Long-Term Safety and Efficacy of Ziprasidone in Subpopulations of Patients With Bipolar Mania

Paul E. Keck, Jr., M.D.; Marcio Versiani, M.D., Ph.D.; Lewis Warrington, M.D.; Antony D. Loebel, M.D.; and R. Lynn Horne, M.D.

Objective: To evaluate long-term safety and efficacy of ziprasidone.

Method: Subjects completing a 21-day placebo-controlled trial of ziprasidone in DSM-IV acute bipolar mania (N = 65) were enrolled in a 52-week open-label extension of flexibly dosed ziprasidone 40 to 160 mg/day, administered b.i.d. Three subjects had missing evaluations (N = 62) but still provided demographic data. Subpopulations with manic (N = 43) or mixed (N = 19) episodes, and with (N = 37) or without (N = 25) psychotic symptoms, were identified. Safety evaluations included adverse event monitoring, electrocardiography, and standard laboratory assessments. Efficacy measures included change from initial study baseline in Mania Rating Scale (MRS) and Clinical Global Impressions-Severity of Illness scale (CGI-S) scores, as well as MRS responder rates (≥ 50% reduction from initial study baseline). The study was conducted from March 1998 to September 1999.

Results: Almost all adverse events (98%) were mild to moderate in severity. The mean ± SD reduction in MRS score at week 55 (last observation carried forward [LOCF]) was –23.5 ± 1.5 ($p < .0001$) from a baseline of 29.4. CGI-S score decreased by 2.32 ± 0.25 at week 55 (LOCF, $p < .0001$) from a baseline of 5.0. MRS and CGI-S reductions were comparable across the subpopulations. The overall MRS responder rate was 86%; subpopulation responder rates were 88% (manic), 79% (mixed), 84% (psychotic), and 88% (nonpsychotic). Long-term improvement within subpopulations was comparable to the overall study population.

Conclusion: Sustained and comparable improvements in symptoms were seen with up to 55 weeks of ziprasidone treatment for patients initially treated for bipolar mania, regardless of whether the baseline episode was manic or mixed or involved psychotic symptoms.

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Received Jan. 9, 2008; accepted July 30, 2008. From the Department of Psychiatry, University of Cincinnati College of Medicine, Ohio (Dr. Keck); Bipolar Disorders Program, Institute of Psychiatry, Federal University of Rio de Janeiro, Brazil (Dr. Versiani); Pfizer Inc., New York, N.Y. (Drs. Warrington and Loebel); and Department of Psychiatry and Behavioral Sciences, University of Nevada School of Medicine, Las Vegas (Dr. Horne).

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Corresponding author and reprints: Paul E. Keck, Jr., M.D., Department of Psychiatry, University of Cincinnati College of Medicine, 231 Albert Sabin Way, P.O. Box 670559, Cincinnati OH 45267-0559 (e-mail: keckpe@ucmail.uc.edu).

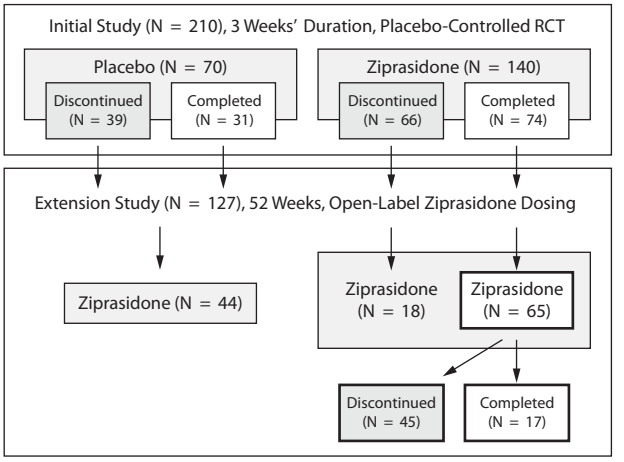
Maintenance therapy for bipolar disorder is required to prevent relapse and reduce the disability and risks associated with subsyndromal symptoms and recurrent illness. Traditional first-line pharmacotherapy for both acute and long-term management of bipolar disorder includes lithium and valproate,[1] although only lithium, lamotrigine, olanzapine, and aripiprazole have indications for the long-term treatment of bipolar I disorder. Although these drugs have generally demonstrated efficacy in controlling both manic and depressive symptoms in both short-term and long-term studies, many patients do not respond well to monotherapy, either initially or as the illness progresses, and require additional medications to control symptoms adequately.

