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Brief Report

A Preliminary Study of the Effects of Treatment with Lithium Versus Quetiapine on Attention of Adolescents with Bipolar Disorder

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Abstract

Objectives: Despite attentional deficits being a prominent feature of bipolar disorder, there are limited data on the effects of common treatments for bipolar disorder on attention. Thus, we sought to compare the effects of lithium versus quetiapine on attention in adolescents with bipolar disorder.

Methods: Adolescents ages 10–17 with bipolar disorder, type I, who were experiencing a manic or mixed episode, were recruited from outpatient settings and the inpatient psychiatric units at Cincinnati Children's Hospital Medical Center during their first manic episode. Healthy comparison subjects were recruited from outreach programs in the community. Patients were randomized to lithium or quetiapine, administered in a double-dummy, double-blinded manner for 6 weeks. Attentional deficits were assessed in all groups using the Identical Pairs Continuous Performance Task at baseline and at week 6.

Results: Patients with bipolar disorder ($n = 79$) had impaired attention relative to the healthy group ($n = 57$) at both baseline and after 6 weeks of treatment. The lithium-treated group ($n = 30$) had poorer attentional performance than the healthy group at week 6. There was a difference in change in performance between lithium- and quetiapine-treated ($n = 49$) groups.

Conclusion: Youth with bipolar disorder may have impaired attention relative to their healthy peers. Conclusions are limited by the high dropout rate in the lithium-treated group.

Keywords: bipolar, pediatric, attention, lithium, quetiapine, cognition

Introduction

Bipolar disorder is a psychiatric disorder characterized by depressive and manic episodes that often first appear during childhood and adolescence (Moreno et al. 2007). In addition to the affective component of the illness, patients also exhibit neurocognitive impairments, which can be present even outside of mood episodes (Martinez-Aran et al. 2000). Indeed, neurocognitive impairments are associated with lower psychosocial functioning, even after controlling for mood symptoms and other clinical variables (Wingo et al. 2009).

One of the difficulties in assessing cognitive impairment in patients with bipolar disorder is the fact that some pharmacologic interventions can produce negative cognitive effects independent of the effects of the illness itself. Notably, lithium may be associated with impaired psychomotor speed and verbal memory in adults (Pachet and Wisniewski 2003). In children with bipolar disorder, treatment with mood stabilizers (including lithium and anticonvulsants) was associated with impaired processing speed and working memory, as well as lower achievement on a timed math test compared with those who are untreated (Henin et al. 2009).

Second-generation antipsychotics have also been shown to impact cognition. A study of euthymic patients with bipolar disorder found that patients taking second-generation antipsychotics performed worse on tasks of semantic fluency and verbal measures than unmedicated patients, with quetiapine being less associated with dysfunction than other antipsychotics (Torrent et al. 2011). In another study, initiation with quetiapine was associated with somnolence and impaired processing speed and attention (Harvey et al. 2007). A controlled study examining cognitive effects of quetiapine in adolescents with bipolar disorder showed similar performance on tasks of information processing and memory between healthy subjects and patients who were treated for 40 weeks (Duffy et al. 2009).

It is often unclear whether cognitive dysfunction is due to the bipolar disorder itself or medication exposure. Studies of youth with bipolar disorder may provide a unique opportunity to resolve this ambiguity. Since many children with bipolar disorder are medication naive at presentation, it becomes easier to determine the

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etiology of their cognitive symptoms. Thus, children are a key population to study when examining the cognitive effects of bipolar disorder and its treatments.

One of the specific cognitive domains that is consistently reported as impaired in bipolar disorder is attention (Dickstein et al. 2004; Doyle et al. 2005). Notably, a study found no difference in attentional impairment between medicated euthymic and unmedicated manic subjects, suggesting these deficits can persist regardless of mood states and may be resistant to treatment (Pavuluri et al. 2006). These studies used some form of a Continuous Performance Task (CPT), which is a measure of sustained attention. Versions of the CPT have been shown to detect deficits in sustained attention in patients with bipolar disorder (Sax et al. 1995; Sax et al. 1999).

