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Tolerability of Oral Ziprasidone in Children and Adolescents with Bipolar Mania, Schizophrenia, or Schizoaffective Disorder

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Abstract

Objective: This study characterizes the tolerability of ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder.
Method: Sixty-three subjects (aged 10–17 years) entered an open-label study consisting of a 3-week fixed-dose period (Period 1) and a subsequent 24-week flexible-dose period (Period 2). In Period 1, subjects received ziprasidone 80 or 160 mg/d in two divided doses, titrated over 10 days. In Period 2, subjects received flexible doses (20–160 mg/d). Tolerability was evaluated using movement rating scales, laboratory tests, and electrocardiograms. Clinical response was assessed using the Young Mania Rating Scale, the Brief Psychiatric Rating Scale-Anchored Version, and the Clinical Global Impressions–Severity scale.
Results: Adverse events (AEs) occurred mostly during dose titration and in the high-dose (160 mg/d) group. The most common AEs during Period 1 were sedation (32%), somnolence (30%), and nausea (25%) and during Period 2 were sedation (30%), somnolence (30%), and headache (25%). The incidence of movement disorder AEs was 22% and 16% during Periods 1 and 2, respectively. Six percent of study participants discontinued study participation due to AEs during Period 1 and 20% discontinued in Period 2. Thirty-three percent of subjects gained ≥7% of their baseline weight. No Fridericia-corrected QT (QTcF) intervals of >450 ms were observed during Period 1 and only one occurred during Period 2. No QTcF increase ≥60 ms from baseline was observed. Symptom reductions were observed in all patient groups.
Conclusions: No unexpected tolerability findings were observed in this prospective trial of ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. On the basis of the results, a starting dose of 20 mg/d titrated to between 80 and 160 mg/d over 1–2 weeks appears optimal for most patients.

Introduction

ATYPICAL ANTIPSYCHOTIC AGENTS are increasingly prescribed to children and adolescents primarily for the treatment of bipolar disorder, schizophrenia, or schizoaffective disorder (Cooper et al. 2004; Curtis et al. 2005; Olfson et al. 2006). As the use of atypical antipsychotics in youth increases, an understanding of their dosing, tolerability, and safety in children and adolescents becomes essential.

Although several studies have demonstrated that ziprasidone is safe and efficacious for the treatment of adults with schizophrenia (Goff et al. 1998; Keck et al. 1998; Daniel et al. 1999) and bipolar disorder (Keck et al. 2003; Potkin et al. 2005), few studies have examined the use of ziprasidone in children and adolescents with psychiatric disorders. However, these studies are limited by their short duration and small sample size (Sallee et al. 2000; Barnett 2004; Staller 2004; Biederman et al. 2007). Nonetheless, the results of these investigations provided a rationale for further studies of ziprasidone in children and adolescents.

With these considerations in mind, the tolerability of low and high doses of ziprasidone was evaluated in a 3-week

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open-label, randomized study followed by a 24-week open-label extension in children and adolescents with bipolar disorder, schizophrenia, or schizoaffective disorder. The primary aim of this study was to determine the appropriate dose and titration schedule for ziprasidone in this population. Preliminary data regarding the efficacy of ziprasidone in children and adolescents with bipolar disorder, schizophrenia, or schizoaffective disorder were also obtained.

Methods

Study design

This study was a multi-center trial involving 13 sites in the United States, of which 10 successfully enrolled subjects. Following screening, eligible subjects (aged 10–17 years) were initially randomized to open-label treatment using either a low or high dosing strategy of ziprasidone monotherapy. After sufficient subjects in the low-dose group had completed Period 1, an informal assessment of tolerability for subjects randomized to treatment within that group was performed. Since the data were adequate to determine the overall tolerability of the low-dose regimen, the group was closed, and additional subjects were enrolled into the remaining treatment group.

All subjects were treated at fixed doses for up to 3 weeks (Period 1) followed by flexible-dose treatment for 24 weeks (Period 2). Scheduled visits occurred at screening, baseline, and during Period 1 (day 4 and weeks 1, 2, 3) and Period 2 (weeks 4, 8, 12, 18, and 27). This study was, in part, a dose-finding trial using constraints and methodology required by the Food and Drug Administration (FDA) and was used to inform a subsequent 4-week, double-blind, placebo controlled phase III trial of the efficacy, safety and pharmacokinetics of flexible doses of oral ziprasidone in children and adolescents with bipolar disorder.

