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A Prospective Open-Label Treatment Trial of Olanzapine Monotherapy in Children and Adolescents with Bipolar Disorder

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ABSTRACT

Objective: **The goal of this study was to assess the effectiveness and tolerability of olanzapine in the treatment of acute mania in children and adolescents.**

Methods: **This was an 8-week, open-label, prospective study of olanzapine monotherapy (dose range 2.5–20 mg/day) involving 23 bipolar youths (manic, mixed, or hypomanic; 5–14 years old). Weekly assessments were made using the Young Mania Rating Scale (YMRS), Clinical Global Impressions Severity Scale (CGI-S), Brief Psychiatric Rating Scale, and Children's Depression Rating Scale. Adverse events were assessed through self-reports, vital sign and weight monitoring, laboratory analytes, and extrapyramidal symptom rating scales (Barnes Akathisia Scale, Simpson–Angus Scale, and Abnormal Involuntary Movement Scale).**

Results: **Twenty-two of the 23 youths (96%) completed the study. Olanzapine treatment was associated with significant improvement in mean YMRS score ($-19.0 \pm 9.2, p < 0.001$). Using predefined criteria for improvement of ≥30% decline in the YMRS and a CGI-S Mania score of ≤3 at endpoint, the overall response rate was 61%. Overall, olanzapine was well tolerated, and extrapyramidal symptom measures were not significantly different from baseline. Body weight increased significantly over the study (5.0 ± 2.3 kg, $p < 0.001$).**

Conclusions: **Open-label olanzapine treatment was efficacious and well tolerated in the treatment of acute mania in youths with bipolar disorder. Future placebo-controlled, double-blind studies are warranted.**

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INTRODUCTION

CHILDHOOD BIPOLAR DISORDER (BPD) is among the most severely disabling psychiatric conditions affecting children (Faedda et al. 1995; Geller et al. 1998; Wozniak and Biederman 1995; Wozniak et al. 1995). It is associated with great severity of illness (e.g., psychosis, mixed mania, high rates of self-injury, and drug abuse) and impairment (Geller et al. 1998; McClellan et al. 1993; Strober et al. 1995; Wozniak and Biederman 1995; Wozniak et al. 1995). Despite the significant morbidity associated with pediatric BPD, however, little has been done to investigate the treatment of this disorder in children (Geller and Luby 1997).

There have been only two prospective studies investigating the safety and efficacy of mood stabilizers in youths with BPD (Geller et al. 1998; Kowatch et al. 2000). Dr. Geller and colleagues found lithium to be moderately helpful for those with BPD and comorbid substance abuse. Dr. Kowatch and colleagues compared open trials of carbamazepine, valproate, and lithium and found that, although somewhat effective, there was a high level of noncompliance with these agents and many subjects dropped out, with only 3 of 42 patients completing the study (Kowatch et al. 2000). These two studies highlight the difficulties in working with this volatile and difficult-to-treat patient population. Comorbid substance abuse and noncompliance are serious problems.

In an effort to gain a better understanding of the therapeutics of pediatric mania naturalistically, a systematic chart review was pursued to capture the clinical experience with this disorder in a pediatric psychopharmacology clinic over an extended period of time (Biederman et al. 1999b). This chart review documented that mood stabilizers (lithium carbonate, carbamazepine, and valproate) were selectively helpful in controlling manic symptoms in children. However, these agents had a slow onset of action and were associated with high rates of relapse (Biederman et al. 1999b). The results of this naturalistic study, combined with the results of the studies conducted by Geller et al. (1998) and Kowatch et al. (2000), prompted the search for alternative agents for the treatment of pediatric BPD. Although typical neuroleptics have been widely used in the acute and chronic management of adults and children with mania, concerns about neuroleptic side effects in general, and tardive dyskinesia in particular, have limited their usefulness (Campbell et al. 1983; Campbell and Spencer 1988; Gelenberg and Hopkins 1996; Gelenberg and Jefferson 1995; Kane and Smith 1982; Tohen and Zarate 1998). In sharp contrast, the atypical agents, because of their unique pharmacological profile of combined dopaminergic and serotonergic action, hold the promise of providing antimanic efficacy with fewer associated adverse reactions than the typical agents and without the requisite blood draw of the mood stabilizers.

