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Clinician's Guide to Medications for PTSD

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Overview

Posttraumatic Stress Disorder (PTSD) has biological, psychological, and social causes and implications. Medications can be used to ameliorate the biological basis for PTSD symptoms along with co-morbid psychiatric diagnoses, and may benefit psychological and social symptoms as well. Studies suggest that cognitive behavioral therapies such as prolonged exposure (PE) therapy and Cognitive Processing Therapy (CPT) have greater effects on PTSD symptoms than medications, but some people may prefer medications or may benefit from receiving a medication in addition to psychotherapy.

It is crucial to consider the level of evidence available for specific medication interventions being considered. Trials which are randomized, placebo-controlled, and double blinded are the gold standard for guiding pharmacotherapy decision making. Less strongly supported evidence includes open trials and case reports. It is vital for the clinician to question the level of evidence supporting the medications being prescribed for PTSD, because there are a variety of influences on prescribing, including marketing, patient preferences, and clinical custom, all of which can be inconsistent with the evidence base.

The current evidence base is strongest for the selective serotonin reuptake inhibitors (SSRIs), and currently only sertraline (Zoloft) and paroxetine (Paxil) are approved by the Food and Drug Administration (FDA) for PTSD (1, 2). All other medication uses are off label, though there are differing levels of evidence supporting their use. For example, there is strong evidence for the SSRI fluoxetine (Prozac) and for the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor) which are first-line treatments in the VA/DoD Clinical Practice Guideline for PTSD. However, 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 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).

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- **Arousal and reactivity.** Examples include angry, reckless, or self-destructive behavior, sleep problems, concentration problems, increased startle response, and hypervigilance.

What is the current understanding 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. Yehuda and others have found that patients with PTSD have hypersensitivity of the HPA axis as compared to patients without PTSD and have a much greater variation in their levels of adrenocorticoids (4).

Other researchers have found differences between patients with PTSD and those without 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 becomes hypersensitive in PTSD and is no longer integrated well with the executive planning and judgment centers in the prefrontal cortex (5). Even minor stresses may then trigger the "fight or flight" response, which leads to increased heart rate, sweating, rapid breathing, tremors, and other symptoms of hyperarousal in patients with PTSD.

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 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 a symptom reduction and are sometimes more effective when used in conjunction with an ongoing program of trauma specific psychotherapy for patients, such as PE or CPT.

What are current clinical tools to measure treatment outcomes?

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 is an example of a patient self-rating form without stressor information, while the CAPS is an example of a structured clinical interview including Criterion A stressor information recorded on the Life Events Checklist. For further information or to obtain these measures, see Assessments.

While the CAPS is preferred for initial evaluation, 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 as a follow up measure for PTSD symptom severity. 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 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. A deficiency in amygdala serotonin transport has been identified in some individuals with PTSD (6). The level of this neurotransmitter in both the peripheral and central nervous systems can be modulated by the selective serotonin reuptake inhibitors (SSRI's). The SSRI's

are the only medications approved by the FDA for PTSD. SSRI's have the strongest empirical evidence for reducing PTSD symptoms with well-designed randomized controlled trials (RCTs), and they are 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, comorbidities, and personal preferences.

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 which could be mitigated by mood stabilization (with anti-epileptic medications) before prescribing SSRIs. 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 SSRI's in the treatment of PTSD 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 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 now a recommended first-line treatment for PTSD in the revised VA/DoD Clinical Practice Guideline for PTSD based upon large multi-site RCTs (7).

There have been smaller RCTs with mirtazapine as well as open trials (8). Mirtazapine has a unique mechanism of action affecting both serotonin and norepinephrine through blockade of the pre-synaptic alpha 2-adrenergic inhibitory autoreceptor for norepinephrine and blockade of post-synaptic 5-HT2 and 5-HT3 receptors. Because of its mechanism of action, it may cause less sexual dysfunction than the SSRI's. 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. A large multisite trial of trazadone is currently in progress.

Nefazodone affects serotonin by blocking the 5-HT2 receptor, and is still available in a generic form but carries a black box warning regarding liver failure (1 per 250,000 patient-years), so liver function tests need to be monitored and precautions taken as recommended in the medication's prescribing information (9,10). Nefazodone has lower levels of sexual dysfunction than the SSRI's and enhances sleep.

