A Randomized, Double-Blind, Placebo-Controlled Study of Ziprasidone Monotherapy in Bipolar Disorder With Co-Occurring Lifetime Panic or Generalized Anxiety Disorder

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ABSTRACT

Objective: Bipolar disorder often co-occurs with anxiety disorders. Evidence suggests that second-generation antipsychotics (SGAs) may be useful in treating both conditions. This study examined the efficacy of ziprasidone in the treatment of these disorders.

Method: This 3-site, randomized, double-blind, placebo-controlled, parallel group, 8-week trial of ziprasidone monotherapy examined 49 subjects with bipolar disorder and lifetime panic disorder (with or without agoraphobia) or generalized anxiety disorder (GAD) experiencing moderately severe anxiety symptoms at entrance into the study. Both bipolar disorder and anxiety diagnoses were based on *DSM-IV-TR* criteria. Patients were screened and randomized from June 25, 2010, through August 23, 2011. Primary outcome measures were the Clinical Global Impressions-21 Anxiety Scale (CGI-21 Anxiety) and the Sheehan Disability Scale (SDS), with secondary measures monitoring anxiety and mood symptoms.

Results: Last-observation-carried-forward analyses demonstrated that patients in the ziprasidone group did not improve significantly more than those in the placebo group on the CGI-21 Anxiety ($F_1 = 0.34$; $P = .564$) or SDS ($F_1 = 0.26$; $P = .611$). Secondary analysis using hierarchical linear modeling found similar results (CGI-21 Anxiety: $F_1 = 1.82$; $P = .178$; and SDS: $F_1 = 0.70$; $P = .408$). Regardless of group, time in the study was associated with significant decrease in anxiety ($F_1 = 11.08$; $P = .001$) and total disability ($F_1 = 26.16$; $P < .001$). Patients in the ziprasidone group showed a greater increase in abnormal involuntary movement, and 81.8% (n = 9) of the subjects who withdrew from the study due to adverse events, serious adverse events, or side effects were in the ziprasidone group.

Conclusions: Results suggest that ziprasidone monotherapy was not associated with a clinically significant improvement in anxiety symptoms or improved function for patients with bipolar disorder, lifetime panic disorder or GAD, and concurrent moderately severe anxiety symptoms, and it was associated with a more negative side-effect profile relative to placebo.

Trial Registration: ClinicalTrials.gov identifier: NCT01172652

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The co-occurrence of bipolar disorder and anxiety symptoms has been demonstrated in epidemiologic,[1,2] clinical,[3–5] and family populations.[4,6] Research suggests that 38%–47% of bipolar patients also have an anxiety disorder.[7,8] Since bipolar disorder may be associated with impaired psychosocial functioning[9–14] even when mood episodes have remitted,[15–17] co-occurring anxiety may put individuals with bipolar disorder at an even greater risk for poor psychosocial functioning. Compared to bipolar disorder patients without anxiety, patients with co-occurring illnesses have been shown to have an earlier age at illness onset, higher rates of mixed states, depressive symptoms, suicidality, and poorer response to lithium-based treatment.[3–5] There is a need to identify agents that can meet both mood stabilizing and anxiolytic goals for patients with bipolar disorder and anxiety.

Research on the use of second-generation antipsychotics (SGAs) suggests that they may be effective at treating symptoms of anxiety in patients with bipolar disorder.[18] Change in anxiety symptoms was assessed as a secondary outcome in 2 large, placebo controlled studies[19,20] of acute bipolar depression. Recent research of patients in this population found that quetiapine extended release (XR) alone[21] and olanzapine when used in addition to lithium[22] were effective at reducing anxiety symptoms. On the other hand, a recent trial[23,24] did not find risperidone to be effective in this population. Research is needed to further study the effectiveness of SGAs that have not been previously evaluated as possible treatments for this population.

The present study investigates the usefulness of ziprasidone as a treatment for co-occurring anxiety and bipolar disorder. There are no placebo-controlled reports addressing the use of ziprasidone for co-occurring anxiety symptoms in patients with bipolar disorder. The current placebo-controlled study treated patients with bipolar disorder, a co-occurring lifetime panic or generalized anxiety disorder (GAD), and current anxiety symptoms (at least moderately severe).

