CME

Pharmacotherapy for PTSD

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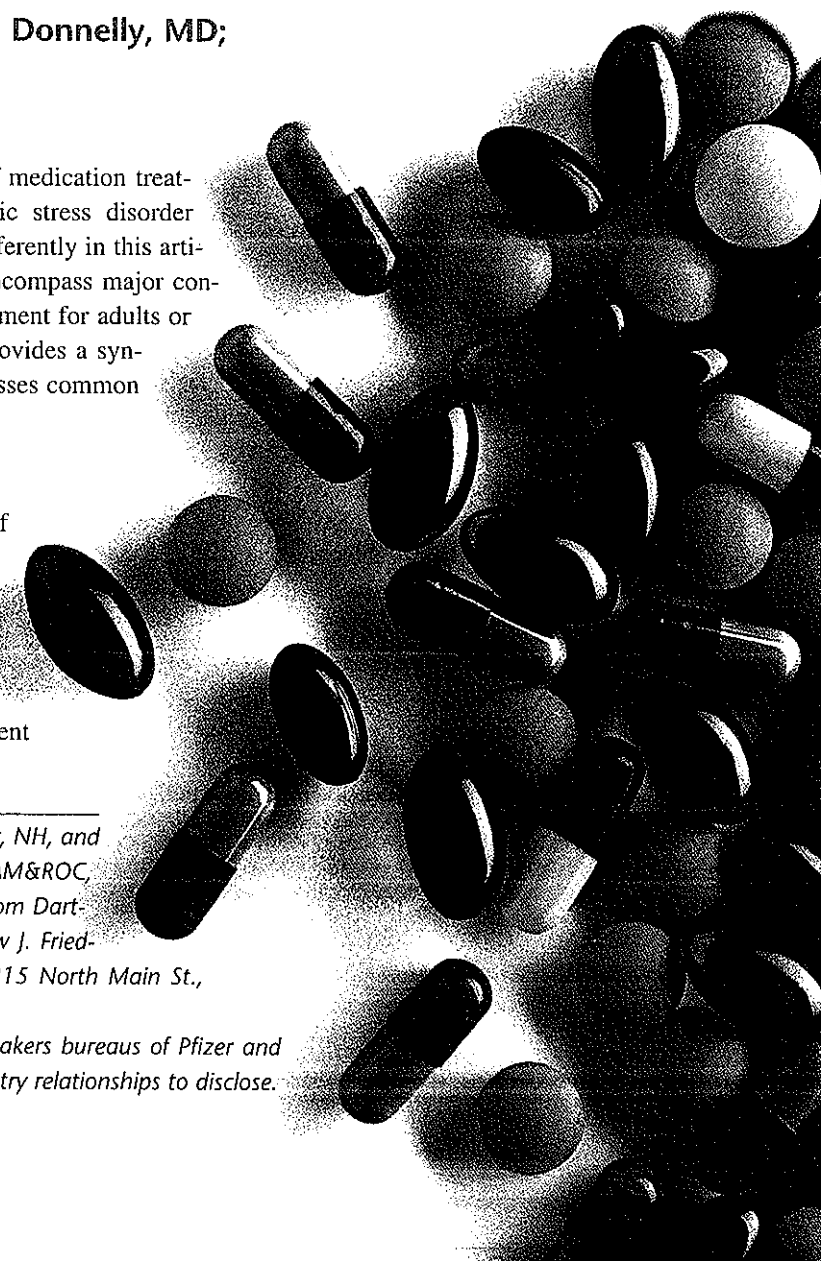

Since each us has previously published reviews of medication treatment for adults and children with posttraumatic stress disorder (PTSD),[1-3] we approach the subject somewhat differently in this article. We ask and answer 11 questions that we believe encompass major concerns of prescribing psychiatrists about medication treatment for adults or children with PTSD. We hope that this presentation provides a synthesis of research literature in a form that directly addresses common clinical decisions.

When Do You Use Medication for PTSD?