Dosing

All subjects and legal guardians were instructed to administer the medication with food. Titration to the assigned dose was accomplished over 10 days. In the low-dose group ($n = 23$), ziprasidone was initiated at 20 mg/d (in two doses) and titrated to 80 mg/d. In the high-dose group ($n = 40$), ziprasidone was initiated at 40 mg/d and increased to 160 mg/d. Once the target dose was achieved, treatment at fixed doses continued for up to 3 weeks (Period 1), after which subjects could enter flexible-dose treatment for 24 weeks (Period 2). Subjects who discontinued from Period 1 early were able to enter Period 2, safety permitting. Ziprasidone dosing in Period 2 was flexible and covered the dose range of 20–160 mg/d. Subjects in Period 2 could remain at the dose achieved in Period 1 or could titrate anywhere within the full range of 20–160 mg/d. Subjects weighing less than 45 kg ($n = 11$) were administered only 50% of the assigned study dose.

Inclusion and exclusion criteria

Children and adolescents, aged 10–17 years, with a manic or mixed episode of bipolar I disorder or with schizophrenia or schizoaffective disorder as defined by the *Diagnostic and Statistical Manual, Fourth Edition-Text Revised* (DSM-IV-TR) (American Psychiatric Association 2000) were eligible for the trial. The diagnosis was confirmed using a Structured Clinical Interview for DSM-IV Childhood Diagnoses (KID-SCID) performed by a child psychiatrist or psychologist. At both screening and baseline visits, subjects with bipolar disorder were required to have a Young Mania Rating Scale (YMRS) (Young et al. 1978) score of $\geq$17. Subjects with schizophrenia or schizoaffective disorder were required to have a Brief Psychiatric Rating Scale–Anchored Version (BPRS-A) (Overall and Gorham 1962) score of $\geq$35, with a score of $\geq$4 on at least one of the following items: unusual thought content, hallucinations, suspiciousness, or conceptual disorganization. Only subjects with a body mass index between the 5th and 95th percentile on the 2000 Centers for Disease Control and Prevention Growth Charts (Centers for Disease Control and Prevention 2000) were considered for study participation.

Potential subjects were excluded from study participation by any of the following: currently on stable well-tolerated treatment; suspected or established substance-induced psychotic disorder; treatment with clozapine within 12 weeks, a depot antipsychotic within 4 weeks, or a monoamine oxidase inhibitor within 2 weeks prior to baseline; imminent risk of suicide or homicide; mental retardation (i.e., documented intelligence quotient (IQ) $<$70); autism or other pervasive developmental disorder; pregnancy, breastfeeding, or unwillingness to use an appropriate method of birth control; any serious unstable medical or neurologic illness; any screening laboratory value that deviated significantly from the upper or lower limits of the normal reference range; clinically significant hypokalemia or hypomagnesemia in the investigator's judgment; a history of cardiac arrhythmias, conduction abnormalities, corrected QT (QTc) prolongation ($>$460 ms), or a genetic risk for prolonged QT syndrome; or DSM-IV–TR-defined psychoactive substance or alcohol abuse or dependence (other than nicotine or caffeine) within the preceding 1 month.

Concomitant mood stabilizers, antidepressants, and stimulants were prohibited during Period 1 but permitted during Period 2. Lorazepam (maximum of 4 mg/d), or a similar benzodiazepine, was allowed for the relief of anxiety, agitation, or insomnia. Benztropine and/or propranolol were permitted to control movement disorders. The washout period for prior antipsychotics was at least 24 hours while approximately four half-lives were required for other prohibited medications.

After study procedures were explained, informed assent and written informed consent were obtained from all study participants and legal guardians, respectively, prior to study participation.

Tolerability assessments

Tolerability assessments, including adverse events (AEs), body weight, and vital signs, were performed at all study visits. AEs were either observed by the investigator or volunteered by the subject. AEs were recorded along with the severity (mild, moderate, or severe) of the events and the investigator's opinion of the relationship to the study treatment. Movement disorders were evaluated using the Simpson-Angus Rating Scale (SARS) (Simpson and Angus 1970), the Barnes Akathisia Rating Scale (BARS) (Barnes 1989), and the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976).

Serum laboratory tests included a complete blood cell count with differential and platelet count, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glucose, prolactin, testosterone, growth hormone, and a urinalysis. All blood samples were taken after an 8-hour fast.

Electrocardiograms (ECGs) were performed at each study visit after approximately 3 hours of fasting and in a supine position for approximately 5 minutes. On the week 3 visit, one ECG was performed prior to the morning administration of ziprasidone to assess the effect of trough levels of ziprasidone on QTc interval, and a second was performed 5–7 hours later to characterize the effect of peak levels of ziprasidone on QTc interval.

ECGs were read and interpreted by a pediatric cardiologist or pediatric intensive care specialist at each site and were also transmitted electronically to a blinded central ECG reader (eResearch Technology, Inc., Philadelphia, PA). Since the Bazett QTc correction formula overcorrects at elevated heart rates (Loebel et al. 2006), only the Fridericia (QTcF) values are reported here. The data were nevertheless also analyzed using the Bazett correction (QTcB), with similar results.

