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Prazosin for Veterans with Posttraumatic Stress Disorder and Comorbid Alcohol Dependence: A Clinical Trial

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Background: Posttraumatic stress disorder (PTSD) is an important and timely clinical issue particularly for combat veterans. Few pharmacologic options are available to treat PTSD, particularly among military personnel, and they are not based on rational neurobiology. The evidence for noradrenergic dysregulation in PTSD is strong, and the alpha-adrenergic agonist prazosin is one of the most promising medications to treat sleep disturbances associated with PTSD as well as PTSD symptoms among both veterans and civilians. Evidence also implicates noradrenergic dysregulation in the pathophysiology of alcohol dependence (AD); prazosin also may have efficacy in treating this disorder. The use of prazosin represents a rational and compelling approach for the treatment of PTSD and comorbid AD. Given the high rates of comorbid AD in trauma survivors with PTSD, and the enormous impact that these comorbid disorders have on psychosocial function and well-being, finding effective treatments for this population is of high clinical importance.

Methods: Ninety-six veterans with PTSD and comorbid AD were randomized to receive prazosin (16 mg) or placebo in an outpatient, randomized, double-blind, clinical trial for 13 weeks. Main outcomes included symptoms of PTSD, sleep disturbances, and alcohol use.

Results: Symptoms of PTSD improved over time, but contrary to the hypothesis, there was no medication effect on PTSD symptoms, or on sleep. Alcohol consumption also decreased over time, but there were no significant differences in outcomes between medication groups.

Conclusions: Prazosin was not effective in treating PTSD symptoms, improving sleep, or reducing alcohol consumption overall in this dually diagnosed group. This does not support the use of prazosin in an actively drinking population and suggests that the presence of a comorbid condition affects the efficacy of this medication. This study highlights the importance of conducting clinical trials in "real-world" patients, as results may vary based on comorbid conditions.

Key Words: Posttraumatic Stress Disorder, Alcoholism, Prazosin, Veterans, Clinical Trial.

POSTTRAUMATIC STRESS DISORDER (PTSD) is a serious mental disorder and a public health issue particularly among military personnel. The risk of developing PTSD among combat-exposed military personnel is very high (Hoge et al., 2006), and screenings of soldiers returning from the recent conflicts in Iraq and Afghanistan have found rates of PTSD up to 24.5% (Hoge et al., 2004, 2006, 2007; Milliken et al., 2007). This is also an issue for the Veterans Health Administration, which has experienced a 3-fold increase in numbers of veterans presenting for treatment over the last 8 years.

The serotonergic reuptake inhibitors (SRI) paroxetine and sertraline are first-line medications and the only medications approved by the Food and Drug Administration (FDA) to treat PTSD. However, their efficacy is modest at best, and they are less effective for combat veterans than for civilian trauma survivors (Hertzberg et al., 2000). SRIs may have limited efficacy for PTSD for a number of reasons (Friedman, 2013): SRIs are nonspecific in their actions and were chosen because they are effective in other disorders such as major depression, rather than based on an understanding of the neurobiology of PTSD.

In contrast, the use of adrenergic agents to treat PTSD represents a rational approach based on preclinical and clinical neurobiological findings. The noradrenergic system is thought to play an integral role in the development and maintenance of PTSD (Southwick et al., 1999). The data from both preclinical and clinical studies are compelling and include evidence for heightened physiologic responsivity to trauma-related cues, elevated 24-hour urinary noradrenaline (NE) excretion, elevated plasma NE, and increased cere-

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