Data have recently emerged documenting the efficacy of the atypical neuroleptics in general, and olanzapine in particular, in the treatment of BPD in adults and children. Olanzapine has been found to be beneficial in the treatment of adults with acute bipolar mania as a monotherapeutic agent or in combination with other agents (Tohen et al. 1999, 2000). The Food and Drug Administration recently approved olanzapine monotherapy for the treatment of acute manic episodes associated with adult bipolar I disorder.

Two recent case series on youths support the potential beneficial effects of olanzapine in the treatment of pediatric mania. These studies reported that olanzapine, in combination with mood stabilizers, led to marked improvement of manic symptomatology. The first study reported on the treatment of seven adolescents (aged 12 to 17 years) with BPD (Soutullo et al. 1999), and the second reported on the treatment of three acutely manic bipolar youths whose symptoms dramatically improved within 5 days on this agent (Chang and Ketter 2000). The results of these reports suggest that olanzapine may have important therapeutic benefits in the treatment of pediatric mania, indicating that more systematic work is needed to evaluate this treatment further.

Although the controlled clinical trial continues to be the "gold standard'' test for the evaluation of any treatment for a mental disorder, before embarking on a randomized clinical trial in children, several preliminary steps are needed to help define the benefits as well as the risks of the proposed new treatment. Case reports pave the way for systematic open trials. The data from an open, prospective trial can then guide the decision as to the wisdom of proceeding to a randomized clinical trial. This three-step approach to drug development in pediatric psychopharmacology is both rational and ethical. To this end, we conducted an open-label, prospective trial of olanzapine monotherapy in the treatment of pediatric BPD. We

hypothesized that olanzapine monotherapy would be well tolerated and effective in the treatment of pediatric BPD (mixed, mania, and hypomania).

METHODS

This was a single-site, prospective, open-label, 8-week study of olanzapine monotherapy in the treatment of youths with mania, aimed at evaluating short-term safety and efficacy, effect size, and time course of treatment response of the medication. The protocol was reviewed by the Institutional Review Board. Parents or legal guardians signed informed consent, and all youths signed informed assent.

Subjects

Subjects were 23 outpatients of either sex, 5 to 14 years old, with a *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV; American Psychiatric Association 1994) diagnosis of BPD (manic, hypomanic, or mixed). Patients were recruited from referrals to a pediatric psychopharmacology program at a major university center. The diagnosis of BPD was determined by the lead author (J.A.F.), an experienced, board-certified child and adolescent psychiatrist, based on clinical evaluation and confirmed by a structured diagnostic interview (Diagnostic Interview for Children and Adolescents-Revised; DICA-R) (de la Osa et al. 1997; Reich 2000).

In addition to satisfying full diagnostic criteria for BPD, eligible and consenting youths were required to have a Young Mania Rating Scale (YMRS) total score of $\geq$15 at baseline to enroll in the treatment trial. Excluded were children with acute suicidality, any unstable medical or neurological condition, a history of severe allergies or multiple drug reactions, pregnancy or lactation, active substance abuse (within 1 month of the study), prior exposure to olanzapine, treatment with a depot neuroleptic, treatment with a monoamine oxidase inhibitor, treatment with fluoxetine or clozapine within 4 weeks, history of schizophrenia or other primary psychotic disorder, or a full-scale IQ of less than 70.

Assessment procedures

Prior to inclusion in the study, patients underwent a standard clinical assessment consisting of a psychiatric evaluation that included obtaining a full history via an interview of the parent or legal guardian and a direct interview of the child by a board-certified child and adult psychiatrist (J.A.F.). In addition, a structured interview, a physical examination, and laboratory assessments were performed (prolactin levels, thyroid function tests, liver function tests, calcium, phosphorus, uric acid, glucose, total protein, albumin, cholesterol, creatinine kinase, electrolytes, hepatitis screen, a urinalysis with urine drug screen, a pregnancy test [for females of childbearing age], and a complete blood cell count). The structured diagnostic interview administered to the child's parents or legal guardian relied on the computerized DICA-R to assess for current diagnosis of BPD and psychiatric comorbidities (Reich 2000). In addition, baseline electrocardiograms, height, weight, supine and standing blood pressure, and heart rate were obtained.