METHOD

Study Design

This study (ClinicalTrials.gov identifier: NCT01172652) is a 3-site, randomized, double-blind, placebo-controlled, parallel-group, 8-week trial of ziprasidone monotherapy in outpatient subjects with lifetime bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified (NOS) and a lifetime panic disorder (with or without agoraphobia) or GAD, currently experiencing at least moderately severe anxiety symptoms (defined as a Clinical Global Impressions-21 Anxiety Scale [CGI-

21 Anxiety] score ≥ 4)[25] and not more than moderately severe bipolar symptoms (defined as a Clinical Global Impression-Bipolar Version [CGI-BP] < 4).[26]

Participants

Eighty-six subjects were consented across 3 sites: (1) Stanford University School of Medicine and VA Palo Alto Health Care System, (2) University of South Florida College of Medicine, and (3) Lindner Center of HOPE, University of Cincinnati College of Medicine. Patients were screened and randomized from June 25, 2010, through August 23, 2011. In total, 49 subjects were randomized into the study. Inclusion criteria specified subjects between the ages of 18 and 65 years; a lifetime bipolar I or II disorder or bipolar disorder NOS diagnosis according to *DSM-IV-TR* criteria, with bipolar disorder current symptoms no worse than moderately severe; and a co-occurring lifetime panic disorder or GAD according to *DSM-IV-TR* criteria, with anxiety symptoms currently at least moderately severe. Exclusion criteria included a current *DSM-IV* diagnosis of delirium or other cognitive disorders; a substance dependence disorder within the past 6 months; clinically significant suicidal or homicidal ideation; and unstable medical illness. After receiving complete description of the study, which was approved by the institutional review boards of each institution, and providing oral and written informed consent, subjects underwent medical screening and a structured clinical interview to confirm diagnoses.[27] Treatment groups were equivalent at baseline on a variety of demographic as well as outcome measures (Table 1).

Intervention

This was a monotherapy study; other than small amounts of adjunctive medication (see below), subjects were discontinued from the study if they required additional psychotropic medications due to lack of response or worsening of clinical symptoms (defined as CGI-BP rating for change of "much worse" or "very much worse," Young Mania Rating Scale (YMRS) score > 21, or Montgomery-Asberg Depression Rating Scale (MADRS) score > 40). Subjects were required to have been off of all regular mood stabilizing, antidepressant, antipsychotic, or anxiolytic medications for at least 1 week prior to baseline; patients who had previously received fluoxetine or depot antipsychotics were required to have stopped taking those medications for at least 4 weeks prior to baseline. Dosing of ziprasidone was flexible to allow for consideration of individual patient symptoms and tolerability. Each patient was required to reach a minimum dose of 120 mg/d by day 14. Allowable doses during study participation ranged from 40 mg to 160 mg per day adjusted to symptoms or side effects (after reaching the required minimum dose of 120 mg, patients could have their medication dosages adjusted back down to as low as 40 mg per day, if necessary). Adjunctive lorazepam (up to 2 mg/d) was permitted during the first 2 weeks of the study for acute management of anxiety symptoms. Zolpidem and zaleplon were permitted throughout the study for insomnia. Benztropine was permitted for management of extrapyramidal symptoms.

Clinical Points

- Anxiety and bipolar disorder often co-occur.
- Evidence suggests that some second-generation antipsychotics may be useful in treating these conditions.
- This study did not find ziprasidone monotherapy to be an effective treatment for current anxiety symptoms in patients with bipolar disorder and a lifetime history of panic disorder or generalized anxiety disorder.

Outcome Measures

Study duration was 8 weeks, and study visits occurred every week (± 3 days). Primary outcome measures were the CGI-21 Anxiety[25] and the Sheehan Disability Scale (SDS).[25] Secondary outcome measures included the 21-item Patient Global Improvement on anxiety symptoms (PGI-21),[25] the Hamilton Anxiety Rating Scale (HARS),[28] and the Sheehan Panic Scale (SPS)[25] to measure anxiety and panic symptoms and the CGI-BP,[26] the Young Mania Rating Scale (YMRS),[29] the Montgomery-Asberg Depression Rating Scale (MADRS),[30] the Sheehan Suicidality Tracking Scale,[31] and the Sheehan Irritability Scale (SIS)[25] to assess mood symptoms. At all visits, the Abnormal Involuntary Movement Scale (AIMS),[32] Simpson-Angus Scale (SAS),[33] and Barnes Akathisia Rating Scale (BARS)[34] were administered to assess extrapyramidal symptoms. Vital signs and weight were measured at every visit. All visits were conducted and measures were administered by blinded raters, who were unaware of which treatment group that each subject was in. At the end of the study, treating clinicians, blinded raters, and patients at the Palo Alto and Lindner sites recorded their impression of which treatment patients had received.

Sample Size Estimation and Randomization

This is the first prospective study to evaluate the efficacy of ziprasidone monotherapy compared with placebo in treating individuals with bipolar disorder and co-occurring anxiety symptoms, and therefore there were no published studies on which to base a power calculation. We chose a goal sample size of 25 evaluable patients per treatment arm. Using a simple *t* test on change from baseline, with a sample size of 50 patients (25/group) and $\alpha = .05$, we estimated an 80% power to detect an effect size of 0.81. Such a sample size provided us with data necessary to conduct a power analysis and calculate the sample size necessary to statistically separate active drug from placebo to inform future large-scale studies in bipolar anxiety. Participants were randomly assigned to study drug by a randomized block design.

