The Art of Prescribing

Pharmacologic Management of Posttraumatic Stress Disorder

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There are growing concerns about the acute and long-term effects on the mental and physical health of individuals exposed to violence and traumatic events such as the terrorist attacks on September 11, 2001, the train bombings in Spain in 2004, and wars in Iraq, Afghanistan, and the Middle East, and natural disasters, such as the 2006 earthquake in Indonesia and hurricane Katrina in 2005. Collectively, these events and global turmoil will increase the prevalence of posttraumatic stress disorder (PTSD) in the next decade. The growing prevalence of trauma and potential acute and chronic responses challenges psychiatric nurses to understand neurobiological underpinnings of PTSD and develop and implement evidence-based interventions—both pharmacotherapy and psychotherapeutic interventions to facilitate early resolution, reduce morbidity and health utilization, and optimize treatment options.

Definition and Prevalence of PTSD

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can occur after experiencing or witnessing a life-threatening or overwhelming traumatic event, such as rape, military combat, violent crimes and assault, and natural disasters (American Psychiatric Association [APA], 2000). By definition, PTSD is threatening and generates a profound fear reaction. Primary symptoms of PTSD include a host of symptoms in three criteria post-exposure to an overwhelming traumatic experience: (a) persistent re-experiencing of the event; (b) marked emotional numbing and avoidance; and (c) hyperarousal. Symptoms must persist more than 1 month after the trauma and be associated with marked social, physical, mental, or occupational impairment (APA, 2000). Approximately 8% of the U.S. general population will experience PTSD at some time in their lives, with women (10.4%) twice more likely than men (5%). The National Center for PTSD estimates the prevalence among Vietnam veterans is 15.2% and 30% in women and men in the recent war zones (National Center for PTSD, 2006). Posttraumatic stress disorder implicates considerable co-occurrence with major depression, other anxiety, and substance-related disorders and is associated with increased morbidity, mortality, and health utilization (Bleich, Koslowsky, Dolev, & Lerer, 1997; Oquendo et al., 2005; Zatzick, Marmar, & Weiss, 1997).

Risk Factors for PTSD

Exposure to trauma is common, affecting about 50% of people in this country. Why some people develop PTSD, while others are more resilient and able to cope and move on, is poorly understood. However, factors that may be helpful in resolving traumatic situations include biological and psychosocial resilience, personality and coping style, quality support systems, and faith (Campbell-Sills, Cohan, Stein, 2006; Davidson et al., 2005). Additional factors that mediate vulnerability to PTSD include:

- Severity of trauma
- Gender (women twice as likely to develop than men)
- Past psychiatric history
- Positive family history of psychiatric illness
- Genetic predisposition
- Decreased cortisol and degree of arousal at time of trauma
- Quality of social support (sense of strong support)
- Reaction at time of trauma
- Witnessing or surviving violent incident
- Education and intelligence level (Rimmö, Åberg, & Fredrikson, 2005)

Neurobiology of PTSD: Target Sites for Pharmacotherapy?

Neurobiological origins of PTSD comprise neurochemical, neuroendocrine, and several neuroanatomical brain regions, such as the amygdala, anterior cingulate cortex, and parts of the limbic system (Iancu, Rosen, & Moshe, 2002; Shin et al., 2004). Decreased hippocampal volume associated with low cortisol levels has also been implicated as a biological marker of PTSD. Twin studies indicate that subtle neurological soft signs

(e.g., smaller hippocampus) may be a pre-existing risk factor for PTSD (Gurvits et al., 2006).

Neuroimaging studies of traumatic recollection and imagery consistently support the premise the amygdala is implicated in the genesis of fear. There appears to be an inverse reaction between the amygdala and the anterior cingulate cortex concerning how fear is ascribed to traumatic events. The amygdala ascribes the degree and output of fear conditioning associated with a traumatic event. Hyperactivation of the amygdala and subsequent hypoactivation of the anterior cingulated cortex increases the risk of PTSD. In contrast, activation of the anterior cingulate cortex produces "protective" or resilient factors and reduces activation of the amygdala and the fear response (Shin et al., 2004). Data also reveal higher regional blood flow (rCBF) in the amygdala and reduced blood flow in anterior/medial frontal gyrus in PTSD and substance-related disorders (Semple et al., 2000).

