

## Ziprasidone in Pediatric Bipolar Disorder: A 6-Week, Open-Label Comparison of Rapid vs. Slow Dose Titration

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### Abstract

**Objective:** This open-label clinical trial evaluated the dosing, safety, and effectiveness of rapid vs. slow titration of ziprasidone in pediatric bipolar disorder over a period of 6 weeks.

**Methods:** Study participants (aged 10-17 years) were diagnosed with bipolar disorder using standardized diagnostic instruments. Additionally, standardized rating scales were used to assess changes in mood, adverse effects, and overall functioning. Twenty-eight participants were randomly assigned to either the rapid- or slow-dose titration of ziprasidone. Linear mixed model analyses of repeated measures—adjusting for the age and respective baseline clinical score—were used to evaluate the main effects and the 2-way interaction effect (incorporating titration group and time). Cox Proportional Hazards Regression, adjusting for age, compared the time-to-treatment response for the rapid- vs. the slow-dose titration of ziprasidone. Treatment response was defined as  $\geq 50\%$  reduction from baseline on the Young Mania Rating Scale total scores for at least two sustained periods.

**Results:** Irrespective of titration group assignment, mean YMRS total scores decreased significantly across the 6 weeks of treatment for the combined groups ( $p=.008$ ). The median time to response was 2 weeks for the rapid titration group and 3 weeks for the slow group, but the two survival curves of treatment response did not differ significantly between the two titration groups ( $p=0.92$ ). Overall, ziprasidone was tolerated well by the study participants in both groups (slow and rapid titration).

**Conclusions:** No significant difference emerged between the rapid- and slow-titration groups over the 6 weeks of ziprasidone treatment on severity of manic symptoms or time-to-response. There was a reduction in manic symptoms in both the rapid and slow titration groups over the 6 week period. A much larger sample is required to test for meaningful differences between the two titration groups, in regards to improving clinical symptoms and minimizing adverse effects from ziprasidone.

**Keywords:** Ziprasidone; Bipolar disorders

### Introduction

Bipolar disorder is a serious, chronic illness that significantly impacts the quality of life of an individual. This disorder has onset in childhood and adolescence [1], which makes it even more important to adequately treat this illness in youth. Recently, atypical antipsychotics have been shown to be effective in treating bipolar disorder in youth [2]. However, many atypicals are known to cause significant weight gain, obesity, diabetes mellitus, and hyperlipidemia. Ziprasidone is often favored over other atypicals, because it lacks the association with these adverse effects [3,4].

Case series, retrospective chart reviews, open-label, and controlled studies suggest that atypical antipsychotic medications result in greater response rates for the treatment of adolescent mania than are found in comparable studies of lithium and antiepileptic [5]. Atypical antipsychotics may be a more effective treatment option and, in some ways, easier to use than the traditional mood stabilizers. Although, the adverse effect profile of ziprasidone appears to be slightly superior to other atypical antipsychotics (particularly with respect to weight gain and metabolic parameters), appropriate dosing strategies, safety parameters, and efficacy of ziprasidone continue to need to be established for pediatric bipolar youth.

Barnett [6] in a case series ( $n=4;7-16$  years), and Biederman et al. [7] in an eight-week, open-label trial with 21 children and adolescents (6-17 years) studied the effects of ziprasidone monotherapy in improving bipolar symptomatology in youths with bipolar disorder. In both studies, treatment with ziprasidone showed clinical improvement in the children/adolescents' bipolar symptomatology, with no significant increase in body weight.

To determine the appropriate dose and titration schedule for ziprasidone in children and adolescents with bipolar disorder type 1, schizophrenia, or schizoaffective disorder, Delbello et al. [8] conducted

