Current and Future Drug Treatment for Posttraumatic Stress Disorder Patients

by MATTHEW J. FRIEDMAN, MD, PhD

There are many challenges to writing an article on pharmacotherapy for posttraumatic stress disorder (PTSD). The most obvious problem is that the published literature on clinical trials is too small and inconsistent for anyone to make recommendations with confidence. Second, what we currently understand about the psychobiology of PTSD is so complicated that it is difficult to predict which classes of drugs might be expected to ameliorate which clusters of symptoms. Third, selecting the best drug must take into consideration the clinical reality that patients with PTSD usually exhibit a spectrum of comorbid diagnoses (for example, depression, anxiety disorders, and chemical abuse/dependency). Despite these many considerations, psychiatrists must wade into this sea of current uncertainties and make the most intelligent decisions they can about which drugs to prescribe for their PTSD patients.

Recognizing that clinicians cannot wait either for the publication of additional randomized clinical trials or for the development of safe new anti-PTSD pharmacologic agents, I will offer some treatment suggestions based on my interpretation of the current evidence. I will do so with the understanding that these are merely tentative suggestions that will surely need to be revised as we continue to learn more about the psychobiology of PTSD and about drug treatment for this disorder. First, however, it is necessary to establish a context and present the evidence on which I will base these recommendations by reviewing what we do know about the pharmacotherapy, psychobiology, and comorbidity of PTSD.

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PHARMACOTHERAPY

Selective Serotonin Reuptake Inhibitors (SSRIs)

In the only published randomized clinical trial of an SSRI (fluoxetine), van der Kolk and associates[1] observed a marked reduction in overall PTSD symptoms, especially with respect to numbing and arousal symptoms among civilian trauma survivors with PTSD but not among veterans with war zone-related PTSD. It is likely that these differences are not the result of civilian versus military trauma, but rather due to the greater PTSD severity and chronicity among the veterans. These results were specifically related to amelioration of PTSD symptoms and could not be attributed to fluoxetine's antidepressant actions.

In addition, a number of successful open trials and case reports have been published concerning SSRIs such as fluoxetine, sertraline, and fluvoxamine (see Friedman[2]). In general, investigators have been impressed by the capacity of SSRIs to reduce the numbing symptoms of PTSD because other drugs tested thus far do not seem to have this property. In two recent open-label studies with fluoxetine in rape trauma survivors[3] and fluvoxamine in Vietnam combat veterans,[4] all three clusters (re-experiencing, avoidance or numbing, and hyperarousal) of PTSD symptoms were dramatically reduced by SSRI treatment. The fluvoxamine study is particularly noteworthy because the veterans complained little about insomnia or arousal side affects as has been the case with other SSRIs tested.

What we currently understand about PTSD is so complicated that it is difficult to predict which classes of drugs might be expected to work for which clusters of symptoms.

Davidson and associates[5] have emphasized the importance of using a global measure of clinical status such as the Clinical Global Impressions Scale (CGI) in drug trials rather than focusing entirely on *Diagnostic and Statistical Manual,* 4th edition (DSM-IV) symptom clusters. In their analysis of drug versus placebo trials, SSRIs generally produced greater CGI improvement than placebo. Even more noteworthy, they showed that most PTSD patients who clearly responded to treatment by the end of a 12-week trial had exhibited marked CGI improvement after only 2 weeks of SSRI administration. Thus, Davidson and colleagues challenge two general assumptions concerning SSRI treatment for PTSD by concluding: (a) SSRIs will ameliorate all symptom clusters of PTSD and also produce (CGI) global improvement, and (b) most drug responders will have exhibited CGI improvement within 2 weeks of SSRI treatment.

SSRIs are also an attractive choice because they reduce alcohol consumption. Indeed, Brady and associates[6] observed significant reductions in both PTSD symptoms and alcohol consumption following sertraline treatment among subjects who were comorbid for PTSD and alcohol dependence. This is an important finding because of high comorbidity rates between PTSD and alcohol abuse/dependence among treatment-seeking patients.

