Efficacy and Safety of Adjunctive Oral Ziprasidone for Acute Treatment of Depression in Patients With Bipolar I Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Objective: To assess efficacy and safety of adjunctive ziprasidone in subjects with bipolar depression treated with lithium, lamotrigine, or valproate.

Method: 298 adult outpatients with bipolar I disorder (*DSM-IV* criteria) were randomized to receive ziprasidone, 20–80 mg twice a day, or placebo twice a day for 6 weeks plus their preexisting mood stabilizer. The primary efficacy variable was change in Montgomery-Asberg Depression Rating Scale (MADRS) total scores from baseline to 6 weeks. The key secondary efficacy endpoint was change from baseline to week 6 in Clinical Global Impressions-Severity (CGI-S) scores. Computer-administered assessments for diagnostic confidence were included for quality control and to evaluate study performance. The study was conducted between October 2007 and December 2008.

Results: The mean ± SD daily dose of ziprasidone was 89.8 ± 29.1 mg. Least squares mean ± standard error changes from baseline to week 6 on MADRS total score for ziprasidone and placebo treatment groups were −13.2 ± 1.2 and −12.9 ± 1.1, respectively, with a 2-sided *P* value of .792. There was no significant difference on the key secondary variable (CGI-S). Adjunctive ziprasidone was well tolerated. Poor quality ratings at baseline were associated with a trend for better improvement on placebo than ziprasidone. Among 43 placebo-treated subjects with poor baseline quality ratings, 29 (67.4%) had baseline MADRS scores > 10 points higher on the computer-administered assessment than the MADRS administered by the site-based rater. The response favoring placebo over ziprasidone observed in this subgroup suggests that poor signal detection in some clinical trials can be a consequence of "subject inflation" as well as "rater inflation."

Conclusions: Adjunctive ziprasidone treatment failed to separate from mood stabilizer alone on primary and secondary endpoints. Possible contributions to this result include enrollment of a substantial number of subjects with low diagnostic confidence, low quality ratings on the MADRS, and overzealous reporting of symptoms by subjects.

Trial Registration: clinical trials.gov Identifier: NCT00483548

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Bipolar I disorder is a common complex, chronic illness that is associated with considerable functional impairment.[1] This dynamic, pleomorphic disorder challenges researchers as well as clinicians and, as a consequence, relatively little high quality data are available to guide clinical practice. The management of depression in patients with bipolar I disorder remains an area of significant unmet need.[2] In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), subjects with bipolar disorder experienced high rates of depressive relapse despite maintenance treatment with lithium, valproate, or other US Food and Drug Administration (FDA)–approved antimanic agents.[3] In view of the unmet need for adjunctive treatments for patients suffering from bipolar depression despite prescribed maintenance treatment at dosages considered adequate, we undertook a study of adjunctive ziprasidone.

Like other agents classified as atypical antipsychotics, ziprasidone is a dopamine D_2 and 5-HT_{2A} antagonist and interacts with numerous other receptors. Ziprasidone shows agonist activity at 5-HT_{1A} receptors and antagonist activity at 5-HT_{1B} and 5-HT_{1D} receptors. The affinity of ziprasidone for 5-HT_{1D} receptors, and its serotonin-norepinephrine reuptake inhibition, is comparable to that of the tricyclic antidepressant imipramine, and provides a rationale for studying ziprasidone as an antidepressant.[4] Data from prior small, open studies suggest that ziprasidone may reduce depressive symptoms associated with bipolar I disorder.[5–7]

Only 2 treatments have FDA approval for treatment of bipolar depression: the atypical antipsychotics quetiapine[8] and olanzapine-fluoxetine combination[9] have demonstrated more efficacy than placebo in reducing depressive symptoms in patients with bipolar I disorder. However, both drugs are associated with undesirable metabolic effects such as weight gain and disturbances of glucose homeostasis.[10,11] Ziprasidone has a lower propensity for weight gain and other metabolic disturbances than olanzapine or quetiapine.[12]

Adjunctive treatment with standard antidepressant medications is the most commonly prescribed intervention for patients with bipolar depression.[13] The STEP-BD showed no benefit, however, for adjunctive treatment with antidepressants (bupropion or paroxetine) compared to mood stabilizer plus placebo. To date, only one placebo-controlled study has succeeded in demonstrating the efficacy of any agent as an adjunct to lithium or valproate.[14] Although successful in an adjunct study[14] and commonly used for maintenance treatment for bipolar disorder, lamotrigine failed to separate from placebo in 5 of 5 bipolar depression monotherapy studies on primary outcome measure and 4 of 5 studies on key secondary outcome measures.[15] Another atypical antipsychotic, aripiprazole, studied for bipolar depression, has also produced negative or failed results.[16]

There are no double-blind data available to guide the care of depressed bipolar patients who have not responded to lithium, lamotrigine, or valproate. As preliminary clinical studies have suggested that

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ziprasidone may have an antidepressant effect in subjects with bipolar disorder or with other psychiatric diagnoses, the present study was designed to investigate the efficacy and safety of ziprasidone as add-on therapy in patients with bipolar I disorder who were treated with lithium, valproate, or lamotrigine. In view of the frequency at which bipolar depression studies have failed or produced negative results, we incorporated an innovative computer-based rating management system into the study design.

METHOD

The study (clinicaltrials.gov registry: NCT00483548) was a randomized, double-blind, placebo-controlled, trial conducted at 78 centers located in Australia (4), India (6), and the United States (68). The protocol was approved by institutional review boards or independent ethics committees at each center, and the trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and all appropriate local regulatory requirements.

The primary aim of the study was to investigate the efficacy and safety of ziprasidone as add-on adjunctive therapy in the treatment of depression associated with bipolar I disorder. Secondary objectives included examination of the effects of ziprasidone on global functioning and quality of life.