Efficacy measures

The YMRS, BPRS-A, and Clinical Global Impressions–Severity scale (CGI-S) (Guy 1976) were administered at screening, baseline, all scheduled visits during Period 1, and weeks 12 and 27 during Period 2. Subjects with bipolar disorder were evaluated using the YMRS; subjects with schizophrenia or schizoaffective disorder were evaluated with the BPRS-A, and all subjects were evaluated with the CGI-S. Clinical Global Impressions-Improvement data were also obtained. Results were similar to CGI-S and are not reported here.

Statistical analysis

Descriptive statistics were used to summarize all tolerability and efficacy data. For YMRS, BPRS-A, and CGI-S, effect sizes (standard mean differences) were calculated by dividing the mean change from baseline to end point by the standard deviation of change from baseline to end point.

Safety-evaluable subjects were those who received at least one dose of study drug. Efficacy-evaluable subjects were those safety-evaluable subjects who had a baseline efficacy assessment in this study, received at least one dose of study medication, and had at least one planned post-dose efficacy assessment in Period 1. Efficacy outcomes were evaluated for subjects who completed an end-of-treatment assessment at the last scheduled visit in the period (week 3 or week 27; "completers") and for subjects who completed an end-of-treatment assessment at any scheduled visit (week 3/early termination (ET) or week 27/ET; last observation carried forward (LOCF)).

Results

Subjects

Of 82 subjects screened, 63 (77%) entered Period 1 (Table 1). Forty-six subjects had a diagnosis of bipolar I disorder, 7 schizophrenia, and 10 schizoaffective disorder. Table 2 de-

Table 1. Subject Disposition by Treatment Group During Periods 1 and 2

	Period 1 (weeks 1–3) (fixed titration)		*Period 2 (weeks 4–27) (flexible dosing)*	
	Low dose (80 mg/d)	*High dose (160 mg/d)*	*From 80 mg/d*	*From 160 mg/d*
All Subjects	23	40	22	34
Completed, n (%)	17 (24)	21 (53)	16 (73)	15 (44)
Discontinued, n (%)	6 (26)	19 (48)	6 (27)	19 (56)
Permanently discontinued due to AEs, n (%)	1 (4)	3 (8)	2 (9)	9 (27)
Bipolar I disorder	15	31	14	25
Completed, n (%)	11 (73)	17 (55)	8 (57)	11 (44)
Discontinued, n (%)	4 (27)	14 (45)	6 (43)	14 (56)
Permanently discontinued due to AEs, n (%)	1 (7)	3 (10)	2 (14)	7 (28)
Schizophrenia or schizoaffective disorder	8	9	8	9
Completed, n (%)	6 (75)	4 (44)[a]	8 (100)	4 (44)
Discontinued, n (%)	2 (25)	5 (56)	0 (0)	5 (56)
Permanently discontinued due to AEs, n (%)	0 (0)	0 (0)	0 (0)	2 (22)

[a]Minor differences between this number and the efficacy data are explained by the different criteria (definitions, windows) used for these tables.

Table 2. Demographic Characteristics of Study Participants by Diagnosis

	Bipolar I disorder (n = 46)		*Schizophrenia or schizoaffective disorder (n = 17)*	
	Low dose (80 mg/d)	*High dose (160 mg/d)*	*Low dose (80 mg/d)*	*High dose (160 mg/d)*
Sex, n (%), boys	7 (47%)	24 (77%)	5 (63%)	6 (67%)
Age, years				
10–13	9	16	2	3
14–15	3	5	2	2
16–18	3	10	4	4
Mean (SD)	13.2 (2.1)	13.8 (2.4)	14.4 (2.3)	14.7 (2.0)

SD = standard deviation.

scribes the baseline demographic characteristics of the subjects. Twenty-three subjects (37%) were allocated to the low-dose group (80 mg/d) and 40 subjects (63%) to the high-dose group (160 mg/d). The mean durations of each diagnosis among subjects in the low- and high-dose groups were 1.1 and 1.3 years for the subjects with bipolar disorder, 1.2 and 4.1 years for the subjects with schizoaffective disorder, and 3.4 and 1.4 years for the subjects with schizophrenia.

Study medications

Seventeen of 23 subjects (74%) in the low-dose group attained the target dose of 80 mg/d, and 21 of 40 subjects (53%) in the high-dose group attained the target dose of 160 mg/d in Period 1.

During flexible dosing between 20 and 160 mg/d in Period 2, 37 of 56 subjects (66%) were prescribed concomitant psychotropic medications and/or movement disorder treatments, most commonly methylphenidate, lorazepam, and benztropine ($n = 10$ each), valproate ($n = 6$), oxcarbazepine, and lithium ($n = 5$ each).