It is also posited that repetitive activation of fear conditioning results in kindling or hypersensitivity in the limbic nuclei and subsequent biological arousal and emotional or psychological impairment (Berlant & van Kammen, 2002). Manifestations of trauma-related kindling phenomenon include distressful recollections, non-hallucinatory flashbacks, nightmares, impulsivity, and aggressive behaviors (Berlant & van Kammen). Promising results from open-label antikindling and anticonvulsant agents, such as topiramate, carbamazepine, valproate, and lamotrigine, suggest that they may be able to prevent sensitization and the kindling phenomenon when administered several hours or days posttrauma (Berlant & van Kammen; Berlant, 2004; Iancu et al., 2002).

Evaluation and Treatment of PTSD

Diagnosis can be determined through a history of exposure to trauma; exhibited symptoms of PTSD (3 *DSM-IV R* diagnostic criteria). Due to the potentially emotionally charged aspect of the evaluation, it is imperative to monitor personal and patient responses to ensure empathy, objectivity, and support during the patient's stressful recollection of the trauma.

Differential diagnosis of co-occurring medical and psychiatric disorders (e.g., major depression, anxiety disorders) requires performing a detailed psychiatric evaluation, including level of dangerousness to self and others and history and physical examination. Results from diagnostic studies, such as complete blood count (CBC) with differential, chemistries, electrolytes, renal, liver, and thyroid panels, urinalysis, and toxicology screens, help rule out medical conditions. Cultural, gender, and age-related considerations must be assessed and integrated into the evaluation and treatment process due to variance of symptom expression.

Apart from the diagnostic criteria of PTSD (APA, 2000) screening instruments are also useful in diagnosing PTSD and monitoring clinical response to pharmacotherapy. Two primary categories of PTSD evaluations are structured interviews and self-report questionnaires. The Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) is among the most widely used types of interviews. It is clinician-friendly and allows for thorough data collections, gathering and evaluation concerning the frequency and intensity of the core PTSD symptoms and associated symptoms, which may have clinical implications for treatment and recovery. The Impact of Event Scale-Revised (IES-R) is also a widely used self-report measure. Additional rating scales include the Clinical Global Impression-Improvement (CGI-I) scale. Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) are also useful in monitoring medication responses to antidepressant medications and co-occurring depression and anxiety disorders.

Pharmacotherapy Management

Antidepressants

Target symptoms for pharmacotherapy in PTSD must focus on three clusters of symptoms, mainly: re-experiencing, avoidance, and hyperarousal. First-line

treatment of PTSD selective serotonin reuptake inhibitor (SSRI) antidepressants is supported by large multi-center randomized controlled trials (Brady et al., 2000; Davidson et al., 2001). Primary advantages of SSRIs in the treatment of PTSD include their broad spectrum properties to reduce three PTSD cluster symptoms; dual efficacy in the treatment of comorbid psychiatric disorders; and tolerability and relatively side-effect profile. Additional advantages of SSRIs in the treatment of PTSD include enrichment of global functioning, mitigation of impulsivity, aggression, sleep disturbances, and suicidality (Maher, Rego, & Asnis, 2006). Specific actions of SSRIs include their modulating effect on norepinephrine activity through actions in the locus caeruleus. These agents also reduce excessive external stimuli and mitigate fear responses and expand a sense of control. Of the SSRIs, sertraline, paroxetine, and fluoxetine have been the most studied and demonstrated efficacy in randomized control trials (Brady et al.), and open-label and double-blind trials (Davidson et al., 2001). Sertraline and paroxetine are the only medications approved for PTSD by the US Food and Drug Administration (FDA); all other drugs are prescribed off-label. Researchers conducting a two multicenter, 12-week, double-blind, flexible dose (50–200 mg/day of sertraline) comparing patients with co-occurring PTSD and depression and controls concluded that sertraline (50–200 mg) was effective in the treatment of co-occurring PTSD and depression or anxiety disorder (Brady & Clary, 2003).

Second-line medications include novel antidepressants such as venlafaxine, bupropion, and mirtazepine, and mood stabilizers or antikindling agents. Venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), enhances the action of serotonin, norepinephrine, and dopamine activity (Asnis, Kohn, Henderson, & Brown, 2004). Primary appeals of mirtazepine lie in its dual enhancement of serotonergic and noradrenergic neurotransmission and blockade of alpha$_2$-adrenoceptors. Mirtazapine also directly blocks 5-HT$_2$ and 5-HT$_3$ receptors, possibly contributing to its anxiolytic and sleep-promoting attribute (Blier, 2001).