Atypical antipsychotic drugs are the most recent class of drugs to be recommended for treatment of moderate-to-severe acute manic episodes, with or without psychotic symptoms, both in combination with traditional agents and as monotherapy. There is a substantial body of evidence supporting their use for the treatment of bipolar mania, including data from a number of randomized, placebo-controlled trials.[2–5] On the basis of these data, most atypical antipsychotic drugs, including ziprasidone, are approved for the treatment of bipolar mania in the United States and many other countries.

In a 3-week randomized controlled trial, ziprasidone produced a rapid and sustained improvement in mania in patients with bipolar I disorder.[4] Subjects included in this study were hospitalized and, on average, were markedly ill at baseline. After 2 days of ziprasidone therapy, a significant reduction in Mania Rating Scale (MRS) scores was seen that continued until study end (day 21).[4]

The efficacy of atypical antipsychotic drugs with respect to predictive clinical features has not been systematically investigated with all available drugs or in long-term studies. Some preliminary evidence, however, suggests that the atypical antipsychotic drug olanzapine is equally effective for acute mania in various bipolar subpopulations.[6] The current post hoc analysis sought to examine the long-term efficacy of ziprasidone in subpopulations of a patient cohort with bipolar I disorder who had participated in the initial pivotal short-term placebo-controlled trial.[4]

Figure 1. Subject Enrollment and Disposition in the 3-Week Placebo-Controlled Initial and 52-Week Open-Label Extension Studies[a]



[a]The groups shown with bold lines are those patients who completed 3 weeks of ziprasidone treatment in the initial study and who entered the extension study. Three subjects had missing baseline or end point evaluations and were excluded from the efficacy evaluable population (N = 62).

METHOD

Study Overview

This report describes an open-label, 52-week extension study of ziprasidone in subjects with bipolar mania. The study was conducted from March 1998 to September 1999. Subjects recruited to this extension study had previously participated in a 21-day, randomized, placebo-controlled trial of ziprasidone in acute bipolar mania.[4] Figure 1 displays the patient recruitment, completion, and discontinuation rates in each treatment arm.

The present report describes only those subjects who were assigned to receive ziprasidone throughout both the initial study and the extension phase (ziprasidone-ziprasidone cohort, N = 65). Subjects included in the present analysis therefore received ziprasidone during the 21-day acute phase of the study[4] and were assigned to receive ziprasidone during the 52-week open-label phase of this investigation, thus receiving a total of up to 55 weeks of ziprasidone treatment. All eligible subjects provided written, informed consent to participate in the extension phase. The original protocol, dated September 25, 1997, and its 2 amendments, dated March 24, 1998 and October 1, 1998, were reviewed and approved by the institutional review board at each site participating in the study.

Patients and Eligibility

To be eligible to participate in the acute study, subjects were required to be inpatients, aged 18 years or older, meeting DSM-IV diagnostic criteria for bipolar I disorder,[7] and experiencing a current manic or mixed episode. Subjects were also required to have an MRS score ≥ 14, with a score ≥ 2 on at least 4 items at baseline and screening. Patients considered at risk of suicide or homicide and women who were pregnant, lactating, or not using a reliable form of birth control were excluded from enrollment. Individuals with a history or serologic evidence of chronic or acute hepatitis or human immunodeficiency virus were also excluded from study participation as were those with clinically significant laboratory or electrocardiogram (ECG) findings at screening or baseline.

Subjects in the extension study were further required to have a willingness and ability to restrict the use of other psychotropic medications (see Concomitant Medications for permitted drugs). Subjects who had experienced any of the following to a serious or clinically significant degree during participation in the initial study were excluded from the extension study: an adverse event (AE) judged by investigators as likely caused by study drug, laboratory abnormality, ECG abnormality, or medical illness.

