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Health-related quality of life as measured by the child health questionnaire in adolescents with bipolar disorder treated with olanzapine

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Abstract

Aim: To examine health-related quality of life (HRQoL) in adolescents with bipolar disorder before and after double-blind treatment with olanzapine or placebo.

Methods: Parents or legal guardians of 160 adolescents with a manic or mixed episode associated with bipolar I disorder were asked to rate their child's health using the Child Health Questionnaire-Parental Form 50 at baseline, before receiving medication, and then again at the end of participation in a 3-week double-blind placebo-controlled study of olanzapine.

Results: Adolescents in both treatment groups began and ended the study with significantly lower scores than normalized values of healthy peers on several HRQoL subscales (lower ratings indicate more impaired functioning), especially those assessing psychosocial factors. However, participants receiving olanzapine exhibited greater improvement than those in the placebo group across multiple HRQoL subscales, including the Behavior, Family activities, and Mental health subscales. Reduction in manic symptoms was associated with improvement in HRQoL values.

Conclusions: As expected, manic adolescents with bipolar disorder exhibit abnormalities in psychosocial, rather than physical factors associated with HRQoL. Treatment with olanzapine had a greater effect on multiple domains of psychosocial functioning compared with placebo, suggesting that in addition to improving manic symptoms, pharmacologic interventions may lessen some of psychosocial deficits experienced by adolescents with bipolar disorder. However, following 3 weeks of treatment, adolescents with bipolar disorder continued to exhibit deficits in several aspects of psychosocial functioning, indicating that additional pharmacologic and psychosocial interventions may be necessary to further improve functional outcome.

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1. Introduction

According to a study of burden of disease, bipolar disorder is the sixth leading cause of disability worldwide [1,2] and has a prevalence rate of 1-2% during adolescence [3,4]. Although pharmacologic interventions reduce manic symptoms in adolescents, youth with bipolar disorder often experience negative psychosocial consequences such as poor academic performance, disruptions in family and social relations, substance abuse, and a high rate of mortality from suicide [5-9]. Indeed, although adolescents with bipolar disorder experience high rates of syndromic recovery in the first year following a manic episode, they exhibit persistent functional impairment [10]. However, few studies have examined whether achieving mood stabilization through pharmacologic intervention leads to improvements in psychosocial functioning (eg, academic performance, social relations, emotional health) in adolescents with bipolar disorder.

One way to assess overall functioning is using measurements of health-related quality of life (HRQoL) which assess the occupational, physical, emotional, and social well-being of an individual [11]. Prior studies report that adults with bipolar disorder exhibit poorer HRQoL as compared to the general population [12–16], even during periods of mood stability [12,16]. However, there have been only 2 studies examining HRQoL in adolescents with bipolar disorder. Specifically, Rademacher, DelBello, Adler, Stanford, and Strakowski [17] used the Child Health Questionnaire-Parent Form [CHQ; [18]] to examine the impact of divalproex and quetiapine on HRQoL among adolescents (n = 23) with a manic or mixed episode during a 28-day study. In another report, Stewart, DelBello, Versavel, and Keller [19] used the CHQ to assess HRQoL among adolescents (n = 63) with a mixed or manic episode who were treated with ziprasidone during a 27-week trial. Overall, both studies found that prior to treatment there was greater impairment in subscales related to psychosocial functioning than in those related to physical health. Additionally, although scores on a majority of the subscales of the CHQ remained significantly lower than national norms following treatment, there were statistically significant improvements in psychosocial aspects of HRQoL in both studies. However, these studies were not placebo controlled, making it difficult to determine whether the pharmacological intervention or other factors related to study participation led to the observed improvements.