Adverse events

The safety-evaluable population included 23 subjects in the low-dose group and 40 subjects in the high-dose group (see Table 1).

Fixed titration (Period 1). In Period 1, 21 of 23 subjects (91%) in the low-dose group and 38 of 40 subjects (95%) in the high-dose group reported treatment-emergent AEs (all causality). The most common AEs (frequency ≥10%) during Period 1 are listed in Table 3. The incidence of new AEs was highest during the titration phase (Fig. 1). Most AEs were rated mild or moderate, with 13 subjects (5 and 8 in low- and high-dose groups, respectively) experiencing severe AEs.

Table 3. Common (>10% in Any Group) Adverse Events, Weight Changes, and Discontinuations in Low-Dose and High-Dose Groups

	Period 1 (fixed titration)		*Period 2 (flexible titration)*	
Adverse event, n (%)	*Low dose (80 mg/d) (n = 23)*	*High dose (160 mg/d) (n = 40)*	*From 80 mg/d (n = 22)*	*From 160 mg/d (n = 34)*
Sedation	5 (21.7)	15 (37.5)	5 (22.7)	12 (35.3)
Somnolence	8 (34.8)	11 (27.5)	8 (36.4)	9 (26.5)
Nausea	5 (21.7)	11 (27.5)	3 (13.6)	2 (5.9)
Headache	3 (13.0)	11 (27.5)	2 (9.1)	12 (35.3)
Dizziness	3 (13.0)	10 (25.0)	2 (9.1)	1 (2.9)
Vomiting	3 (13.0)	8 (20.0)	1 (4.5)	0
Fatigue	4 (17.4)	7 (17.5)	4 (18.2)	4 (11.8)
Weight gain > 7%	3 (13.0)	1 (2.5)	10 (45.5)	10 (29.4)
Discontinuations due to AEs related to study drug	3 (13.0)	16 (40.0)	1 (4.5)	3 (8.8)

AE = adverse event.

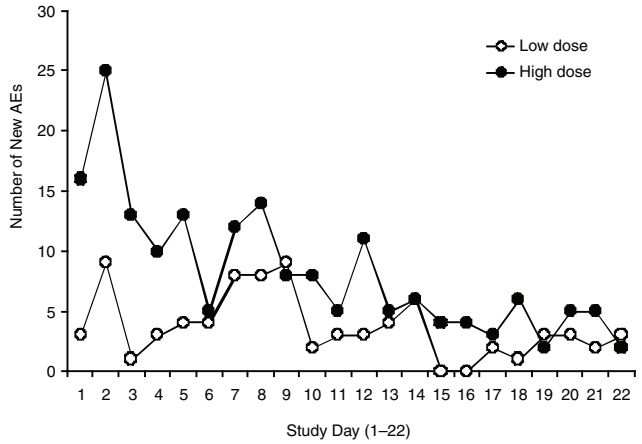

FIG 1. Adverse events (AEs) by study day.

Two subjects in the high-dose group experienced serious AEs (suicidal ideation and exacerbation of mania). Neither was considered to be related to treatment.

Flexible dosing (Period 2). In Period 2, the incidence of AEs was numerically lower than in Period 1, except for sedation and somnolence, which remained at approximately 30% (see Table 3). Most AEs were rated mild or moderate. Seventeen of 56 subjects (30.4%) experienced severe treatment-emergent AEs.

Thirteen subjects reported 19 serious AEs during Period 2. These were exacerbation of bipolar symptoms ($n = 7$), suicidal thoughts or ideation ($n = 4$), aggression ($n = 2$), homicidal ideation ($n = 1$), auditory hallucination ($n = 1$), agitation ($n = 1$), a self-harm attempt ($n = 1$), a drug overdose (880 mg ziprasidone, $n = 1$), and a prolonged QTc interval ($n = 1$). The overdose occurred in a patient who also was experiencing exacerbation of bipolar symptoms.

Movement disorders

The overall incidence of movement disorder AEs during Period 2 was 16.1% (9 of 56 subjects) compared with 22.2% (14 of 63 subjects) in Period 1. Table 4 shows the incidence of dystonia, tremor, akathisia and extrapyramidal symptoms (unspecified), in the different treatment groups. Mean scores on all three scales (SARS, BARS, and AIMS) decreased marginally from baseline to end point (≤0.5 unit) during Periods 1 and 2 (data not shown).

Seven of 63 (11.1%) subjects received benztropine during Period 1 compared with 10 of 56 subjects (17.9%) during Period 2. Table 4 shows the breakdown by dose group.

Discontinuations

Twenty-five subjects (40%) discontinued study participation during Period 1. Subjects were considered to have discontinued if either they left the trial permanently or they stopped taking the prescribed dose and switched to a lower dose. Reasons cited were AEs (19 subjects), lack of response (three subjects), and loss to follow-up or withdrawal of consent (three subjects). Of the 19 subjects who discontinued because of AEs, four discontinued permanently (see Table 1).