Ziprasidone Dosing

Ziprasidone was started at 80 mg/day (dosed b.i.d., with food) on day 1 of the initial study, titrated to 160 mg/day on day 2. Dose adjustments were permitted on days 3 to 21 (limited to a maximum of 40 mg/day within a range of 80–160 mg/day). Mean ± SD ziprasidone dose from days 15 to 28 (end point of the initial study ± 7 days) was 122.4 ± 28.0 mg/day. During the extension study, open-label ziprasidone was administered in flexible doses ranging between 40 and 160 mg/day.

Concomitant Medications

Lithium, carbamazepine, and valproate were permitted during the extension study, as were selective serotonin reuptake inhibitors, bupropion, and venlafaxine. Tricyclic

antidepressants and monoamine oxidase inhibitors were not permitted. Benzodiazepines, such as lorazepam for agitation or insomnia and temazepam for insomnia, were permitted. Anticholinergic drugs and propranolol were permitted as needed to treat extrapyramidal symptoms and akathisia, respectively, but were not to be administered prophylactically.

Extension Study Safety Assessments

All observed or reported AEs were recorded and evaluated for severity, duration, and possible relationship to study drug. Laboratory assessments were conducted at screening and weeks 3, 7, and 55 (or at the time of early discontinuation). Laboratory assessments included complete blood count (with differential and platelet count), urinalysis, and blood chemistries. Clinical assessments were conducted at baseline, week 3, week 7, and week 55 (or at early discontinuation) and included body weight, blood pressure, pulse rate, and 12-lead ECG recordings (also measured at week 31). Abnormal movements were rated using the Simpson-Angus Rating Scale (SAS),[8] Barnes Akathisia Scale (BAS),[9] and Abnormal Involuntary Movement Scale (AIMS)[10] at baseline, week 3, week 7, and week 55 (or early termination).

Efficacy Assessments

Mania Rating Scale.[11] Reduction in initial study baseline MRS score and the proportion of subjects considered to be responders using the MRS (≥ 50% reduction in initial study baseline MRS score)[11] were determined for both the initial study and the open-label extension.

Clinical Global Impressions Scale. Clinical Global Impressions-Severity of Illness (CGI-S)[10] scores were obtained at baseline and during both the initial study and the open-label investigation. The CGI-S scale assesses the severity of the subject's condition on a scale ranging from 1 (normal) to 7 (among the most extremely ill).[10]

Cohort Subpopulations

Although some comparative data are presented from the entire extension study patient group, the present analysis cohort was composed of subjects who completed the 21-day acute randomized, double-blind, placebo-controlled study, during which they were randomly assigned to receive ziprasidone,[4] and who continued taking ziprasidone during the 52-week open-label extension phase of the study. Subpopulations who met DSM-IV criteria for either a manic or a mixed episode at initial study baseline were correspondingly categorized for current analysis purposes as "manic" or "mixed," according to the presenting episode. Similarly, subjects were further categorized into "psychotic" or "nonpsychotic" subpopulations on the basis of the presence or absence of psychotic symptoms at initial study baseline (a score of ≥ 4 on at least 1 of the Positive and Negative Syndrome Scale [PANSS][12] positive items: delusions, conceptual disorganization, and hallucinatory behavior).

Statistical Analysis

Descriptive statistics for initial study baseline and change from initial study baseline were summarized for efficacy variables. The proportion of subjects with clinically significant response (≥ 50% reduction in MRS initial study baseline score) was determined. Efficacy outcomes among the subpopulations were compared using an analysis of covariance model, which included visit and patient subpopulation as main effects, and baseline and study center were used as covariates. Two-sided, single-sample t tests were used to compare each visit with the initial study baseline for efficacy measures. Analyses were restricted to those subjects who were randomly assigned to ziprasidone and completed the 21-day initial study and who continued to receive open-label ziprasidone during the extension investigation. Missing data were handled using the last-observation-carried-forward (LOCF) technique. End point values reported were LOCF; all other time points were reported based on observed cases.