Olanzapine (Zyprexa; manufactured by Eli Lilly and Company) is an atypical antipsychotic that is approved by the United States Food and Drug Administration for the treatment of acute manic or mixed episodes in adolescents with bipolar disorder. Tohen et al [20] reported that adolescents treated with olanzapine (n = 107) experienced greater reduction in the severity of manic symptoms as compared to adolescents receiving placebo (n = 54) during a 3-week multi-center, parallel, double-blind, randomized controlled trial. To our knowledge the impact of olanzapine on HRQoL in adolescents with bipolar disorder has not been previously explored. With these considerations in mind, the aim of our report is to examine HRQoL, as measured by the CHQ in manic adolescents with bipolar disorder before and following treatment with olanzapine. We hypothesized that prior to treatment; manic adolescents with bipolar disorder would exhibit greater impairment in psychosocial domains of CHQ than in physical domains. Additionally, we hypothesized that following treatment with olanzapine, adolescents with bipolar disorder would exhibit greater improvement in CHQ scores than those given placebo.

2. Methods

A complete description of the methods of the 3-week double-blind, placebo-controlled trial along with the primary and secondary outcome measures related to change in mood symptom severity and tolerability measures has been previously published [20]. However, the previously published research did not report aspects related to HRQoL. This multi-center study was conducted from November 2002 to May 2005 in the United States (24 sites) and Puerto Rico (2 sites). Consent and assent was obtained by legal guardians and participants respectively and the study was approved by the appropriate ethical review boards.

2.1. Study participants & design

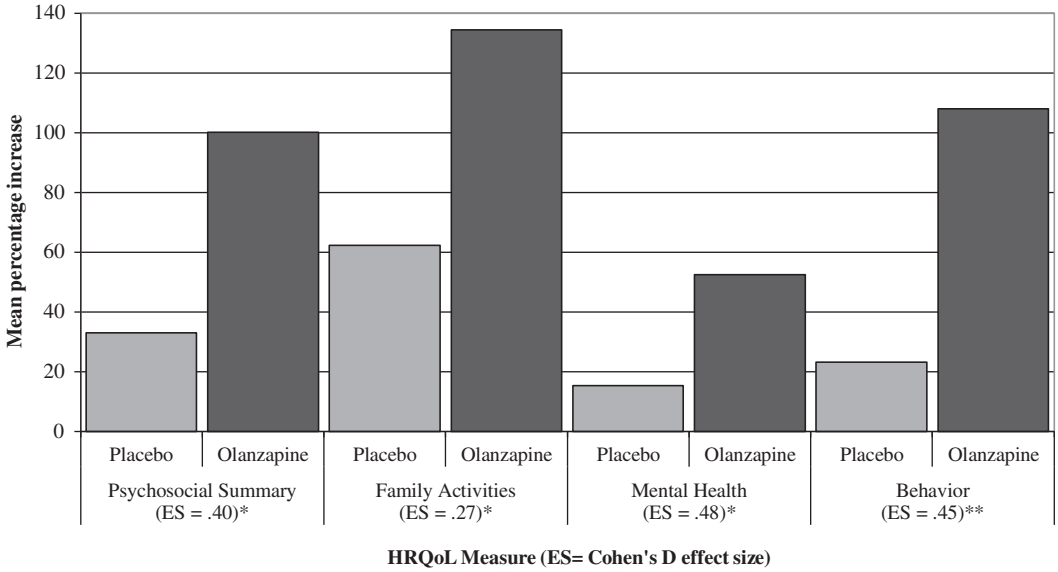
One hundred sixty-one adolescents, ages 13 to 17 years old (mean age = 15.2, SD = 1.3; girls, n = 76, 47%; white, n = 112, 70%) participated in this study. All participants had a *DSM-IV* diagnosis of a manic or mixed episode associated with bipolar disorder, which was confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version [21,22]. Participants were inpatients or outpatients with a total score on the Adolescent Structured Young Mania Rating Scale [YMRS; [23]] of ≥20. Study inclusion and exclusion criteria have been previously published [20].

Written informed assent and consent was obtained from patients and their legal guardians, respectively, prior to study participation. The appropriate ethics review boards approved the study prior to the recruitment of participants.

During the 3-week double blind study, participants were randomly assigned in a 2:1 ratio to olanzapine (2.5-20.0 mg/day) or placebo.

2.2. Measures

The Child Health Questionnaire Parent Form 50 (CHQ) is a parent report HRQoL measure of a child's physical, emotional, and psychosocial well-being, as well as the relative burden of disease on the parents and family [18]. The CHQ is suitable for use in children ages 5 to 18 years and measures the child's well-being over the past month. The 50-item written questionnaire yields 12 subscales which form 2



* Significant difference between olanzapine and placebo groups ($P < .05$).
** Significant difference between olanzapine and placebo groups ($P < .01$).