Many of those who discontinued during Period 1 were unable to tolerate the maximum dose demanded by the study protocol but were nonetheless able to enter Period 2, in which flexible dosing was permitted. In total, 56 subjects (89%) entered Period 2. Eleven subjects permanently discontinued the trial due to AEs during Period 2 (suicide ideation ($n = 2$), exacerbation of symptoms ($n = 3$), overdose ($n = 2$), agitation, fatigue, headache, chest pain, and increased SGOT).

Body weight

At baseline, body weight was similar in the low- and high-dose groups (mean ± standard deviation (SD), 57.7 ± 15.4 and 62.1 ± 19.6 kg, respectively). The mean (±SD) weight gain at week 3 ($n = 61$) was 1.0 ± 1.0 kg, and at week 27 ($n = 47$) was 2.8 ± 6.3 kg. Twenty-one (33.3%) of 63 subjects experienced >7% weight gain during the study, although fewer reported weight gain as an AE (5 of 56 subjects in Period 2). Three subjects had a significant weight increase (gains of 15%, 18%, and 30%).

Laboratory results

No clinically significant changes in lipid profiles were observed. Changes in total cholesterol, HDL, and LDL levels were minimal in both Periods 1 and 2. In Period 1, mean total cholesterol changes (±SD) of −3.5 ± 21.0 mg/dL ($n = 22$) and −5.8 ± 28.2 mg/dL ($n = 36$) were observed in the low-

TABLE 4. MOVEMENT DISORDER ADVERSE EVENTS AND BENZOTROPINE ADMINISTRATION IN LOW-DOSE AND HIGH-DOSE GROUPS

	Period 1 (fixed titration)		*Period 2 (flexible titration)*	
Adverse event, n (%)	*Low dose (80 mg/d) (n = 23)*	*High dose (160 mg/d) (n = 40)*	*From 80 mg/d (n = 22)*	*From 160 mg/d (n = 34)*
Akathisia	1 (4.3)	3 (7.5)	0	2 (5.9)
Dystonia	1 (4.3)	3 (7.5)	1 (4.5)	2 (5.9)
Tremor	2 (8.7)	3 (7.5)	2 (9.1)	1 (2.9)
Extrapyramidal symptoms (unspecified)	0	1 (2.5)	0	1 (2.9)
Received benzotropine	3 (13.0)	4 (10.0)	4 (18.2)	6 (17.6)

and high-dose groups, respectively, with a mean change of −10.4 ± 24.3 mg/dL (n = 37) observed at the end of Period 2. Mean HDL level changes of 0.5 ± 9.9 (n = 22) and −0.9 ± 9.4 mg/dL (n = 36) were observed in the low- and high-dose groups, respectively, in Period 1, with changes of −2.5 ± 10.9 mg/dL (n = 37) in Period 2. In Period 1, mean LDL level changes (±SD) of −1.4 ± 15.0 mg/dL (n = 21) and −0.5 ± 23.9 mg/dL (n = 36) were observed in the low- and high-dose groups, respectively, with a mean change of −5.3 ± 18.4 mg/dL (n = 37) observed at the end of Period 2.

Increased triglyceride levels occurred in 2 (3.4%) of 58 subjects during Period 1. In Period 1, mean triglyceride levels changed from baseline by −9.4 ± 60.6 (n = 22) and −21.7 ± 61.4 mg/dL (n = 36) in the low- and high-dose groups, respectively. In Period 2, there was a mean change in triglyceride levels of −13.20 ± 61.1 mg/dL (n = 37) from baseline.

The mean ± SD change from baseline to end point in fasting serum glucose level was 0.1 ± 20.9 mg/dL (n = 22) in Period 1 and 3.7 ± 11.9 mg/dL (n = 35) in the low- and high-dose groups, respectively, and a mean ± SD change in Period 2 of −1.0 ± 13.1 mg/dL (n = 37) from baseline. No subject had an elevated glucose level (>125 mg/dL) at any point, while two subjects had low fasting glucose values during Period 2.

Elevated prolactin (>1.5 × upper limit of normal (ULN)) was observed in 2 (8.7%) of 23 and 2 (5.0%) of 40 of subjects during Period 1 in the low- and high-dose groups, respectively, while in Period 2, the incidence of elevated prolactin was 9 (16.1%) of 56 subjects. In five subjects (four females and one male), elevated prolactin levels were reported as an AE at week 3. Follow-up results were available for four of those subjects. Two female subjects who received ziprasidone for 86 days and 191 days experienced prolactin elevation at week 3. The prolactin levels for the remaining subjects alternated between elevated and normal values. No subject discontinued the study because of prolactin increases.