Subjects

Adult (≥ 18 years old) outpatients of either sex were eligible for the study if they had a primary diagnosis of bipolar I disorder, with the most recent episode depressed (296.5x), with or without rapid cycling, and without psychotic features, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*).[17] The diagnosis was established by consensus between a certified site-based rater using the Mini-International Neuropsychiatric Interview[18] and an independent expert employed by Concordant Raters Systems in Boston, Massachusetts; Philadelphia, Pennsylvania; or San Francisco, California. The expert was a psychiatrist or psychologist with clinical experience and research experience who reviewed details of prior manic or mixed episodes collected directly from the subject by the computer and who validated the subjects' eligibility for randomization, if at least 1 episode met full *DSM–IV* criteria for mania or a mixed episode. The Bipolarity Index, a measure of diagnostic confidence,[19] was also used for cases in which it was not possible to confirm the diagnosis based on the computer assessment. In these cases, subjects were included only if sufficient additional diagnostic information was obtained from the investigator (or designee) to establish acceptable diagnostic confidence.[20] The onset of the depressive episode was required to be between 2 weeks and 6 months of screening. In addition, subjects were required to have a score of at least 20 on the 17-item Hamilton Depression Rating Scale (HDRS-17)[21] and a score of ≤ 12 on the Young Mania Rating Scale (YMRS)[22] at both screening and randomization.

Clinical Points

- The frequent failure of randomized controlled studies to detect differences between study medication and placebo is a significant obstacle to drug development.
- Although some studies include active comparators, this component alone does little to inform the field as to why randomized clinical trials often lack assay sensitivity.
- Using data from tandem assessments made by site-based raters and computer-administered assessments, this report examined the impact of protocol-specific eligibility criteria, diagnostic confidence, and rating quality on signal detection. The results suggest that variability in study quality can lead to study failure and that future clinical trials could benefit from procedures that do not rely exclusively on assessments made by a single rater.

Subjects were excluded from the study if they had any *DSM-IV-TR* Axis I or Axis II disorder that was clinically unstable or required treatment or if they showed ultrafast rapid cycling (defined as ≥ 8 mood episodes during the 12 months before screening). Other psychiatric exclusion criteria included a suicide attempt within the 3 months before screening or a score of at least 4 on the suicide item of the Montgomery-Asberg Depression Rating Scale (MADRS),[23] *DSM-IV-TR*–defined alcohol or psychoactive substance dependency within 6 months prior to screening or documented abuse of such substances within 3 months before screening, electroconvulsive therapy (ECT) within 3 months before screening, a history of nonresponse to ECT, treatment with any psychotropic medication other than lithium, valproate or lamotrigine within 1 week prior to screening, or depot neuroleptic treatment within the previous 6 months. In addition, subjects were excluded if they had clinically significant electrocardiogram (ECG) abnormalities, a history of QT interval prolongation or any medical condition or treatment that could produce such prolongation, or significant medical conditions, including a history of seizures, cardiovascular disease, neuroleptic malignant syndrome, or tardive dyskinesia that did not respond to treatment. Women of childbearing potential were required to use appropriate contraceptive precautions during the study.

Written informed consent was to be obtained before inclusion in the study. In the case of illiterate subjects, the subject provided an alternative indication, such as a thumbprint, and an impartial witness was required to provide signed confirmation that the informed consent procedure had been appropriate.

Study Design and Treatment

Study subjects comprised (1) subjects already on a mood stabilizer at screening and (2) subjects initiated on a mood stabilizer at screening. In both cases, mood stabilizer treatment had to remain stable, as defined by the protocol

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requirements for lamotrigine dose (100–200 mg/d) or blood concentrations of lithium or valproate (0.6–1.2 mEq/L for lithium or 50–125 μg/mL for valproate), and was to be maintained for at least 4 weeks before randomization. Subjects whose mood stabilizer therapy had remained stable as per-protocol requirements for at least 4 weeks were randomized in a 1:1 ratio to receive adjunctive ziprasidone or placebo for 6 weeks.

Randomization was performed using a unique identification number for each subject and was stratified according to the type of mood stabilizer therapy (lithium, valproate, or lamotrigine). An internet-/telephone-based randomization and drug management system was used to provide the identification number and to assign either ziprasidone or matching placebo capsules to each subject throughout the trial. Blinding was to be broken only in the event of an emergency that required knowledge of the treatment for subject safety. One formal interim analysis was to be performed when approximately 60% of the planned subjects had either completed the study or discontinued prematurely. The Data Safety Monitoring Committee had the option to recommend stopping the study early for efficacy (nominal P value ≤ .0076, 2-sided) or for futility (nominal P value ≥ .5099, 2-sided).

Subjects were instructed to take all study medication with food. The starting dose of ziprasidone was 40 mg in the evening on the day of randomization, followed by 40 mg twice daily on the second day (ie, 80 mg total daily dose). Thereafter, subjects were titrated twice daily with total daily doses in the range of 40–160 mg, depending on symptoms and tolerability. Compliance was assessed by pill counts, and blood levels of lithium and valproate were monitored via samples taken at screening, baseline, and week 6, or at the early termination visit to ensure the subject met the required therapeutic blood level specified in the protocol.

All other psychotropic medications were withdrawn at least 7 days or 4 half-lives (whichever was longer) before randomization. Lorazepam, or an alternative short-acting benzodiazepine, could be given at doses of up to 2 mg/d for up to 4 days per week during screening and the first 2 weeks of the double-blind treatment period to treat agitation or anxiety. Regulatory agency–approved nonbenzodiazepine medications could be used to treat sleep disturbances for up to 4 days per week until the end of the second week of double-blind treatment and for up to 2 days per week thereafter. The benzodiazepines and sleep agents were not to be given on the same day and were not to be used within 24 hours of efficacy assessments. Benztropine (≤ 6 mg/d) or an equivalent agent could be used to treat extrapyramidal symptoms. Propranolol (≤ 120 mg/d) could be used to treat akathisia.