Given that patients with bipolar disorder have impaired attention (Doyle et al. 2005) and may have impaired cognition before their first manic episode (Bora and Ozerdem 2017), it is important to find treatments that maximize potential cognitive improvements or at a minimum, do not worsen cognitive dysfunction. Prior studies of the cognitive effects of pharmacological interventions in bipolar disorder have shown that children with bipolar disorder who are treated pharmacologically may exhibit some improvement in attentional performance. Treatment with aripiprazole for 24 weeks was associated with improved sustained attention in adolescents with bipolar disorder (Wang et al. 2012). Youth with bipolar disorder who were treated for 3 years improved in attention relative to their baseline, but they did not catch up with the performance of their age-matched healthy peers (Pavuluri et al. 2009). A 12-month follow-up study comparing lithium and quetiapine found that lithium-treated participants but not quetiapine-treated participants improved in phonemic fluency over the course of the study (Daglas et al. 2016). No differences between the two treatments were found for any other cognitive domain, including attention and sustained attention.

With these considerations in mind, the aim of this analysis was to identify the differential cognitive effects of treatment with a mood stabilizer (lithium) versus a second-generation antipsychotic (quetiapine) in youth with bipolar disorder. Given prior neurocognitive studies of lithium and quetiapine in youth with bipolar disorder, our hypotheses were as follows: (1) at baseline, patients with bipolar disorder would perform worse on a version of the Identical Pairs Continuous Performance Task (CPT-IP) than healthy subjects and (2) following 6 weeks of treatment, there would be greater impaired attention in the lithium group than the quetiapine group.

Methods

Subjects and clinical data

This study was approved by the University of Cincinnati and Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Boards. All study participants and their legal guardians provided written informed assent and consent, respectively, before participating in the study.

Manic or mixed adolescents, ages 10–17, with bipolar disorder, type I, were recruited from outpatient settings and the inpatient psychiatric units at CCHMC during their first manic episode. Healthy comparison subjects (matched for age, sex, socioeconomic status, race, handedness, and nicotine use) were recruited from outreach programs in the community.

Patients with bipolar disorder were eligible to be included if they met DSM-IV-TR criteria for bipolar disorder, type I, had a baseline Young Mania Rating Scale (YMRS) score ≥20, were less than 2 years from onset of bipolar disorder, had no prior psychiatric hospitalizations, had no lifetime diagnosis of posttraumatic stress disorder, and had an intelligence quotient >70 as measured by the Wechsler Abbreviated Scale of Intelligence (WASI).

DSM-IV-TR diagnoses were made using the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). Symptoms of mania and depression were measured using the YMRS and the Children's Depression Rating Scale-Revised (CDRS-R), respectively. Overall illness severity was assessed using the Clinical Global Impressions-Severity Scale (CGI-S).

Treatment

A randomization schedule was used to assign lithium or quetiapine to manic adolescents. Medication pills were administered in a double-dummy, double-blinded manner. Quetiapine was adjusted based on tolerability to a target dose of 400–600 mg, and lithium was adjusted to a target dose based on a serum level of 1.0–1.2 mEq/L.

Neurocognitive testing

Sustained attention was measured at baseline and week 6 using the CPT-IP. During the CPT-IP, subjects were presented with a random single-digit number for 700 ms at 750 ms intervals, leaving a 50 ms gap between each number's appearances. Subjects were asked to press a button every time an identical number was presented twice in succession. Five blocks of testing were presented. Each active block contained five possible correct pairs, for a total of 25 possible total correct responses. Primary endpoints were total correct responses, total incorrect responses, reaction time to correct responses, and discriminability. Discriminability is a measure of the ability to detect signal from noise, and is calculated as $d = 0.5 + (y - x)(1 + y - x)/4y(1 - x)$ where "x" is the probability of a false alarm and "y" is the probability of a correct response.

To remove subjects who fell asleep during the task, two researchers independently inspected the raw data from each run and determined if the subjects' performance was consistent with them being asleep. Specifically, if the subjects had 0 presses during an active block of the task and also the surrounding control blocks, then they had most likely fallen asleep and they were removed from the analysis.