There is no simple rule that determines the choice of medication use in PTSD. Rather, medication should be considered an option among several potential therapeutic interventions including cognitive behavioral therapy, psycho-education, supportive therapy, and family therapy. Decisions to use medications are appropriately tailored to individual patient needs and influenced by patient concerns and preferences.

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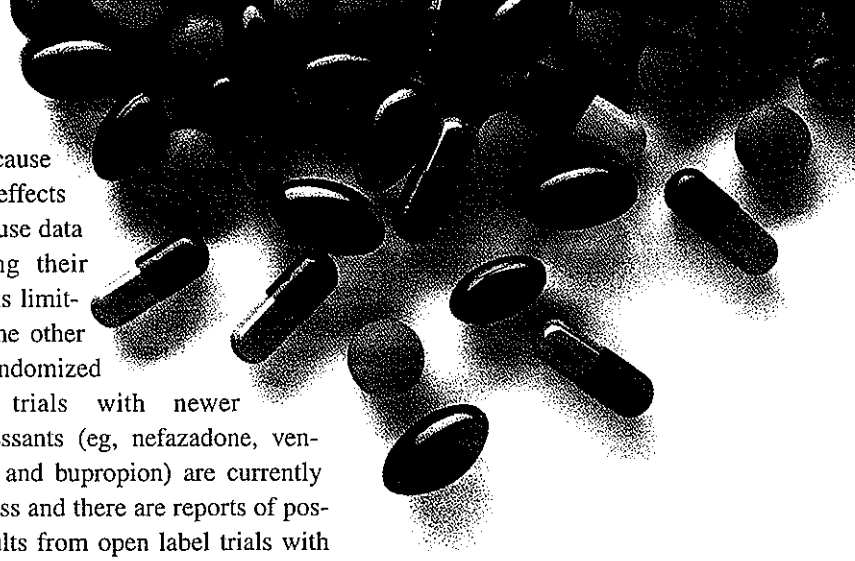
Dr. Friedman is a paid consultant and serves on the speakers bureaus of Pfizer and GlaxoSmithKline. Drs. Donnelly and Mellman have no industry relationships to disclose.



Accordingly, the acceptability of pharmacotherapy and alternative treatment modalities to the patient is one criterion on which to base decisions to prescribe medication. Another might be the presence of significantly severe comorbid psychiatric conditions that are responsive to medications that also treat PTSD. Medication might also be favored as a first line choice when the intensity of PTSD and/or comorbid depression or anxiety symptoms are interfering with a patient's ability to engage in, or tolerate, a psychotherapeutic intervention. Medication treatment may also be indicated when there is no access to competent PTSD-focused psychotherapy and when symptoms persist beyond a reasonable course of treatment.

In What Medications Can We Have Confidence?

At present two medications, the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine, have received approval from the US Food and Drug Administration as indicated treatments for PTSD. Favorable results with other SSRIs such as fluoxetine, fluvoxamine, and citalopram have also been reported. In addition to their broad-spectrum capacity to reduce the severity of all three PTSD symptom clusters, SSRIs have other beneficial properties such as efficacy against disorders frequently comorbid with PTSD (eg, depression, panic disorder, social phobia, and obsessive-compulsive disorder), enhancement of global function, reduction of associated symptoms (eg, suicidality, aggressivity, impulsivity), and a low profile of side effects. Selective serotonin reuptake inhibitors are clearly first line treatment for PTSD.[2,3]

Older antidepressants (eg, tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) have also proven to be effective treatments for PTSD but are less preferred by clinicians because of side effects and because data supporting their efficacy is limited. On the other hand, randomized clinical trials with newer antidepressants (eg, nefazadone, venlafaxine, and bupropion) are currently in progress and there are reports of positive results from open label trials with these agents.[4]

Other classes of medications have not been tested as definitively as the aforementioned antidepressants, although there are both theoretical and empirical reasons to consider anti-adrenergic agents (eg, clonidine, propranolol, guanfacine, and prazosin), anticonvulsants/mood stabilizers (eg, carbamazepine, valproate, lamotrigine, and gabapentin), and atypical antipsychotic agents (eg, risperidone and olanzapine).[2,3]

It must be emphasized that benzodiazepines do not appear to have specific efficacy for PTSD symptoms,[5] although they can improve sleep and improve generalized anxiety.