Assessments

Efficacy assessments were made at baseline (randomization) and at weekly intervals thereafter. The primary efficacy endpoint was the change from baseline to week 6 in the MADRS total score. The key secondary efficacy endpoint was the change from baseline to week 6 in the Clinical Global Impressions-Severity scale (CGI-S)[24] score. Additional secondary efficacy endpoints included change from baseline in Hamilton Anxiety Rating Scale (HARS)[25] total score; change from baseline in YMRS total score; change from baseline in Global Assessment of Functioning (GAF) scale[17] score; change from baseline in Sheehan Disability Scale[26] total score; and change from baseline in Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q)[27] total score.

Only qualified raters who met educational and experience requirements participated in the trial. Prior to the start of the trial, rater training was conducted on-line and at an investigators' meeting for all participating centers. The MADRS data at each study visit were monitored using a remote site management system developed by Concordant Rater Systems, the vendor responsible for rater training and remote site management. Raters completed the training program and then received "provisional certification"; "full certification" was granted on raters demonstrating proficiency with concordance between site-based ratings and computer ratings within the acceptable concordance range over the first 3–6 actual subject ratings. Raters not meeting proficiency requirements were not allowed to enroll additional subjects.

Each site was provided with a laptop computer with the remote site management software (Concordant Rater Systems). The MADRS item scores as determined by the site-based ratings were entered on the laptop. In addition, (without assistance or input from the site rater), the subject completed an interactive interview on the computer, which selected a sequence of questions as necessary to map the subject's responses to the MADRS anchor points for each scale item. A computer-generated score was assigned based on the subject's input. Prior studies have demonstrated that site-based ratings and computer-administered MADRS are highly correlated.[28]

Item ratings scores on which the site-based ratings and computer scores differed by no more than 1 point were considered to be concordant. Concordant Rater Systems contacted raters by telephone to discuss the potential causes for discordant ratings, if the total score differential was ≥ 6 points or more than 2 items with a differential of ≥ 3 points. No further action was taken with raters who provided supporting information for their ratings; however, raters with unresolved discordance received remediation on use of appropriate probes and/or scoring conventions for the MADRS. In all cases, site-based raters were instructed not to change their original scores.

The same procedure was applied to the YMRS data at screening and baseline and to the HDRS-17 data at screening. Rater quality scores were categorized as better quality, lower quality, and poor quality if the absolute value of the difference between the computer- and site-based ratings was ≤ 5, > 5 ≤ 10, or > 10, respectively. The poor quality ratings were designated rater inflation if the site-based ratings score was > 10 points higher than the computer score and subject inflation when the computer score was > 10 points higher than the site-based ratings score. Confidence in the lifetime

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diagnosis of bipolar I disorder was assessed with the Bipolarity Index.[29] This scale quantifies the process suggested by Robins and Guze[30] for validating psychiatric diagnosis by scoring 5 illness domains (episode characteristics, age at onset, response to treatment, course of illness, and family history) on a 0–20 scale, on which higher scores are given to characteristics most associated with the Kraepelinian conception of bipolar disorder. Prior psychometric studies indicate that acceptable confidence for bipolar I disorder lifetime diagnosis corresponds to scores above 60 or having at least 3 domains scored 15 or higher.[20]

Safety and tolerability were assessed by recording of adverse events, physical examination, and measurement of vital signs, 12-lead ECG, and clinical laboratory evaluation. Extrapyramidal symptoms, akathisia, and dyskinesia were assessed by means of the Simpson-Angus Scale,[31] the Barnes Akathisia Scale,[32] and the Abnormal Involuntary Movement Scale (AIMS).[33]

Statistical Analysis

Statistical analyses were performed on the intent-to-treat (ITT) population, which consisted of all subjects who were randomized, received at least 1 dose of double-blind medication, and had at least 1 postbaseline primary efficacy assessment. In addition, the primary and key secondary efficacy endpoints were analyzed in the per-protocol population, which included all subjects in the ITT population with no major protocol violations.

The primary efficacy variable, the mean change in MADRS scores from baseline to week 6, was analyzed using a mixed model repeated measures (MMRM) analysis with fixed categorical effects of treatment, country, type of mood stabilizer, visit and treatment-by-visit interaction, and a fixed, continuous effect of baseline MADRS score; subject effect was included as a random effect. The mixed model repeated measures analysis used the restricted maximum likelihood estimation method, with a sandwich estimator of variance-covariance matrix of the fixed effects parameters. The analysis was performed using the SAS PROC MIXED procedure (SAS Institute Inc, Cary, North Carolina). An unstructured variance-covariance matrix was used in the REPEATED statement. Supplemental analyses of the primary endpoint included analysis of covariance (ANCOVA) of the change in MADRS scores from baseline to week 6, with missing data imputed using last observation carried forward (LOCF) principle; ANCOVA of change from baseline in MADRS scores at week 6 on observed cases only, the primary analysis using log-transformed total MADRS score; and a pattern mixture, mixed model repeated measures analysis of change from baseline in MADRS scores. The change in CGI-S score from baseline to week 6 was analyzed by mixed model repeated measures as described above, and supplementary analyses were performed by ANCOVA on both LOCF and observed cases data. Adjusted for the interim analysis, the *P* value threshold for the primary analysis was .0476. For change from baseline in total score for HARS and YMRS, ANCOVA similar to that for the primary endpoint was conducted at each postbaseline collection time point on the basis of both LOCF and observed cases. For change from baseline in scores for GAF, Sheehan Disability Scale, Q-LES-Q, Simpson-Angus Scale, Barnes Akathisia Scale, and AIMS, ANCOVA similar to that for the primary endpoint was conducted on the basis of the observed cases.