Dosing recommendations for SSRIs, SNRIs, and novel antidepressants in the treatment of PTSD with or without co-occurring depression and anxiety disorder are similar to treating depressive and anxiety disorders. A trial of antidepressant pharmacotherapy (6–12 weeks) is recommended with continuation and maintenance treatment for 6–12 months to prevent relapse. Discontinuation of these agents must be slow taper to avoid rebound anticholinergic syndromes and minimize the risk of relapse. Treatment resistance to antidepressants and persistent and severe symptoms may require alternative or adjunct options such as adrenergic-inhibiting agents, antikindling agents, and antipsychotic medications.

Adrenergic-Inhibiting Agents

Adrenergic-inhibiting agents, such as propanolol, a beta-blocker, have demonstrated promising results in the treatment of adrenergic (norepinephine) dysregulation, a core feature of PTSD. Preliminary data also indicate the efficacy of propranolol (160 mg/day) in divided doses of 40 mg q.i.d. for 10 days in preventing pre-synaptic norepinephrine receptors and reduce cortisol mediated memories may prevent over-encoding or consolidation of traumatic memories and fear conditioning 2 to 3 months posttrauma (Pitman & Delahanty, 2005). Several studies involving immediate pharmacologic intervention with propranolol, within the first 6 h after the traumatic event for 7 to 10 days demonstrated promise in the mitigation of PTSD symptoms or perhaps preventing the development of PTSD (Pitman et al., 2002). In a naturalistic study, propranolol (120 mg/day) in divided doses of 40 mg thrice a day was prescribed 7 days followed by tapering over a 2–8 days period (Vaiva et al., 2003). Preliminary data of alpha$_2$-adrenergic receptor agonists, such as clonidine and prazosin, in the treatment of PTSD symptoms implicate their efficacy in treating sleep problems (e.g., severe nightmares) (Stein, 2005). Management of acute trauma responses with these agents implicates the potential to prevent post-traumatic stress.

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Antikindling Agents/Mood Stabilizers

Open-label studies of antikindling agents/mood stabilizers, such as topiramate, carbamezepine, and lamitrogine, exhibit encouraging findings in the treatment of acute and chronic PTSD (Berlant & van Kammen, 2002). Antikindling or mood stabilizers should also be considered where co-occurrence of bipolar disorder exists, and where impulsivity and anger exist (Asnis et al., 2004). Results from most studies suggest that these agents have been associated with improvement in intrusive thoughts, numbing, and severe nightmares and decrease impulsivity and aggression when used as adjunct treatment with antidepressants or monotherapy.

Antipsychotic Agents

Antipsychotic agents are not routinely prescribed for PTSD. However, patients with comorbid psychotic features, when paranoia and flashbacks, are prominent; treatment refractory PTSD, may benefit from these medications (Asnis et al., 2004; Hammer, Deitsch, & Brodrick, 2003; Petty, Brannan, & Casada, 2001). In these situations, low dose antipsychotic agents may be a useful adjunct to other pharmacotherapy.

Summary

The prevalence of PTSD is expected to rise the next decade and psychiatric nurses must be prepared to recognize and treat acute and chronic symptoms of this complex psychiatric disorder. Understanding neurobiological underpinnings as potential target sites for pharmacologic and psychotherapeutic interventions and genetic and environmental risk factors is critical to symptom management and quality of life after a traumatic event.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders*, 4th ed. (revised). Washington, DC: Author.

Asnis, G. M., Kohn, S. R., Henderson, M., & Brown, N. L. (2004). SSRIs versus non-SSRIs in post-traumatic stress disorder: An update with recommendations. *Drugs, 64*, 383–404.

Berlant, J. L. (2004). Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BioMed Central Psychiatry, 4*:24; doi: 10.1186/1471-244X-4-24. Electronic version http://www.biomedcentral.com/1471-244X/4/24 (Accessed October 30, 2006).

Berlant, J., & van Kammen, D. P. (2002). Open-label topiramate as primary of adjunctive therapy in chronic civilian posttraumatic stress disorder: A preliminary report. *Journal of Clinical Psychiatry, 63*, 15–20.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, E. D., Charney, D. S., et al. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress, 8*, 75–90.

Bleich, A., Koslowsky, M., Dolev, A., & Lerer, B. (1997). Posttraumatic stress disorder and depression: An analysis of comorbidity. *British Journal of Psychiatry, 170*, 479–482.

Blier, P. (2001). Pharmacology of rapid-onset antidepressant treatment strategies. *Journal of Clinical Psychiatry, 62*, Suppl 15, 12–17.