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a multi-site clinical trial. The study included 63 children and adolescents (10-17 years) with the diagnosis of bipolar disorder (manic or mixed, n=46), schizophrenia (n=7), and schizoaffective disorder (n=10). In this study, participants were treated with fixed doses of ziprasidone for up to 3 weeks (Period 1) followed by flexible-dose ziprasidone treatment for 24 weeks (Period 2). During period 1, over 10 days, participants were randomized to either low (n=23) or high (n=40) dose ziprasidone groups. Low dose of ziprasidone was initiated at 20 mg per day and titrated to 80 mg per day, whereas the high dose of ziprasidone was initiated at 80 mg per day and titrated to 160 mg per day. Participants were treated with a fixed dose of ziprasidone for the remainder of the 3 weeks. Children and adolescents weighing less than 45 kg were given half of the doses. In Period I, 91% in the low dose group and 95% in the high dose group reported treatment emergent adverse effects from ziprasidone. The most common adverse effects in any group were sedation, somnolence, nausea, headache, dizziness, vomiting and fatigue. Additionally, it was noted that during Period I, where forced titration of ziprasidone was used, more participants in the high dose group discontinued the study due to adverse effects of the ziprasidone as compared to participants in the low dose group. However, treatment with ziprasidone improved clinical symptoms in children and adolescents with bipolar disorder, schizophrenia and schizoaffective disorder. Therefore, it may be possible that the dosing titration of the medication needs to be re-evaluated so children and adolescents can receive the benefits of the clinical treatment without having the adverse effects.

Delbello et al. study [8] concluded that titration of ziprasidone to 160 mg/day over the first week of therapy may be too rapid for some children and adolescents to tolerate. Additionally, it is plausible that slower titration of the ziprasidone dose may need to be considered for the medication to be tolerated without adverse effects warranting discomfort and discontinuation. Clinicians may benefit from clinical trials in children and adolescents with the bipolar spectrum disorders (BP-I, BP-II and BPNOS not otherwise specified) targeting the manic symptomatology present during this illness. Therefore, we conducted a 6-week, open-label outpatient trial to determine the effectiveness of ziprasidone in decreasing manic symptoms in children and adolescents with the bipolar spectrum disorders by evaluating dosing strategies for the use of ziprasidone in these youth. Specifically, we compared the effectiveness of rapid- versus slow-dose titration of ziprasidone in bipolar youth. We also examined whether bipolar youth on ziprasidone monotherapy (irrespective of titration group assignment) would have a reduction in manic symptoms.

Unlike risperidone, aripiprazole, quetiapine and olanzapine, ziprasidone does not have the Food and Drug Administration approval for the treatment of pediatric bipolar disorder. In the community, off-label usage of ziprasidone is continuing for children and adolescents, therefore an assessment of appropriate dosing regimens and adverse events monitoring of ziprasidone in children and adolescents remains of clinical significance. Finally, we examined whether slower-dose titration of ziprasidone would result in fewer side effects.

## Methods

This was a 6-week, open label investigator initiated study designed to evaluate the dosing, safety, and effectiveness of ziprasidone in children and adolescents with bipolar disorder. The protocol was approved by the University of Texas at Southwestern Medical Center Institutional Review Board. Informed written and verbal consent was obtained from the parent or legal guardian of the study participants, and informed

verbal and written assent was obtained from the participants prior to any study procedure being conducted.

## Participants

Children and adolescents (aged 10-17 years) were recruited from the Child and Adolescent Psychiatry Outpatient Clinic at Children's Medical Center in Dallas, TX, for participation in this study.

## Inclusion criteria for study

Participants were required to meet the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR) [9] criteria for bipolar disorder, type I, II or Bipolar Disorder Not Otherwise Specified (BPNOS) as determined by the Schedule for Affective Disorders and Schizophrenia in School-Age Children-Present/Lifetime (K-SADS-PL) [10]. Participants were experiencing manic, hypomanic or mixed states as determined by a Young Mania Rating Scale (YMRS)  $\geq 14$  and were in good health as determined by medical history, physical examination, and laboratory evaluations [11].

## Exclusion criteria for study

Participants were excluded from the study if they had a lifetime DSM-IV-TR Axis I disorder diagnosis of autistic disorder, schizophrenia, schizoaffective disorder, or other psychotic disorders NOS, alcohol or substance abuse or dependence, anorexia or bulimia within the past 6 months; a serious or unstable medical or neurological conditions which required concomitant medications; known or suspected IQ less than 70; pregnant or nursing female adolescent; a history of syncopal episodes or unexplained loss of consciousness; a history of significant cardiovascular disease or QT prolongation; a known genetic risk for QT syndrome determined by family history in first degree relatives; taking any medications known to interact with ziprasidone or taking any medications which have been consistently observed to prolong the QT interval; a clinically significant ECG abnormality at screening; a persistent QTc (Fridericia) more than or equal to 460 msec at screening; screening laboratory values outside the normal range and judged to be clinically significant by the investigator; patients and families who were Spanish speaking only.