To be given a diagnosis of BPD, the subjects had to meet full DSM-IV criteria for BPD upon psychiatric examination and have the diagnosis confirmed via structured interview. Severity of manic symptomatology was assessed using the YMRS (Young et al. 1978) at baseline and weekly throughout the study. Severity of overall BPD, mania, and depression were assessed using the National Institute of Mental Health Clinical Global Impressions Severity Scale (CGI-S; 1 = *not ill*, 7 = *extremely ill*) (Rapoport et al. 1985). The Brief Psychiatric Rating Scale (BPRS; Overall 1962) was used to assess psychotic symptomatology (1 = *not at all,* 7 = *extremely severe*; converted to a range of 0 to 6) and the Children's Depression Rating Scale (CDRS; 1 = *no symptoms*, 7 = *definite symptoms*) (Poznanski et al. 1984) to assess depressive symptomatology. These ratings were performed at baseline and weekly throughout the study.

Safety was monitored by obtaining a baseline and endpoint physical examination, EKG, weekly blood pressure and heart rate, a comprehensive metabolic battery (liver function tests; hematology; and urinalysis performed at baseline, weeks 2, 4, and 6 and at end point; prolactin assessed at baseline, week 2, and

at endpoint), and weekly weight and height measurements were performed at baseline and endpoint. Reference ranges specific to children and adolescents were used for all quantitative laboratory assessments except those for prolactin, which used sex-specific adult reference ranges (females, 0.06 to 1.05 mmol/L; males, 0.07 to 0.81 mmol/L). Extrapyramidal symptoms were assessed at baseline and at each weekly visit using the Simpson–Angus Scale (Simpson and Angus 1970), the Barnes Akathisia Scale (Barnes 1989; Inada et al. 1996), and the Abnormal Involuntary Movement Scale (AIMS; Rapoport et al. 1985).

Procedures

Patients were assessed during a 2- to 7-day screening period, during which they had screening laboratory tests, a psychiatric history and interview, and a physical examination. All medications that patients were taking upon enrollment in the study were tapered over a 1-week period. Patients were required to discontinue all prior medications for at least 24 hours before initiation of olanzapine treatment.

Olanzapine was initiated at 2.5 mg/day and was increased by 2.5 mg/day every 3 days, depending on the patient's response and adverse reactions. Titration continued throughout the study up to a total of 20 mg/day of olanzapine, administered as a single dose in the evening. Decreases in the dose of olanzapine were allowable in the case of adverse events and could occur by any number of 2.5- to 5-mg tablet decrements to a minimum of 2.5 mg/day. Allowable dose ranges from weeks 2 to 3 were 2.5–10 mg/day; from weeks 3 to 4, 2.5–15 mg/day; and from weeks 4 to 8, 2.5–20 mg/day.

Concomitant use of a benzodiazepine (lorazepam, up to 4 mg/day) as a rescue medication and the anticholinergic agent benztropine for extrapyramidal symptoms (up to 2 mg/day) were allowable. Psychostimulants and α-adrenergic agonists (guanfacine and clonidine) were also allowed for the treatment of attention deficit hyperactivity disorder if patients had been on a stable dose of these medications for at least 1 month prior to enrollment, and no dose changes were allowed during the study. Treatment response was defined a priori as a $\geq$30% decrease in YMRS total score from baseline (visit 2) to the end of the study (visit 10), plus a CGI-S Mania score of $\leq$3 at the end of the study. In addition, we reanalyzed the data using a $\geq$50% decrease in the YMRS total score to compare our results more directly to the 8-week, open-label study on the mood stabilizers conducted by Kowatch and colleagues in youths with BPD (Kowatch et al. 2000).

Statistical analysis

Data were analyzed using the last-observation-carried-forward (LOCF) method, assessing mean change from baseline to endpoint. In addition, an LOCF visitwise analysis was performed. All patients with a baseline and at least one postbaseline measurement were included in the analysis.

Data for all enrolled patients were analyzed for treatment-emergent, self-reported adverse events. The mean changes from baseline to endpoint in laboratory analytes, vital signs, and objective measures of extrapyramidal symptoms were assessed using means and standard deviations. Means and standard deviations were used to evaluate continuous data, and the Student's t test was used to assess within-group changes. Frequencies and proportions were used to characterize nominal data. All tests of hypotheses used a two-tailed alpha level of 0.05 for significance.

RESULTS

Of 78 prospective subjects who were screened by telephone for participation, 62% (n = 48) were ineligible. Of the 30 subjects who were eligible for the study via telephone screen, 23 met the inclusion criteria after an in-person interview. Thus, 23 patients were eligible and signed consent/assent to be included in the study. All 23 individuals met full DSM-IV diagnostic criteria for bipolar I disorder, 44% had psychotic symptoms, and all were outpatients.