Analyses

The primary outcome measures were the CGI-21 Anxiety and the SDS total, work, social, and family disability scores. Secondary anxiety outcome measures were the PGI-21, the

Table 1. Baseline Characteristics of Sample by Treatment Group

Characteristic	Entire Cohort (N = 49)	Ziprasidone (n = 25)	Placebo (n = 24)	Significance Test
Age at baseline, mean (SD), y	36.1 (15.2)	37.6 (17.7)	34.6 (12.2)	$F_1 = 0.477$, $P = .493$
Female gender, n (%)	36 (73.5)	19 (76.0)	17 (70.8)	$\chi^2_1 = 0.168$, $P = .682$
Weight, mean (SD), lb	181.6 (44.0)	184.4 (46.9)	178.7 (41.6)	$F_1 = 0.204$, $P = .653$
Bipolar type, n (%)				
Bipolar I disorder	34 (69.4)	15 (60.0)	19 (79.2)	$\chi^2_2 = 7.329$, $P = .026$ (Fisher exact test)*
Bipolar II disorder	9 (18.4)	8 (32.0)	1 (4.2)	
Bipolar disorder NOS	6 (12.2)	2 (8.0)	4 (16.7)	
Race, n (%)				
White	37 (75.5)	21 (84)	16 (66.7)	$\chi^2_1 = 1.989$, $P = .158$
Other	12 (24.5)	4 (16)	8 (33.3)	
Ethnicity, n (%)				
Non-Hispanic or Latino	40 (81.6)	21 (84)	19 (79.2)	$\chi^2_1 = 0.191$, $P = .725$ (Fisher exact test)
Hispanic or Latino	9 (18.4)	4 (16)	5 (20.8)	
Marital status, n (%)				
Married or living with significant other	9 (81.6)	3 (12)	6 (25)	$\chi^2_1 = 1.380$, $P = .289$ (Fisher exact test)
Single, divorced, widowed, or separated	40 (81.6)	22 (88)	18 (75)	
Education, n (%)				
High school diploma or less	22 (44.9)	14 (56)	8 (33.3)	$\chi^2_2 = 2.644$, $P = .267$ (likelihood ratio test)
Some college to BS/BA	25 (51.0)	10 (40)	15 (62.5)	
More than 4-year degree	2 (4.1)	1 (4)	1 (4.2)	
Employment status, n (%)				
Self-employed, part-time, or full-time	15 (30.6)	6 (24)	9 (37.5)	$\chi^2_1 = 1.051$, $P = .305$
Not employed	34 (69.4)	19 (76)	15 (62.5)	
Sheehan Disability Scale (SDS), mean (SD)				
Total score	15.59 (6.78)	14.92 (8.04)	16.29 (5.25)	$F_1 = 0.496$, $P = .485$
Work/school score	5.14 (3.23)	5.11 (3.77)	5.17 (2.66)	$F_1 = 0.003$, $P = .955$
Social score	5.71 (2.72)	5.68 (3.24)	5.75 (2.13)	$F_1 = 0.008$, $P = .929$
Family/home score	6.00 (2.78)	5.36 (3.00)	6.67 (2.41)	$F_1 = 2.815$, $P = .100$
Sheehan Panic Scale score, mean (SD)	41.76 (20.30)	42.72 (22.58)	40.75 (18.05)	$F_1 = 0.113$, $P = .738$
Hamilton Anxiety Scale score, mean (SD)	21.67 (7.96)	22.80 (8.25)	20.50 (7.64)	$F_1 = 1.022$, $P = .317$
Young Mania Rating Scale score, mean (SD)	9.35 (6.04)	9.18 (6.24)	9.47 (6.09)	$F_1 = 0.015$, $P = .904$
Sheehan Suicide Tracking Scale score, mean (SD)	1.04 (1.81)	1.56 (2.20)	0.48 (1.04)	$F_1 = 4.609$, $P = .037$*
Sheehan Irritability Scale score, mean (SD)	46.31 (13.15)	45.92 (15.35)	46.71 (10.70)	$F_1 = 0.043$, $P = .836$
Montgomery-Asberg Depression Rating Scale score, mean (SD)	24.65 (8.88)	24.96 (8.84)	24.33 (9.09)	$F_1 = 0.060$, $P = .808$
Clinical Global Impressions-Bipolar Version	3.49 (0.96)	3.40 (0.91)	3.58 (1.02)	$F_1 = 0.441$, $P = .510$
Abnormal Involuntary Movement Scale score, mean (SD)	0.08 (0.34)	0 (0)	0.17 (0.48)	$F_1 = 2.997$, $P = .090$
Simpson-Angus Scale score, mean (SD)	0.02 (0.04)	0.02 (0.05)	0.01 (0.03)	$F_1 = 1.683$, $P = .201$
Barnes Akathisia Rating Scale total score for objective and subjective akathisia	0.43 (0.87)	0.52 (0.92)	0.33 (0.82)	$F_1 = 0.564$, $P = .457$
Barnes Akathisia Rating Scale global clinical assessment of akathisia	0.18 (0.53)	0.50 (0.20)	0.56 (0.17)	$F_1 = 0.048$, $P = .828$
Clinical Global Impressions-Severity of Illness scale score, mean (SD)	4.33 (1.00)	4.44 (1.19)	4.21 (0.78)	$F_1 = 0.642$, $P = .427$