In Period 1, no subject had an increase in testosterone in the low-dose group while 2 of 16 (13%) subjects in the high-dose treatment group experienced an increase >1.2 × ULN. The incidence of increased testosterone increased in Period 2 to 5 of 12 (42%) and 3 of 26 (12%) subjects, in the low- and high-dose groups, respectively. Only three subjects had growth hormone measured in the low-dose group. In the high dose group, 2 of 15 (13%) subjects experienced an increase >1.2 × ULN in growth hormone.

Vital signs

The mean changes from baseline through week 27 in supine and standing blood pressure were ≤4.9 mm Hg. In total, 3 (4.9%) of 63 subjects in Period 1 and 4 (7.1%) of 56 subjects in Period 2 experienced a decrease in standing systolic blood pressure ≥30 mm Hg. Also, 3 (4.9%) of 63 subjects in Period 1 and 6 (10.7%) of 56 subjects in Period 2 had a decrease in standing diastolic blood pressure ≥20 mm Hg. No clinically meaningful changes in mean pulse rates were observed during Periods 1 or 2.

QTc interval

Mean changes from baseline in QTcF intervals are summarized in Table 5. QTcB results were similar (data not shown). At baseline, QTcF values were comparable in the low- and high-dose groups. ECG measurements were obtained at week 3 during the time of expected peak exposure to ziprasidone (5–7 hours postdose) and at trough exposure (just prior to dosing). In subjects who completed Period 1 and had ECGs recorded within the protocol-specified time frame, the mean changes from baseline in the peak QTcF interval at the end of week 3 were 1.3 (n = 11) and 11.2 ms (n = 15) in the low- and high-dose groups, respectively. Corresponding values at trough exposure were 6.7 (n = 11) and 9.2 ms (n = 15), respectively.

Random ECG measurements were obtained in Period 2. In subjects who completed Period 2, the mean change from baseline in QTcF interval was 1.9 ms. No QTcF intervals >450 ms were observed during Period 1 and only one was observed during Period 2. No subject had an increase in QTcF interval of ≥60 ms from baseline. Using the Bazett correction, three subjects experienced an increase in QTcB of >60 ms. One subject was discontinued during Period 1 because of a mildly prolonged QTcF interval (34 ms increase in QTcF from baseline to a peak value of 420 ms), which was considered treatment-related.

Table 5. Baseline QTcF (Fridericia Correction) Interval and Mean Change from Baseline by Week During Period 1

	Low dose (80 mg/d)		*High dose (160 mg/d)*	
	n	*Mean (SD)*	*n*	*Mean (SD)*
Baseline, ms	23	395.6 (13.0)	40	388.1 (16.7)
Mean change from baseline, ms				
Week 1	19	1.0 (18.5)	31	9.4 (18.9)
Week 2	17	−4.6 (15.3)	25	5.0 (16.0)
Week 3 completers[a]				
0 hour post-dose (trough)	11	6.7 (21.9)	15	9.2 (17.8)
5–7 hour post-dose (peak)	11	1.3 (24.9)	15	11.2 (16.8)

[a]Subjects who completed Period 1 per protocol and underwent an electrocardiogram within the specified time window pre-dose and post-dose.

SD = standard deviation.

Efficacy rating scales

Of the 23 and 40 subjects assigned to the low-dose and high-dose groups, respectively, the efficacy-evaluable population included 23 subjects in the low-dose group (15 bipolar I disorder, 8 schizophrenia or schizoaffective disorder) and 36 subjects in the high-dose group (27 and 9, respectively; 4 bipolar subjects did not have an end-of-treatment efficacy assessment). Seventeen subjects in the low-dose group (11 bipolar I disorder, 6 schizophrenia or schizoaffective disorder) and 22 subjects in the high-dose group (17 and 5, respectively) completed Period 1.

YMRS was administered to bipolar subjects while the BPRS-A was administered to subjects with schizophrenia or schizoaffective disorder. CGI-S was assessed in all subjects. The results for YMRS, BPRS-A and CGI-I (means ±SD, 95% CI and effect sizes) are summarized by dose group and diagnosis in Table 6. Ziprasidone produced clinically meaningful symptomatic improvements in subjects with bipolar disorder or schizophrenia/schizoaffective disorder as measured by reductions in YMRS, BPRS-A, and CGI-S scores (see Table 6). In most cases, the confidence interval (CI) ranges for changes in YMRS, BPRS-A and CGI-I did not include 0.

Discussion

In general, our findings are consistent with those of previous studies of adult patients with similar disorders (Keck et al. 2003; Addington et al. 2004) and with the recently reported open-label study of ziprasidone in pediatric subjects with bipolar disorder (Biederman et al. 2007). No unexpected tolerability findings were observed in this prospective trial of ziprasidone. However, AEs were numerically more frequent in the high-dose group than in the low-dose group, occurring most commonly during the titration phase. The 10-day titration phase, which was followed by a fixed dose without the possibility of a dose reduction, differed from the more flexible label recommendations since one purpose of the study was investigation of the tolerability of two dosing schedules.

