Continuing Education

Psychopharmacology and Posttraumatic Stress Disorder

Stanley R. Platman, MD

ABSTRACT: *Posttraumatic Stress Disorder (PTSD) is a complex and challenging psychiatric disorder. Its more severe manifestations will require psychopharmacologic intervention. This paper offers guidance in the psychopharmacologic management of PTSD. [International Journal of Emergency Mental Health, 1999, 3, 195-199.]*

KEY WORDS: posttraumatic stress disorder; PTSD; psychopharmacology; treatment

Background

In a Managed Care environment, psychiatrists are increasingly likely to see patients that have been filtered through a non-physician or primary care physician. In general, this will mean that the patient is not doing well and has failed to respond to counseling, behavioral intervention, or a variety of anti-anxiety or anti-depressant medications. Individuals with an Acute Stress Disorder might present initially in an Emergency Room and because of the nature of the traumatic stressor or the degree of dissociation, anxiety and/or dysfunction, be considered for inpatient care. More commonly, the psychiatrist will see the individual in the chronic posttraumatic stage (beyond three months since the initial stressor). As the label of PTSD is being applied for a great variety of reasons and symptoms, it is essential that the primary task of the psychiatrist is to perform a complete evaluation. Medical conditions, substance abuse, depression, and psychotic disorders must be excluded. Malingering is always an important variable and many such referred cases are in the process of litigation or compensation issues.

The syndrome of PTSD is one in which there is still little agreement scientifically, and there is a low concordance in terms of diagnosis and prognosis. In 1980 in DSM III, the term PTSD was introduced as if it were a new discovery to psychiatry. In fact it was one with a long and checkered history, commonly referred to as posttraumatic neurosis or accident neurosis (Trimble, 1981). Consequently, there is no single answer to the question, "What is PTSD?" as posed in a recent journal (Hales & Zatzick, 1997).

Stanley R. Platman, MD. Address correspondence concerning this article to Stanley R. Platman, MD, Department of Psychiatry, Union Memorial Hospital, 3333 North Calvert St., Baltimore, MD 21218.

Perhaps the most consistent research finding in PTSD is that of physiological arousal. Patients may exhibit baseline increases in heart rate, blood pressure, or may show enhanced reactivity to traumatic stimuli (Freidman, 1991). These physiological responses track activation of the sympathetic nervous system as part of a larger stress response of the organism. This response includes behavioral, neural, endocrine, and metabolic adaptations that help the organism cope with a dangerous situation. Several animal models of stress shed some light on possible pharmacological treatments for PTSD.

Fear-enhanced Startle

PTSD patients frequently exhibit an increased startle response. A similar response mediated by a relatively small number of brain stem pathways involving the thalamus and amygdala has been shown in animals (Krystal et al., 1989). It appears that fear enhancement is an associative learning process that may be blocked by a variety of agents, including clonidine, benzodiazepines, alcohol, opiates, and neuroleptics. Treatment with anti-depressants (tricyclics and monoamine oxidase inhibitors) does not block fear-enhanced startle (Krystal et al., 1989). These results may underlie the clinical reports suggesting a role for clonidine in the treatment of PTSD.

Inescapable Shock

Exposing animals to inescapable shock procedures produces a syndrome of "learned helplessness" characterized by behavioral depression, impaired learning, decreased appetite, decreased reproductive behavior, decreased immunity, and increased ulcer formation (Krystal et al., 1989). This pattern, reminiscent of changes seen in major depression, is likened to PTSD (van der Kolk, 1987). Clonidine, benzodiazepines, tricyclics, and monoamine oxidase inhibitors all prevent the development of learned helplessness (Krystal et al., 1989). These agents can also reduce the intensity of deficits induced by

learned helplessness once it is established. These results are consistent with a role for noradrenergic systems in learned helplessness and might account for the reported usefulness of these agents in PTSD and depression.

Kindling

Kindling has been proposed as a mechanism for the generation of seizures, affective disorders, and PTSD (Friedman, 1991). Repeated traumatization through actual events or reexperiencing phenomena, may be the kindling stimulus in PTSD. Carbamazepine, a drug that prevents kindling in animals, has also been reported to have efficacy in PTSD in an open trial (Lipper et al., 1986). If this mechanism has relevance, early and chronic pharmacological intervention may be important in preventing long-term complications of acute PTSD.

General Considerations

Posttraumatic stress disorder may develop after exposure to severe stress, such as combat, accidents, assaults and natural disasters. Pharmacotherapy can be a useful adjunct in the comprehensive treatment of these patients. The presence of comorbid conditions, including depression, panic disorder, substance abuse and traumatic brain injury, should be carefully evaluated. Symptoms of PTSD that are associated with central nervous system hyperarousal or reexperiencing of the traumatic event appear to be the most responsive to pharmacotherapy. Social withdrawal and dulled responsiveness have not been shown to be alleviated through standard pharmacological interventions.

Pharmacotherapy can assist in the patient's ability to participate in psychotherapy. Panic attacks, fear, hallucinations, insomnia, and other disturbing symptoms can interfere with the patient's ability to participate meaningfully in the intellectual and emotional tasks of psychotherapy. By reducing the intensity of these debilitating symptoms, medications can actually facilitate the psychotherapeutic process, permitting symptom reduction to be achieved. In PTSD complicated by comorbidity, medications can alleviate conditions such as mania and depression, which make psychotherapy impossible. In the most severe and psychotherapy-refractory patients, medications may be the only viable alternative. Patients with disabling flashbacks, nightmares, startle, panic, and other debilitating symptoms may find some relief only in psychotropic medication. Although we have several animal models that reflect aspects of PTSD, there is no one model that clearly parallels all the symptoms of PTSD.