Finally, SSRIs may be clinically useful because a number of symptoms associated with PTSD may be mediated by serotonergic mechanisms. These include rage, impulsivity, suicidal intent, depressed mood, panic symptoms, obsessional thinking and behaviors associated with alcohol or drug abuse/dependency.[7]

OTHER SEROTONERGIC AGENTS

Trazadone and nefazadone are serotonergic antidepressants with both SSRI and 5-HT_2 blockade properties. A recent open trial of trazadone on six Vietnam veterans[8] resulted in clinically significant reductions in all PTSD symptom clusters with specific improvement in re-experiencing and arousal symptoms. Trazadone has received renewed attention recently because of its capacity to reverse the insomnia caused by SSRI agents such as fluoxetine and sertraline. As a result, many PTSD patients receiving SSRI treatment also receive trazadone (25-500 mg) at bedtime. Trazadone's advantages over conventional hypnotics is that its major serotonergic mode of action is synergistic with overall SSRI treatment, its sedative properties promote sleep, and its REM suppressant action may reduce traumatic nightmares.[9]

Nefazadone is closely related to trazadone with respect to mechanism of action but appears to have greater potency. There are no current published reports on nefazadone as a treatment for PTSD although multisite trials are currently in progress.

Buspirone is a nonsedating anxiolytic that acts as a 5-HT_{1A} partial agonist that reduced anxiety, insomnia, flashbacks, and depressed mood in three male war-zone veterans with PTSD.[10]

Cyproheptadine is a 5-HT antagonist that reportedly can suppress traumatic nightmares. In case reports of six PTSD patients, cyproheptadine reduced nightmares but no other PTSD symptoms.[2] There have been no further publications on this finding.

ANTIADRENERGIC AGENTS: PROPRANOLOL, CLONIDINE, AND GUANFACINE

It is well established that adrenergic dysregulation is associated with chronic PTSD.[11,12] Therefore, it is surprising that there has been little research with the beta-adrenergic antagonist, propranolol, or with the alpha-2 agonist, clonidine, despite the fact that positive findings with both drugs were reported as early as 1984.[13] Indeed, there are no randomized clinical trials with either drug, although there is one report[14] in which propranolol was administered to 11 physically and/or sexually abused children with PTSD in an A-B-A design (6 weeks off-6 weeks on-6 weeks off medication). Significant reductions in re-experiencing and arousal symptoms were observed during drug treatment but symptoms relapsed to pretreatment severity after discontinuation of medication. There are only two other published reports on propranolol treatment for PTSD[15]: a successful open trial in which re-experiencing and arousal symptoms were reduced in Vietnam veterans and an unsuccessful open trial with Cambodian refugees with PTSD.

There are four reports on open trials with the alpha-2 adrenergic agonist, clonidine,[15] in which successful reduction of many PTSD and associated symptoms was observed such as traumatic nightmares, intrusive recollections, hypervigilance, insomnia, startle reactions, and angry outbursts. In addition, patients in these trials reported improved mood and concentration. It is noteworthy that three different clinical populations participated in these trials: Vietnam veterans, abused children, and Cambodian refugees. In the latter study, a clonidine/imipramine combination was more effective than either drug alone. It has also been reported[16] that preschool (3-6-year-old) children may tolerate a clonidine

patch replaced every 5 days better than an oral dose of 0.1 mg once or twice a day.

Sometimes patients who have a favorable initial response to clonidine appear to develop tolerance to this drug resulting in a return of PTSD symptoms. There are two recent case reports in which clonidine was replaced by the adrenergic alpha-2 agonist, guanfacine (which has a longer half-life: 18-22 hours) after tolerance had developed. In both cases, complete suppression of PTSD symptoms was again achieved and was maintained over the subsequent course of treatment.[17,18]

Despite positive findings, most clinicians are reluctant to prescribe MAOIs for PTSD because they are concerned patients may ingest contraindicated substances or not adhere to necessary dietary restrictions.

