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Psychopharmacology of Posttraumatic Stress Disorder

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In psychopharmacology literature, there is limited information about posttraumatic stress disorder (PTSD), since the drug treatment of this disorder has been admixed with the literature on the treatment of anxiety, panic disorder, depression, and borderline personality disorder (all of which include trauma survivors). As those of us who work in the trauma field know, our patients meet the criteria for a number of DSM-IV diagnoses. These may include not only PTSD, but also the anxiety disorders, mood disorders, dissociative disorders, substance abuse/dependence, somatoform disorders, sexual disorders, sleep disorders, eating disorders, and personality disorders within clusters A, B, and C. In addition, there are often significant medical illnesses in Axis III (as mentioned in the previous article). As knowledge in this field grows, we are looking at the umbrella of Complex Posttraumatic Stress Disorder as described by Herman in 1992 (this is not yet a DSM diagnosis, but should be included in ICD-10), particularly for survivors of repeated traumatization.

The concept of Complex PTSD comes from both clinical experience and field trials. It describes a clinical syndrome in survivors of prolonged, repeated trauma within a framework of captivity and coercive control. The disorder encompasses a multiplicity of symptoms including affective changes, somatization, dissociation, characterological sequelae with pathological changes in relationships and identity, and repetition of harm (self-mutilation and revictimization). Synthesis of Axis I and II disorders here makes more clinical sense than compartmentalization, particularly in looking at both the complexity of the

disorder and the possibility of subtypes (e.g. anxious or depressed subtype) rather than separate disorders.

As an introduction to clinical research in this area, it is important to know that most randomized clinical trials (drug vs. placebo treatment) have been done with combat veterans. Open trials are now being conducted with non-combat PTSD patients. No trials have explored the differences between single vs. repeated traumatization or acute vs. chronic PTSD. There is only one reported study with traumatized children. Questions have been raised as to what we should be measuring - target symptoms within the three PTSD clusters or global improvement.

Classes of Medications Used with PTSD

- The **tricyclic antidepressants** (TCAs) have been the most studied medications used in the treatment of PTSD. Three random clinical trials have been published; amitriptyline, imipramine and desipramine, were studied. Results were mixed and of moderate efficacy. In a summary analysis of randomized trials, open trials, and case reports involving TCA treatment for PTSD, 45% of patients showed moderate to good global improvement.
- A comprehensive review of all published findings on **monoamine oxidase inhibitors** (MAOIs) showed moderate to good global improvement in 82% of patients with PTSD. There was reduction of re-experiencing symptoms, but not those of avoidance/numbing, hyperarousal, or depression/anxiety. In contrast, there is a growing literature on the use of MAOIs for "treatment-resistant depression", which includes many trauma survivors. When the new reversible MAOIs (e.g., moclobemide, not yet on

the market) are available, there will be less risk of hypertensive crisis with tyramine-containing foods.

- **Selective serotonin reuptake inhibitors** (SSRIs) have been successful in one randomized clinical trial (fluoxetine), open trials, and case reports (fluoxetine, sertraline, paroxetine and fluvoxamine). All of the SSRIs in open trials of significant length have reduced core symptoms in all three PTSD clusters, in contrast to other antidepressants which do not markedly affect numbing. A recent study of paroxetine in chronic PTSD (non-combat), the first such clinical report, also showed a 43% reduction in dissociative symptoms (note: the term "dissociative symptoms" used in this study needs clarification). My own clinical experience is that medication has little or no effect on dissociative defenses, particularly amnesic barriers. There are several reports showing the efficacy of SSRIs in PTSD with comorbid substance abuse.
- Trazodone and nefazodone, the **other serotonergic antidepressants**, have and are being studied. A recent open trial of trazodone in Vietnam veterans showed significant reduction in all PTSD symptom clusters. Trazodone, in small doses, has been used extensively to counteract the sleep disturbance of PTSD. Multisite studies are in progress on nefazodone as a treatment for PTSD. There is one open trial report showing a 32% reduction of PTSD symptoms with nefazodone. Like trazodone, nefazodone is helpful in treating insomnia. Buspirone, an anxiolytic, also has serotonergic properties; it has been shown in one study to be useful.

- **Benzodiazepines** are antianxiety agents

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which exert their effect by enhancing the concentration of inhibitory gamma-aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter synthesized by large numbers of brain cells. It is the brake on the excitatory pathways and thus results in decreased anxiety and arousal. Open trials of alprazolam and clonazepam have suggested efficacy in treating hyperarousal in some patients. However, despite the extensive use of benzodiazepines in clinical practice, the results are mixed and fraught with the danger of prescription abuse and dyscontrol. It is wise to use them cautiously and with careful control of prescribed amounts. I have found that small doses on a routine basis give more consistent results than p.r.n. usage. The new anticonvulsant, tiagabine, is a GABA reuptake inhibitor that has benzodiazepine-like properties, but is not addictive. It may be a useful adjunct in the future treatment of PTSD.