The most common AEs were sedation, somnolence, and nausea. The frequency of these AEs is higher than is generally observed in adults (Keck et al. 2003). This may indicate a greater sensitivity of children and adolescents to certain AEs. However, a higher incidence of AEs in this trial may be related to the forced titration used in this study. Over the course of Period 2, doses between 80 and 160 mg/d were generally well tolerated, but the target dose of 160 mg/d in the high-dose group was not well tolerated by some subjects in Period 1.

Serious AEs were reported for 2 subjects in Period 1 and 13 subjects in Period 2. Mostly the symptoms reported (suicidal ideation, exacerbation of mania, exacerbation of bipolar symptoms, and hallucinations) are suggestive of poor bipolar or schizophrenic symptom control by ziprasidone rather than de novo symptoms caused by the medication. However, cases of mania have been reported following initiation of ziprasidone (Baldassano et al. 2003).

Table 6. Mean Change from Baseline to End of Period 1 in Rating Scales

	Bipolar mania		*Schizophrenia/ Schizoaffective disorder*	
	Low dose (40 mg twice daily)	*High dose (80 mg twice daily)*	*Low dose (40 mg twice daily)*	*High dose (80 mg twice daily)*
	YMRS		*BPRS-A*	
Baseline: mean ± SD	29.2 ± 5.4	26.2 ± 6.9	51.5 ± 13.6	52.8 ± 12.6
(95% CI)	(26.2, 32.2)	(23.6, 28.7)	(40.1, 60.9)	(43.1, 62.5)
(n)	(n = 15)	(n = 31)	(n = 8)	(n = 9)
Completed: mean change ± SD	−17.2 ± 8.2	−13.1 ± 8.9	−9.5 ± 11.0	−15.2 ± 3.2
(95% CI)	(−22.7, −11.7)*	(−17.7, −8.6)*	(−21.0, 2.0)	(−19.2, −11.2)*
(n) [effect size]	(n = 11) [2.10]	(n = 17) [1.47]	(n = 6) [0.86]	(n = 5) [4.75]
Completed/discontinued mean change ± SD	−14.9 ± 9.7	−11.1 ± 9.3	−9.0 ± 9.3	−14.0 ± 6.7
(95% CI)	(−20.2, −9.5)*	(−14.8, −7.4)*	(−16.8, −1.2)*	(−19.2, −8.8)*
(n) [effect size]	(n = 15) [1.54]	(n = 27) [1.19]	(n = 8) [0.97]	(n = 9) [2.09]
	CGI-S			
Baseline: mean ± SD	5.3 ± 0.6	4.7 ± 0.6	4.6 ± 0.9	4.9 ± 0.8
(95% CI)	(4.9, 5.6)	(4.5 (4.9)	(3.9, 5.4)	(4.3, 5.5)
(n)	(n = 15)	(n = 31)	(n = 8)	(n = 9)
Completed: mean change ± SD	−1.6 ± 1.4	−1.7 ± 1.2	−0.7 ± 0.8	−0.8 ± 0.5
(95% CI)	(−2.6, −0.7)	(−2.3, −1.1)*	(−1.5, 0.2)	(−1.4, −0.2)*
(n) [effect size]	(n = 11) [1.14]	(n = 17) [1.42]	(n = 6) [0.89]	(n = 5) [1.60]
Completed/discontinued mean change ± SD	−1.5 ± 1.5	−1.3 ± 1.2	−0.8 ± 0.7	−0.9 ± 0.9
(95% CI)	(−2.3, −0.6)*	(−1.8, −0.8)*	(−1.3, −0.2)*	(−1.6, −0.2)*
(n) [effect size]	(n = 15) [1.00]	(n = 27) [1.81]	(n = 8) [1.14]	(n = 9) [1.00]

*CI does not include 0

BPRS-A, Brief Psychiatric Rating Scale—Anchored; YMRS, Young Mania Rating Scale; CGI-S, Clinical Global Impressions–Severity; SD, standard deviation; CI, confidence interval.