MONOAMINE OXIDASE INHIBITORS (MAOIS)

Phenelzine produced excellent reduction of PTSD symptoms during an 8-week randomized clinical trial[19] but was less effective than placebo in a 4-week crossover study[20] where the high dropout rate may have subverted the study's validity. The negative findings in the latter study may have been the result of the study design, the duration of treatment, or the unusually high placebo response. In addition, there have been two successful open trials of phenelzine, a number of positive case reports,[21] and one recent negative open trial with phenelzine.[22] With the exception of one case report on successful treatment of Indo-Chinese refugees with tranylcypromine or isocarboxazid, all published results on MAOI treatment for PTSD concern phenelzine.[21]

A comprehensive review of all published findings on MAOI treatment[23] found that MAOIs produced moderate to good global improvement in 82% of all patients, primarily as a result of reduction in re-experiencing symptoms such as intrusive recollections, traumatic nightmares, and PTSD flashbacks. Insomnia also improved. No improvement was found, however, in PTSD avoidant/numbing, PTSD hyperarousal, or depressive or anxiety/panic symptoms.

Despite these positive findings, most clinicians are reluctant to prescribe MAOIs because they are concerned that PTSD patients may ingest alcohol or pharmacologically contraindicated illicit drugs or that they may not adhere to necessary dietary restrictions. Hopefully, there will be renewed interest in this class of drugs when reversible MAO-A inhibitors such as moclobemide become more available. Unlike phenelzine, these drugs are free of hepatoxicity and have a low risk of producing hypertension when combined with tyramine-containing foods. Indeed, moclobemide produced significant reductions in PTSD re-experiencing and avoidant symptoms in a recent open trial with 20 patients.[24]

Brofaromine

Brofaromine is an investigational drug that is both an SSRI and a reversible MAO-A inhibitor. Two multicenter trials with this drug have been disappointing[25,26] and, as a result, the drug has not been made available commercially. Given the positive SSRI and suggestive MAOI results reviewed previously, it is surprising that brofaromine did not prove more effective for PTSD. A careful review of the data shows that an unusually high rate (30%) of improvement within the placebo group may have obscured brofaromine's efficacy. Furthermore, at the end of the trial, 55% of patients who received brofaromine versus 26% of placebo patients no longer met full diagnostic criteria for PTSD following 14 weeks of treatment. This suggests that the drug may indeed have been clinically superior to placebo.[26] It would seem that further studies with drugs of this nature should be conducted in the future.

Tricyclic Antidepressants (TCAs)

There have been three randomized clinical trials as well as numerous case reports and open trials with TCAs.[27] Results have been mixed and generally modest in magnitude. Imipramine produced statistically and clinically significant global improvement and reduction in re-experiencing symptoms after an 8-week trial.[19] Amitriptyline produced clinically significant improvement in a PTSD global rating; it also produced significant but modest reduction in avoidant/numbing but not re-experiencing or arousal symptoms after 8 weeks of treatment.[28] Finally, desipramine was no better than placebo after a 4-week crossover trial.[29] In their analysis of 15 randomized trials, open trials, and case reports involving TCA treatment for PTSD, Southwick and associates[23] found that 45% of patients showed moderate to good global improvement after treatment whereas MAOIs produced global improvement in 82% of patients who received them. As with MAOIs, most improvement was the result of reductions in re-experiencing rather than avoidant/numbing or arousal symptoms. It also appeared that a minimum of 8 weeks of treatment with either TCAs or MAOIs was necessary to achieve positive clinical results in veterans of military combat.