Fig. Comparison of mean percentage increase from baseline to end point in HRQoL measures of the Child Health Questionnaire-Parent Form between placebo and olanzapine treated adolescents.

global summary scores known as the Physical and Psychosocial Component Scores. The CHQ scoring algorithm calculates a norm-based score for each participant in the clinical trial. This score enables the comparison of the observed scores to a representative sample of community-based children ages 5 to 18 years drawn from the general US population. Lower scores on the CHQ indicate greater impairment in functioning. Population means and standard deviations for the CHQ are reported in The CHQ User's Manual [18]. In this study, the CHQ-PF 50 was completed by a parent (or legal guardian) at baseline and again at the end of the individual's participation in the double-blind study.

2.3. Statistical analysis

For descriptive statistics, means and standard deviations were used to describe continuous variables. One sample, 2-sided *z*-tests were used to compare CHQ scores between study participants and tabulated population values. Paired *t* tests were used to compare CHQ scores at baseline to those at the end point within treatment groups. Comparison of changes in CHQ scores due to *treatment group* also employed an analysis of covariance models which included *treatment group* as a *fixed effect* and change in either *YMRS* or Children's Depression Rating Scale, Revised (CDRS-R; [24]) from baseline to end point as a covariate. SAS 9.2 and MS Excel were used for data analysis. Statistical significance was based on $\alpha = .05$.

3. Results

One hundred and seven participants were randomly assigned to receive olanzapine and 54 participants were assigned to placebo (see Table 1 for participant demographics within each treatment group). One subject in the olanzapine group was eliminated from the analysis due to lack of baseline measurements, thus reducing the number of olanzapine participants to 106. Statistical analysis revealed no significant differences in demographic variables between treatment groups.

3.1. Baseline CHQ scores compared with population means

Table 2 compares baseline and end of study CHQ scores for both treatment groups in relation to population values. While Table 2 shows that the olanzapine group had lower scores at baseline than the placebo group, these differences were not statistically significant (except scales noted below) and likely reflect normal differences due to randomization. Further, baseline scores for both treatment groups were significantly different from population values on the CHQ-psychosocial summary scale ($P = .0009$) but not on the physical summary scale. Post hoc analyses revealed that scores for both treatment groups were significantly different

Table 1
Participant demographics by treatment group

	Placebo (n = 54)		Olanzapine (n = 107)	
	N	%	N	%
Sex, girls	30	56	46	43
Race, White	41	76	71	66
	Mean	SD	Mean	SD
Age (y)	15.4	1.2	15.1	1.3

Table 2
Comparison to population values for subscales of the CHQ-PF50 at baseline and at the end point for each treatment group

HRQoL Measure	Population		Placebo				ES	Olanzapine				ES
	μ	Σ	Baseline (n = 54)		End point (n = 52)			Baseline (n = 106)		End point (n = 99)		
			Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Psychosocial Summary	51.2	9.1	26.0**	10.8	32.5*	12.6	.55	21.0**	11.8	31.7*	12.9	.87
Physical Summary	53.0	8.8	53.1	11.5	53.7	9.1	.06	50.4	12.0	50.4	10.3	.00
Psychosocial scales												
Family Activities	89.7	18.6	**36.6****	24.8	**47.4***	27.7	.41	**32.2****	24.5	**51.8***	28.9	.78
Parental Impact-Emotional	80.3	19.1	**37.7***	15.6	**47.4***	20.8	.53	**32.5****	21.3	**43.8***	25.7	.48
Mental Health	78.5	13.2	**52.4***	15.3	58.8	18.2	.38	**43.2****	18.6	**55.9***	20.9	.64
Self-Esteem	79.8	17.5	**46.1***	24.6	54.4	22.9	.35	**42.9***	22.8	**50.9***	24.8	.34
Behavior	75.6	16.7	**39.9***	15.5	48.6	20.8	.48	**33.5****	19.9	51.8	24.5	.82
Role/Social-Emotional/Behavioral	92.5	18.6	**49.6***	37.5	65.0	35.4	.42	**39.3****	34.6	65.5	35.0	.87
Parental Impact-Time	87.8	19.9	58.0	24.9	67.3	25.9	.37	**52.5***	27.1	62.1	28.5	.35
Family Cohesion	72.3	21.6	50.2	29.9	53.3	29.9	.10	48.8	28.5	56.3	26.8	.27
Physical scales												
Bodily Pain	81.7	19.0	71.3	20.9	80.0	19.9	.43	67.3	27.9	74.2	23.6	.27
General Health	73.0	17.3	69.7	15.5	70.4	16.0	.04	63.1	17.2	70.6	17.2	.43
Physical Functioning	96.1	13.9	89.6	23.2	93.4	12.5	.20	89.3	20.4	86.3	21.3	.14
Role/Social-Physical	93.6	18.6	88.9	26.1	89.1	20.8	.01	82.4	29.7	88.0	23.3	.21

