Biological Therapies for Posttraumatic Stress Disorder: An Overview

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Both core and secondary symptoms of posttraumatic stress disorder (PTSD) respond to medication, a valuable part of overall PTSD treatment. Treatment options include antidepressants, anxiolytics, anticonvulsants, and mood stabilizers. A growing data base of results from double-blind, placebo-controlled clinical trials supports the use of antidepressants, especially tricyclics, monoamine oxidase inhibitors (MAOIs), and serotonin selective reuptake inhibitors (SSRIs). Although heightened anxiety is characteristic of PTSD, benzodiazepines have not yet proved useful in controlled trials and may be associated with a rebound effect on discontinuation. The small, open studies of anticonvulsant drugs indicate moderate to good improvement with these agents. Tricyclic, SSRI, and MAOI antidepressants have demonstrated efficacy in larger, longer-term controlled trials. Drug/psychotherapy combinations may enhance the usefulness of psychotherapeutics in the management of PTSD. Studies with tricyclics and fluoxetine indicate that magnitude and type of trauma may determine the degree of response.
(J Clin Psychiatry 1997;58[suppl 9]:29–32)

Because posttraumatic stress disorder (PTSD) involves a person's psychobiological reaction to an environmental event, it is not surprising that psychopharmacology plays an important role in management and constitutes a major area of PTSD research. However, despite recent rapid growth, our knowledge of psychopharmacology for PTSD is still at an early stage, especially when compared with that for disorders like depression, schizophrenia, or even obsessive-compulsive disorder.

GOALS OF PHARMACOTHERAPY

Sealing Over Versus Uncovering the Pain

There are two possible roles for medication in treating patients with PTSD. One is to seal over the pain and distress, eliminating symptoms so that the patient can resume his or her normal life. The other approach consists of uncovering the pain in order to facilitate resolution of the traumatic experience. In this approach, medication is used as an adjunct to help the patient confront the trauma and work through any resulting distress.

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Previously presented at the symposium "Repairing the Shattered Self: Recovering From Trauma," held May 5, 1996, New York, N.Y., sponsored by the American Psychiatric Association and supported by an unrestricted educational grant from the Roerig Division of the U.S. Pharmaceuticals Group, Pfizer Inc.

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Sealing over. One of the earliest references to the use of medication in PTSD comes from Sargant and Slater, who gathered a great deal of experience in managing acute PTSD patients in World War II.[1] They were also pioneers in biological treatments. In the 1960s, they observed:

> "In recent years we have found that patients, of the kind we used to abreact, have done very well by other means, used with the aim of putting traumatic material under the surface rather than bringing it out. When we are well, we mostly repress our fears, which are eventually forgotten, and do not normally need to ventilate them. As a general approach to this group of patients, we have found the MAOI and tricyclic antidepressants more valuable than abreactive therapies."[1]

This insight, however, was largely disregarded at the time.

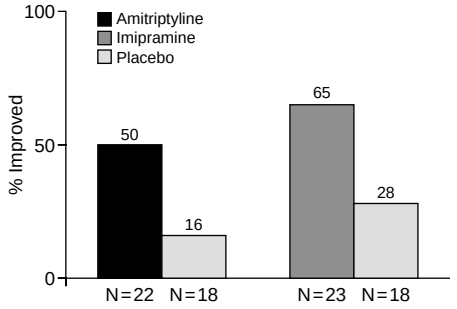
Uncovering the pain. On the other hand, in 1981, Hogben and Cornfield[2] wrote that phenelzine seemed to enhance psychotherapy in five combat veterans by stimulating an intense abreaction not achieved by earlier therapies with or without psychotropic medication. They stated that "rage was the primary emotion expressed . . . followed by depression and, finally, a short period of elation."[2]

The individual situation must determine which of these goals to follow, depending on what might most benefit the particular patient, what kind of contract or understanding patient and therapist have between them, and what their expectations of therapy are.