To summarize, TCAs appear to reduce PTSD re-experiencing and/or symptoms but have not demonstrated the efficacy of SSRIs or MAOIs. Furthermore, their side effects are not

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tolerated well by many PTSD patients. It is because of their relative lack of potency, their side effects, and their failure to reduce avoidant/numbing symptoms that TCAs have been replaced by SSRIs as first-line drugs in PTSD treatment. This may be a rush to judgment, however, because TCAs have been tested primarily on veterans with severe and chronic PTSD whereas SSRIs have been mostly tested on nonveteran cohorts. Indeed, TCAs have actually outperformed SSRIs in reducing PTSD severity among combat veterans.[5]

Benzodiazepines

Although benzodiazepines have been prescribed widely for PTSD patients in some clinical settings, there are only four publications on benzodiazepine treatment for PTSD. In a randomized clinical trial with alprazolam[30] and two open trials with alprazolam and clonazepam, respectively, no improvement was observed in core PTSD re-experiencing, avoidant, or numbing symptoms. In each study, however, patients reported reduced insomnia, anxiety, and irritability. Finally, in PTSD patients who suffered from dissociative identity disorder, clonazepam successfully reduced insomnia, nightmares, and panic attacks in five patients but not in many others without reducing avoidant or dissociative symptoms.[15,31] In summary, benzodiazepines appear to offer little for PTSD intrusion or avoidant/numbing symptoms although they may reduce anxiety, arousal, irritability, and insomnia. In addition, there is a risk of prescribing these agents for many patients with comorbid alcohol or drug abuse/dependence and a serious withdrawal syndrome has been reported after abrupt discontinuation of alprazolam among PTSD patients.[14]

Anticonvulsants

It has been proposed that after exposure to traumatic events, limbic nuclei become kindled or sensitized so that, henceforth, they exhibit excessive responsivity to less intense trauma-related stimuli.[32] As a result, there have been a number of open trials with anticonvulsant/antikindling drugs with PTSD patients. In five studies, carbamazepine produced reductions in re-experiencing and arousal symptoms, whereas in three studies valproate produced reductions in avoidant/numbing and arousal (but not re-experiencing) symptoms.[15] This is clearly a promising area for future research.

Narcotic Antagonists

Glover,[33] having hypothesized that emotional numbing in PTSD results from excessive endogenous opioid activity, conducted an open trial of the narcotic antagonist nalmafene. Consistent with this hypothesis, eight of 18 Vietnam veterans with PTSD exhibited reduced numbing whereas the other 10 patients showed either no improvement or a worsening of anxiety, panic, and hyperarousal symptoms, which might have been caused by inhibition of numbing by nalmafene.

McGee[34] prescribed the narcotic antagonist, naltrexone, to a borderline patient to prevent a hypothesized elevation in opioid levels after self-mutilation which McGee suggested might be reinforcing her repetitive tendency to cut her arms with a razor during periods of stress. As predicted, 50 mg naltrexone per day prevented any further self-cutting behavior and was also associated with continuous sobriety for over 1 year.

Antipsychotics

Before the empiric and conceptual advances achieved during the past 15 years, PTSD patients were often considered to have a psychotic disorder because of their intense agitation, hypervigilance/paranoia, impulsivity, and dissociative states. Times have changed, however, and the current thinking is that most of these symptoms will respond to antiadrenergic or antidepressant drugs and that antipsychotic medications should only be prescribed for the rare PTSD patient who exhibits psychotic symptoms.[15] Such a conclusion may be premature, however, because clinicians have begun to prescribe atypical antipsychotics (for example, risperidone, olanzepine, quetiapine, and others) for refractory PTSD patients. Some preliminary anecdotal observations have been encouraging. This is certainly a research area to watch in the future.

Although it has been suggested that there is a psychotic subgroup of PTSD patients characterized by physical aggression, social isolation, poor self-esteem, and trauma-related hallucinations who are refractory to neuroleptic treatment,[15] there are two published case reports describing successful treatment of PTSD patients with comorbid psychosis with thioridazine[35] and clozapine,[36] respectively. This also is an area needing further research, especially with atypical antipsychotic drugs.

