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Research paper

Failed efficacy of ziprasidone in the treatment of post-traumatic stress disorder

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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) is a chronic anxiety disorder that is often difficult to treat. Patients suffering from PTSD often fail to respond to antidepressants and may have a high incidence of positive symptoms of psychosis, though antipsychotic medications have been minimally studied in this population. The aim of this study was to assess the impact of the atypical antipsychotic ziprasidone (Geodon) on PTSD symptom clusters, as well as comorbid major depressive disorder. To our knowledge, this is the first completed randomized controlled trial investigating the potential efficacy and tolerability of ziprasidone in patients with chronic PTSD.

Methods: We conducted a 9-week prospective, randomized, double-blind, placebo-controlled trial of ziprasidone in 30 patients diagnosed with PTSD and comorbid depression. After screening and randomization, patients completed nine weekly study visits at which treatment safety and efficacy were evaluated. Primary measures of efficacy included total and subscale scores from the Clinician-Administered PTSD Scale (CAPS), while the Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Scale (HAM-A), Clinical Global Impression (CGI), and Treatment Outcome PTSD Scale (TOP-8) were implemented as secondary efficacy measures.

Results: We observed no significant effect of treatment on reduction of PTSD or depression symptoms from pre- to post-treatment.

Conclusions: Our findings suggest that ziprasidone treatment may not significantly improve symptoms of PTSD or comorbid depression, though further study is needed.

1. Introduction

Post-traumatic stress disorder (PTSD) is a chronic anxiety disorder with a high lifetime prevalence of 7.8% (10.4% for women and 5% for men) [1] that is often difficult to treat. PTSD is characterized by symptoms in three clusters: intrusive, avoidant, and hyperarousal. The intrusive symptom cluster, which includes flashbacks, nightmares, intrusive thoughts, and physiological and psychological arousal upon reminders of the trauma, is considered unique to PTSD and not seen in any other psychiatric condition. Additionally, the intrusive symptom cluster has proved difficult to treat successfully with conventional psychotherapeutic and pharmacotherapeutic approaches.

Presently, two medications, sertraline (Zoloft) [2,3] and paroxetine (Paxil) [4,5] have U.S. Food and Drug Administration (FDA) approval for the indication of treating PTSD. Unfortunately, many patients with PTSD are unresponsive, have only moderate or marginal responses, or have troubling side effects to first-line selective serotonin reuptake inhibitor (SSRI) treatment. In addition, current SSRI trials have found that more than 50% of patients still have significant residual symptoms, which can be highly incapacitating.

Recent studies suggest that patients suffering from combat-associated PTSD may have a high incidence of positive symptoms of psychosis [6–9], and these patients especially frequently fail to

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respond to antidepressants. Antipsychotic medications have been minimally studied; however, some research suggests their usefulness in PTSD patients with marked paranoia, anger, and/or flashbacks [10–13]. That hypothesis is also supported by biological study findings of abnormal dopamine function [14] and reports of elevated peripheral (urinary and plasma) dopamine levels in PTSD patients [15].

Ziprasidone (Geodon) is a new-generation (atypical) antipsychotic with a benign side effect profile (e.g., extrapyramidal side effects comparable to placebo). To date, there is little evidence concerning the efficacy and tolerability of ziprasidone in PTSD, though one report [16] suggests that ziprasidone can be effective and well tolerated in this population. There is one reported randomized placebo-controlled trial of ziprasidone as add-on to SSRI treatment for PTSD [17], though the trial was terminated early, making it difficult to draw conclusions regarding the efficacy of ziprasidone.

We conducted a 9-week, prospective double-blind trial of ziprasidone specifically designed to assess the impact of ziprasidone on PTSD symptom clusters. Also, as PTSD has an extensive comorbidity with major depressive disorder [18], the clinical trial of ziprasidone in PTSD was intended to help delineate its potential antidepressant spectrum of efficacy and anxiolytic profile. To our knowledge, this is the first completed randomized controlled trial investigating the potential efficacy and tolerability of ziprasidone in patients with chronic PTSD.

2. Materials and methods

2.1. Participants

Participants were recruited from the outpatient mental health clinic at Creighton University and community referrals. The diagnosis of PTSD was made during a comprehensive screening evaluation for PTSD program entry. The study protocol was approved by the Creighton University Institutional Review Board. Informed consent of all participants was obtained after the nature of the procedures had been fully explained and prior to study participation.