RESULTS

Subjects

Of 210 subjects who entered the 21-day, double-blind initial study, 127 entered the 52-week, open-label extension study, with ziprasidone flexibly dosed 80 mg/day to 160 mg/day. The demographics of these subjects are shown in Table 1. Of 140 subjects who had been assigned to the ziprasidone treatment arm of the initial study, 65 successfully completed the initial study and entered the extension trial (ziprasidone-ziprasidone cohort) and were evaluated for safety and efficacy. Three subjects had missing baseline or end point evaluations and were excluded from the efficacy evaluable population. Of the remaining 62 subjects, 19 met criteria for a mixed episode at baseline and 43 met criteria for a manic baseline episode. A total of 37 subjects had psychotic symptoms at baseline. Baseline demographic and clinical characteristics of the subject subpopulations were statistically comparable in terms of sex distribution, weight, and ethnicity (Table 1). Most subjects were moderately to severely ill at baseline, with the ziprasidone-ziprasidone cohort as a whole having a mean MRS (± standard error of the mean [SEM]) score of 29.4 ± 1.0 and a CGI-S score of 5.03 ± 0.11.

Ziprasidone Dosing

The median daily dosage of ziprasidone in the ziprasidone-ziprasidone cohort throughout the long-term extension study was 130 mg/day (mean ± SD = 125.2 ± 31.9 mg/day). Doses did not change significantly over the

Table 1. Baseline Demographic and Clinical Characteristics of the Extension Study Population and Subpopulations

Characteristic	Overall Extension Study Cohort (N = 127)	Ziprasidone-Ziprasidone Cohort (N = 62/65)[a]	Subpopulations of Ziprasidone-Ziprasidone Cohort			
			By Episode Type		By Psychotic Symptoms	
			Manic (N = 43/46)[a]	Mixed (N = 19)	Psychotic (N = 37)	Nonpsychotic (N = 25/28)[a]
Age, mean ± SD, y	38.9 ± 11.0	38.3 ± 10.7	39.0 ± 10.8	36.4 ± 10.6	38.3 ± 9.2	38.2 ± 12.6
Weight, mean ± SD, kg						
Men	82.3 ± 19.3	78.4 ± 19.4	79.6 ± 21.1	75.3 ± 14.5	78.0 ± 13.2	78.0 ± 25.9
Women	69.5 ± 14.4	66.5 ± 13.3	67.7 ± 14.3	63.9 ± 10.9	65.8 ± 14.2	67.5 ± 12.5
Men, N (%)	61 (48)	32 (49)	23 (50)	9 (47)	18 (49)	14 (50)
Race, N (%)						
White	101 (79.5)	50 (76.9)	34 (73.9)	16 (84.2)	27 (73.0)	23 (82.1)
Black	12 (9.4)	7 (10.8)	6 (13.0)	1 (5.3)	5 (13.5)	2 (7.1)
Asian	2 (1.6)	1 (1.5)	1 (2.2)	0 (0.0)	1 (2.7)	0 (0.0)
Other	12 (9.4)	7 (10.8)	5 (10.9)	2 (10.5)	4 (10.8)	3 (10.7)
MRS score, mean ± SD	27.8 ± 7.4	29.4 ± 7.9	31.1 ± 7.9	25.6 ± 7.0	30.8 ± 8.5	27.4 ± 7.0
CGI-S score, mean ± SD	4.94 ± 0.89	5.03 ± 0.87	5.2 ± 0.78	4.7 ± 1.00	5.2 ± 0.91	4.7 ± 0.80

[a]Three subjects in the extension study had missing baseline or end point evaluation and hence were excluded from the efficacy evaluable population (MRS and CGI-S) but still provided demographic data.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, MRS = Mania Rating Scale.

Table 2. Adverse Events Reported by ≥ 5% of Patients Over the 55 Weeks of Initial and Extension Study Periods

Adverse Event	All Subjects[a] (N = 127), N (%)	Ziprasidone-Ziprasidone Cohort (N = 62), N (%)
Somnolence	46 (36.2)	26 (41.9)
Dizziness	20 (15.7)	14 (22.6)
Headache	17 (13.4)	12 (19.4)
Tremor	17 (13.4)	8 (12.9)
Akathisia	14 (11.0)	9 (14.5)
Extrapyramidal syndrome	14 (11.0)	7 (11.3)
Insomnia	12 (9.4)	4 (6.5)
Dystonia	11 (8.7)	7 (11.3)
Nausea	11 (8.7)	8 (12.9)
Constipation	8 (6.3)	6 (9.7)
Diarrhea	8 (6.3)	5 (8.1)
Agitation	7 (5.5)	4 (6.5)
Dyspepsia	6 (4.7)	5 (8.1)

[a]All subjects group includes subjects who received placebo during the initial study.

course of the extension period: mean ± SD = 122.6 ± 36.3 mg/day (days 29–90), 118.4 ± 39.9 mg/day (days 91–180), and 123.6 ± 38.5 mg/day (days 181–364).