## Procedure and measures

Upon completion of the informed consent/assent process, all participants underwent a 1-2 week screening process. During this time, diagnoses were confirmed through the K-SADS-PL, and severity and functioning were assessed using the YMRS, the Quick Inventory of Depressive Symptomatology- Adolescent-Clinician Rated (QIDS-A-C) [12] and the Quick Inventory of Depressive Symptomatology- Adolescent-Clinician Rated (Parent) (QIDS-A-C (P)), The Children's Depression Rating Scale - Revised (CDRS-R) [13], The Overt Aggression Scale (OAS) [14] The Clinical Global Impression Scales -Severity and Improvement (CGI-S and CGI-I) [15]. Physical examination, including an electrocardiogram, weight, Body Mass Index (BMI), serum lipid, glucose, prolactin and a serum pregnancy test from adolescent females were also performed at the screening and baseline visits. Participants who met inclusion criteria were gradually tapered off of their other psychiatric medications. They were allowed to take over the counter medication diphenhydramine (benadryl) in doses ranging from 25-50 mg per night, or ativan (lorazepam) in doses ranging from 0.25 mg-2 mg per day if they experienced symptoms of agitation, insomnia or restlessness during this taper. Lorazepam and Benadryl could be continued for the first fifteen days of the trial. Participants were allowed to be on stimulants only if they were on the stimulant

prior to beginning the study. Participants who met all inclusion and no exclusion criteria were randomized to slow or rapid dose titration, and were then assessed weekly for 6 weeks by the treating psychiatrist.

### Titration groups

Twenty-eight participants met the inclusion criteria and thus were randomly assigned to either the rapid (n=13) or slow-dose (n=15) titration of ziprasidone treatment. Ziprasidone was started at 20 mg daily for all participants see (Table 1) for dosing schedules. The maximum dose of ziprasidone for those participants who weighed 45 kg or more was 160mg and the maximum dose of ziprasidone for those who weighed less than 45 kg was 80 mg. In the rapid dose group, the maximum dose of ziprasidone was reached at the beginning of week 3, whereas in the slow dose group, the maximum dose of ziprasidone was reached at the beginning of week 4.

### Outcomes

The primary outcome for this study was manic symptom severity as measured by the YMRS total score. Secondary outcomes were depressive symptom severity as measured by the QIDS-A-C, QIDS-A-C (P), and CDRS-R. Response was defined as the Clinical Global Impression-Improvement (CGI-I) score of  $\leq 2$ . Safety was also assessed weekly using The Abnormal Involuntary Movement Scale (AIMS) [16], the Barnes Akathisia Rating Scale (BARS) [17], and the Systematic Assessment for Treatment Emergent Events (SAFTEE) Adverse Symptoms Checklist.

### Statistical analysis

Demographic and clinical characteristics for the entire sample and for both titration groups were first described using the sample mean and standard deviation for continuous variables, and the frequency and percentage for categorical variables. Two-independent sample *t*-test (for continuous variables) and Fisher's exact test (for categorical variables) were used to compare the two titration groups (rapid vs. slow) on the various demographics and baseline clinical characteristics.

The primary data analysis was a linear mixed model analysis of repeated measures. A separate mixed model analysis was conducted on each clinical outcome as well as on each side effect measure. Age and the respective baseline clinical measure were included as covariates in each respective mixed model analysis. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used, with the Kenward-Roger correction [18] applied to the first-order autoregressive covariance structure. The main effects of Titration Group and Time (least squares means across the 6-week trial) and the Titration Group  $\times$

Time interaction effect were examined. Simple Titration Group effects (and least squares means) at each time (week) were also assessed. Cohen's *d* was calculated and interpreted as the effect size estimator for the between-subjects Titration Group effect.

