ORIGINAL RESEARCH

Key Words: posttraumatic stress disorder, guanfacine, noradrenergic, norepinephrine, pharmacologic treatment

A Placebo-Controlled Trial of Guanfacine for the Treatment of Posttraumatic Stress Disorder in Veterans

By Lori Davis, MD, L. Charles Ward, PhD, Ann Rasmusson, MD, Jason M. Newell, PhD, Elizabeth Frazier MS, and Steven M. Southwick, MD

ABSTRACT ~ Objective: *Preclinical and clinical studies demonstrate a hyperactivity of the norepinephrine system in patients with posttraumatic stress disorder (PTSD). α(2) adrenergic agonists have been shown to ameliorate symptoms of PTSD, likely because of their ability to dampen noradrenergic tone. This study tests the ability of the α(2) adrenergic agonist, guanfacine, to reduce the symptoms of PTSD.* ***Experimental Design:*** *Patients with chronic PTSD were randomized (1:1) to an 8-week double-blind, placebo-controlled treatment of guanfacine followed by a 2–month, open-label extension phase. Patients were maintained on their stable doses of allowed antidepressants during the trial. Efficacy was measured by the following assessment scales: Clinician Administered PTSD Scale (CAPS), Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), and Davidson Trauma Scale (DTS, self-report).* ***Principal Observations:*** *There were no significant differences in the drug versus placebo responses for the clinician-administered or patient self-report outcome measures in this small sample of predominantly male combat veterans with PTSD. However, the medication was well tolerated.* ***Conclusion:*** *Similar to previous findings, this small pilot study failed to show differences in the response to guanfacine versus placebo in a small sample of predominantly male combat veterans with PTSD.* Psychopharmacology Bulletin. *2008;41(1):8-18.*

Dr. Davis is affiliated with VA Medical Center, Tuscaloosa, AL and is also affiliated with University of Alabama School of Medicine, Department of Psychiatry, Birmingham and Tuscaloosa, AL. Dr. Ward is affiliated with VA Medical Center, Tuscaloosa, AL. Dr. Rasmusson is affiliated with Boston VA Healthcare System, Boston, MA, VA Connecticut Health Care System, West Haven, CT, and Department of Psychiatry, Yale University, New Haven, CT. Mr. Newell is affiliated with VA Medical Center, Tuscaloosa, AL and is also affiliated with The University of Alabama School of Social Work, Tuscaloosa, AL. Ms. Frazier is affiliated with VA Medical Center, San Francisco, California. Dr. Southwick is affiliated with VA Connecticut Health Care System, West Haven, CT is also affiliated with Department of Psychiatry, Yale University, New Haven, CT.

To whom correspondence should be addressed: Lori L. Davis, MD, VA Medical Center (151), 3701 Loop Road East, Tuscaloosa, AL 35404, USA; Tel: 205-554-2000; Fax: 205-554-2877; E-mail: lori.davis@med.va.gov

INTRODUCTION

There is extensive preclinical and clinical evidence that supports noradrenergic (NE) dysregulation in the pathophysiology of posttraumatic stress disorder (PTSD).[1–5] Rigorous psychophysiologic studies have clearly demonstrated heightened sympathetic nervous system arousal in patients with PTSD,[6] including higher 24-h urinary NE excretion in combat veterans with PTSD compared to controls,[1] a significant downregulation of platelet α(2) adrenergic receptors in combat veterans with PTSD compared to normal controls,[7] and increased flashbacks and panic attacks following a pharmacologic challenge with yohimbine, an α(2) adrenergic antagonist that increases NE release.[8]

Medications that dampen the centrally hyperactive NE state can be beneficial in the treatment of PTSD, including those that decrease NE release (i.e., centrally acting α(2) agonists such as clonidine and guanfacine)[9,10] and those which block postsynaptic NE receptors (e.g., centrally acting α(1) or β receptor antagonists such as prazosin or propranolol).[11–13]

Based on the previous research described earlier, clinical investigators have hypothesized that guanfacine may be as efficacious in reducing PTSD symptoms. Clinically, guanfacine has demonstrated efficacy in other conditions involving catecholamine dysregulation, including some forms of hypertension[14] and attention-deficit hyperactivity disorder.[15–17] To date, there have been case studies describing amelioration of PTSD-related nightmares and other sleep disturbances with guanfacine treatment.[18,19] More recently, an 8-week, double-blind, placebo-controlled trial of guanfacine for the treatment of PTSD was conducted by Neylan et al.[20] in a sample of veterans with chronic PTSD, who were either medication-free or on stable pharmacotherapy. The results of this study failed to show significant differences between guanfacine and placebo in improving the symptoms of PTSD, sleep quality, or general mood.

This paper is a report of a placebo-controlled study of guanfacine as either monotherapy or as an adjunctive medication to SSRI treatment for PTSD in veterans. The study was conducted simultaneously to the Neylan et al.[20] study and serves as an additional and independent examination of the potential efficacy of guanfacine in treating PTSD.