Sixty of 62 subjects (97%) took at least 1 concomitant medicine. The most common concomitant medications used by this cohort were hypnotic, sedative, and anxiolytic drugs (N = 53, 86%); antipsychotics (N = 5, 8%); antimanic drugs (N = 4, 6%); nonemergency antiepileptic drugs (N = 11, 18%); antidepressants (N = 17, 27%); analgesics (over the counter or prescription) (N = 26, 42%); drugs to treat allergic disorders (N = 9, 15%); antimuscarinic drugs used in parkinsonism (N = 25, 40%); and drugs used in rheumatic diseases and gout (almost entirely anti-inflammatory analgesics, N = 26, 42%).

Five patients in the ziprasidone-ziprasidone cohort took an additional antipsychotic medication during the extension study (2 subjects received 1 day of haloperidol, 2 subjects received 1 day of chlorpromazine, and 1 subject received quetiapine throughout the extension study).

Safety and Tolerability

Of 127 subjects in the extension study, 104 (82%) experienced treatment-related AEs. Of 377 AEs reported, only 16 (4%) were rated severe. The most common treatment-emergent and treatment-related AEs are summarized in Table 2 and included somnolence, dizziness, and headache.

A similar profile was seen in the ziprasidone-ziprasidone cohort. Adverse events judged by investigators to be treatment related were reported in 87% (54/62) of subjects. Again, the vast majority (98%) were graded mild or moderate in severity. Of 216 AEs reported, only 5 (2%) were rated severe. These were chest pain, bradycardia, insomnia, somnolence, and abnormal thinking.

A total of 101 of 127 subjects (80%) discontinued treatment during the 52-week extension study. Of these 101, 25 subjects (25%) discontinued for reasons related to study treatment. Ten of these 25 (40%) discontinued because of insufficient clinical response, and 15 (60%) discontinued because of treatment-related AEs, including 1 subject who discontinued because of an increase in the Bazett-corrected QT interval of 61 ms (at day 204) from a baseline of 408 ms.

Seventy-five of 127 subjects (59%) discontinued for reasons unrelated to study drug. Of these 75, 44 subjects (59%) either withdrew consent or were lost to follow-up, 12 (16%) discontinued due to AEs, and 19 (25%) discontinued for other reasons, including protocol violations and relocation of residence.

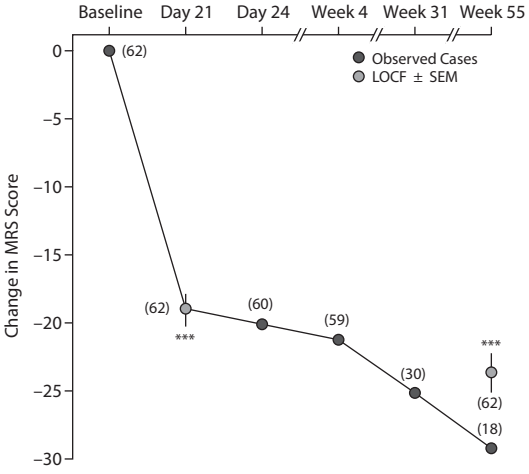
The ziprasidone-ziprasidone cohort showed a similar profile of discontinuations, with 45 of 62 subjects (73%) discontinuing treatment during the study. Only 9 of these 45 subjects (20%) discontinued for reasons related to

Table 3. Weight, Laboratory Assessments, and Abnormal Movement Scores

Measure	Baseline Value Mean ± SD	N	Change From Baseline at Study End Point Mean ± SD	N
Body weight, kg	72.3 ± 17.8	62	–5.9 ± 20.6	23
Fasting laboratory values, mg/dL				
Cholesterol	187.0 ± 37.1	61	0.8 ± 33.5	53
Triglycerides	169.8 ± 136.2	61	–37.7 ± 112.3	53
Abnormal movement scores				
SAS	0.28 ± 0.57	53	0.11 ± 1.66	53
BAS	0.32 ± 0.83	53	0.08 ± 0.85	53
AIMS	0.16 ± 0.47	53	0.06 ± 0.69	53

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, SAS = Simpson-Angus Scale.