Goals of Therapy

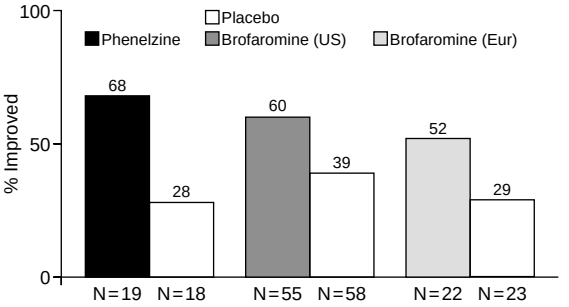
Regardless of the conceptual model, the goals of pharmacotherapy are the same: to reduce intrusive symptoms and the tendency to interpret stimuli as recurrences of

Figure 1. Efficacy of Tricyclic Antidepressants in PTSD*



*Two separate studies measured efficacy.
Left: Data from Davidson et al.[4] The advantage of amitriptyline over placebo approached significance (p = .06).
Right: Data from Kosten et al.[5] Imipramine was significantly more effective than placebo (p = .02).

Figure 2. Efficacy of MAOIs in PTSD*



*Three sparate studies measured efficacy.
Left: Data from Kosten et al.[5] Phenelzine versus placebo.
Center: Data from Baker et al.[10] Brofaromine versus placebo, U.S. study.
Right: Data from Katz et al.[11] Brofaromine versus placebo, European study.

trauma; to lessen avoidance behavior; to improve numbing, estrangement, and mood; and to reduce phasic hyperarousal, in response to exposure to a reminder, and tonic hyperarousal, the enduring hyperarousal. Another goal of treatment should be to decrease impulsivity and psychotic or dissociative symptoms.[3]

The following discussion focuses on the overall effectiveness of different classes of medication used in PTSD, their effects on specific symptoms, the duration of treatment, the importance of particular populations investigated in research, and important management issues.

CLASSES OF MEDICATION

Antidepressants

Tricyclics. Since the late 1980s, many studies have investigated the use of tricyclics in PTSD. Two of the largest studies, published in the early 1990s, involved combat veterans. One, conducted by our group in North Carolina, compared amitriptyline and placebo.[4] The other, from the Veterans Administration (VA) Hospital in West Haven, Conn., compared imipramine with phenelzine or placebo.[5] Figure 1 summarizes the results of both studies.

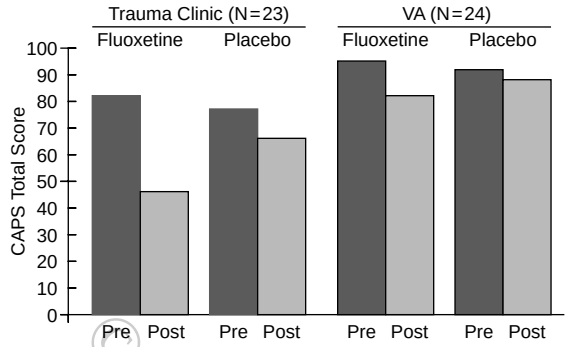
Both trials lasted 8 weeks. The North Carolina trial involved inpatients and outpatients; all were veterans of World War II or the Vietnam war. This group may have been more symptomatic and more severely disturbed than the Connecticut VA patients, who were all outpatient Vietnam veterans. Both studies found a difference of approximately 35% between the tricyclic drug and placebo in number of patients improved. Other, briefer trials had shown modest or negative results, indicating that length of treatment may be a factor.[6–9]

There was an important inverse relationship between the intensity of the trauma exposure and the success of treatment. Even in the World War II veterans, whose combat exposure had occurred 35 years earlier, its influence still persisted, and it affected responsiveness to treatment.[7] Similarly, the severity of symptoms on a variety of scales inversely predicted response to treatment.[7] The more severe the symptoms were, the less well the patients responded.[7] Other predictors of response were severe depression, neuroticism, anxious mood, impaired concentration, somatic symptoms, feelings of guilt, and one intrusion and four avoidance symptoms of PTSD.[7]