Research on medication for children with PTSD is quite limited (for review see Donnelley and Amaya-Jackson[1]). Children present unique challenges in that their PTSD may be comorbid with attention-deficit/hyperactivity disorder, school phobia, illicit drug use. and other externalizing, disruptive, or oppositional defiant disorders. Often, it is the disruptive behavior, aggressiveness, or impulsive acting out in children with PTSD that is the chief treatment target. Helping children to gain better self-control through treatment of these externalizing behavioral symptoms with stimulants (dextroamphetamine or methylphenidate), alpha-2 agonists (clonidine or guanfacine), or the antidepressant bupropion, is often a precursor to the treatment of their PTSD per se. As discussed below, children merit special consideration in the pharmacologic management of PTSD and often require the use of multiple medications.

Do Medications Have a Role In Alleviating Acute Traumatic Distress and Preventing PTSD?

We are at a preliminary stage in research on acute pharmacotherapy as an early intervention for acutely traumatized individuals, with very little scientific information to guide us.

It is reasonable to postulate that antidepressant medications, for which there is demonstrated efficacy in PTSD (see below), could be useful in an early stage of the disorder. The only published data concerns the treatment of children with acute stress disorder related to burn injuries in which 83% of the 12 cases treated with imipramine responded favorably, in comparison to only 38% of the 13 cases who received chloral hydrate.[6]

Although one might expect that benzodiazepines would ameliorate acute traumatic distress, this was not demonstrated in the published controlled study of this question which involved alprazolam and clonazepam.[7]

Based on findings linking noradrenergic activity to fear-enhanced memory, Pitman and colleagues conducted a placebo-controlled trial of propranolol administered to emergency department patients.[8] Propranolol intervention ex-

hibited a beneficial trend, although most statistical comparisons were nonsignificant. However, it is interesting that early propranolol treatment significantly reduced physiological reactivity to trauma stimuli among the patients who received this medication shortly after their acute traumatization.

What Is the Best Way to Monitor Clinical Response and to Determine an Adequate Response to Treatment?

Strictly speaking, clinical response is best monitored with instruments that measure PTSD symptom severity. There is a wide choice of both self-rating scales and structured clinical interviews that may be used with both adults and children. Selection of a given instrument will depend on the balance between time available, patient compliance, clinical concerns, and scientific necessity.

For rigorous research protocols, we recommend more labor-intensive structured interviews such as the Clinician Administered PTSD Scale (CAPS)[9] or PTSD Symptom Scale Interview (PSS-I)[10] for adults or CAPS for Children (CAPS-C)[11] that provide greater completeness and accuracy in exchange for the extra effort. There are also a number of reliable and valid self-rating questionnaires for measuring PTSD symptom severity that have good psychometric properties.[11-13]

Since PTSD is usually associated with comorbid diagnoses and impaired functional status, it is not uncommon to monitor other psychopathological indices along with PTSD per se. It has become state of the art for treatment trials for PTSD to define optimal outcomes in terms of reduced severity of anxiety and depression in addition to PTSD per se, global improvement, and to include measurement of general function and quality of life.

What Are the Major Considerations Regarding Medication Tolerability for PTSD Patients?