Figure 2. Changes in Mania Rating Scale (MRS) Score Over 55 Weeks (N = 62)[a]



[a]Changes in MRS scores in subjects who received ziprasidone throughout the initial study (baseline to 21 days) and extension phase (up to week 55). The number of patients (observed cases/LOCF) at each time point is shown in parentheses.
***p < .0001 versus baseline.
Abbreviations: LOCF = last observation carried forward, SEM = standard error of the mean.

study treatment; 3 of 45 (7%) discontinued due to insufficient clinical response and 6 (13%) because of treatment-related AEs. No subjects discontinued because of an increase in corrected QT. Thirty-six of 62 subjects (58%) discontinued for reasons unrelated to study drug: 23 of the 36 subjects (64%) either withdrew consent or were lost to follow up, 6 (17%) discontinued due to AEs, and 7 (19%) discontinued because of protocol violations or relocation.

Average values (means ± SD) for key laboratory assessments and abnormal movement scores at baseline and end point in the ziprasidone-ziprasidone subject cohort are summarized in Table 3. Changes from baseline in body weight and serum chemistry were generally not clinically significant.

Efficacy Assessments

Figures 2 through 4 display the changes in MRS variables over the course of the trial for the 62 subjects who received ziprasidone throughout the initial and extension phases. Figure 2 shows data from the entire ziprasidone-ziprasidone cohort: MRS scores decreased by 19 at 21 days (the end of the initial study) and by 29 at 55 weeks, from the initial study baseline of 29 (Figure 2, observed cases). The mean ± SD reduction in MRS score at 55 weeks (LOCF) for the cohort as a whole was –23.5 ± 1.5 ($p < .0001$ vs. initial study baseline). Criteria for MRS response (≥ 50% reduction in initial study baseline MRS score) were met by 86% of cohort subjects at 55 weeks compared with 73% at 21 days.

Mean CGI-S score decreased by 2.2 and 2.3 at 21 days and 55 weeks, respectively, from the initial study baseline of 5.0. The mean CGI-S score at 55 weeks (LOCF) for the cohort as a whole was 2.7 ± 0.2, reflecting a mean decrease of 2.32 ± 0.25 ($p < .0001$ versus initial study baseline).

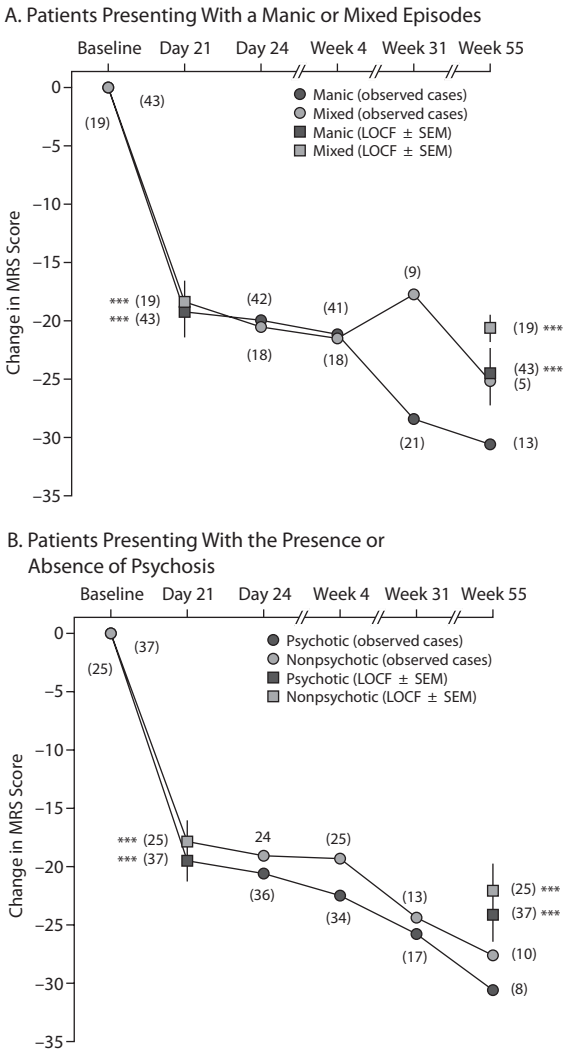
Mania Rating Scale scores were compared in manic and mixed episode subjects and in those with and without baseline psychotic symptoms. Mania Rating Scale scores in all subpopulations of the ziprasidone-ziprasidone cohort declined sharply in the initial 21-day double-blind trial. This decline was sustained through week 55 of the open-label extension period (Figure 3A and 3B). Similar reductions in MRS scores were observed in the manic, mixed, psychotic, and nonpsychotic subpopulations.