Cox Proportional Hazards Regression, adjusting for age, compared the time-to-treatment response for the rapid- vs. the slow-dose titration of ziprasidone. Treatment response was operationally defined as  $\geq 50\%$  reduction from baseline on the YMRS total for at least two sustained periods. As part of the survival analysis, right censoring was used in the current study. Censoring occurred when incomplete information was available about the survival time (i.e., time-to-response) of a given participant (the information was incomplete because the participant did not have an event during the time that the participant was part of the study period). In our study, censoring (or a censored observation) meant a participant who dropped out of the study without responding or who completed the study period without responding. Overall, during the 6-week treatment study period, 25.0% of the participants in the current trial were censored for time-to-response. We conducted all of the statistical analyses using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). The level of significance for all tests was set at  $\alpha = 0.05$  (two-tailed) and, because of the pilot nature of this study, *p*-values were not adjusted for multiple testing.

## Results

### Participant characteristics

There were a total of 28 participants in this study, amongst which 15 (53.6%) were randomized to slow-dose titration and 13 (46.4%) to rapid-dose. About 57% (n=16) of the patients were male. The mean age of the participants was  $13.4 \pm 2.5$  years (slow titration group:  $13.53 \pm 2.62$ ; rapid titration group:  $13.38 \pm 2.50$ ) (Table 2, for participant characteristics between groups).

For the 28 youth, the mean baseline YMRS total score was  $22.9 \pm 7.0$ , mean baseline OAS total score was  $65.9 \pm 69.1$ , mean baseline OAS aggression total score was  $60.0 \pm 67.7$ , mean baseline QIDS-A-C total score was  $8.2 \pm 5.6$ , mean baseline CDRS-R total score was  $38.2 \pm 8.1$ , and the mean baseline CGI-S score was  $4.7 \pm 0.70$ . The mean baseline weight was  $54.7 \pm 14.7$  kg for the 28 bipolar youth. Clinical characteristics of the entire sample at baseline and at week 6 are shown in (Table 3).

### Titration group and clinical outcomes

The results from the linear mixed model analysis revealed that, while controlling for age and baseline YMRS total score, the overall adjusted least squares means (LSM  $\pm$  SE) for manic severity symptoms (YMRS total scores) were not significantly different between the rapid- and slow-titration groups over the 6 weeks of ziprasidone treatment ( $12.70 \pm 1.41$  vs.  $12.57 \pm 1.32$ ,  $p=0.95$ , Cohen's  $d=0.02$ ). No significant simple effects emerged at any prospective week ( $p>0.23$ ); however, the adjusted YMRS total scores, on average, were lower at week 1 for the rapid- vs. the slow-titration group ( $15.01 \pm 1.98$  vs.  $18.26 \pm 1.84$ ,  $p=0.23$ ) but then the pattern of YMRS total scores reversed direction in favor of the slow titration group (lower adjusted YMRS scores) starting with week 2 and persisting throughout the trial until week 6 albeit not statistically significant (Figure 1).

Adjusted YMRS scores, on average, decreased significantly over the six weeks of treatment within the Slow dose group ( $p=0.002$ ), but not within the Rapid dose group ( $p=0.13$ ). However, with both groups combined, we found a significant within-subjects Time effect (over

Day	Rapid Dose Titration							
	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-42
Week	1	1	1	2	2	2	2	3-6
Maximum Daily Dose, $\geq 45$ kg (mg)	20	40	60	80	100	120	140	160
Max. Daily Dose, $<45$ kg (mg)	20	20	40	40	60	60	80	80
Day	Slow Dose Titration							
	1-3	4-7	8-10	11-14	15-17	18-21	22-24	25-42
Week	1	1	2	2	3	3	4	4-6
Max. Daily Dose, $\geq 45$ kg (mg)	20	40	60	80	100	120	140	160
Max. Daily Dose, $<45$ kg (mg)	20	20	40	40	60	60	80	80