Examples of antidepressants with novel mechanisms of action prescribed 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 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 (11).

Mood stabilizers for PTSD

These medications, also known as anticonvulsants or anti-epileptic drugs, affect the balance between the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter gamma-amino-butyric acid (GABA) by acting at their neuronal receptor sites. 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 (13,14). 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 (15,16). 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 are needed regarding the place of topiramate in PTSD treatment (17). A recent meta-analysis showed strong support for the use of topirimate in PTSD finding it to be similar to paroxetine in its efficacy (18). Additionally, 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 (19).

As for other mood stabilizers for PTSD, few published results are negative or mixed. Despite some promising open label data, two RCTs have been negative for divalproex in treating PTSD (20, 21). A small trial of lamotrigine in 15 individuals with PTSD demonstrated possible benefit (22). In summary, the effectiveness of mood stabilizers, as a class, remains uncertain.

Mood stabilizers are definitely indicated for bipolar disorder whether or not it is comorbid with PTSD, through both mood stabilization of the bipolar disorder and avoiding precipitation of a manic episode with the SSRI's. 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

While 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. The antipsychotics ameliorate 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 (23). 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 (24). As a result the recent VA/DoD PTSD Clinical Practice Guideline has been revised as follows:

- 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 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. This is logical given its blockade of the neurotransmitter norepinephrine at the post-synaptic alpha-1 receptor. Its effectiveness for PTSD symptoms other than nightmares has not been determined at this time (25). However, a recent trial with military personnel using prazosin during the day in addition to bedtime for nightmares shows a significant reduction in daytime PTSD symptoms as well as nightmares (26). This research provides a possible extension of the therapeutic effects of prazosin in PTSD.

The tricyclic antidepressants and 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 (27, 28). However, a recent study demonstrated no difference between desipramine and paroxetine in reducing PTSD symptoms (29). While there are RCTs supporting their use, these medications are not used as first-line agents due to their safety and side effect profiles. This is because tricyclics have quinidine-like effects on the heart and 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.

The MAOI phenezine has been shown to be effective in PTSD. The MAOI's increase a number of neurotransmitters, such as serotonin, norepinephrine, and dopamine, through inhibition of their degradation by the enzyme monoamine oxidase. 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 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 block the effects of adrenalin (epinephrine) at the post-synaptic beta-adremergic receptor located 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 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 (30, 31). 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, and addiction. 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 (32). Because of these potentially negative effects, it is recommended that benzodiazepines must be used with great caution in PTSD. When they are used, short term use (e.g., no more than five days) with frequent re-evaluation for side effects is recommended. Examples of commonly used benzodiazepines are listed below:

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

What are some future research directions for pharmacotherapy?

The pathophysiological mechanism of PTSD in the nervous system is 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 has implicated supplemental cortisol in reducing PTSD symptoms (33).

In addition to corticotropin releasing factor (CRF) and adrenocorticotropin hormone (ACTH), other neuropeptides such as Substance P and Neuropeptide Y (NPY) have been implicated in PTSD (34). 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, but researchers have delivered the neuropeptide oxytocin intranasally through the olfactory pathway in veterans with PTSD and have demonstrated decrease in hyperarousal symptoms (35).

D-cycloserine (DCS) has been used in panic disorder, specific phobia and social anxiety disorder, to enhance the effects of exposure therapy (36). 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 (37). A recent study of DCS did not demonstrate a significant treatment benefit by adding the drug to PE. There were some interesting caveats, though of DCS reducing cortisol and startle reactivity more than placebo when combined with PE requiring further research (32). This line of research recognizes a paradigm shift in the use of pharmacotherapy as the major treatment modality for reducing PTSD symptoms to an adjunctive role of facilitating learning during psychotherapy , especially with regard to prolonged exposure (PE) therapy (38).

Memantine (Namenda) is a drug of potential interest in preventing neurodegeneration by protecting against glutamatergic destruction of neurons through its antagonism of the NMDA receptor. 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.

Ketamine is an anesthetic agent which modulates the balance between glutamanergic 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 trials currently (39). A recent trial showed beneficial effects in PTSD as well (40). 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 mechanisms of action distinct from serotonin and norepinephrine for treatment of PTSD.

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 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 adherence can improve outcomes to medications. 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

Final thoughts about medications for treatment of 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 and PE based upon the effect sizes in the literature. 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.

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