Specific Considerations

During World War II, amobarbital sodium and thiopental sodium were used in the treatment of acute "combat exhaustion" and "war neurosis" (Kolb, 1985) largely for purposes of abreaction and sedation. More recently, clinicians and researchers have employed a wide variety of psychopharmacological agents to treat the acute and chronic symptoms of traumatic stress with mixed results.

Despite the prevalence of PTSD in our society few empirical studies exist to define the efficacy of different treatment approaches (e.g. Breslau et al., 1991 found a lifetime rate of 9.1% although Davidson et al., 1991 found a lifetime rate of 1.3% in a community unselected for risk and in which 46% become chronic). Multiple psychopharmacological agents have been advocated for PTSD. Solomon et al., 1992 reviewed 255 English language treatment reports and found only 11 randomized, clinical trials for treatment of well diagnosed PTSD. These included a handful of medication trials together with a mixture of behavioral, cognitive-behavioral, and behavioral-psychodynamic approaches.

Controlled trials indicate that tricyclic anti-depressants (Davidson et al., 1990; Frank et al., 1988; Reist et al., 1989), monoamine oxidase inhibitors (Frank et al., 1988), and serotonin re-uptake blockers (van der Kolk et al., 1994) provide significant improvement in intrusive and hyperarousal symptoms with less effect on avoidant symptoms. Advantages for medications within these trials are often limited. Shestatsky et al. (1988) found no difference between phenelzine, a monoamine oxidase inhibitor, and placebo. Van der Kolk's 1994 study with fluoxitane was criticized by Hillel Glover in a letter to the editor (Glover, 1996) and noted that the impact on the symptom of numbing in PTSD might be difficult to distinguish from apathy as a side effect of fluoxitane. Thus, although numerous anecdotal and clinical reports suggest a useful role for anti-depressants, the evidence from controlled trials is limited even in the comorbid depressed group and lacking in the pure PTSD group.

Open trials with other medications, such as clonidine (Kinzie and Leung 1989; Kolb et al., 1984), propranolol (Famularo et al., 1988; Kolb et al., 1984), and carbamazepine (Lipper, 1990), suggest that certain patients may have positive responses to these medications. There are limited reports on the efficacy of lithium monotherapy for the treatment of PTSD. Studies suggest possible efficacy on the positive symptoms of PTSD (Sutherland, 1994). There are increasing reports on the potential benefits of Divalproex Sodium and the

theoretical model is based on the concept of PTSD being a stress-activated kindling disorder (Fesler, 1991, Szymanski, 1991). Controlled studies are lacking in the use of naltrexone (Bills, 1993), trazodone (Hertzberg, 1996), Bupropion (Canive, 1998), Nefazodone (Davidson, 1998) and buspirone. There are only case study reports using typical and atypical antipsychotic medications.

Investigators have recently explored the use of benzodiazepines in PTSD, particularly the high-potency benzodiazepine alprazolam. High potency benzodiazepines are of particular interest because they reduce arousal, inhibit memory consolidation, and have antipanic properties (Barbee, 1993). By reducing the amount of distress and anxiety, they may also facilitate the mental processing of traumatic events (Hommer, 1991). This approach is fraught with problems because of the high incidence of comorbid alcohol and drug abuse in some individuals with PTSD. Although there has been some indication of significant efficacy in decreasing symptoms of hyperarousal (Braun et al., 1990), there was no impact on the core PTSD symptoms. Furthermore, another report documented severe withdrawal symptoms following discontinuation of alprazolam in chronic PTSD veterans who have been maintained on 2-9 mgs of alprazolam per day for 1-5 years. During gradual withdrawal, all patients had severe reactions including sleep disturbance, rage reactions, intrusive thoughts, and homicidal ideation (Risse et al., 1990). An open study using alprazolam or clonazepam in 13 trauma survivors with a matched control population failed to show any salient beneficial effect even though their use was given initially in the acute stage (Gelpin et al., 1996). Vargas and Davidson (1993) have offered a review of putative psychopharmacologic agents relevant to the treatment of PTSD.

Conclusion

Clearly, more research is required before we can approach the pharmacotherapy of PTSD in the same informed fashion in which we approach the pharmacotherapy of depression or anxiety. In addition, no prospective double-blind studies have looked at combinations of medications, treatment-resistant patients, related substance abuse problems, treatment duration or relapse, or likely response rate.

A paper written for the American Society of Clinical Psychopharmacology (Marshall, 1995) outlined some guidelines for the use of psychotropic medications in PTSD. They are:

- Serious comorbid conditions known to respond to medication: psychosis, major depression, panic disorder, social phobia, etc.
- Preexisting conditions that are medication responsive.
- A history of prior failure of an adequate trial of psychotherapy (approximately three months).
- Individuals who are not psychologically minded, who prefer medication treatment, or who otherwise appear unable to enter into a collaborative psychotherapeutic relationship.
- A patient's inability to tolerate the acute distress sometimes associated with PTSD psychotherapy.

Table 1 represents a listing of psychopharmacologic agents that may be considered in the treatment of PTSD.

Table 1: Psychopharmacologic Considerations in the Treatment of PTSD

Learned Helplessness
Clonodine
Benzodiazepines
Tricyclics
MAOIs
Hyperstartle
Clonodine
Intrusive Ideation
MAOIs
Selective serotonergic reuptake inhibitors (SSRIs)
Tricyclics
Panic
Alprazolam
Clonazepam
Depressed Mood and Avoidance
SSRIs. e.g., sertraline
Impulsive Rage
Lithium
Carbamazepine
Sleep Disturbance
Trazodone

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