The sample size calculation was performed with EAST 4 software (Cytel Inc, Cambridge, Massachusetts) to account for a preplanned interim analysis, when approximately 60% of the planned number of subjects had either completed the study or discontinued prematurely. It was calculated that a sample size of 141 subjects per group (282 in total) would provide 85% power to detect a treatment difference in the mean change in MADRS scores from baseline to week 6 of 4.0 points, with a standard deviation of 11.0, using a 2-sided test at a significance level of .05.

Rating Quality Data Analysis

After completion of the efficacy analysis, the study sponsor sent unblinded treatment assignments to Concordant Rater Systems and matched with the rater quality data files. The files were reviewed for accuracy, and analyses were carried out using Stata version 11.0 statistical software.

The analysis plan compared key results from the efficacy analysis to those derived from the Rater Quality data set and evaluated a list of a priori competing hypotheses. These involved comparing results from prespecified subgroups defined by variables derived from computer-administered scales.

Quality ratings were defined based on the absolute value of the difference between the computer- and site-based ratings scores on the MADRS: better quality (difference ≤ 5), low quality (absolute value of difference from 5–10), or poor quality (difference > 10). Baseline MADRS ratings in which the site-based ratings score was > 10 higher than the computer scored were classified as indicating likely rater inflation. Baseline MADRS ratings in which the site-based ratings score was > 10 lower than the computer scored were classified as indicating likely subject inflation.

RESULTS

Between October 2007 and December 2008, 792 subjects were screened, of whom 298 were randomized and 294 (147 in each group) received treatment (Figure 1). Of the 294 who received treatment, 102 subjects discontinued treatment, mainly due to adverse events and protocol violations. Thus, 192 subjects (88 in the ziprasidone group, 104 in the placebo group) completed the study (Figure 1). The sample characteristics are summarized in Table 1.

Interim Analysis

The interim analysis was performed on 168 subjects (84 subjects in each treatment group; 59.6% of the planned final sample size). At the interim analysis, the least squares mean ± standard error (SE) changes from baseline to week

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Figure 1. Study Profile

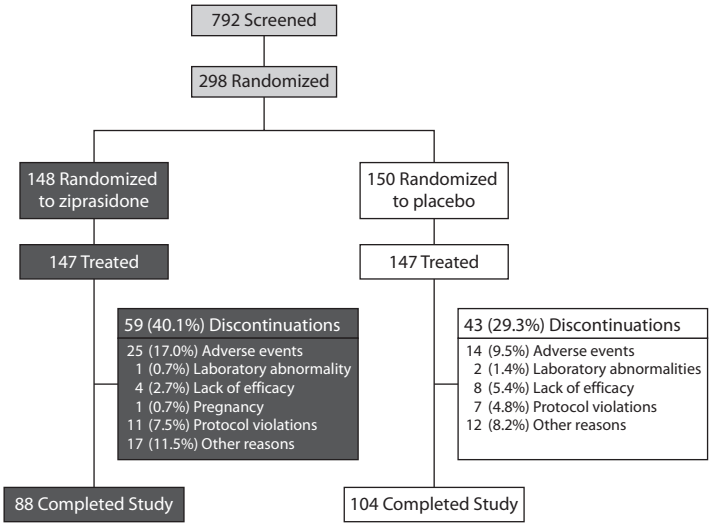

Table 1. Baseline Characteristics

Characteristic	Ziprasidone (n = 147)	Placebo (n = 147)
Sex, n (%)		
Male	58 (39.5)	56 (38.1)
Female	89 (60.5)	91 (61.9)
Race, n (%)		
White	116 (78.9)	111 (75.5)
Black	19 (12.9)	20 (13.6)
Asian	7 (4.8)	11 (7.5)
Other	5 (3.4)	5 (3.4)
Age, mean ± SD (range), y	40.4 ± 11.4 (18–64)	40.4 ± 11.9 (18–66)
Weight, mean ± SD (range), kg	84.3 ± 21.4 (45.0–156.1)	89.9 ± 23.2 (45.4–174.8)
Height, mean ± SD (range), cm	168.2 ± 10.2 (138.0–188.0)	168.0 ± 10.0 (139.7–195.0)
Time since first diagnosis of bipolar I disorder, mean (range), y	16.2 (0.07–50.7)	16.6 (0.1–45.2)
Duration of current episode, mean (range), d	76.2 (15–254)	82.9 (16–207)
No. of episodes in previous 12 mo, mean (range)	2.7 (0–20)	2.3 (0–10)
Suicidal ideation in previous 12 mo, n (%)	60 (41.4)	45 (31.5)
History of suicide attempt in previous 12 months, n (%)	6 (4.1)	4 (2.8)
Mood stabilizer, n[a]		
Lithium	53	54
Valproate	52	52
Lamotrigine	41	41

[a]One subject in the ziprasidone group did not receive a mood stabilizer during the double-blind period and was therefore excluded from the analysis.

6 on the MADRS for the ziprasidone and placebo treatment groups were −11.3 (2.18) and −13.3 (2.06), respectively, with a 2-sided *P* value of .2690 favoring placebo.

Enrollment in the study was faster than expected, and the results of the interim analysis were not available until enrollment was almost completed. On the basis of the results of the interim analysis, the Data Safety Monitoring Committee recommended that, due to study futility, already randomized subjects could complete the study but that no further subjects should enter the trial. Enrollment was completed before this recommendation was implemented.

Efficacy

Table 2 describes changes in efficacy rating scores. At baseline, there were no significant differences between the groups on any efficacy measure. The mean ± SD daily dose of ziprasidone was 89.8 ± 29.1 mg.