The clinical and demographic characteristics of the 23 participating patients are outlined in Table 1. The mean age upon study entry was 10.3 $\pm$ 2.9 years. The sample consisted of 13 male and 10 female patients. Most patients (91.3%) were White. Of the 23 participating youths, 22 had experienced prior unsuccessful

Table 1. Demographics of Pediatric Bipolar Patients ($n = 23$)

Demographics	
Age at time of study (years)	10.3 ± 2.9[a]
Range	5.4–14.7
White	21 (91%)
Male	13 (57%)
Characteristics of mania	
Age of onset of mania (years)	6.0 ± 3.5[a]
Age of onset of depression (years)	6.0 ± 3.1[a]
Onset of depression prior to mania	6 (29%)[b]
Mean duration of illness (years)	4.3 ± 2.5[a]
Manic/hypomanic episodes	12.7 ± 21.3[a]
Positive family history of bipolar disorder	3 (13%)
Positive family history of depression	12 (52%)
Positive family history of substance abuse	11 (48%)
Neuroleptic-naïve	15 (65%)
Bipolar disorder	23 (100%)
Mixed presentation	17 (74%)
Psychotic	10 (44%)
First episode	5 (22%)

[a]Mean ± SD.
[b]Six of 21 patients: 2 patients were missing data.

medication trials. Trials using different agents included stimulants ($n = 29$), mood stabilizers ($n = 20$), serotonin reuptake inhibitors and selective serotonin reuptake inhibitors ($n = 13$), tricyclic antidepressants ($n = 10$), α-adrenergic agonists ($n = 9$), benzodiazepines ($n = 5$), typical antipsychotics ($n = 4$), atypical antipsychotics ($n = 4$), venlafaxine ($n = 2$), buspirone ($n = 2$), and hydroxyzine ($n = 1$).

Three children (13%) had first-degree relatives diagnosed with BPD, 12 children (52%) had a family history of major depression, and 11 (48%) had first-degree relatives with substance-use disorders. The mean age at onset of bipolar symptoms was 6.0 ± 3.5 years. The mean age at onset of depression was 6.0 ± 3.1 years in 21 cases (2 cases were missing onset data). Depression occurred before mania in 6 of 21 cases (29%). The mean duration of bipolar illness was 4.4 ± 2.5 years. Seventy-four percent had a mixed presentation, and 22% were in their first episode. As measured with the DICA-R, 44% had psychotic features. Patterns of comorbidity were characterized by extremely high rates of oppositional defiant disorder (100%), attention deficit hyperactivity disorder, (see Table 2) (78%), phobia (57%), separation anxiety disorder (52%), overanxious disorder (48%), conduct disorder (35%), and obsessive-compulsive disorder (35%).

The mean dose of olanzapine at endpoint was 9.6 ± 4.3 mg/day (0.21 ± 0.1 mg/kg/day; range 2.5–20 mg/day). All but four children received olanzapine once a day (qhs). The four patients that required twice-daily dosing (with the higher dose given in the evening) were relatively young (one was 6 years old, two were 10, and one was 12). Concomitant medications used during the study included stimulants (35%), benzodiazepines (13%), and benztropine (9%).

Efficacy analysis

A significant improvement was observed in symptoms of mania, as reflected in the YMRS total score (LOCF) decrease of 19 points (62% improvement) from baseline to endpoint ($p < 0.001$; Fig. 1). Significant improvement was seen at the end of week 1, and sustained improvement was seen throughout the 8-week duration of the study (Fig. 1). Patients showed an improvement at endpoint relative to baseline on all items of the YMRS scale. Significant improvement was seen in the following YMRS items: elevated mood, increased motor activity–energy, sleep, irritability, speech, language–thought disorder, thought content, disruptive–aggressive behavior (all ps < 0.001), and insight ($p = 0.018$). The CGI-S of Bipolar Disorder also

TABLE 2. COMORBID DIAGNOSES IN 23 YOUTHS WITH BIPOLAR DISORDER

Diagnosis	
Disruptive behavioral disorders	
Oppositional defiant disorder	23 (100%)
Attention deficit disorder	18 (78%)
Conduct disorder	8 (35%)
Anxiety disorders	
Two or more comorbid anxiety disorders	13 (57%)
Obsessive-compulsive disorder	8 (35%)
Avoidant	7 (30%)
Psychosis	10 (44%)
Other	
Enuresis	7 (30%)
Encopresis	2 (9%)[a]
Bulimia	1 (4%)