Mean reduction in MRS score from baseline at week 55 of ziprasidone treatment (LOCF) was statistically significant ($p < .0001$), comparable among the subpopulations (range, –20.8 to –24.7), and similar to that in the overall ziprasidone-ziprasidone study cohort.

At week 55, MRS response (≥ 50% reduction in initial study baseline MRS score) rates were statistically similar among the patient subpopulations (88% in manic, 79% in mixed, 84% in psychotic, and 88% in nonpsychotic subjects) (Figure 4). These response rates were comparable to those observed in the 21-day double-blind phase.

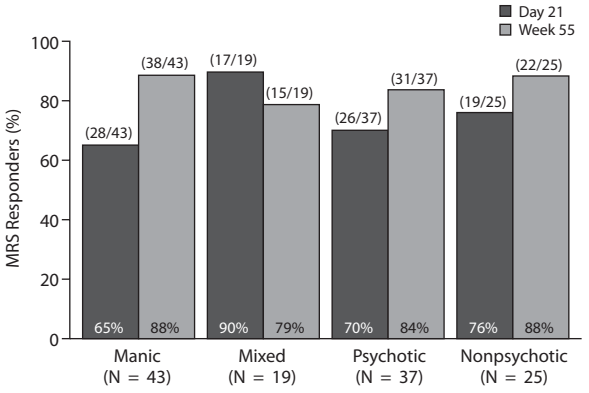
Clinical Global Impressions-Severity of Illness scores also declined sharply in the initial double-blind trial. This decline was sustained throughout the open-label extension period. Clinical Global Impressions-Severity of Illness scores fell to similar values in manic, mixed, psychotic, and nonpsychotic subpopulations. With 21 days of ziprasidone therapy, mean ± SEM CGI-S scores (LOCF) were significantly ($p < .0001$) improved from initial study baseline among the patient subpopulations (manic: –2.2 ± 0.2; mixed: –2.2 ± 0.3; psychotic: –2.2 ± 0.2; nonpsychotic: –2.2 ± 0.4). With up to 55 weeks of ziprasidone therapy, mean ± SEM CGI-S scores (LOCF) were significantly

Figure 3. Changes in Mania Rating Scale (MRS) Score in Patient Subgroups (N = 62)[a]



[a]Changes in MRS scores in subjects who received ziprasidone throughout the initial study (baseline to 21 days) and extension phase (up to week 55). The number of patients (observed cases) at each time point is shown in parentheses.
***p < .0001 versus baseline.
Abbreviations: LOCF = last observation carried forward, SEM = standard error of the mean.

Figure 4. Mania Rating Scale (MRS) Responders at 21 Days and 55 Weeks (N = 62)[a]



[a]Proportion of MRS responders (≥ 50% reduction from initial study baseline MRS score) in subjects who received ziprasidone throughout the initial study (baseline to 21 days) and extension phase (up to week 55). The number of responders (last observation carried forward) at each time point is shown in parentheses for manic, mixed, psychotic, and nonpsychotic subjects (left to right).

improved from initial study baseline among the patient subpopulations (manic: –2.5 ± 0.3; mixed: –1.8 ± 0.5; psychotic: –2.4 ± 0.3; nonpsychotic: –2.2 ± 0.4). Apart from the mixed group at week 55 ($p < .005$), all values were significantly different from acute study baseline at the $p < .0001$ level.

DISCUSSION

This long-term extension study provides important data regarding the safety and tolerability profile observed with long-term use of ziprasidone. For most subjects, ziprasidone treatment was generally safe and well tolerated; the AE profile (Table 2) was mostly unexceptional, with somnolence and dizziness the most commonly reported AEs. The prevalence of akathisia and agitation was comparatively high, which may suggest some activation. Most AEs were mild or moderate in severity.