MAOIs. The Connecticut VA study also found a highly significant difference between phenelzine and placebo,[5] with the phenelzine group having a higher rate of patients improved (68% vs. 28% for placebo) and better treatment retention (7.4 weeks vs. 5.6 weeks for imipramine and 5.5 weeks for placebo) (Figure 2). Phenelzine-treated patients also showed greater improvement (44%) than patients taking imipramine (25%) or placebo (28%, $p < .02$), as assessed globally. Intrusive symptoms in these patients improved significantly; avoidance symptoms improved slightly but not significantly, although phenelzine tended to produce the greatest effect.[5]

Two other large trials investigated brofaromine, a selective reversible inhibitor of monoamine oxidase type A (RIMA) and the uptake of serotonin, one of the so-called second-generation RIMA drugs not yet available in the United States.[10,11] This class of medications offers the promise of greater safety and tolerability, and freedom from the interaction with tyramine. As Figure 2 shows, the larger study, conducted in the United States, showed some evidence of a drug effect, as measured by Clinical Global Improvement (CGI) outcomes, although other measures of PTSD failed to demonstrate a drug versus placebo difference.[10] In the European study, the drug effect was more marked.[11] A difference in study populations may explain the difference between the U.S. and European studies: most of the U.S. patients were combat veterans, whereas only a small proportion of the European patients had seen combat. Unfortunately, the manufac-

Figure 3. Treatment Outcome: Effect in Two Trauma Populations*



*Reproduced with permission from van der Kolk et al.[15] Results are expressed as percentage of improvement on the Clinician-Administered PTSD Scale (CAPS) score.
Trauma Clinic = Massachusetts General Hospital Trauma Clinic; VA = Boston Veterans Administration Outpatient Clinic.

turer of brofaromine has decided not to continue with clinical trials, and brofaromine is no longer available anywhere.

MAOIs such as phenelzine are likely to prove helpful in treating patients with PTSD. Because of the risks of hypertensive crisis attendant with their use, however, the currently available MAOIs must be considered third- or fourth-line drugs in treating PTSD.

Serotonin Selective Reuptake Inhibitors (SSRIs)

These drugs, probably the most widely used agents in PTSD, have been studied in open-label trials and in a few double-blind controlled investigations. Published research papers have discussed sertraline, fluvoxamine, and fluoxetine, but not paroxetine.

Sertraline. The many open trials of SSRIs include two using sertraline: a small study of rape victims by Rothbaum et al.[12] and a study of combat veterans by Kline and colleagues.[13] Both showed promising results. In the study by Rothbaum et al., four of the five completers responded to sertraline, despite PTSD of long duration (mean = 15.6 years after the rape). In the Kline study, 12 (63%) of the 19 veterans who were prescribed sertraline after other agents had failed had positive responses.[13] A large double-blind, multicenter controlled trial comparing sertraline with placebo is under way. With more than 200 patients enrolled, this is the largest data set to date, but the results of this study are not yet available.

Fluvoxamine. Our center has recently seen very positive results with this drug in civilians with PTSD, as have Marmar et al.[14] in veterans.

Fluoxetine. In a recently completed study of fluoxetine versus placebo, we found evidence for a robust drug effect in civilians with chronic PTSD over a 12-week period. Results of this trial are now undergoing comprehensive analysis. Van der Kolk and colleagues compared fluoxetine with placebo in two populations: civilians in a trauma clinic, most of whom were victims of sexual trauma, and combat veterans in a VA hospital (Figure 3).[15] The civilians improved greatly on medication, but not on placebo. The veterans, who overall had a higher level of symptomatology than the civilians, improved only slightly more with medication than with placebo, but the difference was not significant.

Because results are not necessarily applicable across populations, future research must involve a much broader cross section of the community. Nonetheless, the two positive studies on tricyclics discussed above were conducted in combat veterans, suggesting that under some circumstances antidepressants can yield positive results in this population. Does this mean that tricyclic drugs may be more efficacious than SSRIs in such patients? Will other populations achieve the same results? How do the older drugs that affect multiple neurotransmitter systems compare with the newer, more selective agents? These questions deserve closer examination.

Anxiolytics

In patients who are very anxious, jittery, hyperaroused, easily startled, insomniac, and autonomically unstable, the benzodiazepines—particularly high-potency drugs—seem a logical choice. But, in fact, there is very little evidence for their efficacy.