[a]Two of 22 patients: 1 patient was missing data.

improved significantly (38% improvement, $p < 0.001$; Fig. 2), as well as the CGI-S of Mania (40% improvement, $p < 0.001$). In addition, significant improvement was observed from baseline to endpoint for depression ratings, as measured by the CGI-S of Depression (37% improvement, $p = 0.002$) and the CDRS (32% improvement, $p < 0.001$), for BPRS total scores (62% improvement, $p < 0.001$), and positive psychotic symptomatology subscore (90% improvement, $p = 0.008$). The within-group change from baseline was significant at every visit for all variables, except at week 1 for the BPRS positive psychotic symptomatology subscore. There were no significant differences in the treatment response, either on the CGI or on the YMRS, between the BPD youths with and without psychosis.

Using the a-priori definition of treatment response of a ≥30% decline on the YMRS and a CGI-S Mania score of ≤3, 14 patients (61%) were considered responders. Median time to response, when assessed

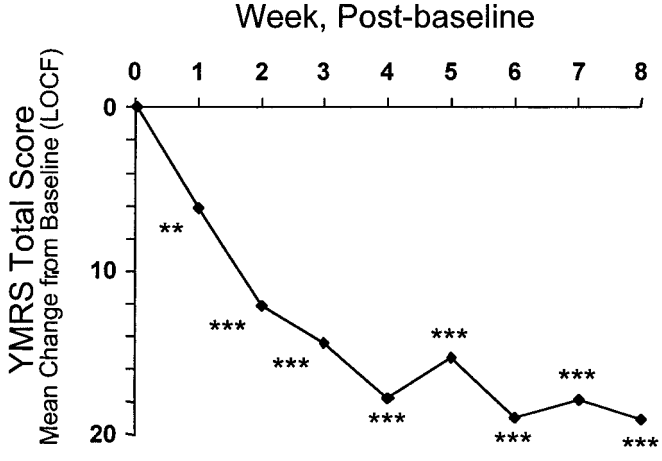

FIG. 1. Mean change from baseline (last observation carried forward; LOCF) in mean Young Mania Rating Scale (YMRS) total score in 23 pediatric patients with bipolar disorder receiving olanzapine. Significant improvement was seen by the first time point at the end of week 1 (**, $p = 0.001$) and was sustained throughout the rest of the 8-week study (***, $p < 0.001$).

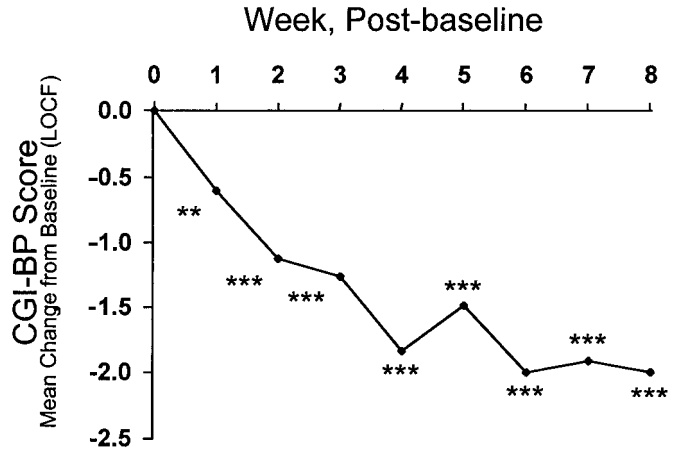

FIG. 2. Mean change from baseline (last observation carried forward; LOCF) in mean Clinical Global Impressions–Severity of Bipolar Disorder (CGI-S-BP) total score. Significant improvement was seen by the first time point at the end of week 1 (**, $p = 0.002$) and was sustained throughout the rest of the 8-week study (***, $p < 0.001$).

over time according to the definition of treatment response, was 30 days. Applying the response rate criteria used in Kowatch et al. (2000), 17 youths (74%) had a ≥50% change in YMRS.

Safety analysis

Overall, olanzapine treatment was generally well tolerated. Only one patient discontinued the study after 6 weeks of treatment due to increased depressive symptoms with accompanying suicidal ideation, which resulted in an inpatient hospitalization. There were no significant baseline-to-endpoint changes in the Simpson–Angus, Barnes Akathisia, or AIMS scores. However, two patients (9%) displayed treatment-emergent akathisia, based on their Barnes Akathisia Scale scores.