Table 1: Dosing Guidelines for Ziprasidone

	Titration Group		Test Statistic and <i>p</i> value
	Rapid	Slow	
	( <i>n</i> = 13)	( <i>n</i> = 15)	
Age, M ± SD	13.38 ± 2.50	13.53 ± 2.62	<i>t</i> (26) = -0.53, <i>p</i> = .88
Gender (Male), % ( <i>n</i> )	53.85 (7)	60.00 (9)	Fisher's test, <i>p</i> = 0.99
Ethnicity, % ( <i>n</i> )			Fisher's test, <i>p</i> = 0.60
Caucasian	84.62 (11)	73.33 (11)	
African American	7.69 (1)	20.00 (3)	
Hispanic	7.69 (1)	0.00 (0)	
Other	0.00 (0)	6.67 (1)	
Diagnosis, % ( <i>n</i> )			Fisher's test, <i>p</i> = 0.32
Bipolar I	69.23 (9)	53.33 (8)	
Bipolar II	7.69 (1)	0.00 (0)	
Bipolar NOS	23.08 (3)	46.67 (7)	
Co morbid Diagnoses, % ( <i>n</i> )			
Major Depressive Disorder	46.15 (6)	26.67 (4)	Fisher's test, <i>p</i> = 0.43
Psychosis	7.69 (1)	6.67 (1)	Fisher's test, <i>p</i> = 0.99
Generalized Anxiety Disorder	15.38 (2)	13.33 (2)	Fisher's test, <i>p</i> = 0.99
ADHD	61.54 (8)	46.67 (7)	Fisher's test, <i>p</i> = 0.25
	Titration Group		Test Statistic and <i>p</i> value <sup>a</sup>
	Rapid	Slow	
	( <i>n</i> = 13)	( <i>n</i> = 15)	
Oppositional Defiant Disorder	30.77 (4)	0.00 (0)	Fisher's test, <i>p</i> = 0.03
Conduct Disorder	7.69 (1)	6.67 (1)	Fisher's test, <i>p</i> = 0.99
Family History, % ( <i>n</i> )			
Bipolar Disorder	53.85 (7)	53.33 (8)	Fisher's test, <i>p</i> = 0.71
Depression	38.46 (5)	60.00 (9)	Fisher's test, <i>p</i> = 0.45
Alcohol/Substance Abuse	23.08 (3)	20.00 (3)	Fisher's test, <i>p</i> = 0.99
Anxiety	0.00 (0)	20.00 (3)	Fisher's test, <i>p</i> = 0.23
ADHD	30.77 (4)	26.67 (4)	Fisher's test, <i>p</i> = 0.99
Schizophrenia	0.00 (0)	6.67 (1)	Fisher's test, <i>p</i> = 0.99
Antisocial Personality Disorder	7.69 (1)	6.67 (1)	Fisher's test, <i>p</i> = 0.99
Other	15.38 (2)	13.33 (2)	Fisher's test, <i>p</i> = 0.99
Baseline Weight (kg), M ± SD	52.93 ± 11.65	56.31 ± 17.23	<i>t</i> (26) = -0.60, <i>p</i> = 0.56
Baseline YMRS, M ± SD	25.23 ± 8.81	20.93 ± 4.46	<i>t</i> (17.20) = 1.59, <i>p</i> = 0.13
Baseline OAS, M ± SD	78.09 ± 82.45	57.00 ± 58.91	<i>t</i> (26) = 0.76, <i>p</i> = 0.45
Baseline QIDS-SR-A, M ± SD	7.83 ± 6.54	9.07 ± 4.94	<i>t</i> (26) = -0.78, <i>p</i> = 0.45
Baseline CDRS, M ± SD	37.15 ± 6.63	39.20 ± 9.31	<i>t</i> (26) = -0.66, <i>p</i> = 0.52
Baseline CGI-S, M ± SD	4.85 ± 0.69	4.67 ± 0.72	<i>t</i> (26) = 0.67, <i>p</i> = 0.51

<sup>a</sup>Test of mean difference between the two titration groups on each demographic and baseline clinical characteristic.