There was no significant difference on the primary outcome variable, the key secondary variable (CGI-S), or most of the other secondary measures, including YMRS, HARS, and Q-LES-Q. There was, however, a significant difference favoring ziprasidone over placebo on the GAF scale and the Sheehan Disability Scale.

The least squares mean ± SE change from baseline at week 6 in MADRS total score for ziprasidone- and placebo-treated subjects was −13.2 ± 1.2 and −12.9 ± 1.1, respectively (Table 2), corresponding to a least squares mean ± SE treatment difference of −0.36 ± 1.37 (95% CI, −3.07 to 2.34) that was not statistically significant (*P* = .7921). The results of the per-protocol analysis (*P* = .3989) and the sensitivity analysis

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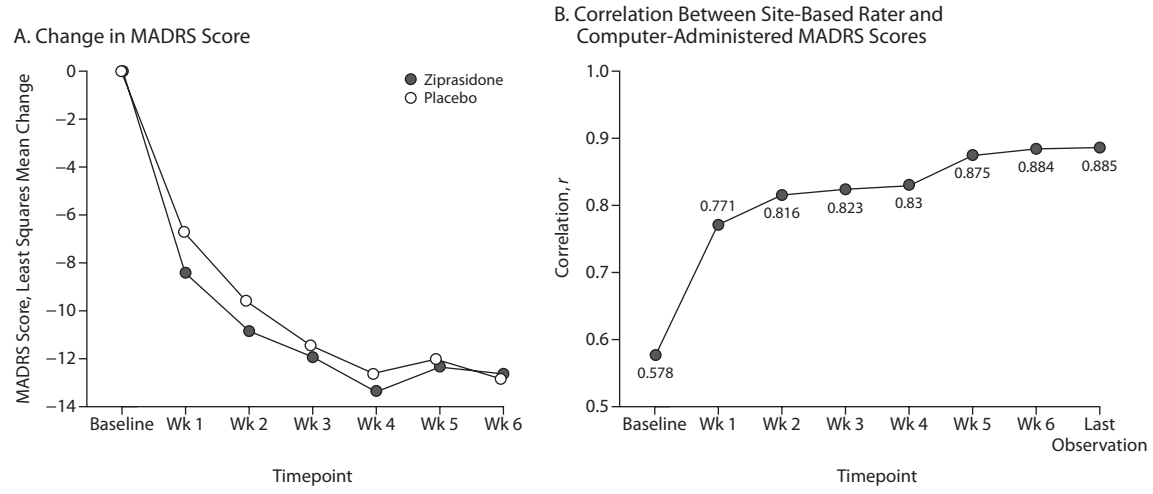
Table 2. Changes in Efficacy Rating Scores

Scale	Ziprasidone (n = 145)	Placebo (n = 145)	Treatment Difference, LS Mean ± SE (95% CI)	*P* Value
MADRS[a]				
Baseline score, mean ± SD	30.0 ± 5.5	28.8 ± 6.1		
Change from baseline to week 6, LS mean ± SE	−13.2 ± 1.2	−12.9 ± 1.1	−0.4 ± 1.4 (−3.1 to 2.3)	.7921
CGI-S[a]				
Baseline score, mean ± SD	4.4 ± 0.5	4.4 ± 0.7		
Change from baseline to week 6, LS mean ± SE	−1.4 ± 0.2	−1.4 ± 0.2	0.1 ± 0.2 (−0.3 to 0.4)	.7223
YMRS[b]				
Baseline score, mean ± SD	6.8 ± 3.1	7.1 ± 3.0		
Change from baseline to week 6, LS mean ± SE	−0.8 ± 1.1	−1.0 ± 1.0	0.2 ± 0.7 (−1.1 to 1.5)	.7647
HARS[b]				
Baseline score, mean ± SD	20.1 ± 6.2	19.9 ± 7.0		
Change from baseline to week 6, LS mean ± SE	−8.6 ± 1.4	−9.2 ± 1.3	0.6 ± 0.9 (−1.1 to 2.3)	.4770
GAF[c]				
Baseline score, mean ± SD	52.4 ± 7.5	52.1 ± 6.9		
Change from baseline to week 6, LS mean ± SE	16.8 ± 2.4	12.5 ± 2.3	4.2 ± 1.7 (1.0 to 7.5)	.0108
Sheehan Disability Scale[c]				
Baseline score, mean ± SD	18.1 ± 7.1	16.9 ± 7.3		
Change from baseline to week 6, LS mean ± SE	−7.4 ± 2.1	−2.8 ± 2.1	−4.6 ± 1.4 (−7.2 to −1.9)	.001
Q-LES-Q[c]				
Baseline score, mean ± SD	41.4 ± 15.2	43.2 ± 16.6		
Change from baseline to week 6, LS mean ± SE	12.1 ± 4.6	10.6 ± 4.5	1.5 ± 2.5 (−3.5 to 6.5)	.5519

[a]Mixed model repeated measures.
[b]Last observation carried forward.
[c]Observed cases.
Abbreviations: CGI-S = Clinical Global Impressions-Severity scale; GAF = Global Assessment of Functioning; HARS = Hamilton Anxiety Rating Scale; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; Q-LES-Q = Quality of Life, Enjoyment, and Satisfaction Scale; SE = standard error; YMRS = Young Mania Rating Scale.

Figure 2. (A) Least Squares Mean Change in Montgomery-Asberg Depression Rating Scale (MADRS) Scores (last observation carried forward) and (B) Correlation Between Site-Based Rater and Computer-Administered MADRS Scores Over the Course of the Study



were consistent with this result. Figure 2A shows change in MADRS score with time.

