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Brief report

Characterizing relapse prevention in bipolar disorder with adjunctive ziprasidone: Clinical and methodological implications

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ABSTRACT

Background: Ziprasidone, adjunctive to either lithium or valproate, has previously been shown to be associated with a significantly lower risk of relapse in bipolar disorder compared with lithium or valproate treatment alone.
Methods: This placebo-controlled outpatient trial with ziprasidone adjunctive to lithium or valproate or lithium and valproate alone, for subjects with a recent or current manic or mixed episode of bipolar I disorder, comprised a 2.5- to 4-month, open-label stabilization period, followed by a 6-month, double-blind maintenance period. These post hoc analyses characterize the relapse outcomes by dose, relapse types and timing as well as all-reason discontinuations during the maintenance period.
Results: Time to relapse and all-reason discontinuation were both statistically significant in favor of the ziprasidone 120 mg/day group compared with placebo ($p=0.004$ and 0.001, respectively) during the 6-month double-blind period. There was no difference in time to relapse in the 80 and 160 mg/day dose groups compared with placebo ($p=0.16$ and 0.40, respectively) and, likewise, for time to all-reason discontinuation ($p=0.20$ for both doses). The majority of relapses in each group occurred prior to week 8, and most were depressive in nature.
Limitations: The primary study was not designed to compare relapse rates by dose groups.
Conclusions: These analyses confirm the effectiveness of ziprasidone (80–160 mg/day) in preventing relapses in subjects with bipolar disorder, with the 120 mg/day dosage appearing to have the highest relapse prevention rate.

1. Introduction

Only 30% of bipolar patients on mood stabilizer monotherapy experience long-term symptom control (Bowden, 2005). Atypical antipsychotics can be effective as concomitant therapy with mood stabilizers and are recommended by the American Psychiatric Association guidelines as add-on therapy in bipolar disorder for partial responders (American Psychiatric Association, 2002; Miller et al., 2001).

Ziprasidone is an atypical antipsychotic with established efficacy as monotherapy in acute bipolar, manic or mixed episodes (Keck et al., 2003, 2009; Potkin et al., 2005; Vieta et al., 2010). In a long-term study in bipolar disorder, ziprasidone plus lithium or valproate significantly reduced the risk of relapse compared with lithium or valproate alone. Ziprasidone maintenance therapy at doses between 80 and 160 mg/day for up to 10 months was well tolerated, with no evidence of metabolic disturbances or clinically meaningful weight gain (Bowden et al., 2010).

2. Objective

These post hoc analyses explore relapse events and baseline disease severity by dose and characterize the timing and types of relapse by dose observed for ziprasidone adjunctive to lithium or valproate in subjects with bipolar disorder in a 6-month maintenance trial (Bowden et al., 2010).

3. Materials and methods

3.1. Study design

The methodology and primary results of this study (NCT# 00280566) have been previously published (Bowden et al., 2010).

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Briefly, this placebo-controlled outpatient trial evaluated the maintenance effects of ziprasidone in subjects (≥ 18 years) with a recent or current manic (*Diagnostic and Statistical Manual of Mental Disorders,* 4th edition [*DSM-IV*] 296.4x) or mixed (*DSM-IV* 296.6x) episode of bipolar I disorder with a Mania Rating Scale (MRS) score ≥ 14 (scores of ≥ 2 on ≥ 4 items), responding to ziprasidone plus lithium or valproate (American Psychiatric Association, 1994; Young et al., 1978). The trial comprised a 2.5- to 4-month open-label period followed by a 6-month, double-blind maintenance period. Subjects had to remain symptomatic (MRS score ≥ 14) despite therapeutic levels of lithium or valproate (lithium, 0.6–1.2 mEq/L or valproate, 50–125 μg/mL) for ≥ 2 weeks prior to study enrollment. During the open-label phase, ziprasidone (flexible dose of 80–160 mg/day, i.e., 40–80 mg twice daily) was added to this treatment regimen for up to 16 weeks.

For eligibility in the double-blind phase, subjects had to be stabilized, defined as Clinical Global Impression-Improvement (CGI-I) score ≤ 3 for 8 weeks and with stable doses of ziprasidone and lithium or valproate for at least the last 4 weeks. All stabilized subjects were randomized in the double-blind maintenance period to two groups: ziprasidone with lithium or valproate, or placebo with lithium or valproate. Subjects randomized to continue on adjunctive ziprasidone were maintained on the dose (fixed dose of 80, 120 or 160 mg/day) on which they had been stabilized, while subjects randomized to placebo had ziprasidone titrated gradually over 1 week.

Psychiatric assessment during the double-blind period was done at 1, 2, 4, 8, 12, 16, 20 and 24 weeks using the MRS scale, Montgomery–Åsberg Depression Rating Scale (MADRS) and the CGI-I scale (Guy, 1976; Montgomery and Asberg, 1979). The primary endpoint was the time to intervention for a relapse. Subjects were discontinued from the trial when they had a relapse. Relapse criteria were: the investigator decided discontinuation was in the best interests of the subject; a loss of effect and/or requirement for an alteration to the treatment regimen (in the investigator's judgment); any time a subject was hospitalized for disease under study; an MRS rating of ≥ 18 for two consecutive visits scheduled ≤ 10 day apart; or an MADRS rating of ≥ 18 for two consecutive visits scheduled ≤ 10 day apart. The key secondary endpoint was the time to all-reason discontinuation.