**Table 2:** Demographic and Baseline Clinical Characteristics.

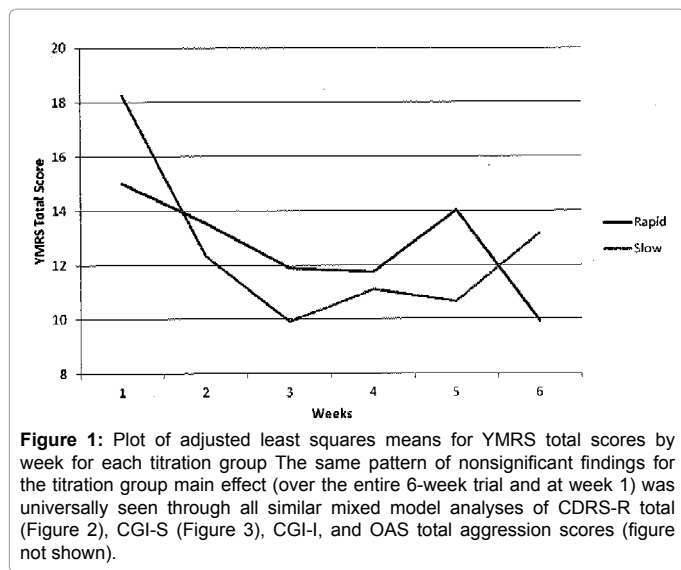
Clinical Measures	Baseline ( <i>n</i> =28)	Week 6 ( <i>n</i> =28)	<i>p</i> value <sup>a</sup>
	Mean (Standard Deviation)	Mean (Standard Deviation)	
Weight (kg)	54.74 (14.74)	56.00 (17.10)	0.37
YMRS Total	22.93 (7.04)	11.64 (8.27)	<0.0001
OAS Total <sup>b</sup>	65.92 (69.11)	31.96 (35.45)	0.01
QIDS-A-C <sup>b</sup>	8.29 (5.69)	4.68 (4.26)	0.005
CDRS-R Total	38.25 (8.10)	31.61 (10.28)	0.006
CGI-S	4.75 (0.70)	3.18 (1.34)	<0.0001

<sup>a</sup>Test of mean difference between week 6 and baseline on each demographic and clinical characteristic.

<sup>b</sup>The sample size at week 6 for OAS total and QIDS-A-C was 24 and 25, respectively.

**Table 3:** Clinical characteristics of the entire sample at baseline and at week 6.





the 6 weeks of treatment) on adjusted YMRS total scores ( $p=0.008$ ). In other words, irrespective of titration group assignment, adjusted LS mean YMRS total scores decreased significantly across the 6 weeks of treatment for the overall (combined) sample of youth (Periods 1-6 adjusted LS means, respectively: 16.6 vs. 12.9 vs. 10.9 vs. 11.4 vs. 12.3 vs. 11.5).

### Hazard of response

Cox Proportional Hazards Regression, adjusting for age, revealed that the two survival curves of treatment response did not differ significantly between the two titration groups—that is, rapid- vs. slow-titration of ziprasidone did not have a significant effect on the response time over 6 weeks of ziprasidone treatment (hazard ratio = 1.15, 95% CI = 0.49 to 2.72;  $\chi^2 = 0.11$ ,  $p=.73$  (Figure 4)). The median time to response was 2 weeks for the rapid titration group and 3 weeks for the slow titration group.

### Safety

Twenty (71.4%) participants completed the study. Among the rapid group, 2 (15.4%) discontinued prior to the completion of the study; while 6 (40%) of the slow group discontinued early.

