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Efficacy of ziprasidone monotherapy in patients with anxious depression: A 12-week, randomized, double-blind, placebo-controlled, sequential-parallel comparison trial

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ABSTRACT

Anxious depression, defined as major depressive disorder (MDD) accompanied by high levels of anxiety, seems to be difficult to treat with traditional antidepressant monotherapy. The purpose of this study was to assess the efficacy of ziprasidone monotherapy in patients with anxious depression versus non-anxious depression. One hundred and twenty outpatients were enrolled in a 12-week study that was divided into two 6-week periods according to the sequential parallel comparison design. Patients were randomized in a 2:3:3 multi-ratio to receive ziprasidone for 12 weeks, placebo for 6 weeks, followed by ziprasidone for 6 weeks, or placebo for 12 weeks. Efficacy was measured according to the 17-item Hamilton Depression Rating Scale (HRDS-17), Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR). Anxious depression was defined as a score of $\geq$7 on the HDRS-17 anxiety/somatization subscale. In phase I and II, ziprasidone monotherapy led to no significant changes compared with placebo on the HDRS-17 and QIDS-SR scores in patients with both anxious and non-anxious depression. In the pooled analysis, ziprasidone monotherapy also produced no significance on the HDRS-17 ($Z = 0.25$, $P = 0.80$) and QIDS-SR ($Z = 0.43$, $P = 0.67$) in patients with anxious depression. In conclusion, treatment with ziprasidone monotherapy may produce no significant improvement compared with placebo in patients with in anxious depression.
Trial registration: ClinicalTrials.gov identifier: NCT00555997.

1. Introduction

Major depressive disorder (MDD) consists of heterogeneous subtypes that are related to treatment outcome (Vrieze et al., 2014). Anxious depression, is defined as MDD accompanied by a high level of anxiety, nervousness, and the somatic correlates of these states (Fawcett and Kravitz, 1983), and is found in about half of MDD patients (Fava et al., 2004). The DSM-5 classification added 'anxious distress specifier' to MDD diagnosis (American Psychiatric Association, 2013). The presence of anxious depression has been associated with greater severity of depressive illness and functional impairment (Joffe et al., 1993), higher suicide risk (Tollefson et al., 1994), and poorer response to antidepressants, including significantly lower response and remission rates, more frequent and intense side effects, despite changes in medication or augmentation techniques (Fava et al., 2008; Papakostas et al., 2012a; Papakostas and Larsen, 2011; Seo et al., 2011).

Ziprasidone is an atypical antipsychotic with several pharmacologic properties suggestive of antidepressant actions, including 5-HT_{2A}, 5-HT_{2C}, 5-HT_7, 5-$HT_{1B/D}$ and α_2 antagonism and dopaminergic receptor antagonism. It additionally inhibits norepinephrine and serotonin reuptake (Nemeroff et al., 2005; Stahl and Shayegan, 2003). Ziprasidone possesses a high 5-HT2A/D2 affinity ratio (Richelson and Souder, 2000; Tatsumi et al., 1999) and acts as a 5-HT_{2A} receptor antagonist. Ziprasidone additionally acts as a 5-HT_{1A} receptor partial agonist. 5-HT_{1A} receptor partial agonists have

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demonstrable antianxiety and antidepressant properties (Robinson et al., 1990). Ziprasidone appears to be suited for study as monotherapy in anxious depression, since it has a unique affinity for several monoaminergic receptors and transporters. However, no previous clinical trials have examined the effect of ziprasidone monotherapy in anxious depression patients.

The purpose of the present study was to examine the comparative efficacy of ziprasidone monotherapy for treatment of patients with anxious depression and non-anxious depression.

2. Methods

This study involved a post-hoc analysis utilizing data from a 12-week, multicenter, randomized, double-blind, placebo-controlled, SPCD trial of oral ziprasidone monotherapy for MDD (ClinicalTrials.gov identifier: NCT00555997) (Papakostas et al., 2012b). The results of the original study were reported elsewhere (Papakostas et al., 2012b). The original study involved enrollment of 120 patients with MDD from 8 centers in the United States. Institutional review board–approved written informed consent was obtained from all study patients before commencing the study. Eligibility was assessed by trained psychiatrists, primarily, during the screening visit, and, secondarily, during the baseline visit, which occurred 14 days after the screening visit.

Anxious depression was defined as a score of $\geq$7 on the anxiety/somatization subscale of 17-item Hamilton Depression Rating Scale (HRDS-17) (Fava et al., 2011; Ionescu et al., 2013). The anxiety/somatization subscale were derived from a factor analysis of the HDRS-17 scale conducted by Cleary and Guy (Cleary and Guy, 1977), which includes 6 items from the original 17-item version: item 10 – Anxiety (psychic); item 11 – Anxiety (somatic); item 12 – Somatic Symptoms (Gastrointestinal); item 13 – Somatic Symptoms (General); item 15 – Hypochondriasis; item 17 – Insight.