Patients had to meet the following inclusion criteria: (1) male or female patients aged 19–64 years meeting DSM-IV criteria for PTSD; (2) competent to provide informed consent; (3) able to attend weekly clinic appointments; (4) if female, using an approved contraceptive if of childbearing potential. Patients were excluded from the study if they had any of the following: (1) history of prior treatment with ziprasidone; (2) medical condition that may prevent safe administration of ziprasidone, such as clinically significant/severe hepatic, cardiac, kidney, or pulmonary disease and seizure disorders, with the exception of childhood seizure disorders; (3) primary major psychotic disorder (i.e., schizophrenia, schizoaffective disorder, or bipolar disorder); (4) suicidal or homicidal ideation or other clinically significant dangerousness; (5) change in psychotropic medication within 90 days of study entry.

2.2. Study procedures

During the screening evaluation, patients received a comprehensive psychiatric evaluation, as well as a physical examination and urine drug screen. Laboratory tests (clinical chemistry and hematology) were also performed if indicated by the patient's medical history. Patients who met eligibility criteria were randomized either to ziprasidone group or placebo group. Patients completed a total of nine weekly study visits and were provided with a pager number to contact the study coordinator 24 h per day for adverse event reporting. The beginning dose of ziprasidone was 20 mg administered twice daily. The dose was increased in 20 mg increments twice daily, up to 80 mg twice daily. Concomitant antidepressant and other psychotropic (including antipsychotic) medications were permitted if they were maintained at a constant dose for at least 3 months before baseline visit.

2.3. Assessment of effectiveness

The primary outcome measure was the Clinician-Administered PTSD Scale (CAPS), which was administered at study visits 1, 7, and 9. The CAPS is a clinician-administered scale used to assess the core PTSD symptoms of the DSM-IV. Higher scores on the CAPS indicate greater severity of PTSD symptoms. The primary efficacy variable was the change from visit 1 (baseline) to visit 9 (endpoint) in the global scores on the CAPS. Clinically significant improvement on the CAPS score was defined a priori as at least a 50% decrease from baseline to endpoint. We also examined the number of patients showing at least a 30% decrease on the CAPS over the course of the study.

The Hamilton Anxiety Scale (HAM-A), Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression (CGI), and Treatment Outcome PTSD Scale (TOP-8) were administered as secondary outcome measures at each study visit. Higher scores on the HAM-A reflect greater severity of anxiety symptoms, while higher scores on the HAM-D reflect greater severity of depression symptoms. The CGI is a clinician-administered scale with two items used to rate illness severity (CGI-S) and global improvement from baseline (CGI-I). Higher scores on the CGI-S reflect greater illness severity, while lower scores on the CGI-I indicate greater improvement. Higher scores on the TOP-8 reflect greater severity of PTSD symptoms. Utilizing the secondary measures, the data also helped to determine whether the improvement in PTSD symptoms was entirely a function of treating depression and/or anxiety symptoms, or whether there were additional effects on PTSD. The change from baseline to endpoint was measured. At the end of the acute phase, patients who elected to continue in treatment in the research clinic were administered open-label ziprasidone at individual doses for an additional 12 weeks.

2.4. Assessment of safety and tolerability

Adverse events and vital signs were evaluated at each visit. Each patient had a pager number to contact the study coordinator 24 h per day for adverse event reporting.

2.5. Statistical analyses

Categorical data, including demographics, were assessed with descriptive statistics. Treatment group was compared over time with repeated measures, mixed-effects models. The outcome measures of interest were total CAPS score, and CAPS B (Intrusion), C (Avoidance), and D (Hyperarousal) subscale scores. The repeated measures model included treatment, visit (as a categorical variable), and treatment*visit interaction fixed effects. An unstructured covariance matrix was used to fit the within-patient repeated measures. Pairwise comparison p-values from the mixed models were adjusted with Tukey's method. Fisher's exact test was also used to compare treatment response between groups.

Paired t-tests were used to compare the change on secondary efficacy measures between the treatment groups from baseline to visit 9. For the primary outcome variable a p-value less than 0.05 is considered to be statistically significant, while other statistical comparisons are exploratory. SAS software version 9.1 (SAS Institute, Cary, NC) was used for the analyses.