Although discontinuations were high (73%), only 3 patients in the extension study cited insufficient clinical response as a reason for discontinuation, while 6 left the trial due to adverse events. Mostly, subjects left the study for reasons unrelated to the study drug.

Concerns have been raised about the tolerability and safety of long-term atypical antipsychotic use and certain atypical antipsychotic drugs have been linked to weight gain and metabolic dysfunction.[13–15] Analyses of available data indicate clear differences among available atypical antipsychotic drugs for weight gain and metabolic dysregulation,[16] with the highest risks posed by clozapine and olanzapine and the lowest risks associated with aripiprazole and ziprasidone.[14] In the present study, no significant changes in vital signs, body weight, or blood laboratory values were seen with long-term ziprasidone administration (Table 3). Extrapyramidal symptoms were detected in 11% of the participants, and few subjects discontinued because of treatment-related AEs. Our findings suggest that side effects, such as weight gain, metabolic dysfunction, and extrapyramidal symptoms, may be minimized with ziprasidone.

Among clinically distinct subpopulations of patients with bipolar I disorder, ziprasidone therapy administered for up to a total of 55 weeks was comparably efficacious.

Mania Rating Scale scores and improvements in CGI-S ratings were similar, regardless of whether the initial episode was predominantly manic or mixed or whether psychotic symptoms were present or absent. The majority of subjects in this analysis exhibited a sustained improvement in manic symptoms; overall, 86% of subjects at the 52-week extension study end point met criteria for MRS response, defined here as ≥ 50% reduction from initial study baseline in total MRS score. In line with this, at end point, the mean reduction from initial baseline MRS score was 24 points, or 80% of the mean initial study baseline score.

These findings are consistent with other recent reports concerning longer-term efficacy of atypical antipsychotic drugs in patients with bipolar I disorder.[17–19] In a 9-week open-label investigation of risperidone in patients with bipolar I disorder, Young MRS scores were decreased by a mean of 30 points from double-blind baseline.[17] In a much longer, 49-week, extension trial, open-label olanzapine therapy was associated with an 18-point decrease in Young MRS scores.[18] More recently Tohen and colleagues[19] described results of a 48-week placebo-controlled, randomized trial of olanzapine in patients with bipolar I disorder who achieved remission from mania during acute treatment with olanzapine. A significantly lower relapse rate was seen among olanzapine-treated patients (47%) than among patients who received placebo (80%).[19]

None of the recent long-term studies described or examined clinical subpopulations, as in the present analysis. In a meta-analysis of 2 short-term controlled trials in patients with bipolar I disorder who received olanzapine,[6] short-term therapy was equally effective in reducing acute manic symptoms among patients with manic or mixed episodes or among those with or without psychotic symptoms. Our observations indicate that, like olanzapine, ziprasidone is also broadly effective for these subpopulations of bipolar I patients but, in addition, they suggest that clinical features at the time of acute presentation of mania in bipolar I disorder are unlikely to influence long-term outcomes with ziprasidone therapy. These findings contrast with outcome data for lithium or valproate, which have indicated that clinical features may have a significant impact on therapeutic outcome with these drugs.[20]

Limitations

The open-label design of the current study and use of concomitant psychotropic agents makes it difficult to draw definitive conclusions about the long-term efficacy of ziprasidone, which must remain provisional given the absence of a control group. Since concomitant medications were permitted during the open-label phase of the trial, conclusions regarding the specific role of ziprasidone in maintaining the improvements observed should be made with caution.

CONCLUSIONS

For patients with acute bipolar mania, up to 55 weeks of treatment with ziprasidone demonstrated comparable levels of sustained efficacy in each of 4 defined subpopulations: manic, mixed, psychotic, or nonpsychotic at presentation. Ziprasidone was generally well tolerated; no clinically significant changes in body weight or serum lipid levels were seen in this subpopulation or in the larger overall study population.[4,21] Regardless of episode type, most patients exhibited long-term response to ziprasidone, with persistent, significant reductions in mania and illness severity at study end.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Innopran, Inderal, and others), quetiapine (Seroquel), risperidone (Risperdal and others), temazepam (Restoril and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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