Rater Quality

Results from 1 or more computer-administered scales were available for 282 subjects at 66 of the 78 sites participating in the trial. Results from at least 1 postrandomization visit were available for 265 subjects (placebo, n = 137; ziprasidone, n = 128). Overall, the rater quality data produced results (Table 3) similar to the overall results of the efficacy analysis. The mean ± SD Bipolarity Index score was 71.7 ± 10.1. The correlation between site-based rater and computer-administered MADRS scores improved consistently over the course of study visits (Figure 2B).

None of the subgroup analyses based on the computer assessments found statistically significant differences between adjunctive placebo versus adjunctive ziprasidone.

The computer assessments, however, suggest that many subjects were enrolled who did not meet protocol-specified eligibility criteria. On the basis of the computer assessments, about 30% of all participants failed to meet severity criteria (computer-administered HDRS score < 20 criteria n = 22)

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Table 3. Impact of Eligibility Criteria Based on Computer Assessments: Comparison of Last Observation Carried Forward Site-Based Rater and Computer-Administered Montgomery-Asberg Depression Rating Scale (MADRS) Change Scores

	Placebo		Ziprasidone			
Variable	Change From Baseline MADRS, Mean (SD)	n	Change From Baseline MADRS, Mean (SD)	n	Difference	*P* Value, 2-Sided *t* Test
Full sample						
Site-based rater	−11.1 (11.0)	137	−11.4 (11.2)	128	+0.3	> .80
Computer	−10.3 (12.7)	137	−11.4 (12.3)	128	+1.1	> .48
Baseline $HDRS_{Comp} \geq 20$						
Eligible						
Site-based rater	−10.7 (11.1)	115	10.9 (11.1)	108	+0.20	> .89
Computer	−10.3 (12.5)	115	11.2 (12.3)	108	+0.94	> .57
Not eligible						
Site-based rater	−13.0 (10.5)	22	−14.3 (11.6)	20	+1.3	> .72
Computer	−10.7 (13.6)	22	−12.5 (12.2)	20	+1.8	> .66
Baseline $YMRS_{Comp} < 3$ symptoms of mania						
Eligible						
Site-based rater	−11.5 (10.9)	114	−12.3 (11.2)	104	+0.8	> .60
Computer	−11.0 (12.8)	114	−12.6 (12.7)	104	+1.6	> .34
Not eligible						
Site-based rater	−9.0 (11.7)	23	−7.8 (10.7)	24	−1.2	> .70
Computer	−7.2 (12.0)	23	−6.2 (8.6)	24	−1.0	> .74
Diagnostic confidence (Bipolarity Index mean score = 71.7)						
Above mean						
Site-based rater	−10.9 (12.3)	58	−11.7 (9.9)	56	+1.2	> .67
Computer	−10.8 (13.7)	58	−13.0 (10.2)	56	+2.2	> .34
Below mean						
Site-based rater	−11.2 (11.1)	79	−11.2 (12.1)	72	0	> .98
Computer	−10.0 (12.0)	79	−10.2 (13.6)	72	+0.2	> .92
Criteria for eligibility with high confidence						
Meets all						
Site-based rater	−11.5 (11.5)	46	−11.9 (10.6)	43	+0.4	> .83
Computer	−11.0 (13.4)	46	−13.6 (10.6)	43	+2.6	> .33
Does not meet all						
Site-based rater	−10.9 (10.8)	91	−11.2 (11.9)	85	+0.3	> .86
Computer	−10.0 (12.3)	91	10.3 (12.7)	85	+0.3	> .86
Rater quality						
Better						
Site-based rater	−11.7 (10.7)	64	−11.3 (11.1)	69	−0.4	> .83
Computer	−11.5 (11.5)	64	−11.8 (12.1)	69	+0.3	> .89
Lower						
Site-based rater	−10.5 (11.3)	73	−11.5 (11.4)	59	1.0	> .60
Computer	−9.3 (13.6)	73	−11.0 (12.5)	59	1.7	> .47
Poor						
Site-based rater	−10.2 (12.2)	43	−9.1 (11.2)	30	−1.2	> .67
Computer	−8.4 (14.7)	43	−5.5 (11.2)	30	−2.9	> .35
Eligible by MADRS, high confidence diagnosis, and rater quality not poor						
Meets all						
Site-based rater	−13.4 (11.4)	37	−12.1 (9.8)	37	−1.3	< .60
Computer	−13.3 (12.7)	37	−15.0 (10.1)	37	+1.7	> .53
Does not meet all						
Site-based rater	−10.2 (10.8)	133	−11.2 (11.7)	126	+1.0	> .91
Computer	−9.2 (12.5)	133	−10.0 (10.1)	126	+0.8	> .76
Poor quality rating at baseline						
Rater inflation						
Site-based rater	−15.5 (9.5)	14	−9.6 (8.7)	11	−6.1	< .11
Computer	−3.1 (10.2)	14	−0.36 (6.8)	11	−3.4	> .34
Subject inflation						
Site-based rater	−7.1 (14.3)	29	−0.33 (9.8)	19	−6.8	< .30
Computer	−19.4 (15.2)	29	−8.5 (11.7)	19	−10.9	> .13

Abbreviations: HDRS = Hamilton Depression Rating Scale, YMRS = Young Mania Rating Scale.

and/or met criteria for a current mixed episode (3 clinically significant symptoms on computer-administered YMRS, n = 23). Only 89 (33.6%) of the 265 subjects met the eligibility requirements based on the computer ratings. The computer ratings demonstrated numerically greater differences favoring ziprasidone over placebo in subgroups meeting eligibility requirements, those having higher confidence bipolar diagnosis, and those having better quality ratings.

Among subjects meeting eligibility requirements based on the MADRS score ≥ 20, high diagnostic confidence, and high rater quality, the computer change from baseline scores show a small numerical advantage for ziprasidone, while the site-based raters found a difference favoring placebo of similar magnitude (see Table 3).