CHQ-PF50, Child Health Questionnaire Parent Form 50. ES, Cohen's D effect size.
* $P < .05$ when compared to population.
** $P < .01$ when compared to population.

from population values on the following CHQ-psychosocial subscales: Behavior, Family activities, Mental health, Parental impact-emotional, Role/social-emotional/behavioral, and Self-esteem. In addition, at baseline, individuals in the olanzapine group were also significantly different from population values on the Parental impact-time subscale (Table 2). Although both groups were significantly different from population values on the aforementioned subscales, individuals who were assigned to the olanzapine group had significantly lower CHQ-psychosocial summary, Mental health, and Behavior baseline subscale scores than those assigned to placebo. Since subjects were randomly assigned to treatment, the baseline treatment group differences in CHQ subscales are likely due to chance.

3.2. End point CHQ scores compared with population means

Comparisons of end of study scores (Table 2) indicate that participants in both treatment groups remained statistically significantly different from population values on the Psychosocial summary scale ($P = .017$) but not on the Physical summary scale. Post hoc analyses showed that participants in both groups remained different from population values on the Family activities and Parental impact-emotional subscales. Additionally, participants in the olanzapine group also remained significantly different from population values at the end of the study on the Self-esteem and Mental health subscales.

3.3. Group differences in improvement in CHQ scores

Although participants in both groups showed improvement over time across most subscales, individuals in the olanzapine group exhibited significantly greater improvement in the Psychosocial summary score from baseline to end point compared with those in the placebo group (10.2 vs. 6.2 point change, $P < .05$). Specifically, the Behavior, Family activities, and Mental health subscales showed significantly greater improvement in mean scores in the olanzapine group than the placebo group (Fig.).

3.4. Associations between CHQ scores and Rating scale scores

For the 2 treatment groups combined, change in YMRS score from baseline to end point was significantly inversely correlated with change in the Psychosocial summary scale score ($b = -14.5$, $P < .001$) but not change in the Physical summary scale score. Further post hoc analyses revealed that change in YMRS had a significant inverse association with change in Behavior ($b = -19.7$, $P < .001$), Family activities ($b = -26.9$, $P < .001$), Mental health ($b = -17.3$, $P = .002$), Parental impact-emotional ($b = -13.1$, $P = .02$), Parental impact-time ($b = -14.1$, $P = .03$), role/social-emotional/behavioral ($b = -22.0$, $P = .002$), and Self-esteem ($b = -14.5$, $P < .001$).

Change in Children's Depression Rating Scale, Revised (CDRS-R; [24]) from baseline to end point was significantly inversely related to change in Psychosocial summary scale score ($b = -1.43$, $P < .01$), but not Physical summary scale score. Post hoc analyses also showed that change in CDRS-R had a significant inverse relationship with change in Family activities ($b = -249$, $P < .01$), Mental health ($b = -.86$, $P = < .001$), and Self-esteem ($b = -63$, $P = .04$) subscale scores. There were no statistically significant treatment group differences in change in Psychosocial or Physical summary score after controlling for change in YMRS score.