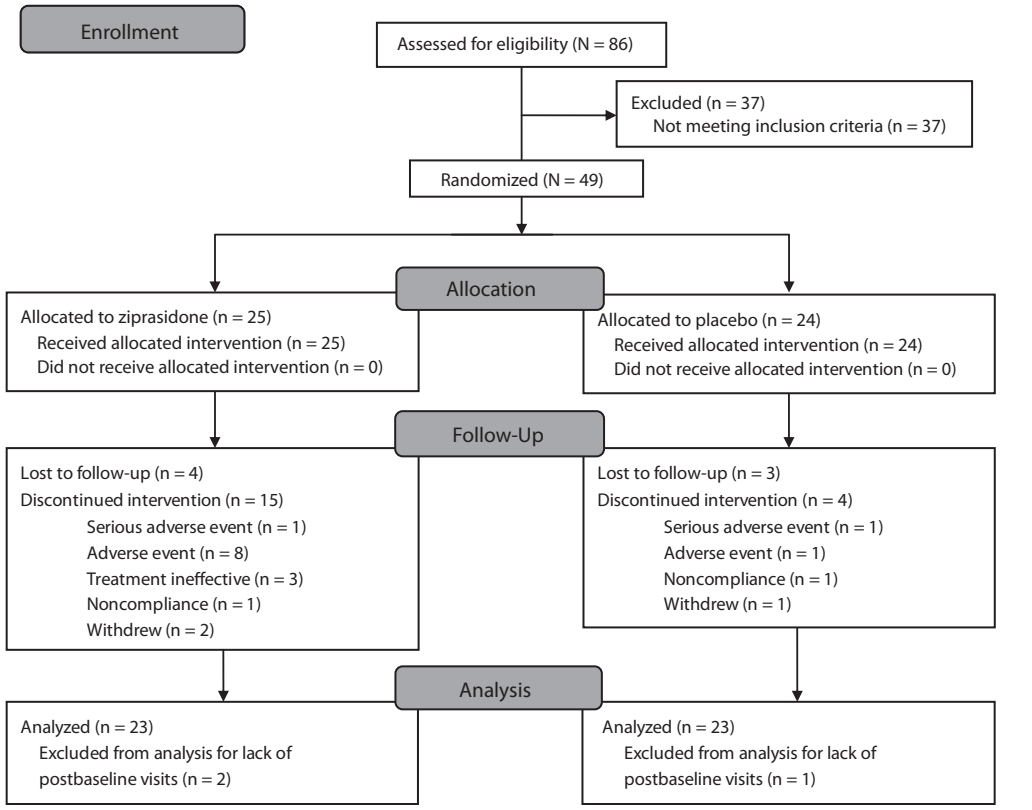
*Significant at $P < .05$.
Abbreviations: BA = bachelor of arts, BS = bachelor of science, NOS = not otherwise specified.

HARS, and the SPS. Secondary mood outcome measures included the CGI-BP, the YMRS, the MADRS, the Sheehan Suicidality Tracking Scale, and the SIS. The AIMS, the SAS, and the BARS were used to measure side effects including extrapyramidal symptoms and akathisia.

Efficacy analyses were based on the intent-to-treat population (ITT) (N = 49). The ITT population was defined as all patients who received at least 1 dose of study medication and had at least 1 postbaseline assessment. The primary analysis, last observation carried forward (LOCF), was conducted on all outcome measures to compare difference in scores between baseline and study end point. To understand the trajectory of change over the course of the study, hierarchical linear modeling was conducted on all outcome measures, with predictor variables defined for group (ziprasidone or placebo), time (natural log of weeks + 1), study site, a group-by-site interaction, and a group-by-time interaction. This group-by-time interaction term was used to determine whether, over time, ziprasidone subjects behaved differently than or similarly to placebo subjects. The natural log of weeks from baseline was used to give a more nearly linear relationship of outcome scores to time. Hierarchical linear modeling is a more sensitive analysis than LOCF analysis of variance, with greater power to detect differences between treatment groups at baseline and over time. Differences were detected between sites and groups at baseline; hierarchical linear modeling takes these baseline differences into account in the analysis.