As shown in Table 3, the most frequently reported adverse events were increased appetite ($n = 14$), somnolence ($n = 10$), abdominal pain ($n = 7$), and weight gain ($n = 7$). Although only seven patients reported weight gain by self-report, all patients gained some weight over the course of the study (mean increase: 5.0 ± 2.3 kg, $p < 0.001$) and continued to gain weight throughout the 8 weeks of active treatment (Fig. 3). Mean change from baseline in body mass index (BMI) was 2.4 ± 1.3 kg/m^2 ($p < 0.001$) during the 8-week study. Using a definition of obesity of BMI > 30 kg/m^2, no patient was considered obese at baseline, but 3 of 22 (14%) met criteria for obesity at endpoint. Weight gain showed no relationship to either age or sex,

TABLE 3. TREATMENT-EMERGENT ADVERSE EVENTS AS REPORTED BY THE PATIENTS (≥20%)

Event	*Number of patients*	*Percentage*
Increased appetite	14	60.9
Somnolence	10	43.5
Abdominal pain	7	30.4
Weight gain	7	30.4
Depression	6	26.1
Diarrhea	5	21.7
Infection	5	21.7
Fever	5	21.7

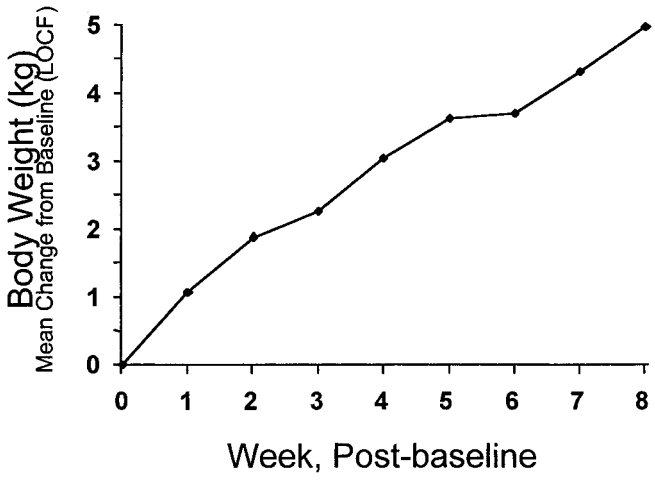

FIG. 3. Mean change from baseline (last observation carried forward; LOCF) in body weight (kg). Change from baseline was significant at every time point ($p < 0.001$).

and there was no difference in weight gain or clinical response between children who remained on stimulants ($n = 8$) and those not on stimulants ($n = 15$) during the course of the olanzapine trial. One patient had an increased cholesterol level at endpoint, and no patients were noted to have nonfasting blood glucose abnormalities.

Although small but statistically significant decreases from baseline to endpoint were observed in hematocrit, hemoglobin, and mean cell volume, all endpoint hematologic values were within normal limits. Likewise, although significant increases from baseline to endpoint were also observed for Alanine Transferase (ALT), all but two cases had endpoint ALT values within normal limits; the two cases (8.7%) had endpoint ALT values slightly above the normal range ($p = 0.009$). There was a statistically significant mean change from baseline to endpoint in prolactin levels (0.4 ± 0.5 mmol/L, $p = 0.002$), and endpoint values were above range in 6 of the 21 patients (28.6%) with normal levels at baseline. Of these six cases of treatment-emergent increased prolactin, there was a single case where the prolactin level (2.18 mmol/L) exceeded twice the upper limit of the reference range. The six cases of treatment-emergent hyperprolactinemia consisted of four males and two females. Clinically, none of the subjects had any signs or symptoms associated with the prolactin elevation.

Small but statistically significant baseline-to-endpoint increases were observed in supine pulse rate (baseline, 84.5 ± 13.5 beats per minute [bpm]; change, 9.8 ± 14.5 bpm; $p = 0.004$) and standing pulse rate (baseline, 97.8 ± 18.9 bpm; change, 10.3 ± 13.0 bpm; $p < 0.001$). Likewise, EKG data showed a small but statistically significant increase in heart rate (baseline, 82.7 ± 16.8 bpm; change, 11.3 ± 14.9 bpm; $p = 0.002$). There were no significant changes in any other EKG parameter.