Medication tolerability affects adherence to pharmacotherapy over the course of treatment. Favorable tolerability findings from the recent large scale studies that led to Food and Drug Administration approval for sertraline and paroxetine are not surprising in view of the now well-established safety and side effect profile of the SSRI medication class. Multicenter studies have shown variable rates of side effects such as asthenia, diarrhea, abnormal ejaculation, impotence, nausea, dry mouth, insomnia, and somnolence.[14-17] These side effects are often mild and transient and do not typically necessitate discontinuation of treatment. While recent large multi-site trials have provided more extensive information on SSRI tolerability in PTSD patients, clinicians should consider tolerability issues for other medications used in PTSD treatment.[2] For example, TCAs can produce anticholinergic effects, orthostatic hypotension, and prolong cardiac conduction. Monoamine oxidase inhibitors necessitate dietary and medication restrictions to avoid hypertensive crisis. Antiadrenergic agents can lower blood pressure and anticonvulsants can produce gastrointestinal and hematological problems. Atypical antipsychotic agents, while free of the neurological toxicity of conventional neuroleptics, still have the potential to cause sedation and, variably, weight gain and problems with glucose regulation.

It is important that the outset to define realistic goals for treatment that are both desirable and obtainable.

There may be ways in which specific tolerability issues for psychiatric medications interact with the diagnosis of PTSD. For example, the sexual side effects of SSRIs may serve as barriers to sexual intimacy within the context of PTSD-related emotional numbing and diminished closeness with others. It is important that clinicians inform patients of these potential side effects and assess the status of sexual functioning on an ongoing basis. Another tolerability concern is the propensity for SSRIs and other antidepressants to produce activation side effects which may exacerbate PTSD-related arousal symptoms. It is therefore prudent to adopt the strategy of "starting low and going slow" with potentially activating medications because they may exacerbate or produce physical restlessness and insomnia during the course of treatment.

What's the Next Step When the Response to First Line Medications Is Inadequate?

It is important at the outset to define realistic goals for treatment that are both desirable and obtainable.[18] Although clinical trials tend to emphasize reduction in PTSD symptom severity, it may be that the management of suicidal behavior, substance misuse, social isolation, and comorbid psychopathology is the first order of business, and improvements in global function and quality of life the ultimate goal.

When treatment goals are achieved, medication should be continued for a reasonable interval (see question below). When treatment has been completely ineffective or has produced intolerable side effects it should be discontinued. A more typical scenario is when an adequate clinical trial of a medication has been partially successful but improvement falls far short of treatment

goals and the clinician is faced with the decision of whether to switch from or add to the initial medication. If further improvement is achieved after adding a medication, it is important to determine ultimately whether the improvement was related to the second medication alone or the combination. Such determinations are aided by gradually reducing the initial medication with the patient's consent while monitoring clinical status. Due to the diffuse nature and frequent partial responsiveness of symptoms that present with PTSD, and what appears to be frequent use of medication combinations, periodic evaluation of ongoing efficacy is of paramount importance.

While recent trials have established SSRIs as first line medications for PTSD, there is little empirical research to guide choices for second line interventions, and it seems reasonable to consider the unique psychopathology of an individual patient to guide these decisions. The following recommendations are based primarily on theoretical considerations and clinical experience for second line interventions (some of which have previously been proposed elsewhere[1,19]), assuming that initial treatment was an SSRI:

Patients who are excessively aroused, hyperreactive, or having dissociative episodes might benefit from antiadrenergic agents (eg, clonidine, guanfacine, propranolol, or prazosin).

Fearful hypervigilant, paranoid, and psychotic patients might benefit from atypical antipsychotic agents.

- Patients with comorbid major depression might benefit from TCAs, MAOIs, nefazadone, venlafaxine, or bupropion.
- Patients who had an excellent clinical response to SSRI treatment but experienced intolerable side effects might benefit from discontinuing the SSRI and switching to nefazadone (because of its 5-HT2 receptor antagonism).
- Labile, impulsive, and/or aggressive patients might benefit from anticonvulsant/mood stabilizers or atypical antipsychotic agents.
- Children and adolescents with impulsive, externalizing behavioral disorders such as ADHD and ODD may benefit from treatment with stimulants, clonidine or bupropion.
- Children with sleep onset anxiety and, or traumatic nightmares may benefit from imipramine.