For each outcome variable, effect size was calculated using Cohen *d* and a continuous number needed to treat (NNT)/number needed to harm (NNH). Improvement from baseline to final visit was calculated, and continuous NNT was estimated at $1/(2 \times \text{area under the receiver operating characteristic curve} - 1)$, where AUC is the area under

Figure 1. CONSORT Diagram



the receiver operating characteristic (ROC) curve.[35] All statistical tests were 2-tailed and carried out at an α level of .05.

RESULTS

Enrollment

Patients were screened and randomized from June 2010 through August 2011. Forty-nine patients were randomized to receive ziprasidone (n = 25) or placebo (n = 24; Figure 1). A significant portion of the sample had bipolar I disorder (69.4%).

Of the 49 patients enrolled and randomized, 3 (ziprasidone, n = 2; placebo, n = 1) did not return for a postbaseline visit and therefore were not included in the ITT efficacy analyses. The mean time to study termination was 5.25 weeks (SD = 3.06). The most common reasons for early termination were adverse events (ziprasidone, n = 7; placebo, n = 1) and lost to follow-up (ziprasidone, n = 4; placebo, n = 3).

Dosing of Ziprasidone

After the initial titration period, the mean (SD) peak dose of ziprasidone was 131.77 (52.47) mg/d. At week 2, the mean peak dose of ziprasidone was 127.06 (51.45) mg/d; at week 3, the mean peak dose was 146.67 (26.05) mg/d; the week 4 mean peak dose was 149.09 (18.68) mg/d; the week 5 and 6 mean peak dose was 148.00 (19.32) mg/d; the week 7 mean peak dose was 146.67 (20.00) mg/d; and the week 8 mean peak dose of ziprasidone was 146.67 (20.66) mg/d.

Primary Efficacy Outcomes

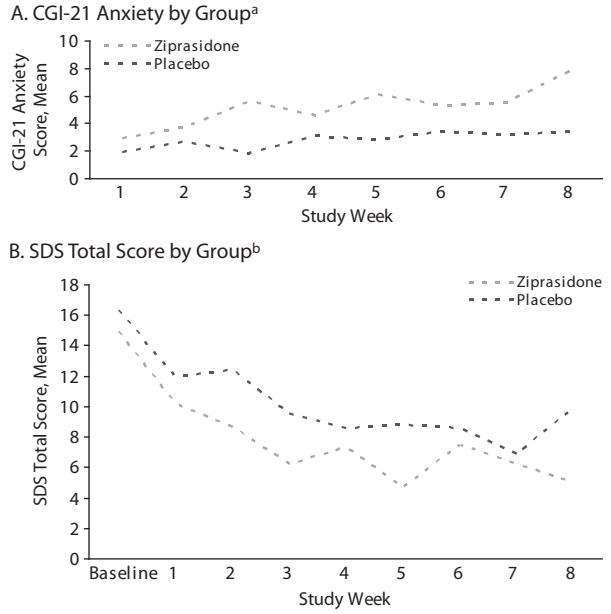
CGI-21 Anxiety. The ziprasidone group did not show greater improvement than the placebo group in ratings of overall anxiety severity when either the LOCF analyses of mean change from baseline to study end point ($F_1 = 0.34$; $P = .564$) or hierarchical linear modeling ($F_1 = 1.82$; $P = .178$) was used (Figure 2A). There was an effect of study week such that, regardless of group, a decrease in anxiety was observed over time ($F_1 = 11.08$; $P = .001$).

When the ITT sample was used, the NNT according to the CGI-21 Anxiety was 9.51 and Cohen *d* was 0.19, indicating a small clinical effect size between ziprasidone and placebo. Given this effect size and an α of .05, a sample size of 934 (467 per treatment group) would be necessary to have power of 0.8.

SDS. The ziprasidone group did not show greater improvement than the placebo group in ratings of overall functional disability when either the LOCF analyses ($F_1 = 0.26$; $P = .611$; Figure 2B) or hierarchical linear modeling ($F_1 = 0.70$; $P = .408$) was used. There was also an effect of study week such that, regardless of group, SDS total score decreased over time ($F_1 = 26.16$; $P < .001$).

For the SDS total score, the NNT was 12.07 and Cohen *d* was 0.15, indicating a small clinical effect size difference between ziprasidone and placebo. With this effect size and an α of .05, a sample size of 2,090 (1,045 per treatment group) would be necessary to have power of 0.8. Similar results were seen with SDS subscales.