DISCUSSION

This is the first systematic prospective, open-label treatment trial of olanzapine monotherapy for acute pediatric mania. The 23 youths with DSM-IV bipolar mania who participated in this study improved significantly from baseline to endpoint in both manic and depressive symptomatology. In total, 61% of patients were classified as responders, defined a-priori as a decline of $\geq$30% in the YMRS total score plus an endpoint CGI-S of Mania score $\leq$3. These encouraging results support the impetus for future controlled trials of olanzapine and other atypical neuroleptics in the treatment of pediatric mania.

The positive results observed with olanzapine in the treatment of children and adolescents with mania are consistent with emerging evidence documenting that olanzapine is effective in treating acute mania in adults. In a recent placebo-controlled study, Tohen et al. (1999) found that 49% of 70 adult bipolar patients responded

to olanzapine monotherapy with significant reduction in their manic symptoms, as rated on the YMRS. Furthermore, our results documenting that olanzapine had similar efficacy in treating the manic symptoms in youths with and without psychotic features are also consistent with the adult study by Tohen (1997) and support the notion that the reduction of manic symptoms by olanzapine is not due only to its antipsychotic effects.

Also consistent with the adult study is the finding that the spectrum of benefits from olanzapine treatment in these youths was not limited to manic symptoms but extended to depressive symptoms as well. In fact, we observed a statistically significant reduction in depressive symptomatology, as measured through the CDRS. The positive impact on depressive symptomatology is particularly important for the management of mania in youths, considering its frequently mixed presentation with prominent depressive features (Wozniak and Biederman 1985; Wozniak et al. 1985). Considering the hazards associated with the use of antidepressants in bipolar patients, further studies regarding the efficacy of olanzapine in improving symptoms of depression are extremely important.

Equally important is the effect of olanzapine in reducing aggressive symptoms. Although we did not have specific scales to address the measurement of aggression, the YMRS aggression subscale change score demonstrated significant improvement. In addition, this was the one symptom complex that parents repeatedly described as significantly improved. Hyperaggressive symptoms are a major source of morbidity and disability in youths with mania and are among the most disabling and dangerous manifestations of this disorder in youths. Severe outbursts of irritability in manic children often result in threatening or aggressive behavior (McGlashan 1988). As has been recently documented, severe aggressive behavior frequently leads to the diagnosis of conduct disorder in bipolar youths. In a recent study of children (Biederman et al. 1999a), a large and bidirectional overlap between BPD and conduct disorder was noted. These results suggest that some youths with conduct disorder with prominent affective dysregulation and aggressive symptomatology may suffer from BPD and that the treatment of the underlying mood disorder could have a large impact on quality of life of these highly disturbed youths, who are at very high risk for highly adverse outcomes.

Our results with olanzapine treatment are particularly encouraging, given the outcomes in the two prospective studies that exist in the literature of mood stabilizers in youths with BPD. Geller et al. (1998) reported the first double-blind, placebo-controlled treatment trial of a mood stabilizer (6 weeks; using a Children's Global Assessment Scale of $\geq$65 for response) in BPD youths (mean age 16.2 $\pm$ 1.2 years; range 12–18 years), documenting that lithium was effective in the treatment of BPD with secondary substance abuse in 46% of patients. Notable side effects in the Geller study included thirst, polyuria, nausea, vomiting, and dizziness (no objective measures of weight gain were given).

More recently, Kowatch et al. (2000) reported results from an 8-week (2-week lead-in phase followed by a 6-week active-treatment phase) open study comparing divalproex, carbamazepine, and lithium in the treatment of 42 BPD children (aged 8–18 years; mean age 11.4 years). The Kowatch et al. study was similar to our olanzapine monotherapy study in pediatric BPD in that it was an open-label trial of mood stabilizers (6 weeks on active treatment) and provides clear response criteria. In the Kowatch study, treatment response was defined as a change from baseline to endpoint, with a score of 1 or 2 on the CGI Improvement of Bipolar Disorder Scale *or* a $\geq$50% improvement in the YMRS score. The present study relied on the CGI-Severity scale, rather than the Improvement scale, precluding meaningful comparison of our CGI data with those of Kowatch et al. However, using only the YMRS response criteria, Kowatch et al. obtained a 53% response rate for valproate, 38% for lithium, and 38% for carbamazepine. In comparison, we obtained a 74% response rate using the $\geq$50% YMRS improvement criterion with olanzapine.