SUMMARY

Results of drug trials are summarized in Table 1. As we review this table, it is important to recognize that we are dealing with a number of complex systems that interact with one another. The fact that an SSRI might produce symptom relief does not necessarily mean that the primary problem is a 5-HT system abnormality. It may mean that 5-HT neurons exert indirect rather than direct effects through their

Table 1
Summary of Drug Actions Against PTSD and Associated Symptoms

Drug Class	Probable PTSD Actions	Possible PTSD Actions	Possible Associated Symptoms
SSRI	C (numbing)	B, D	Rage, impulsivity, suicidality, depression aggression, panic/anxiety, obsessional thoughts, chemical abuse/dependency
Antiadrenergic	B, D	C (dissociation)	Rage, aggression, panic/anxiety
MAOI	B	D (insomnia)	Depression, panic/anxiety
TCA	B	D (insomnia)	Depression, panic/anxiety
Benzodiazepines	—	B, D	Panic/anxiety
Anticonvulsants	D	B, C	Impulsivity, aggression
Narcotic antagonists	B (numbing)	—	Chemical abuse/dependency (may make B&D symptoms worse)
Antipsychotics	—	D (hypervigilance)	Psychotic symptoms

Abbreviations:
B, PTSD B symptoms: intrusive recollections, traumatic nightmares, flashbacks, and so on; C, PTSD C symptoms: avoidant behavior, psychic numbing, dissociation, and so on; D, PTSD D symptoms: insomnia, irritability, startle, hypervigilance, hyperarousal, and so on; SSRI, selective serotonin reuptake inhibitor; MAOI—monoamine oxidase inhibitor; TCA—tricyclic antidepressant.

modulation of other neurobiologic systems (for example, HPA, opioid) whose disruption is the direct cause of these specific PTSD symptoms. Practically speaking, this might explain why SSRIs may effectively ameliorate many PTSD and related symptoms that are not primarily serotonergic in nature (Table 2).

As with serotonergic drugs, adrenergic agents may indirectly precipitate flashbacks and dissociative symptoms. They do this through their actions on glutamatergic mechanisms that appear to be the major mediators of dissociation.[37] The fact that the adrenergic alpha-2 antagonist yohimbine can provoke dissociation in PTSD patients may explain why, in my own clinical experience, the adrenergic alpha-2 agonist, clonidine, appears to be a useful treatment for dissociative symptoms.

PSYCHOBIOLOGY

As reviewed earlier in this issue and elsewhere,[11,12,38] a number of animal models and psychologic mechanisms have been proposed for PTSD including fear conditioning, resistance to habituation/extinction, sensitization/kindling, fear-potentiated startle, uncontrollable/unpredictable/inescapable stress, peritraumatic dissociation, early developmental maternal neglect, a neurobiologic shift from homeostasis to allostasis, and stress-induced hippocampal neurodegeneration. It appears that PTSD is a complex disorder that is associated with stable and profound alterations in many psychobiologic systems that have evolved for coping, adaptation, and survival of the human species. Fundamental psychobiologic functions such as information processing, conditioning, appraisal, and memory appear to be altered in PTSD patients. It may be that PTSD is not a unitary psychobiologic abnormality but that (as with fever and edema) there are a number of possible mechanisms through which this disorder might evolve. Another possibility is that there are different psychobiologic subtypes of a common PTSD disorder. Indeed, some investigators have concluded that because of this complexity, there is no single animal model that is applicable to PTSD.[38]

Table 2 summarizes psychobiologic abnormalities in PTSD that involve specific neurotransmitter, neurohormonal, or neuroendocrine systems.[11,12,38] Such information is relevant to current or future pharmacotherapeutic strategies in which specific classes of drugs should be selected because of their actions on specific psychobiologic systems. Whereas some proposed psychobiologic abnormalities listed in Table 2 are well established (for example, adrenergic hyperreactivity and HPA-enhanced negative feedback), other proposed mechanisms have little empiric support or are primarily theoretical at this time. They are indicated by question marks in Table 2 as are suggested pharmacologic treatments that can only be considered speculative at this time.

Adrenergic hyperreactivity appears to be associated with hyperarousal, re-experiencing, panic/anxiety symptoms, and probably dissociation and rage/aggression. Based on my clinical observations, the drug of choice would be an alpha-2 adrenergic agonist such as clonidine or a beta-adrenergic antagonist such as propranolol.