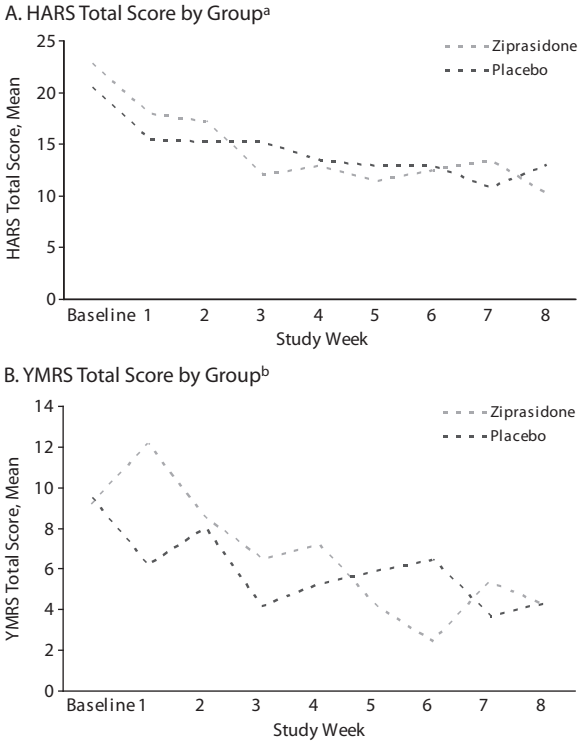
Figure 2. Mean Scores on Clinical Global Impressions-21 Anxiety Scale (CGI-21 Anxiety) and Sheehan Disability Scale (SDS) Total Score by Group



[a]The CGI-21 Anxiety ranges from –10 (very bad, could not be worse) to +10 (major improvement, back to normal self). When hierarchical linear modeling was used, a significant group-by-time interaction was not observed for CGI-21 Anxiety total scores ($F_1 = 1.82$; $P = .178$), indicating that subjects in the ziprasidone group did not experience reduction of anxiety symptoms at a faster rate than those in the placebo group. Importantly, a reduction in anxiety symptoms was observed in both treatment groups over time in the study ($F_1 = 11.08$; $P = .001$).

[b]When hierarchical linear modeling was used, a significant group-by-time interaction was not observed for SDS total scores ($F_1 = 0.70$; $P = .408$), suggesting that the rate of improvement for the 2 treatment groups was not different. Importantly, a reduction in disability was observed in both treatment groups over time in the study ($F_1 = 26.16$; $P < .001$).

Figure 3. Hamilton Anxiety Rating Scale (HARS) and Young Mania Rating Scale (YMRS) Total Scores by Group



[a]The rates of improvement on the HARS for the 2 treatment groups were not significantly different ($F_1 = 1.35$; $P = .251$). There was a significant effect of group (regardless of time in the study), signifying that the ziprasidone group had higher scores at baseline than the placebo group ($F_1 = 5.92$; $P = .017$); a significant effect of site ($F_2 = 50.05$; $P < .001$); and a significant effect of time ($F_1 = 29.22$; $P < .001$) such that scores decreased over time regardless of group.

[b]For YMRS total scores, the rates of improvement were similar for the 2 treatment groups ($F_1 = 0.03$; $P = .872$). There was a significant difference between groups ($F_1 = 5.19$; $P = .025$), indicating that patients in the ziprasidone group had higher symptoms of hypomania at baseline than the placebo group; a significant effect of site ($F_2 = 9.53$; $P = .001$) indicated that there were differences in sites on hypomania scores at baseline, and a significant effect of time ($F_1 = 4.33$; $P = .050$) indicated that mood symptoms decreased over time regardless of treatment group.

Secondary Efficacy Outcomes: Anxiety

HARS, SPS, and PGI-21 outcome. The ziprasidone group did not show greater improvement than placebo in ratings of overall anxiety or panic symptoms. Last-observation-carried-forward analyses found no significant differences between groups on HARS ($F_1 = 0.00$; $P = .988$) or SPS ($F_1 = 0.29$; $P = .594$) ratings from baseline to study end point. There were also no group-by-time interactions on the HARS ($F_1 = 1.35$; $P = .251$; Figure 3A) or SPS ($F_1 = 0.03$; $P = .872$), suggesting that the rate of improvement for the 2 treatment groups was not different. There was a significant effect of time such that scores decreased over time regardless of group. There were no significant differences between treatment groups on PGI-21 ratings from baseline to study end point ($F_1 = 0.24$; $P = .628$) and no group-by-time interaction ($F_1 = 0.11$; $P = .740$), suggesting that the rates of improvement were similar for the 2 treatment groups.