Subjects with mixed episodes (n = 23 for placebo and n = 24 for ziprasidone) had a numerically better outcome on placebo than ziprasidone. In contrast, among those eligible by this criterion, the numerical difference favored ziprasidone, particularly so when based on the computer ratings. Similarly, separation between ziprasidone and placebo was greater for subjects with high diagnostic confidence (n = 114) than lower diagnostic confidence. The separation was numerically greater based on the computer ratings for those subjects (n = 89).

Poor quality ratings at baseline were associated with a trend for better improvement on placebo than ziprasidone. This observation was true overall and among subjects meeting all eligibility requirements and having high diagnostic confidence. Among the 73 subjects with poor quality ratings at baseline, placebo was numerically superior to ziprasidone. The largest differences were seen for the subgroup with subject inflation.

Safety

Adverse events were reported by 122 subjects (83.0%) in the ziprasidone group and 108 (73.5%) in the placebo group (Table 4); adverse events that were considered to be treatment related occurred in 107 subjects (72.8%) and 69 subjects (46.9%) in the ziprasidone and placebo groups, respectively. More than 80% of adverse events in each group were mild

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Table 4. Summary of Treatment-Emergent Adverse Events

Variable, n (%)	Ziprasidone (n = 147)	Placebo (n = 147)
Subjects with adverse events	122 (83.0)	108 (73.5)
Subjects with treatment-related adverse events	107 (72.8)	69 (46.9)
Subjects with severe adverse events	27 (18.4)	11 (7.5)
Subjects with serious adverse events	1 (0.7)	6 (4.1)
Discontinuations due to adverse events	27 (18.4)	16 (10.9)
Adverse events occurring in ≥ 5% of subjects in either group		
Diarrhea	7 (4.8)	11 (7.5)
Nausea	16 (10.9)	8 (5.4)
Fatigue	19 (12.9)	6 (4.1)
Akathisia	8 (5.4)	2 (1.4)
Dizziness	19 (12.9)	9 (6.1)
Headache	17 (11.6)	14 (9.5)
Sedation	21 (14.3)	7 (4.8)
Somnolence	33 (22.4)	7 (4.8)
Tremor	13 (8.8)	10 (6.8)
Anxiety	9 (6.1)	1 (0.7)
Insomnia	17 (11.6)	10 (6.8)
Restlessness	8 (5.4)	2 (1.4)

or moderate in severity (Table 4). Overall, 27 ziprasidone-treated subjects (18.4%), and 16 (10.9%) of those in the placebo group, discontinued treatment because of adverse events: discontinuations were similar whether the mood stabilizer was valproate (12/104, 11.5%), lamotrigine (12/82, 14.6%), or lithium (19/107, 17.8%), irrespective of adjunctive therapy. The most common adverse events (those occurring in at least 5% of subjects in either group) are summarized in Table 4.

Five subjects in the ziprasidone treatment group experienced adverse events that were considered to be possibly suicide related: suicidal ideation (n = 3), overdose (n = 1), and suicide attempt (n = 1). Five subjects in the placebo treatment group also experienced possibly suicide-related adverse events: suicidal ideation (n = 2), suicide attempt (n = 1), intentional self-injury (n = 1), and bipolar I disorder (n = 1). With regard to possibly suicide-related adverse events by mood stabilizer, there were 7 (6.5%) in the group treated with lithium, 2 (2.4%) in the lamotrigine group, and none in the divalproex group. Three subjects in each group discontinued treatment because of these possibly suicide-related adverse events.

A total of 9 serious adverse events (defined as death, risk of death, significant disability/incapacity) in 8 subjects were reported. Ziprasidone subjects experienced 3 serious adverse events (suicide attempt, overdose, dyspnea), and placebo subjects experienced 6 serious adverse events (palpitations, suicidal ideation, parasuicide, bipolar depressive episode, manic symptoms, manic episode). Eight events were treatment emergent, and 1 event (suicide attempt) occurred posttreatment (ie, > 6 days after the final dose of study drug).

Ziprasidone treatment was not associated with any consistent abnormalities in clinical laboratory evaluations, physical examination, vital signs, or ECG. Mean fasting glucose increased by 6.6 mg/dL for ziprasidone and 2.4 mg/dL for placebo (lamotrigine group), by 2.7 mg/dL for ziprasidone and 1.5 mg/dL for placebo (lithium group), and by 8.0 mg/dL for ziprasidone and 2.9 mg/dL for placebo (valproate group). Two subjects in the ziprasidone group and 1 subject in the placebo group experienced mild adverse events of decreased weight. Increased weight was reported more frequently as an adverse event: 5 subjects in the ziprasidone group and 3 subjects in the placebo group experienced adverse events of increased weight.

Movement disorder scores were similar over time. Mean (SD) scores at baseline were 0.3 (1.1) in the ziprasidone group and 0.2 (0.7) in the placebo group (Simpson-Angus Scale), 0.2 (0.4) in both groups (Barnes Akathisia Scale), and 0.1 (0.4) in both groups (AIMS), and there were minimal apparent postbaseline differences between the ziprasidone group and placebo group. Benztropine and/or propranolol were allowed as treatment for extrapyramidal symptoms during the study period; therefore, movement disorders that developed and were treated between assessment days would not have been captured by the Simpson-Angus Scale, Barnes Akathisia Scale, or AIMS.

DISCUSSION

This study found no statistically significant difference between placebo and ziprasidone as adjuncts for bipolar depressed subjects treated with valproate, lithium, or lamotrigine on the primary outcome measure and most of the secondary measures of antidepressant efficacy. Subjects receiving adjunctive ziprasidone, however, had significantly better improvement on the GAF and Sheehan Disability Scale compared to subjects receiving placebo.

