though there is little empirical evidence in support of this. Buspirone acts on serotonin and might reduce anxiety in PTSD without sedation or addiction. There are some case reports supporting its use. Beta blockers block the effects of adrenalin (epinephrine) on organs such as the heart, sweat glands, and muscles. There is interest in using beta blockers to prevent PTSD, though the evidence at the current time does not support this. Beta blockers reduce the 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 phobia for example.

Benzodiazepines and PTSD

Benzodiazepines act directly on the GABA system which produces a calming effect on the nervous system. This is the only potentially addictive group of medications discussed. Studies have not shown them to be useful in PTSD treatment as they do not work on the core PTSD symptoms (23, 24). There are several other concerns with the benzodiazepines including potential disinhibition, difficulty integrating the traumatic experience, interfering with the mental processes needed to benefit from psychotherapy, and addiction. Because of their potential for addiction and disinhibition, they must be used with great caution in PTSD. Examples are listed below:

- Lorazepam (Ativan)
• Clonazepam (Klonopin)
• Alprazolam (Xanax)

Developing new medications for PTSD

The pathophysiological mechanism of PTSD in the nervous system is unknown, but there are several interesting areas 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 hypothalamic-pituitary-adrenal axis or at the level of the glucocorticoid receptors in the brain to modulate the effects of stress and the development of PTSD. Neuropeptides such as Substance P and Neuropeptide Y (NPY) have been implicated in PTSD as well (25). Combat troops exposed to stress have been found to have lower levels of NPY. Perhaps altering this neuromodulator could improve the resiliency of the brain to the effects of trauma. One challenge with this new focus research is dealing with the blood-brain barrier for introducing neuropeptides into the brain.

D-cycloserine (DCS) has been used in panic disorder, specifically phobia and social phobia, to enhance the effects of exposure therapy (26). 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 (27). This line of research recognizes a paradigm shift in the use of pharmacotherapy to assist learning during psychotherapy as opposed to directly affecting PTSD symptoms (28).

Memantine (Namenda) is a drug of much interest in preventing neurodegeneration by protecting against glutamatergic destruction of neurons. It has been approved for use in certain neurodegenerative conditions such as Alzheimer’s disease. This drug could be potentially useful in preventing hypothesized neurodegeneration in the hypothalamus and memory loss in PTSD.

Current research is looking towards the possibility of one day intervening early in the course of PTSD with a combination of psychotherapy and pharmacotherapy that would prevent the development of the pathophysiology of PTSD in the brain.

Common barriers to effective medication treatment in PTSD

There are several common barriers to effective medication treatment for PTSD which are listed below. These need to be addressed with patients 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 taking the medications consistently can improve adherence. A simple intervention of setting up a pill organizer weekly can go a long way to improve adherence.

• Fear of possible medication side effects including sexual side effects
• Feeling medication is a “crutch” and that taking it is a weakness
• Fear of becoming addicted to medications
• Taking the medication only occasionally when symptoms get severe
• Not being sure how to take the medication
• Keeping several pill bottles and not remembering when the last dosage was taken
• Using "self medication" with alcohol or drugs with prescribed medications

A final word regarding medications and treatment for PTSD

A more comprehensive discussion of pharmacotherapy can be found online in the VA/DoD PTSD Clinical Practice Guidelines. Based upon current knowledge, most prescribing clinicians view pharmacotherapy as an important adjunct to the evidenced based psychotherapies for PTSD. While there are few direct comparisons of pharmacotherapy and psychotherapy, the greatest benefits of treatment appear to come from evidenced based therapies such as CPT, PE, and patients need to be informed of the risks and benefits of the differing treatment options. 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.

Important Considerations

- Patients with anxiety disorders including PTSD may be very aware of their somatic reactions, and it is important to start low and go slow often on dosage adjustments to improve patient adherence.
- Be sure to ask female patients of childbearing age about contraception when prescribing medication.
- Be sure to ask all patients about substance abuse as well.
- 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.

References


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