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics program version 25 and the SAS program version 9.4. Group comparisons for demographic variables were evaluated using chi-square or analysis of variance (ANOVA) tests. Comparisons of group performance in the CPT-IP were assessed using ANOVAs, with group as the independent variable and performance measures as the dependent variable. Associations between clinical improvement (YMRS, CDRS, CGI-S) and change in CPT-IP performance were assessed using Pearson correlations. Statistical significance was set at the 0.05 level for all tests.

Results

Sixty quetiapine-treated, 56 lithium-treated, and 59 healthy subjects were enrolled in this study. Of those enrolled, 26 lithium-treated and 11 quetiapine-treated subjects did not complete the study. In the lithium group, subjects dropped out due to the following: adverse events ($n = 5$), lost to follow-up ($n = 6$), withdrawal of consent ($n = 6$), lack of efficacy ($n = 3$), medication noncompliance ($n = 3$), incarceration ($n = 1$), technical difficulty with CPT-IP ($n = 1$),

Table 1. Demographic and Clinical Characteristics of Healthy, All Bipolar, Lithium-Treated, and Quetiapine-Treated Adolescents

Variable[a]	*Healthy* (n = *57*)	*All bipolar* (n = *79*)	*Lithium* (n = *30*)	*Quetiapine* (n = *49*)
Age, years, mean (S.D.)	14.8 (1.9)	14.4 (2)	15.0 (2.1)	14.1 (1.8)
Sex, females, *n* (%)	32 (56)	51 (65)	21 (70)	30 (61)
Race, Caucasian, *n* (%)	38 (67)	60 (76)	22 (73)	38 (78)
Duration of illness, weeks, mean (S.D.)	NA	15.1 (23.7)	12.6 (18.3)	16.7 (26.6)
Age of onset, years, mean (S.D.)[a]	NA	13.2 (2.2)	14.0 (2.1)	12.6 (2.1)
Psychosis, *n* (%)	0 (0)	12 (15)	4 (13)	8 (16)
Anxiety disorders, *n* (%)	0 (0)	18 (23)	6 (20)	12 (24)
Attention-deficit/hyperactivity disorder, *n* (%)	0 (0)	33 (42)	10 (33)	23 (47)
YMRS at baseline, mean (S.D.)	0 (1)	27.7 (5.5)	27.8 (5.7)	27.6 (5.2)
YMRS at week 6, mean (S.D.)	0 (1)	10.2 (6.5)	11.8 (7.1)	8.6 (6)
IQ, mean (S.D.)	111 (13)	104 (12)	106 (12)	103 (13)

[a]Significant difference: ANOVA $F(1, 75) = 8.449$, $p = 0.005$, lithium > quetiapine.
ANOVA, analysis of variance; IQ, intelligence quotient; NA, not applicable; S.D., standard deviation; YMRS, Young Mania Rating Scale.

and moving out of town ($n = 1$). In the quetiapine group, subjects dropped out due to the following: adverse events ($n = 4$), lost to follow-up ($n = 4$), lack of efficacy ($n = 1$), medication noncompliance ($n = 1$), and moving out of town ($n = 1$).Within the patient group and within treatment groups, there were no differences in sex, ethnicity, age, baseline YMRS and CDRS-R scores, duration of illness, age of onset of illness, nor rates of comorbid attention deficit/hyperactivity disorder, psychosis, and comorbid anxiety disorders between completers and noncompleters.

Of those who completed, ANOVA testing revealed a significant difference in age of onset between lithium-treated and quetiapine-treated patients, with the lithium group having an older age of onset [mean (standard deviation): 14.0 (2.1) vs. 12.6 (2.1), ANOVA: $F(1, 75) = 8.0$, $p = 0.005$]. Otherwise, groups were closely matched on demographic variables (Table 1).

At baseline, there were significant differences between healthy subjects and patients for percent correct [88.6 (8.0) vs. 84.4 (12.3), ANOVA: $F(1, 134) = 5.1$, $p = 0.025$] and discriminability [0.969 (0.022) vs. 0.955 (0.040), ANOVA: $F(1, 134) = 5.4$, $p = 0.022$]. Between treatment groups, there were no differences in CPT performance at baseline.