3. Inclusion criteria

Patients were eligible for study participation according to the following inclusion criteria: aged 18–65 years; satisfied MDD criteria during the screening and baseline visits, per the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), and scored at least 14 on the HDRS-17 (Hamilton, 1960) and 10 on the Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR) (Trivedi et al., 2004) at the baseline visits.

4. Exclusion criteria

Patients were excluded from the study if they were on antidepressants, antipsychotic, or anticonvulsant agents up to 2 weeks prior to the screening visit and if they had been taking lithium for up to 2 weeks prior to the screening visit. Patients receiving psychotherapy were also excluded. Breastfeeding women, pregnant women, and women of childbearing potential who were not using a medically accepted means of contraception were excluded, as well as patients who demonstrated a >25% decrease in depressive symptoms as reflected by the QIDS-SR total score between the screening and baseline visits. Patients who were at serious risk for suicide or homicide, had unstable medical illness as assessed by an evaluating clinician, or had active alcohol or drug use disorders within the month prior to screening were also excluded. Furthermore, patients with a history of mania, hypomania (including antidepressant-induced), psychotic symptoms, or seizure disorders were excluded.

Also excluded were patients who had failed to experience sufficient symptom improvement following more than 2 antidepressant trials during a current major depressive episode, who had a course of ziprasidone or intolerance to ziprasidone at any dose, or who had used any investigational psychotropic drug within the prior 3 months.

5. Study procedures

Once patients agree to participate in the study by signing the informed consent document, a full medical and psychiatric history will be taken and a physical examination will be performed. Screen rating scales will be performed. Screened and eligible patients will be asked to return two weeks later for a baseline visit when they will be randomized to double-blind treatment with placebo or ziprasidone. The 12-week, double blind treatment was divided into 2 phases of 6 weeks in accordance with the SPCD design (Fava et al., 2003) (Fig. 1). During the first phase of double-blind treatment, eligible patients were randomized to 6 weeks of treatment with either ziprasidone (n = 29) or placebo (n = 91), using a 2:3:3 multiratio for random assignment to the following treatment sequences: drug/drug, placebo/placebo, and placebo/drug. Post-baseline study visits occurred every 7 days, with a study visit window of ±3 days. Ziprasidone was initiated at 20 mg orally, twice a day and increased, at the treating psychiatrist's clinical discretion, by weekly increments of 20 mg orally, twice a day up to a maximum of 80 mg orally, twice a day. Decreases in the ziprasidone dose were allowed if the patient showed intolerance. However, subjects who were unable to tolerate ziprasidone at the minimum 20 mg orally, twice a day, were withdrawn from the study. Placebo-treated subjects followed a similar titration schedule. Trained psychiatrists administered the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) at the baseline visit, and the HDRS-17 (Hamilton, 1960) and QIDS-SR (Trivedi et al., 2004) during all post-screening visits. For the purposes of the present, post-hoc analysis, patients were dichotomized into 2 groups: anxious and non-anxious depression at baseline. The primary and secondary outcome measures for this analysis were differences in the degree of change in the HDRS-17 and QIDS-SR scores, respectively, between ziprasidone- and placebo-treated patients.

6. Statistics

SPCD is a clinical trial design paradigm aimed at reducing both the placebo response rate and sample size requirement (Fava et al., 2003). The basic idea is to have 2 phases of treatment. The first phase involves an unbalanced randomization between placebo and active treatment with more patients randomized to placebo. Non-responders treated with placebo are re-randomized in the second phase to either active treatment or placebo.

The subjects were divided into 2 groups, anxious and non-anxious depression, and SPCD analyses were applied to compare efficacy of drug and placebo in each group. A standard, intent-to-treat (ITT)/last-observation-carried forward (LOCF) analysis approach was employed for phase I. According to the SPCD model, the phase II dataset of interest was limited to patients treated with placebo during phase I, who had completed phase I and had no clinical response (response defined as a reduction of $\geq$50% from baseline and scoring at least 14 on the HDRS-17 and 10 on the QIDS-SR). In the phase II, non-responders treated with placebo are re-randomized to either active treatment or placebo. Since patients on the second phase have already 'failed placebo', their placebo response will be reduced. The ITT/LOCF approach was then applied to the analysis of the phase II dataset, as defined by the SPCD, with the final visit of phase I/first visit of phase II serving as the baseline