How Should the Presence of Comorbid Disorders Influence Medication Choices?

There is a high likelihood that at least one other psychiatric condition will be present along with PTSD.[20] The presence of such associated disorders will often influence the choice of medication selected to treat PTSD. Comorbid conditions, such as depression or anxiety, or specific trauma related symptoms, such as insomnia, may suggest a wide variety of treatment options for clinicians to consider for initial medication intervention.

Relapse rates were quite low in the subgroup that achieved initial remission status quickly.

As a general principle, broad-spectrum agents such as SSRIs are a good first choice. Selective serotonin reuptake inhibitors have efficacy in treating both the core symptoms of PTSD and conditions such as the anxiety disorders and depression which commonly co-occur with PTSD. These agents also improve social and occupational functioning as well as an individual's perception of improved quality of life.[14-16] Although SSRIs are generally effective for a broad spectrum of problems, clinicians should systematically monitor for the persistence of symptoms not responsive to these agents. For example, despite significant improvements in core PTSD symptoms in one study using sertraline, little improvement was seen in patients' comorbid anxiety and depressive symptoms.[15] This finding demonstrates the value of continuous symptom monitoring and shows that residual or comorbid symptoms may require a different medication to augment effective SSRI treatment for PTSD.

How Long Do You Continue Medications for PTSD?

Evidence from treatment research for other disorders indicates that long-term medication use prevents relapse of a number of chronic psychiatric disorders. A recent report on continuation treatment for PTSD with the SSRI sertraline suggests that this may also be the case for PTSD.[21] In this study, PTSD patients who had had a successful response to sertraline after 36 weeks of treatment were randomized to either sertraline or placebo groups for an additional 28 weeks of pharmacotherapy. Patients in the sertraline continuation group exhibited a relapse rate of only 5% in contrast to the 26% relapse rate observed among patients who had been switched from sertraline to placebo. This study shows that for some patients, sustaining medication treatment for 64 weeks produced a lower relapse rate than when similar treatment was provided for a shorter period of time. It is noteworthy that relapse rates were quite low in the subgroup that achieved initial remission status quickly (within 4 weeks of starting sertraline treatment). Therefore, treatment duration exceeding 1 year may thus be beneficial in many cases but individuals who exhibit robust or

rapid responses should be given consideration for shorter durations of medication treatment.

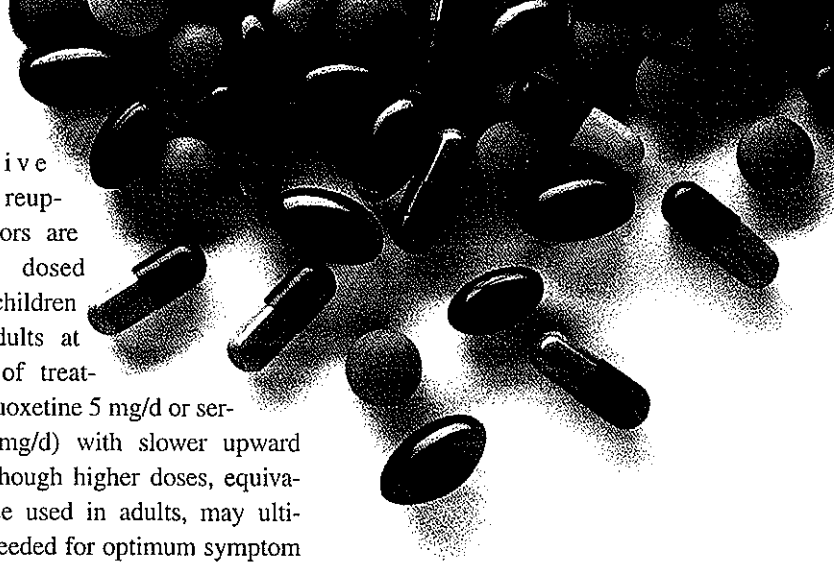
Are There Special Considerations for Treating Children and Adolescents?