4. Discussion

Consistent with prior studies [17,19], our findings indicate that adolescents with bipolar disorder exhibit worse CHQ scores in psychosocial domains compared to population norms, particularly in areas such as disruptions to family activities and parents' emotional distress. More specifically, researchers found that individuals receiving divalproex remained significantly below the national norms at the end of the study on all subscales except physical functioning and role/social limitations-physical [17]. In this same study, individuals who received quetiapine remained significantly below the national norms at the end of study on all scales except behavior, bodily pain, self-esteem, general health, physical functioning, and role/social limitations-physical [17]. Although Stewart et al. did not report how participants varied across subscales when receiving ziprasidone, they noted that participants exhibited greatest impairment in psychosocial aspects of HRQoL, which is consistent across studies [19]. These aspects of psychosocial function may be more difficult to normalize because they involve treating the patient as well as their family members. This notion has been well documented in samples of children who have chronic illnesses [25–28]. Findings from the current study suggest that increased focus on improving family related functioning may improve the adolescents overall well-being while providing support to other family members. Indeed, Family-Focused treatment [29] has been found to be effective as adjunctive treatment to pharmacotherapy for adolescents with bipolar disorder and their families.

Regardless of treatment group, our results suggest that a reduction in manic symptoms was associated with improved psychosocial functioning. Results also revealed that while participants in the olanzapine group (end point mean = 16.9; SD = 9) and the placebo group (end point mean = 24; SD = 9.7) completed the study with clinically elevated YMRS scores, participants in the olanzapine group exhibited a greater reduction (mean change = 16.1; SD = 10) in YMRS scores from baseline to end point than participants in the placebo group (mean change = 7.8; SD = 9.6). Therefore, because the olanzapine group demonstrated a greater reduction in mania compared to the placebo group, individuals in the olanzapine group may have exhibited greater improvement in psychosocial functioning. Nonetheless, although improvements in manic symptoms were associated with improvements in CHQ scores, these scores did not necessarily normalize. As noted previously, other social systems influence an adolescent's psychosocial health and correcting disruptions to these systems may require more than alleviation of manic symptoms. It should also be noted that this study lasted only 3 weeks and full remission of HRQoL deficits may take longer. Future research to determine HRQoL changes associated with more chronic treatment is needed. Additionally, although adolescents in both treatment groups did not show improvement on the physical health scales (e.g., physical functioning and general health), our results generally indicated that values on physical health scales began and ended within normal levels.

4.1. Limitations

This study has several limitations. First, the results of this study reflect a brief window of time following a manic episode. Results may be different when assessing adolescents with bipolar disorder over a longer time period. Second, the recall period for the CHQ in this study was the past month (at baseline) or the time in study (at end point). Our results at end point, which represent changes from baseline, may be skewed by the different recall period than the normative data, which is prior month and thus should be interpreted with caution. Third, individuals in the placebo group exhibited improvement in psychosocial functioning despite continuing to experience clinically significant levels of mania, which limits our findings because it may suggest that some aspects of psychosocial functioning are not related to symptoms of mania. However, it is important to note that treatment with placebo is not equivalent to not receiving treatment because subjects participating in a double blind placebo controlled study with weekly visits may inadvertently receive supportive therapy during study visits. Moreover, the improvement in psychosocial functioning among the placebo group likely also reflects benefits from family and school meetings, increased awareness of the individuals' difficulties, and other non-pharmacologic follow-up care that occurs for most patients regardless of study participation. Fourth, psychosocial and physical functioning was based on parent-report; adolescents may have reported differently. Additionally, information was not available regarding which participants began the study as inpatients vs. outpatients or how long inpatient participants remained hospitalized. Indeed, participants who were inpatients at baseline and those who had longer hospitalization stays may have had worse CHQ scores and, thus, may have skewed our results.

Despite these limitations, this study is the first placebo controlled study to measure the HRQoL among adolescents with bipolar. Our results suggest that several aspects of psychosocial functioning are impaired in manic adolescents with bipolar disorder and improve with olanzapine treatment. However, our findings suggest that psychosocial impairment does not normalize despite treatment and that additional family interventions might lead to further improvements in psychosocial function. In contrast, our findings showed that domains of physical health largely remained intact and primarily unchanged despite treatment.

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