Secondary Efficacy Outcomes: Mood

CGI-BP, YMRS, and MADRS outcome. The ziprasidone group did not show greater improvement than placebo on ratings of overall bipolar illness severity or depressive and manic mood symptoms. There were no significant differences between groups from baseline to study end point on the CGI-BP ($F_1 = 0.34$; $P = .563$), YMRS ($F_1 = 0.19$; $P = .668$), or MADRS ($F_1 = 0.63$; $P = .432$). There were also no significant group-by-time interactions on the CGI-BP ($F_1 = 0.13$; $P = .717$), YMRS ($F_1 = 0.03$; $P = .872$; see Figure 3B), or MADRS ($F_1 = 0.25$; $P = .618$), suggesting that the rates of improvement were similar for the 2 treatment groups. There was a significant effect of time such that mood symptoms decreased over time.

STS and SIS outcome. The ziprasidone group did not show greater improvement than placebo on ratings of suicidality (STS; $F_1 = 1.88$; $P = .176$) and irritability (SIS; $F_1 = 3.34$; $P = .073$). There was a significant effect of time such that irritability scores decreased over time ($F_1 = 57.54$; $P < .0001$), regardless of treatment group.

Study Attrition and Completion Rates

Twenty-three patients completed all 8 weeks (ziprasidone, n = 6; placebo, n = 17), with significantly fewer patients in

the ziprasidone group completing the entire 8-week study ($\chi^2_1 = 10.78$; $P = .001$). The disposition of consented subjects is illustrated in the CONSORT figure (Figure 1). Three patients in the ziprasidone group withdrew from the study, stating the treatment was ineffective.

Adjunctive Medication

Four patients (ziprasidone, n = 2; placebo, n = 2) were prescribed 0.5–1 mg/d of lorazepam as needed for symptoms of anxiety, insomnia, or both during the first 2 weeks of the study. Six patients (ziprasidone, n = 3, placebo, n = 3) were prescribed 2.5–10 mg/d of zolpidem or zaleplon as needed for symptoms of insomnia, and 6 patients were prescribed benztropine (ziprasidone, n = 2, placebo, n = 4) for management of extrapyramidal symptoms.

Movement Side Effects: Clinical Scale Results

AIMS, SAS, and BARS outcome. There was a significant difference in the change from baseline to end point AIMS scores between the ziprasidone and placebo groups ($F_1 = 9.92$; $P = .003$). The AIMS scores at study end point were not in the clinically significant range for either the ziprasidone (mean = 1.12, SD = 3.24) or placebo (mean = 0.4, SD = 0.20) groups. No between-group differences were observed for akathisia as measured by BARS total change scores ($F_1 = 2.77$; $P = .103$).

Serious adverse events, adverse events, and side effects. Eleven patients withdrew from the study due to serious adverse events, adverse events, or side effects. Of those, 9 (81.8%) were from the ziprasidone group ($\chi^2_1 = 5.38$; $P = .020$). Two patients (ziprasidone, n = 1; placebo, n = 1) discontinued treatment due to serious adverse events, including hospitalizations for illness-related violence (placebo) and considerable anxiety, depression, and possible suicidal risk (ziprasidone).

The ziprasidone group reported more sleep disturbances than the placebo group ($\chi^2_1 = 4.50$; Fisher exact test $P = .040$) and, specifically, the ziprasidone group reported more sedation and somnolence than the placebo group ($\chi^2_1 = 4.41$; Fisher exact test $P = .049$). Finally, the placebo group reported more headaches than the ziprasidone group ($\chi^2_1 = 6.60$; Fisher exact test $P = .019$). The ziprasidone group gained more weight over the course of the study than the placebo group (mean weight gain was 3.92 [SD = 16.31] and 0.08 [SD = 5.97] pounds, respectively; $F_1 = 4.60$; $P = .035$).

Blinded Guess of Treatment: Ziprasidone Versus Placebo

Blinded treatment impressions were collected at 2 of the 3 sites and by 3 cohorts of raters: treating clinician, blinded rater, and patient. There were no significant differences in the accuracy of treatment impression between the 3 groups of raters. Treating clinicians were accurate 47.6% of the time, with better accuracy within the ziprasidone group (66.7% accuracy). The blinded raters were accurate 42.3% of the time. The patients were accurate 71.4% of the time, with those in the placebo group guessing correctly 100% of the time, while patients in the ziprasidone group guessed accurately 66.7% of the time (likelihood ratio test$_3$ = 8.69; $P = .034$).

DISCUSSION

Our results suggest that ziprasidone monotherapy is not associated with a clinically significant improvement in anxiety symptoms or functional status in patients with bipolar disorder and lifetime panic disorder (with or without agoraphobia) or GAD. The effect sizes were found to be small, and large sample sizes would be necessary to have enough statistical power to detect differences between the 2 treatment groups on primary outcome measures. The results also suggest that ziprasidone monotherapy was associated with increased side effects relative to placebo.