At week 6, significant differences remained between healthy subjects and patients for percent correct [90.0 (9.3) vs. 84.2 (13.9), ANOVA: $F(1, 134) = 7.4$, $p = 0.007$] and discriminability [0.974 (0.024) vs. 0.957 (0.040), ANOVA: $F(1, 134) = 8.0$, $p = .005$]. ANOVA testing revealed significant treatment group differences at week 6 for percent correct [ANOVA: $F(2, 133) = 5.1$, $p = 0.008$] and discriminability [ANOVA: $F(2, 133) = 4.5$, $p = 0.013$]. *Post hoc* testing revealed that lithium-treated subjects had lower percent correct [81.4 (13.5) vs. 90.0 (9.3), $p = 0.006$] and discriminability [0.952 (0.034) vs. 0.974 (0.024), $p = 0.016$] than the healthy subjects. There were no significant performance differences between lithium- and quetiapine-treated subjects, or between quetiapine-treated and the healthy subjects.

For change in score from baseline to week 6, ANOVA revealed significant treatment group differences for change in discriminability [ANOVA: $F(2, 133) = 3.1$, $p = 0.050$]. *Post hoc* testing revealed a difference between the lithium-treated and quetiapine-treated subjects for change in discriminability [–0.008 (0.030) vs. 0.007 (0.030), $p = 0.05$]. There were no other significant differences in change in performance measures between groups. CPT performance results are summarized in Table 2.

Pearson correlations revealed no significant relationship between change in CPT-IP scores from baseline to week 6 and change in symptom rating scales (measured by YMRS, CDRS, and CGI-S) for either lithium or quetiapine (all $p > 0.08$).

Discussion

The attentional performance of patients with bipolar disorder in this study was significantly impaired relative to healthy subjects at

Table 2. Continuous Performance Task Performance in the Healthy, All Bipolar, Lithium-Treated, and Quetiapine-Treated Adolescents

Variable	*Healthy* (n = *57*)	*All Bipolar* (n = *79*)	*Lithium* (n = *30*)	*Quetiapine* (n = *49*)
Baseline performance				
Average reaction time, ms, mean (S.D.)	562 (93)	562 (84)	555 (82)	566 (86)
% correct, mean (S.D.)[a]	88.6 (8.0)	84.4 (12.3)	84.6 (11.5)	84.3 (12.8)
% false alarm, mean (S.D.)	0.9 (1.7)	1.3 (3.2)	0.6 (0.5)	1.8 (4.0)
Discriminability, mean (S.D.)[b]	0.969 (0.022)	0.955 (0.040)	0.959 (0.030)	0.953 (0.045)
Change in performance from baseline to week 6				
Average reaction time, ms, mean (S.D.)	–15 (51)	–1 (58)	7 (72)	–6 (47)
% correct, mean (S.D.)	1.3 (8.3)	–0.2 (11.3)	–3.2 (11.7)	1.6 (10.7)
% false alarm, mean (S.D.)	–0.5 (1.7)	–0.5 (11.3)	–0.1 (0.7)	–0.7 (2.8)
Discriminability, mean (S.D.)[c]	0.005 (0.020)	0.001 (0.031)	–0.008 (0.030)	0.007 (0.030)

[a]Significant difference, ANOVA: $F(1, 134) = 5.112$, $p = 0.025$, healthy > all bipolar.
[b]Significant difference, ANOVA: $F(1, 134) = 5.358$, $p = 0.022$, healthy > all bipolar.
[c]Significant difference, ANOVA: $F(2, 133) = 3.071$, $p = 0.050$, quetiapine > lithium.
ANOVA, analysis of variance; S.D., standard deviation.

baseline. This impairment in attentional performance remained significant after 6 weeks of treatment with lithium or quetiapine. Other studies have found similar results. In a 2009 study by Pavuluri et al., patients with bipolar disorder exhibited poorer performance on a cognitive battery than did their healthy peers. After 3 years of treatment, their performance remained impaired relative to their healthy peers. The cognitive battery in this study included the Trail Making Task and the Penn CPT as measures of attention.