Brady, K. T., & Clary, C. M. (2003). Affective and anxiety comorbidity in post-traumatic stress disorder treatment trials of sertraline. *Comprehensive Psychiatry, 44*, 360–369.

Brady, K., Pearlstein, T., Asnis, G. M., Baker, D., Rothbaum, B., et al. (2000). Efficacy and safety of sertraline treatment of posttraumatic stress disorder: A randomized controlled trial. *Journal of the American Medical Association, 283*, 1837–1844.

Campbell-Sills, L., Cohan, S. L., & Stein, M. B. (2006). Relationship of resilience to personality, coping and psychiatric symptoms in young adults. *Behaviour Research and Therapy, 44*, 585–599.

Davidson, J. R., Payne, V. M., Connor, K. M., Foa, E. B., Rothbaum, B. O., Hertzberg, M. A., et al. (2005). Trauma, resilience, and saliostasis: Effects of treatment in posttraumatic stress disorder. *International Clinical Psychopharmacology, 20*, 43–48.

Davidson, J. R., Rothbaum, B. O., van der Kolk, B. A., Sikes, C. R., & Farjel, G. M. (2001). Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Archives of General Psychiatry, 58*, 485–492.

Gurvits, T. V., Metzger, L. J., Lasko, N. B., Cannistraro, P. A., Tarhan, A. S., et al. (2006). Subtle neurologic compromise as a vulnerability factor for combat-related posttraumatic stress disorder: Results of a twin study. *Archives of General Psychiatry, 63*, 571–576.

Hamner, M. B., Deitsch, S. E., Brodrick, P. S., et al. (2003). Quetiapine treatment in patients with posttraumatic stress disorder: An open adjunctive therapy. *Journal of Clinical Psychiatry, 23*, 15–20.

Iancu, I., Rosen, Y., & Moshe, K. (2002). Antiepileptic drugs in post-traumatic stress disorder. *Clinical Neuropharmacology, 25*, 225–229.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C. B. (1995). Posttraumatic disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 52*, 1048–1060.

Maher, M. J., Rego, S. A., & Asnis, G. M. (2006). Sleep disturbances in patients with post-traumatic stress disorder: Epidemiology, impact and approaches to management. *CNS Drugs, 20*, 567–590.

National Center for Posttraumatic Stress Disorder. Retrieved June 3, 2006, from http://www.ncptsd.va.gov/facts/general/fs_epidemiological.html

Oquendo, M., Brent, D. A., Birmaher, B., Greenhill, L., Kolko, D., et al. (2005). Posttraumatic stress disorder comorbid with major depression: Factors mediating the association with suicidal behavior. *American Journal of Psychiatry*, *162*, 560–566.

Petty, F., Brannan, S., Casada, J., et al. (2001). Olanzapine treatment for posttraumatic stress disorder: An open-label study. *International Clinical Psychopharmacology*, *16*, 331–337.

Pitman, R. K., & Delahanty, D. L. (2005). Conceptually driven pharmacologic approaches to acute trauma. *CNS Spectrum*, *10*, 99–106.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healey, A. R., Cheema, F., Lasko, N. B., et al. (2002). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biological Psychiatry*, *51*, 189–192.

Rimmö, Ö., Åberg, P.-A., & Fredrikson, M. (2005). Trauma exposure and post-traumatic stress disorder in the general population. *Acta Psychiatrica Scandinavica*, *111*, 291–299.

Semple, W. E., Goyer, P. F., McCormick, R., Donovan, B., Muzic, R. F. Jr et al. (2000). Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry*, *63*, 65–74.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S., Macklin, M. L., Lasko, N. B., et al. (2004). Regional blood flow in the amygdale and medical prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Archives of General Psychiatry*, *61*, 168–176.

Stein, M. B. (2005). Anxiety disorders: Somatic treatment. In B. J. Sadock & V. A. Sadock (Eds.) *Kaplan & Sadock's Comprehensive Textbook of General Psychiatry*, 8th ed. (pp. 1780–1788). Philadelphia: Lippincott Williams & Wilkins.

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., et al. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after Trauma. *Biological Psychiatry*, *54*, 947–949.

Zatzick, D. F., Marmar, C. R., & Weiss, D. S. (1997). PTSD and functioning and quality of life outcomes in a nationally representative sample of male Vietnam veterans. *American Journal of Psychiatry*, *154*, 1690–1695.