• The **mood stabilizers**, carbamazepine and valproate, have also been studied. These two medications are both anticonvulsant/antikindling. Carbamazepine reduced re-experiencing and arousal symptoms in five studies; valproate produced reductions in avoidant/numbing and arousal symptoms in two studies. The newer anticonvulsant mood stabilizers, lamotrigine and gabapentin, are being used clinically, but it is too early to determine their efficacy. Surprisingly enough, there are no controlled trials on the use of lithium in the treatment of PTSD. However, there are reports of improvement in affective instability and irritability/outbursts in the literature. Lithium is commonly prescribed to augment antidepressant therapy in PTSD.

• **Antiadrenergic agents** suppress the symptoms of arousal, anxiety, insomnia, startle, vigilance, and irritability. Surprisingly, although these are prominent symptoms of PTSD, little controlled research has been done on these medications. However, propranolol and clonidine have been noted to be effective in open trials. There is one study in which propranolol was administered to abused children; significant reductions in re-experiencing and arousal symptoms were noted during six weeks of drug treatment, but there was relapse after discontinuation of the medication. Clonidine has been shown to be useful in decreasing traumatic

nightmares, intrusive recollections, and startle reactions. Since there is adrenergic hyperreactivity in PTSD, all adrenergic agents should be used with caution. Many patients have gotten into difficulty with the use of asthma medications or amphetamine augmentation of an antidepressant.

• The **opioid antagonists** have been suggested to counteract the stress release of endogenous opiates, which result in psychic numbing and stress-induced analgesia. There is a literature which supports the use of naltrexone as a treatment for self-mutilation; two reports suggest improvement in PTSD symptoms in a small number of subjects.

• **Antipsychotics** have no specific efficacy in the treatment of PTSD and are generally not recommended because of their short- and long-term side effects. What happens, more often than not, is that intense intrusive symptoms, suspiciousness, and dissociation are erroneously diagnosed as psychosis. Antipsychotics, in fact, may cause increased dysphoria in PTSD or less control of the switching process in patients with dissociative identity disorder. The new atypical antipsychotics (risperidone, olanzapine, quetiapine) have fewer side effects and, we hope, less risk of tardive dyskinesia. They are now being used for disorganized PTSD patients at times of intense agitation and crisis, but are not recommended for long term treatment.

Suggested Treatment Algorithm

My own treatment algorithm for PTSD is to start with an SSRI, usually sertraline or paroxetine, with a small dose of trazodone for sleep. This is first-line treatment in terms of efficacy, with a focus on safety and few side effects. If there is no response, I will usually switch to another SSRI or augment with buspirone or bupropion (small dose). If a benzodiazepine is needed to control anxiety, I prefer the use of clonazepam, which is longer-acting and has fewer withdrawal problems. If the SSRIs have been exhausted, I will try mirtazapine or venlafaxine (with awareness of the adrenergic properties). I am cautious about the use of TCAs and MAOIs, because of the lethality of small doses. Either clonidine or propranolol is useful to treat intense hyperarousal if there are no medical contraindications. A mood stabilizer, usually valproate or gabapentin, may be added. I have

sometimes found valproate more useful than benzodiazepines for hyperarousal and anxiety. Gabapentin, given at night, is helpful for sleep. I use the atypical antipsychotics sparingly and for short periods of time.

There are many frustrations in the psychopharmacological treatment of PTSD, including the “poop-out syndrome” (descriptive term courtesy of Dr. Norman Sussman). “Poop-out” refers to the loss of effectiveness of a medication that had previously resulted in a clinical response. Whether this is due to the biological complexity of the disorder itself or downregulation of neuroreceptors (thus, decreased sensitivity) is not clear. Before moving on to another medication, I have learned to check out what’s happening in psychotherapy and look at the external stressors.

In summary, the literature and research are obviously too meager to make strong recommendations, but our everyday clinical experience and sense of direction are growing. In comparing notes with my psychiatric colleagues in the field, the axioms appear to be “keep it simple” and “trial and observation.” I always tell patients that psychotherapy is the heart of the treatment, and that medication is adjunctive. I have sometimes jested that if I prescribe more than three medications, I am treating my own “rescuer” countertransference (these patients are in great distress). In this era of “co-pharmacy and tweaking receptors”, I might consider four!

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