In terms of pharmacologic treatment, children are not simply small adults. Medications may have different efficacy, side-effect profiles, and may be metabolized differently in children versus adults.[22] Also, there is far less empirical evidence to guide clinical practice in childhood versus adult PTSD. Although 15 open-label trials have been carried out, there have been no randomized controlled trials of medication use in children with PTSD.

It should be emphasized that the initial treatment of choice for pediatric PTSD is probably cognitive behavioral therapy with play-based components for young children. To date, it appears less risky than medication treatment and has more supportive evidence favoring its use.[23,24]

However, medication use is sometimes warranted when severe agitation, disruptive aggression, or depression limits the behavioral functioning of the child. Medication may serve to stabilize debilitating symptoms allowing children to more effectively engage traumatic material in therapy and to cope better with life stressors.

Several uncontrolled trials with children report that agents such as SSRIs,[25] mood stabilizers,[26] and anti-adrenergic agents[27,28] can be effective in reducing PTSD symptom severity in youth. For example, in one of the best studies in children to date Seedat et al.[25] reported the effectiveness of the SSRI citalopram in a 12-week open-label trial in eight adolescents with moderate to severe PTSD. Subjects in their trial exhibited a 38% reduction in PTSD symptoms at the end of treatment.



Selective serotonin reuptake inhibitors are typically dosed lower for children than for adults at the outset of treatment (eg, fluoxetine 5 mg/d or sertraline 25 mg/d) with slower upward titration, although higher doses, equivalent to those used in adults, may ultimately be needed for optimum symptom control. The stimulants (methylphenidate, dextroamphetamine, mixed dextroamphetamine salts) and α-2 agonists (clonidine and guanfacine) that target specific externalizing behavior disorders common in children with PTSD, such as attention-deficit/hyperactivity disorder and oppositional defiant disorder, may need to be used along with other agents that treat core PTSD symptoms.

How and When Do You Integrate Medication Treatment With Psychotherapy?

Although all published PTSD treatment research has focused on monotherapy (eg, treatment with either a single medication or a single psychotherapeutic approach), most patients who are prescribed medication in clinical practice also receive a psychosocial intervention. There is no empirical evidence comparing monotherapy to combined treatments; therefore it is not known whether there is added benefit from combining treatments.

Without empirical evidence to guide us, a systematic approach where only one treatment component is changed at a time can be helpful for determining the need for combined approaches. If the initial therapeutic approach (medication or psychotherapy) is completely successful, there is no need for an additional treatment. If the initial treatment is completely unsuccessful, it should be discontinued so something else can be tried.

If, however, the initial treatment is partially successful following an adequate therapeutic trial, the optimal approach may be to maintain the initial treatment (eg, medication) and add a second (eg, cognitive behavioral therapy). If combined treatment produces complete remission of PTSD-related problems, it is worthwhile to determine whether both treatments are needed to maintain this clinical improvement.

Where Do We Go From Here?

We are on the threshold of a very exciting period in the development and testing of pharmacotherapeutic agents for PTSD. Without exception, every medication that has been discussed in this article was originally developed as treatment for some other psychiatric or medical disorder and later tested with PTSD patients. Most of these medications were initially developed and marketed for treating depression (eg, SSRIs, TCAs, MAOIs, etc.) although anticonvulsants/mood stabilizers, anxiolytics, antiadrenergic agents, and atypical antipsychotics have also been mentioned.

Our expanding scientific understanding of the pathophysiology of PTSD continues to suggest novel targets for pharmacological interventions. These include corticotropin-releasing-factor antagonists, neuropeptide Y agonists, selective serotonergic agents (eg, 5-HT1A agonists), selective opioid agents,

substance P antagonists, glutamatergic modulators, and brain-derived neurotropic factor enhancers.[29]

In short, we can look forward to a future in which PTSD pharmacotherapy will employ medications that have been specifically designed and selected to treat the unique patterns of psychobiological abnormalities associated with PTSD.

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