HPA-enhanced negative feedback is probably associated with the low tolerance for stress seen in PTSD patients and is probably mediated by upregulation of glucocorticoid receptors. Theoretically one might predict that an etiologic treatment would be to downregulate these receptors with a glucocorticoid such as pred-

Table 2
Possible Ideological Treatments for Psychobiological Abnormalities Theoretically Associated With PTSD

Proposed Psychobiologic Abnormality	Possible Clinical Result	Possible Pharmacologic Treatment
Adrenergic hyper-reactivity	Hyperarousal, re-experiencing dissociation, rage/aggression panic/anxiety	Alpha-2 adrenergic agonists Beta-adrenergic antagonists MAOI? TCA?
HPA-enhanced negative feedback	Stress intolerance	Glucocorticoids? SSRIs?
Opioid dysregulation	Numbing chemical abuse/dependency	Opioid antagonists SSRIs?
Elevated CRF levels	Hyperarousal, re-experiencing panic/anxiety	CRF antagonists Neuropeptide Y enhancers? Alpha-2 adrenergic agonists?
Sensitization/kindling	Hyperarousal, re-experiencing	Carbamazepine, valproate
Glutamatergic dysregulation Impaired information & memory processing	Dissociation	NMDA facilitators?
Serotonergic dysregulation hyperarousal associated symptoms*	Numbing, re-experiencing MAOI? TCA?	SSRIs, buspirone?
Increased thyroid activity	Hyperarousal	Beta-adrenergic blockers

*Associated symptoms include rage, aggression, impulsivity, depression, panic/anxiety, obsessional thoughts, chemical abuse/dependency.
Abbreviations: HPA—hypothalamic-pituitary-adrenocortical; CRF—corticotropin-releasing factor; NMDA—n-methyl-d-aspartate; SSRIs—selective serotonin reuptake inhibitors; MAOIs—monoamine oxidase inhibitors; TCAs—tricyclic antidepressants.

nisone. SSRIs might also be beneficial because 5-HT modulates the HPA system.

Opioid dysregulation might be associated both with psychic numbing and with a greater risk for chemical abuse/dependency. A narcotic antagonist might be effective for some patients but not for others because it might exacerbate re-experiencing and hyperarousal symptoms as shown by Glover.[33]

Elevated corticotropin-releasing factor (CRP) may etiologically be the most important abnormality in PTSD. Because CRF is uniquely positioned to simultaneously ignite a cascade of adrenergic, HPA, immunologic, and other biologic responses to stress. Appropriate treatment, theoretically, would be direct blockade (with experimental drugs such as CRF antagonists) or through enhancement of other neurobiologic mechanisms that attenuate CRF activity (for example, experimental neuropeptide Y enhancers or clinically available alpha-2 adrenergic agonists that attenuate locus coeruleus activity).

Antikindling agents such as carbamazepine and valproate have shown promise in a number of studies but no randomized clinical trials have been carried out with such agents.

Glutamatergic dysregulation has been postulated as etiologically responsible for dissociation as well as the information and memory processing abnormalities associated with PTSD. Normalization could theoretically be achieved with drugs that enhance NMDA (n-methy-d-aspartate) synaptic mechanisms.

As noted in Table 1, 5-HT appears to have a direct or indirect role in mediating a number of core (B, C, and D) PTSD as well as associated symptoms that are clinically relevant. This may be why SSRIs have shown early promise as effective drugs for PTSD.

Although elevated in PTSD, increased thyroid activity is usually in the high normal rather than thyrotoxic range. Therefore, it would probably be inadvisable to consider an antithyroid agent, but rather to consider using a beta-adrenergic antagonist such as propranolol to reverse hyperarousal symptoms possibly resulting from this abnormality.