Bipolar disorder frequently co-occurs with anxiety, and this clinically distinct and challenging combination may put these individuals at an even greater risk than usual for poor psychosocial functioning.[9,10,12–14] However, as noted by Kauer-Sant'Anna et al,[36] the majority of studies investigating treatments for bipolar disorder with anxiety examine anxiety symptoms as a secondary outcome within a trial focused on symptoms of bipolar disorder.[19,20,22] The only 2 published randomized placebo-controlled, double-blind, monotherapy trials we are aware of that specifically examined bipolar disorder with anxiety found SGAs (risperidone and quetiapine) to have mixed effectiveness in terms of treating anxiety.[21,23] The results of the present analysis appear to further support the limited findings that not all SGAs are effective for treating anxiety symptoms in bipolar disorder patients with a lifetime panic disorder or GAD.

However, further research is warranted. This study examined the efficacy of ziprasidone as monotherapy; it is possible that ziprasidone, or another SGA, could be efficacious in conjunction with a mood stabilizer. Additionally, one study[21] found significant improvement in primary outcomes of anxiety for quetiapine XR monotherapy, suggesting that other SGAs may be more effective in bipolar and panic disorder or GAD than ziprasidone.

The results of this study suggest that ziprasidone may, in fact, be more poorly tolerated than placebo. The lower completion rate in the ziprasidone group, greater increase in AIMS side effect symptoms in that group, and high percentage of ziprasidone patients among those who failed to complete due to adverse events, serious adverse events, and side effects suggest that ziprasidone monotherapy may be not only ineffective but contraindicated in this population.

Limitations

One limitation of this study may be the length of the treatment with a longer study potentially finding greater group differences. Additionally, the sample size was a limiting factor in this study. Given the small effect sizes of ziprasidone compared to placebo on both the CGI-21 Anxiety and SDS scales, a much larger sample size would be necessary to have sufficient power to detect these effects.

One other possible limitation to consider is that this study looked at patients with panic disorder, GAD, or both, while social phobia and obsessive-compulsive disorder have been found to be of particular prevalence and pathophysiology in patients with bipolar disorder.[37,38] Future studies could focus specifically on the intersection of social phobia, obsessive-compulsive disorder, or both with bipolar disorder in order to hone in on an important subsample of this population.

CONCLUSIONS

Results from this study suggest that ziprasidone monotherapy is not more effective than placebo for short-term treatment of either anxiety symptoms or psychosocial impairment in patients with bipolar disorder and co-occurring panic disorder, GAD, or both panic disorder and GAD and current moderately severe anxiety symptoms.

Drug names: benztropine (Cogentin and others), fluoxetine (Prozac and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), zaleplon (Sonata and others), ziprasidone (Geodon and others), zolpidem (Ambien, Edluar, and others).

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Potential conflicts of interest: **Dr Suppes** has received grants or medications for clinical grants from AstraZeneca, Pfizer, Sunovion, Elan Pharma International Limited, VA Cooperative Studies Program, and the National Institute of Mental Health (NIMH); has served on advisory boards of Sunovion; has received royalties from Jones and Bartlett (formerly Compact Clinicals); and has received travel expenses from Sunovion. **Dr McElroy** has been a principal or co-investigator within the past year on research studies sponsored by Abbott, Agency for Healthcare Research and Quality, Alkermes, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Jazz, Marriott Foundation, the National Institute of Mental Health, Orexigen, Pfizer, Shire, Takeda, and Transcept; and has been a consultant to, or member of the scientific advisory board of Alkermes, AstraZeneca, Eli Lilly, Jazz, Pfizer, and Shire. Dr McElroy is also inventor on US patent no. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patent's assignee, University of Cincinnati, Cincinnati, OH, has received payments from Johnson & Johnson Pharmaceutical Research & Development, which has exclusive rights under the patent. **Dr Sheehan** has served on advisory boards of Roche Sagene Pharma, Otsuka, Forest, Novadel, Labopharm Neuronetics, and International Society for CNS Drug Development; has been a scientific consultant to Sagene Pharma, Neuronetics, Janssen, MAPI, Prime Education, ProPhase, NovaDel, xCenda, Targacept, and Quadrant HealthCom; has received honoraria and travel expenses for lectures and presentations from Pfizer, Eli Lilly, Glaxo, Labopharm Angelini, Merck, PharmaNeuroBoost, Quintiles, Hikma, United BioSource, Janssen, INC Research, and Otsuka; and holds stock in Medical Outcome Systems. **Dr Hidalgo** has received grant support from Shire, Otsuka, Cephalon, Cenerx, Sunovion/DSP, Repligen, Eli Lilly, Takeda, AstraZeneca, Labopharm, Sanofi-Synthelabo. **Dr Cosgrove** and **Mss Gwizdowski** and **Feldman** have no potential conflicts of interest to disclose.

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