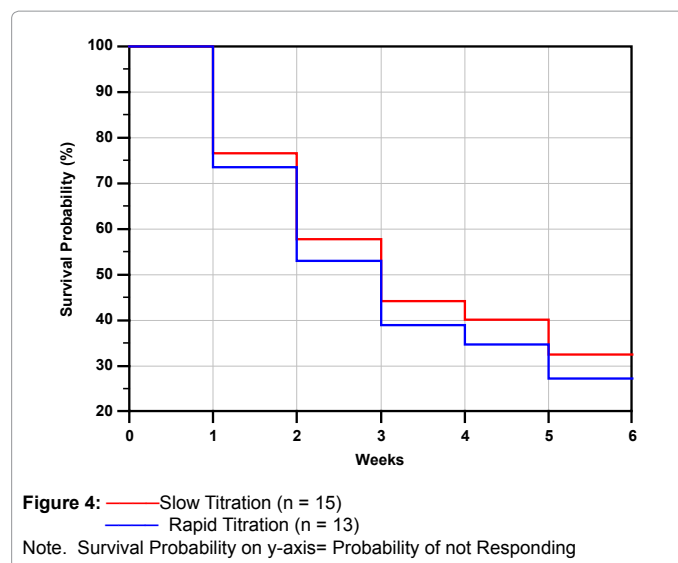
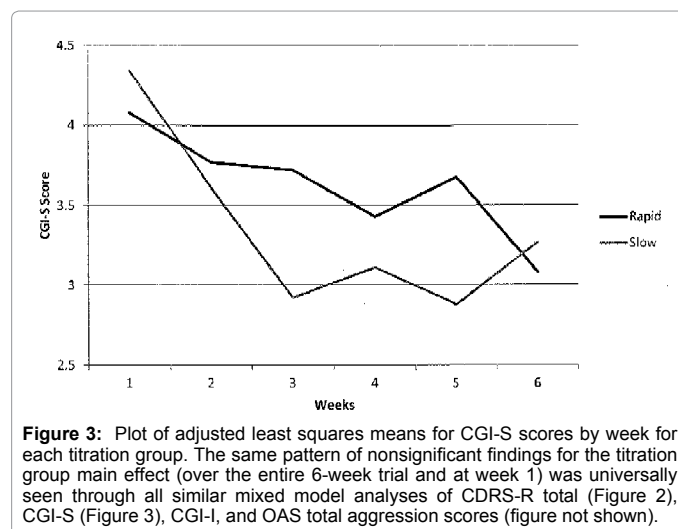
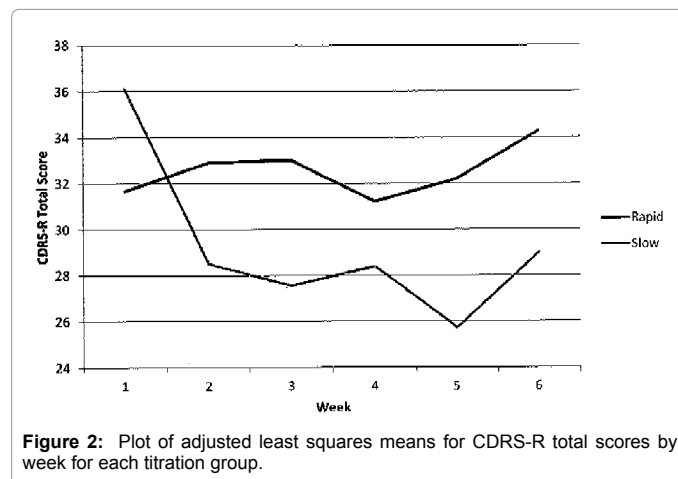
Reasons for discontinuation were similar for the 2 groups. Among the rapid group, one patient was withdrawn for non-compliance (week 2), and one was withdrawn due to adverse events (week 2). Among the slow group, 2 were withdrawn due to lack of improvement (week 4 and week 5), 2 withdrew due to adverse events (week 2 and week 5), 1 withdrew consent (week 4), and 1 was lost to follow-up (week 2).

Thus, three (10.7%) of the 28 participants (1/13 (7.7%) in the rapid group and 2/15 (13.3%) exited the study due to adverse events of the study medication. No serious adverse events were experienced during the study by any participant.

Over the 6 weeks of ziprasidone treatment (LSM  $\pm$  SE), patients in the rapid- and slow-titration groups were similar in weight ( $55.34 \pm 0.31$  vs.  $54.95 \pm 0.29$ ,  $p=0.37$ ). Patients in the rapid- and slow-titration groups were also similar in side effects profile as measured by the Global Clinical Rating of Akathisia (BARS) ( $0.11 \pm 0.05$  vs.  $0.06 \pm 0.04$ ,  $p=0.46$ ), AIMS total score ( $0.20 \pm 0.15$  vs.  $0.32 \pm 0.14$ ,  $p=0.54$ ), and SAFTEE (interference of side effects with daily activities;  $0.32 \pm 0.09$  vs.  $0.46 \pm 0.08$ ,  $p=0.28$ ).