3.2. Statistical analyses

The intent-to-treat (ITT) analysis set was used for these post hoc analyses (unless otherwise specified) and was defined as those subjects randomly assigned to treatment within the 6-month, double-blind maintenance period who received a least one dose of study medication and had at least one postrandomization observation.

We analyzed relapses by drug and dose, all-reason discontinuations by drug, and type of relapse across treatment groups. Kaplan–Meier survival analysis was performed for each ziprasidone dose versus placebo using the Kaplan–Meier product-limit estimator and log-rank test. Baseline scores for the MRS, MADRS, and CGI-I scores were analyzed by the stabilized dose groups in the open-label period and compared using one-way analysis of variance by dose groups. Subjects were grouped according to the ziprasidone dose on which they had been stabilized within the open-label phase. For subjects who relapsed, scatter plots were generated for mixed/manic and depressive episodes depicting the time to relapse or time to all-reason discontinuation with the corresponding last observed MRS or MADRS scores. These figures also included aggregate plots presenting the cumulative proportion of relapses by dose group.

4. Results

4.1. Baseline disease severity for subsequently stabilized subjects

In the ITT analysis set ($n=238$), 127 stabilized subjects remained on ziprasidone adjunctive to lithium or valproate ($n=60$, 40 and 27 on 80, 120, or 160 mg/day ziprasidone, respectively), and 111 stabilized subjects ($n=48$, 35 and 28 on 80, 120, or 160 mg/day ziprasidone, respectively, in open-label phase) were treated with placebo adjunctive to lithium or valproate in the double-blind phase. In the open-label period, 108, 75 and 55 subjects were stabilized on adjunctive ziprasidone doses of 80, 120 and 160 mg/day, respectively, and were subsequently randomized into the double-blind period (ITT analysis set). Among these subjects, the baseline MADRS total score for the open-label period was significantly higher for the subjects stabilized on the 160 mg/day dosage compared with those stabilized on the 80 and 120 mg/day dosages ($p<0.05$; Table 1).

4.2. Rate of discontinuations and relapses by dose

The time to relapse was statistically significant in favor of ziprasidone 120 mg/day compared with placebo ($p=0.004$; Fig. 1a) based on Kaplan–Meier survival analyses. For the ziprasidone 80 and 160 mg/day dose groups it did not reach statistical significance ($p=0.16$ and $p=0.40$, respectively). All-reason discontinuations based on Kaplan–Meier survival analyses also showed a similar pattern by dose ($p=0.001$ for 120 mg/day and $p=0.20$ for both 80 mg/day and 160 mg/day; Fig. 1b). Subjects remained on ziprasidone therapy with the 120 mg/day dosage for a longer period than placebo (Fig. 1c).

4.3. Timing of discontinuations and relapses

Subjects within the placebo group were more likely to discontinue therapy for any reason than those receiving ziprasidone (Fig. 2a). By week 12, most of the discontinuations within the ITT placebo (40/57) and ziprasidone (29/43) groups had occurred. In the safety analysis set, a total of 58 subjects (52%) randomized to the placebo group discontinued therapy compared with 43 subjects (34%) randomized to the ziprasidone group. Also in the safety analysis set, the most common reason for discontinuing placebo was lack of efficacy (22 subjects), followed by adverse events (15 subjects). In comparison, 9 and 11 subjects discontinued ziprasidone therapy as a result of lack of efficacy or adverse events, respectively.

Relapse occurred in 23% of subjects receiving ziprasidone 80 mg/day (14/60), 10% receiving ziprasidone 120 mg/day (4/40), 26% receiving ziprasidone 160 mg/day (7/27), and in 32% receiving

Table 1
Open-label baseline symptom severity scores by subsequent stabilization dose groups.

	Ziprasidone open-label stabilization dose groupings					
	80 mg/day		120 mg/day		160 mg/day	
Baseline score[a]	N[b]	Mean (95% CI)	N[b]	Mean (95% CI)	N[b,c]	Mean (95% CI)
MRS	108	21.4 (20.1, 22.6)	75	21.4 (19.8, 23.1)	54	21.5 (19.7, 23.3)
MADRS	108	9.2 (7.6, 10.9)	75	9.6 (7.4, 11.7)	53	15.7 (13.4, 18.0)[d]
CGI-S	108	4.0 (3.9, 4.1)	75	4.1 (3.9, 4.3)	54	4.2 (4.0, 4.5)

CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; MRS, Mania Rating Scale.

[a] Baseline is day 1. First day of study treatment is day 1 of open-label period.

[b] Only includes subjects who were stabilized to 80, 120 and 160 mg/day ziprasidone and were in the intent-to-treat analysis set in the double-blind phase.

[c] One subject each for MRS and CGI-S and two subjects for MADRS had missing baseline scores.

[d] $p<0.05$ each when compared with 80 mg/day or 120 mg/day groups.