The only randomized, double-blind, crossover trial compared alprazolam with placebo in a group of 10 Israeli patients, including both combat veterans and civilians traumatized by accidents or terrorism.[16] Patients met DSM-III criteria for PTSD and had treatment-resistant illness. Alprazolam relieved anxiety symptoms more than placebo, but only to a modest extent. Mean ± SD scores on the observer-rated PTSD scale fell from 30.9 ± 8.50 at baseline to 26.6 ± 7.44 after 5 weeks of therapy for alprazolam patients, and from 30.0 ± 9.34 to 28.8 ± 8.16 for placebo patients; the difference was not significant.

Short-acting benzodiazepines often produce withdrawal symptoms on discontinuation. Although the pattern of these symptoms is very well known, case reports[17] indicate that they might pose a special problem in patients with PTSD. Of 116 combat veterans with PTSD receiving long-term alprazolam therapy, 79 tried to taper or gradually discontinue the medication. A rebound phenomenon consisting of clinically significant withdrawal symptoms—anxiety, sleep disturbance, rage reactions, hyperalertness, nightmares, and intrusive thoughts—occurred in 34 (43%) and was severe in 8 (10%). Six of these eight patients developed prominent rage and homicidal ideation.[17]

The role of benzodiazepines in PTSD remains to be determined; in particular, questions concerning when and how to discontinue them remain to be answered. A longer acting benzodiazepine such as clonazepam might prove useful in this setting and warrants further study.

Anticonvulsants

The kindling model of PTSD makes the anticonvulsants a very promising group of drugs, but no controlled clinical trials have been conducted. Two small open-label studies, however, did show positive results.

The first, by Lipper and colleagues, involved a trial of carbamazepine in Vietnam combat veterans.[18] As shown on the CGI scale, 7 of the 10 patients showed moderate to very much improvement. Nightmares, flashbacks, and intrusive recollections became less intense and/or frequent, according to a self-rating PTSD index.

A later study by Fesler investigated the efficacy of valproic acid in 16 Vietnam combat veterans with PTSD: 11 reported significant improvement in hyperarousal/hyperreactivity symptoms and 9 in avoidance/withdrawal symptoms.[19] The first noticeable benefit, reported by nine patients, was improved quality and length of sleep. Combining the results of the two studies shows that 65% of the patients responded to anticonvulsant therapy for PTSD.

Other Considerations

According to the epidemiologic survey of Kessler and colleagues, patients in a community sample who received treatment for PTSD had a mean duration of illness of 36 months; in contrast, in untreated patients the disorder lasted 66 months, almost twice as long.[20] Kessler's survey does not state what kind of treatment these patients received, how appropriate it was, how specific, or how effective. As diagnosis and individual assessment improve and we become better skilled at selecting treatments, we will probably have an even greater impact on PTSD. Through behavioral therapy or long-term pharmacotherapy plus supportive therapy, some patients may learn self-management of their PTSD.

Many patients will not reach this point; they will continue to need long-term medication and psychotherapy. One of our challenges is to gain a better understanding of who is most capable of full recovery and how best to accomplish it. Do certain kinds of people have a greater or lesser predisposition to recover? Is early intervention more critical than a specific therapy? These questions warrant further research.

CONCLUSION

From the data presented here, we can conclude that overall the tricyclic, MAOI, and SSRI antidepressants are effective in treating PTSD, although the extent of their efficacy is debatable. They affect all of the symptom groups in PTSD, but have not yet been shown to improve functioning or disability. Medications may strengthen resiliency and coping skills. Finally, civilian populations may respond differently than veterans; however, we do not yet know why or how severity, type of trauma, length of time before treatment, or other factors may contribute to differences in response.

Other important unanswered questions include the overall time needed for response, relapse rates after therapy discontinuation, relative efficacy of pharmacotherapy and psychotherapy, effects of anticonvulsants and other drugs, role of different psychotropic drug combinations, and relative costs and benefits of effective pharmacotherapy.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clonazepam (Klonopin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), valproic acid (Depakene and others).

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