## Discussion

This is a 6 week open-label pilot study evaluating the dosing, safety, and effectiveness of ziprasidone in pediatric bipolar disorder. Twenty-



eight participants were randomly assigned to either the rapid (n=13) or slow-dose (n=15) titration of ziprasidone treatment. The current study found that no significant difference emerged between the rapid- and slow-titration groups over the 6 weeks of ziprasidone treatment on severity of manic symptoms or time-to-response. However, the results from this study found that all study participants on ziprasidone monotherapy (irrespective of titration group assignment) had a reduction (improvement) in manic symptoms. Slower-dose titration of ziprasidone compared to rapid-dose titration did not result in fewer side effects. Overall, ziprasidone was tolerated well by the study participants in both groups (slow and rapid titration). Over six weeks of treatment, all participants had a significant decrease in their manic symptoms and the YMRS total scores were not significantly different between the rapid- and slow-titration groups. The study found that rapid titration of ziprasidone may slightly decrease manic symptoms more in the first week, but overall, there was no difference in reduction in mania by week 6 in manic symptoms in both groups. Two participants (13.3%) in the slow titration group withdrew due to lack of improvement, while none of the rapid titration participants withdrew for this reason.

In this pilot study, the most common adverse effects were nausea and vomiting. One child had a dystonic reaction, and after discontinuing the ziprasidone and giving benadryl, the dystonia resolved. Three of the 28 study participants discontinued the study due to adverse effects from the ziprasidone. Within the slow dose group, there were 2 study participants who discontinued due to worsening of mood symptoms and an inadequate response to the treatment.

Given the dire need for comparing pharmacological agents for the treatment of mania in children, Geller et al. [19] conducted an 8 week randomized, controlled multi-site outpatient clinical trial in 279 children with bipolar type I disorder, aged 6- 15 years who were in a manic or mixed phase. In this Treatment of Early Age Mania (TEAM) [19] study, the participants were randomized to either lithium, risperidone or divalproex sodium, to explore which medication should be given first to treat antimanic medication-naïve children and adolescents.

The TEAM study found risperidone to be much more efficacious than lithium or divalproex sodium for initially treating mania in children. However, participants treated with risperidone had significantly more weight gain and increase in their body mass index in comparison to those than those treated with either lithium or divalproex.

Another study, The Treatment of Early Onset Schizophrenia (TEOSS) [20] was a randomized, double-blind multisite 8 week clinical trial designed to compare the efficacy and safety of molindone with olanzapine and risperidone in the treatment of early onset schizophrenia, in which, olanzapine and risperidone were associated with significantly greater weight gain. Additionally, treatment with olanzapine was associated with increases in lipid and insulin levels and liver function tests, and treatment with risperidone was associated with elevated prolactin levels.

Taken together, atypical antipsychotics, i.e., risperidone and olanzapine, improve symptoms of mania and psychosis in children and adolescents. However, these atypicals increase serum lipids and glucose and have a propensity for clinically significant weight gain and the potential for significant long-term morbidity. In this regard, ziprasidone has been found to have a favorable metabolic profile and does not result in significant increases in weight. Importantly, ziprasidone does improve manic and psychotic symptoms. Therefore, finding the appropriate dosing strategy for ziprasidone in the pediatric population is of clinical significance [5-7].

Overall, the results from the current pilot study indicate that there was a reduction in manic symptoms in both the rapid- and slow-dose titration groups over the 6 week period. Additionally, in the first week on treatment, the rapid titration group showed a greater decrease (or had lower scores) in YMRS (Figure 1), aggression, CDRS-R (Figure 2), and CGI (Figure 3) than did the slow titration group, although this was not statistically significant. Thus, if a patient requires a rapid reduction in manic or aggressive symptoms which can possibly delay hospitalization then a rapid titration of ziprasidone may be of benefit. Of note, only 3 of the 28 participants discontinued the study due to adverse effects of ziprasidone. The results of this pilot study are promising and future studies should include a randomized, clinical trial with a larger sample size to determine if this dosing titration of ziprasidone will allow for clinical improvements in manic symptoms without increased adverse effects of the medication.

The limitations of this study which affect its internal validity are its small sample size, open label design, and heterogeneous group, as the study included youth with bipolar spectrum disorders (BPI, BPII and BPNOS). A larger sample is required to test for meaningful differences between the rapid and slow titration groups. However, the preliminary results from this pilot study can be helpful to a clinician while dosing ziprasidone in youths with bipolar disorder.

## Statistical Expert

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