COMORBIDITY

PTSD rarely occurs alone. Patients with PTSD usually exhibit at least one other Axis I psychiatric disorder. Most frequently PTSD is comorbid with depression, anxiety disorders, and/or chemical abuse/dependency. When selecting the best drug, the clinician must try to prescribe a drug that might be expected to ameliorate PTSD and the comorbid disorder at the same time. An excellent example is Brady's successful use of the SSRI sertraline to treat PTSD and alcohol abuse/dependence[6] simultaneously.

We actually know little about how the pres-

ence of one or more comorbid disorders should influence our choice of which drug to prescribe. This is because most drug trials have not attempted to balance the various experimental groups with regard to comorbid disorders. Taken as a whole, the comorbid disorders most frequently associated with PTSD are disorders that respond to SSRI treatment. These include depression, panic disorder, obsessive-compulsive disorder, and chemical abuse/dependency. Furthermore, a number of clinically significant symptoms that are often associated with PTSD include rage, aggression, impulsivity, and suicidal behavior. These comorbid disorders and associated symptoms may all reflect inadequate serotonergic activity, and all are known to respond to SSRIs and other 5-HT enhancers.

RECOMMENDATIONS

The published literature on pharmacotherapy for PTSD is small and inconsistent. As shown in Table 2, there are a number of future drugs that must be developed and drug trials that must be conducted with agents that act directly on the HPA, opioid, CRF, and NMDA systems. Furthermore, additional randomized clinical trials are needed with all drugs mentioned in this review. We are at too preliminary a stage in our development of a solid empiric body of knowledge on drug treatment for PTSD for anyone to make recommendations with confidence.

However, patients need treatment today. They cannot wait for all this research to be completed. Therefore, I recommend that for the present we consider SSRIs and antiadrenergic as first-line drugs for PTSD patients. Current evidence suggests that SSRIs may reduce PTSD core (B, C, and D) symptoms, comorbid (depression, panic, obsessive-compulsive, chemical abuse/dependency) disorders, and clinically significant associated symptoms (such as rage, aggression, impulsivity, and suicidal behavior). However, there remain a number of important questions about SSRI treatment. Whereas earlier studies suggested that it may take a month or two before SSRIs exert their effects,[15] more recent studies suggest that drug-responsive patients will exhibit improvement after only 2 weeks of treatment.[5] Whereas earlier studies suggested that SSRIs might be less effective against re-experiencing and arousal than they are against avoidant/numbing symptoms,[15] more recent studies suggest that SSRIs may effectively ameliorate all PTSD symptom clusters and also produce global improvement.[5] In addition, when prescribing SSRIs, it is important to recognize that they sometimes have undesirable side effects that are particularly intolerable for PTSD patients such as arousal and insomnia.

Antiadrenergic agents (such as alpha-2 agonists or beta blockers) have received little systematic attention in clinical trials despite overwhelming evidence for adrenergic dysregulation in PTSD. In my own practice, I usually prescribe clonidine first. More often than not, clonidine will reduce hyperarousal and re-experiencing symptoms. In addition, reduced adrenergic activity is often accompanied by dramatic reductions in dissociative symptoms, even among adults with complex PTSD as a result of repeated sexual abuse during childhood. The advantage of using clonidine or a beta-adrenergic antagonist is that the clinician can titrate the drug over the course of a week or two. It is readily apparent (in a much shorter time than with an SSRI) whether this drug will work. When a clonidine responder appears to develop tolerance to the drug, switching to guanfacine (an alpha-2 agonist with a longer half-life) often restores the therapeutic effect.

I recommend that for the present we consider SSRIs and antiadrenergic agents as first-line drugs for PTSD patients.

To summarize, I recommend starting with an antiadrenergic agent. If symptoms persist, as they often do, after optimal titration, the next drug to prescribe is an SSRI. If patients develop insomnia and/or agitation, as they often do, the next choice is to add trazadone at bedtime. If there are still clinically significant symptoms after an 8-10-week trial of the SSRI at its optimal dose, it is time to go back to the drawing board. Try to make sense of the refractory symptoms from a pathophysiological perspective and cautiously consider other classes of drugs that have been mentioned in this review.

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