Twenty-one (33.3%) of 63 subjects experienced >7% weight gain. Although 7% is a standard threshold for weight gain, these figures should be interpreted with caution in growing subjects (Tohen et al. 2007) . Numerous studies in adults have demonstrated that ziprasidone results in minimal, if any, change in body weight. Specifically, in a 6-week randomized, double-blind, placebo-controlled, fixed-dose trial of ziprasidone in adult subjects with schizophrenia and schizoaffective disorder, the median weight gain from baseline to end point was 1 kg in subjects receiving 80 mg/d and 0 kg in subjects receiving 160 mg/d (Daniel et al. 1999). Other controlled trials in adults (Addington et al. 2004; Lieberman et al. 2005; Simpson et al. 2005) and uncontrolled studies in pediatric patients (Barnett 2004; Cohen et al. 2003) have also shown a weight-neutral profile for ziprasidone. A recent open-label trial of ziprasidone in 21 pediatric subjects with bipolar disorder found no statistically significant change in weight over the 8 weeks of the study (Biederman et al, 2007). Future double-blind, placebo-controlled trials of treatment-naãve patients are necessary to determine more accurately the effect of ziprasidone on body weight in children and adolescents.

No clinically significant changes in serum lipid or fasting glucose levels occurred during the 27 weeks of our study. Studies in adult populations (Lieberman et al. 2005; Simpson et al. 2005) have shown similar findings, with ziprasidone associated with significantly lower median increases in total cholesterol and LDL levels than olanzapine, and even with reductions in lipid and glucose levels, over a period of 6 months to 1 year. Indeed, the laboratory results were essentially unremarkable except for the modest incidence of prolactin elevation in both groups. These prolactin increases were not extreme and often tended to normalize with time.

In general, movement disorder symptoms as evaluated using SARS, BARS and AIMS scales were infrequent and declined or remained close to the baseline level during the 27 weeks of the study, in both the low- and high-dose treatment groups. Only one subject discontinued due to a movement disorder (akathisia and extrapyramidal syndrome during Period 1 in the high-dose group).

We also evaluated the effect of ziprasidone on the QTc interval. The ECG data from this study were collected under controlled conditions and, to our knowledge, provide the most thorough information to date on the cardiac safety of ziprasidone in children and adolescents. No QTc value exceeded 500 ms and only one was greater than 450 ms. Furthermore, no subject experienced an increase in QTc interval over baseline that exceeded 60 ms (using Fridericia correction formula), suggesting that no subject was put at risk of a QTc-related cardiac event. Similar results were obtained with the Bazett correction, but with three subjects experiencing an increase in QTc of >60 ms.

A recent report of an open-label study of 20 diagnostically heterogeneous, nonpsychotic pediatric subjects treated with a maximum of 40 mg/d of ziprasidone (mean dose, 30 ± 13 mg/d) (Blair et al. 2005) reported mean QT interval changes greater than those observed in this study. However, in the latter study ECGs were not collected under standardized conditions to control for diurnal effects or the effects of food and posture. The study used the Bazett correction for QT values. However, this method overcorrects QT (yielding larger values) at faster heart rates, which are common in children (Loebel et al. 2006). Additionally, the QTc interval changes reported were based on the difference between a random baseline measurement and the highest measurement of multiple subsequent random ECG measurements. This method could lead to a high probability of detecting changes in QTc that are based on within-subject variability (e.g., time of day, food effect, sympathetic tone, heart rate). By contrast, the ECGs in the present study were obtained with the subjects supine, under standardized conditions for fasting, postural changes, activity, and dosing, and at peak and trough plasma ziprasidone levels. Our results are more consistent with those of Biederman et al (2007) who found no significant change in QTc in bipolar pediatric subjects receiving a mean ziprasidone dose of 57 ± 34 mg/d. Caution is nonetheless necessary in extrapolating these findings to other contexts.

Although assessing efficacy was not the primary aim of the present study, and the investigation was limited by its open-label design, the results provide preliminary data to suggest the potential efficacy of ziprasidone for the treatment of children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. Improvements in CGI-S scores, observed during Period 1, were maintained through week 27 in all subjects. Among subjects with bipolar disorder, mean YMRS scores improved at weeks 3 and 27 in subjects initially receiving either high or low doses of ziprasidone. Improvements were also noted in BPRS-A scores at weeks 3 and 27 in subjects with schizophrenia or schizoaffective disorder, with numerically greater improvements from baseline in the high-dose group. Although efficacy measures were not subjected to formal statistical analysis, the CI ranges of changes in YMRS, BPRS-A and CGI-S did not include 0 in the majority of cases. However, mood stabilizers such as valproate, oxcarbazepine, and lithium were taken by many subjects during Period 2, making the efficacy ratings difficult to interpret.

The results of this study should only cautiously be compared with those of other studies of antipsychotics in children and adolescents. In contrast to other studies, the present study involved a fixed-dose phase, thus perhaps exaggerating the AE profile. There are several limitations to this study, including the lack of a placebo control group and the open-label design, which limits the interpretability of the findings. Nonetheless, although some adolescents gained weight, no other new tolerability or safety findings emerged relative to the AE profile already established for adults. Despite these limitations, the results of this study suggest that ziprasidone may be useful for the treatment of mania and psychotic symptoms in children and adolescents.

Disclosures

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