There was a difference in the change in attentional performance between lithium- and quetiapine-treated subjects as measured by discriminability. One study comparing the cognitive performance of lithium- versus quetiapine-treated young adults with new-onset bipolar disorder found no difference in attention between the two groups at 12 months (Daglas et al. 2016). The sample in the Daglas et al. had a mean age of 21 years, whereas our study had a mean age of 14 years. It is possible that earlier age at onset correlates with different cognitive morbidity and treatment responsiveness. It is also possible that the 6-week treatment yields different outcomes in cognition than the 12-month treatment.

The lithium-treated group in our study had poorer attentional performance at week 6 than the healthy group. Previous studies have found no negative effect of lithium on attention. A study of pediatric bipolar disorder showed no difference in attention between medication-naive patients and patients taking lithium plus risperidone; both groups were similarly impaired relative to healthy subjects (Pavuluri et al. 2006). Age of onset, length of illness, and co-occurring treatment may be confounding factors, as there was a younger age of onset and longer length of illness in the Pavuluri study. In addition, patients were also taking risperidone. Furthermore, when lithium was administered to healthy subjects for 3 weeks, attention was not significantly impaired (Stip et al. 2000). Finally, one recent review did not find an association between lithium use and impaired attention in patients with bipolar disorder, although lithium use was associated with impaired psychomotor speed (Paterson and Parker 2017). This review focused on adults; it is possible that age affects the cognitive effects of lithium.

In our study, quetiapine did not negatively affect overall attentional performance from baseline to week 6 relative to the healthy group. Data on the cognitive effects of quetiapine in bipolar disorder vary. One study found that in patients with bipolar disorder, initiation with quetiapine was associated with impaired processing speed and attention relative to risperidone, as well as more somnolence (Harvey et al. 2007). A naturalistic study of the cognitive effects of antipsychotics in bipolar disorder found that quetiapine-treated patients performed worse on a Backward Digit Span Task of attention relative to healthy subjects, and worse on a Trail Making Task than unmedicated subjects (Torrent et al. 2011). One of the difficulties in comparing different studies is the use of a variety of tests of cognition. A recent meta-analysis found that when different measures of attention were grouped, euthymic youth with bipolar disorder did not have deficits in attention relative to healthy peers. However, impaired attention was found when meta-analyses of individual tests were performed, highlighting the importance of considering heterogeneity in attention measures (Elias et al. 2017). Our study used the CPT-IP to measure attention, while Torrent et al. used the Digit Span and Trail Making Test. The Trail Making Task involves more visual scanning than does the CPT-IP, meaning they measure slightly different facets of attention, which could explain some of the differences in findings.

Our study has some important limitations. The lack of an unmedicated comparison group with bipolar disorder makes it difficult to definitively say if the attentional decline in the lithium group was related to the natural course of the illness or if it was a direct medication effect. Also, many more lithium-treated participants failed to complete the study than quetiapine-treated participants, which introduces bias and limits the power of the study. Lack of systematic collection of serum drug levels makes it difficult to determine whether serum drug levels were associated with performance changes. In addition, lack of adherence measures, other than self-report, reduced our ability to detect patients who were nonadherent to their medication regimen. Finally, the lithium group had an older age of onset of illness than the quetiapine group (14 vs. 12.6, respectively). This introduces age of onset as a confounding factor and limits our ability to draw conclusions from the comparison of these two groups.

Conclusions

Despite the fact that cognitive deficits are a prominent feature of bipolar disorder, data on the cognitive effects of common treatments are lacking, particularly for quetiapine. In this preliminary study, patients with bipolar disorder remained impaired in attention relative to healthy peers after 6 weeks of treatment. Lithium-treated subjects had poorer attentional performance at week 6 than the healthy subjects. This study has a few important limitations, including a disproportionately high dropout rate in the lithium-treated group. Thus, the interpretability of our results is limited and further studies are needed.

Clinical Significance

In this study, youth with bipolar disorder had impaired attention relative to their healthy peers. Further studies comparing the cognitive effects of lithium and quetiapine are needed.

Disclosures

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