

ORIGINAL RESEARCH

Key Words: PTSD, aripiprazole, atypical antipsychotics

Prospective Study to Evaluate the Efficacy of Aripiprazole as a Monotherapy in Patients with Severe Chronic Posttraumatic Stress Disorder: An Open Trial

By Gerardo Villarreal, MD, Lawrence A. Calais, RN, CCRC, Jose M. Cañive MD, S. Laura Lundy, BS, Jacob Pickard, MA, and Gregory Toney, PharmD

ABSTRACT ~ The objective of the study was to assess the efficacy and safety of aripiprazole in outpatients with posttraumatic stress disorder (PTSD) on a 12-week, open-label trial. Twenty-two subjects with DSM-IV diagnosis of PTSD participated; 16 were combat veterans. The primary outcome measure was PTSD symptom severity assessed with the Clinician Administered PTSD Scale (CAPS). Secondary outcome measures included the Positive and Negative Symptoms Scale and the Hamilton Depression and Anxiety Scales. All subjects had a CAPS score of ≥ 60 at baseline. Lifetime history of psychotic disorders or bipolar illness was exclusionary. The overall analysis across time was Repeated Measures ANOVA, using Bonferroni corrections. Fourteen subjects completed 12 weeks of treatment. Eight subjects dropped-out due to side effects. For patients who discontinued, missing values were estimated using "the last observation carried forward" method. Significant improvements were seen on: CAPS total, all its subscales, positive symptoms, anxiety and depression scores. Fourteen participants were classified as responders, defined by 20% or greater improvement on CAPS total score. Of the 13 subjects who completed final ratings, CAPS total scores improved significantly ($P = .011$). Two subjects attained remission of PTSD ($CAPS < 20$), and three had a final $CAPS \leq 26$. The mean daily dose of aripiprazole was 12.95 mg. The most common side effects were somnolence

Dr. Villarreal and Dr. Cañive are affiliated with the PTSD Program, New Mexico VA Health Care System, Albuquerque, New Mexico, USA and Departments of Psychiatry and Neurosciences, University of New Mexico School of Medicine, Albuquerque, New Mexico. Mr. Calais is affiliated with Biomedical Research Institute of New Mexico, Albuquerque, New Mexico, USA. Ms. Lundy is affiliated with Department of Psychology, University of New Mexico, Albuquerque, New Mexico, USA. Mr. Pickard is affiliated with Department of Psychology, University of South Dakota, Vermillion, South Dakota, USA. Dr. Toney is affiliated with PTSD Program, New Mexico VA Health Care System, Albuquerque, New Mexico, USA.

To whom correspondence should be addressed: José M. Cañive, MD, Director of Psychiatry Research, New Mexico VA Health Care System (116A), 1501 San Pedro SE, Albuquerque, NM 87108, USA; Tel: (505) 265-1711 ext. 2133; Fax: (505) 256-5474; E-mail: jose.canive@va.gov

ARIPRAZOLE IN PTSD

(54.5%), restlessness (50%), insomnia (36.4%), and asthenia (31.8%). These results indicate that aripiprazole was effective in about two thirds of subjects that tolerated this medication. The initially high dropout rate may be related to intolerability due to a high starting dose (10 mg), suggesting beginning treatment at lower doses. These preliminary results are encouraging; a double blind study seems warranted. *Psychopharmacology Bulletin*. 2007;40(2):6-18.

INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is a common anxiety condition that affects individuals who have been exposed to psychological trauma, such as combat or rape. Characteristic symptoms encompass reexperiencing memories of traumatic events, persistent avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent hyperarousal.¹ The general population lifetime prevalence of PTSD is <8% or up to 25 million individuals in the United States,² while the lifetime prevalence of PTSD among Vietnam combat veterans is about 30%.³ A recent reanalysis of the National Vietnam Veterans Readjustment Study (NVVRS) adjusted the lifetime prevalence of PTSD among Vietnam veterans at 18.7% with 9.1% who are currently suffering from PTSD.⁴ PTSD has a significant impact on a person's well being and is often associated with increased health service utilization, poor social and occupational functioning, and substantial cost to society, especially among people who experience combat trauma or sexual assault.⁵⁻⁷ Hoge and et al.⁸ in their recent survey reported that 12.2-12.9% of active-duty veterans returning from Iraq met screening criteria for PTSD as compared with their Afghanistan counterparts (6.2%) that correlated directly with rates of combat exposure. Treatment guidelines for PTSD cite a group of selective serotonin reuptake inhibitor (SSRI) antidepressants as the first line of treatment.^{9,10} Currently, there are two SSRI (sertraline and paroxetine) that are U.S. FDA-approved for PTSD.¹⁰ However, many chronic PTSD patients, especially male combat veterans, have a partial or minimal response to antidepressants.¹¹⁻¹⁴ These studies underscore that PTSD among combat veterans is difficult to treat and often requires additional psychotropic medications.^{11,15} In addition, there is an evidence that 36-46% of patients with PTSD also suffer from psychotic symptoms.¹⁶⁻¹⁹

There is an increasing interest in the use of atypical antipsychotics (AAP) to treat PTSD. A series of double-blind, placebo-controlled studies of AAP as adjunct treatment in PTSD report benefit from risperidone.²⁰⁻²³ Only one of these studies focused on PTSD patients with psychotic symptoms.²¹ An 8-week, double-blind, placebo-

7

Villarreal, Calais,
Canive, et al.

ARIPIPRAZOLE IN PTSD

controlled study demonstrated that adjunctive olanzapine was effective in reducing PTSD symptoms and depression in combat veterans with PTSD without psychotic symptoms who had minimal response to an SSRI.²⁴ Open-label trials of risperidone,²⁵ olanzapine,²⁶ and quetiapine²⁷ also reported beneficial effects. In another study, olanzapine was not superior to placebo.²⁸

PTSD is probably associated with abnormalities in serotonin, norepinephrine, and dopamine systems, among others.²⁹ Aripiprazole is a novel and efficacious antipsychotic with 5-HT_{2A} antagonist effect and partial agonist activity at the 5-HT_{1A} and D₂ receptors, which may confer a favorable effect on anxiety along with less extrapyramidal symptoms.^{30,31} Aripiprazole has been proven effective in schizophrenia and was not associated with extrapyramidal side effects, prolactin elevation, weight gain, or QT_c interval prolongation as compared with placebo.^{32,33} A recent report indicated that four out of five PTSD cases benefited from open-label aripiprazole treatment,³⁴ indicating the potential usefulness of this medication in PTSD. The pharmacological profile of aripiprazole, the insufficient evidence about its efficacy in PTSD and the hopes that it may be an effective compound among veterans who appear not to respond to FDA-approved agents led us to study its efficacy in PTSD in the hopes of eventually conducting a double-blind study. To our knowledge, this is the first monotherapy design clinical trial of aripiprazole using standardized rating scales in the treatment of PTSD. We report the results of a twelve-week, open-label, flexible dose trial of aripiprazole monotherapy conducted to assess its efficacy in core PTSD symptoms and associated psychiatric symptoms, including anxiety, depressive and positive psychotic symptoms.

8

Villarreal, Calais,
Canive, et al.