The apparent lack of antidepressant efficacy for ziprasidone in this trial may have occurred for several reasons. First and most obvious is the possibility that ziprasidone is not effective as adjunctive treatment for bipolar depression. Although ziprasidone has been shown to have serotonin-norepinephrine reuptake inhibition comparable to imipramine, this mechanism may not be germane to efficacy for bipolar depression. Depression and the depressive phase of bipolar disorder follow different time courses and may have different neurochemical substrates. While monoamine uptake blockade may be pertinent to the former, recent data suggest that its relevance to bipolar disorder is more equivocal. It is difficult to extrapolate from in vitro studies of drug concentrations associated with reuptake inhibition to predict dosages required to achieve monoamine transporter blockade in vivo.

The present study contrasts with earlier open trials that have shown ziprasidone to be effective when used as monotherapy against schizophrenic symptoms in patients with schizophrenia,[34] or as adjunctive therapy against depressive symptoms in depression or bipolar disorder,[5–7] and with studies using other atypical antipsychotics for bipolar I disorder.[8,9,35] It is possible that the dose of ziprasidone used in this study was too low to show a significant effect: the mean daily dose was 89.8 mg, which is lower than the mean dose of 112 to 132 mg achieved in successful ziprasidone monotherapy trials that evaluated bipolar mania.[36,37]

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A third possibility is that ziprasidone failed to show efficacy in this trial due to flaws inherent in the design or execution of the study. This possibility is consistent with experience in prior studies of adjunctive treatments for bipolar depression. In this context, high placebo response represents response to an active monotherapy, which may greatly reduce the power to see a response to an active adjunct. The entry requirements were designed to allow subjects to enter based on the assumption that they had not responded to an adequate course of treatment with lithium, valproate, or lamotrigine. This assumption may be false in many cases and the protocol-specified dosing guidelines for lithium, valproate, and lamotrigine may have increased the likelihood that subjects were exposed to a therapeutic level of these agents. A similar outcome was obtained in STEP-BD, in which most subjects received mood stabilizers prior to randomization but had numerically better outcomes when treated with adjunctive placebo than when treated with adjunctive antidepressant medication.[38]

The nature of the subject cohort is an important consideration in understanding the results. Here the rater quality data can shed some light on which problems may have impacted the study. This study attempted to mitigate the potential for baseline inflation by using a separate scale to qualify subjects (HDRS) from that used as the primary outcome (MADRS). On the basis of the computer ratings, about 16% of the sample in both treatment groups may have had inflated baseline scores. It does not, however, appear that qualifying subjects based on inflated HDRS scores hurt the study as much as other factors. In fact, both the site-based ratings and the computer found a nonsignificant trend for these less severely depressed subjects to improve more and have greater separation between ziprasidone and placebo than those meeting the HDRS criteria at baseline. The study was more disadvantaged by the inclusion of subjects for whom computer ratings indicated should have been ineligible due to their having mixed episodes (3 or more symptoms of mania), low confidence in their bipolar diagnosis, and poor quality ratings. The largest separations of any subgroup were observed in the subjects meeting criteria for poor quality with subject inflation and favored placebo. This brings to light a previously underappreciated problem for clinical trials. Subjects overzealous in their desire to enter a clinical trial may obscure drug-placebo differences by reporting extreme symptoms.

In summary, the computer ratings suggest that this study was impacted by inclusion of a substantial number of ineligible subjects and poor quality of ratings at baseline. The considerable improvement in concordance after baseline suggests changes in the incentives for raters and subjects after randomization and that substantial disagreement between the computer and site-based ratings at baseline may signal problematic rater-subject pairs.

Ziprasidone was well tolerated in this study. In particular, it had neutral effects on body weight and glucose metabolism, as previously reported.[39] This is in contrast to some other atypical antipsychotics that have been shown to produce clinically significant weight gain and increases in plasma glucose.[10,11]

When designing possible future studies, it will be important to put greater emphasis on assessing protocol-specified eligibility, assuring high diagnostic confidence, and achieving high quality ratings. Criteria can be developed to help site-based ratings avoid baseline inflation and identify overzealous subjects. In hindsight, it may not have been helpful in the present trial to use the HDRS to qualify subjects and the MADRS scale as the primary outcome measure. The use of the 2 scales did not produce a sample free from baseline inflation, and their use came at the cost of allowing subjects with low MADRS scores and low diagnostic confidence into the study. Only 74 of 256 subjects had reasonable MADRS scores and good quality ratings. In future studies, it may be useful to use computer and site-based ratings in tandem to determine eligibility at study entry and to maintain high quality ratings over the course of the protocol. The results of the present trial should nonetheless be seen against a background of several failed trials for this indication and in the context of wider recent clinical trial failures in psychiatry.

Drug names: benztropine (Cogentin and others), bupropion (Wellbutrin, Aplenzin, and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine-fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), propranolol (Inderal, InnoPran, and others), quetiapine (Seroquel), ziprasidone (Geodon).

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Author contributions: Statistical analyses were performed by Dr Schwartz. The article was written by the authors.

Potential conflicts of interest: **Dr Sachs** is a founder and an employee of Concordant Rater Systems; has been a consultant to Astellas, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Otsuka, Pfizer, Sepracor, Takeda, Wyeth, and Repligen; has served on speakers or advisory boards for Astellas, Bristol-Myers Squibb, GlaxoSmithKline, Sanofi, Pfizer, Sepracor, Takeda, and Wyeth; and is a stock shareholder in Concordant Rater Systems. **Drs Ice**, **Schwartz**, and **Vanderburg** are employees of and stock shareholders in Pfizer. **Dr Chappell** is an employee of Pfizer. **Dr Kasuba** has been an employee of Pfizer (2006–2009), has been employed at Concordant Rater Systems since 2009, and is a stock shareholder in Pfizer. **Dr Gurtovaya** reports no financial or other relationships related to the subject of the article.

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