In addition, in sharp contrast to our 96% completion rate for the full 8 weeks of active treatment in this study and the scarce need for rescue medicines, Kowatch et al. (2000) had only 3 of the 42 randomized youths (7%) complete the full 8 week study, and more than half of their patients did not respond to monotherapy with any of the three mood stabilizers. Notable side effects in the Kowatch et al. study included nausea, increased appetite (reported on lithium; no objective measures of weight gain were given), sedation (on carbamazepine and valproate), rash, dizziness on carbamazepine, and polyuria and diarrhea on lithium. Clearly, more work is needed to further evaluate the role of traditional mood stabilizers and atypical neuroleptics in the management of youths with BPD. Direct comparisons in a randomized trial would be of benefit.

In this study, olanzapine treatment was well tolerated, with a high level of compliance. Only one patient

discontinued the treatment trial, due to worsening depression at week 6. Also encouraging are the data regarding treatment-emergent extrapyramidal symptoms. Only two patients (9%) were noted to have mild treatment-emergent akathisia, and there were no significant baseline-to-endpoint changes in Simpson–Angus, Barnes Akathisia, or AIMS scores. These results are encouraging, given the purportedly higher rate of extrapyramidal effects of the typical antipsychotics in children (Campbell et al. 1983) and adults with affective disorders.

Although prolactin levels were not reported to be significantly different from placebo in adult patients treated with olanzapine over a 6-week period (Crawford et al. 1997), mild prolactin elevations (defined as less than two times above the normal range) were found in nearly one third of our patients. These were asymptomatic, and only one child had an elevation that was greater than two times the upper end of the laboratory norm. This relatively mild elevation of prolactin is consistent with one other olanzapine study in youths (Sikich et al. 1999) and could represent a developmental pharmacodynamic difference in responsivity/sensitivity of children to the D_2 effects of antipsychotic agents, possibly due to the greater D_2 receptor density found in the striatum, which might reflect a generalized increase in D_2 receptor density in children (Seeman et al. 1987). This point notwithstanding, and considering the unknown clinical significance of prolactin elevation on growth and development in children and adolescents, more work is needed to evaluate further the implication of this finding in the overall analysis of risks and benefits of olanzapine treatment in pediatric mania.

The most significant adverse event observed was the marked increase in weight and BMI that occurred during the 8 weeks of the study. Three patients met the criterion for obesity at the end of this treatment trial. Given the potentially serious health problems that are inherently associated with obesity, more efforts are clearly needed to evaluate the etiology of weight gain in youths treated with olanzapine.

These results are consistent with an emerging literature documenting the beneficial effects of atypical neuroleptics in the treatment of manic symptomatology, including aggressive behavior, in patients with BPD. For example, clozapine has been described as an effective monotherapeutic agent for the treatment of BPD in adults (Zarate et al. 1995), targeting not only thought disorder but also the dysphoric and manic mood components. Olanzapine has also been found to be beneficial in the treatment of adults with acute mania as a monotherapeutic agent or in combination with other agents (Tohen et al. 1999, 2000). In addition, a retrospective chart review documented that the atypical neuroleptic risperidone was markedly helpful in reducing symptoms of mania, psychosis, and aggression in youths with BPD (Frazier et al. 1999). The results of the study reported by Frazier et al. were particularly remarkable given the severity of illness and the prior treatment refractoriness of these youths to multiple medication trials, including mood stabilizers and typical antipsychotics. Taken together, the findings of these studies and the data from this study support the therapeutic benefits of atypical neuroleptics in the treatment of manic and aggressive symptoms associated with BPD, with and without psychotic symptomatology, not only in adults but also in children.

The findings in this report should be viewed against some methodological limitations. This was an open study; therefore, the assessments were not blind to treatment. However, the benefits associated with olanzapine therapy in these patients are particularly striking considering that, upon enrollment in the study, these patients remained sufficiently ill despite receiving as many as four to six concomitant medications, with the majority of these youths having a history of failing multiple prior medication trials and of refractoriness to medication.

Clearly, the results of this study need to be considered preliminary due to its uncontrolled nature. These results do suggest the potential efficacy of olanzapine monotherapy in the treatment of acute pediatric BPD. Although firmer conclusions regarding the role of olanzapine in the treatment of pediatric mania await results from randomized, double-blind, controlled clinical trials, open studies such as this represent an essential step in a rational drug development program aimed at pediatric mania. As such, these positive results lay the foundation for further investigation of olanzapine in the treatment of pediatric mania in the form of a randomized, controlled clinical trial.

Despite the limitations of this study, our results show that olanzapine monotherapy had beneficial effects on manic, depressive, psychotic, and aggressive symptoms in youths with acute BPD (manic type). The streamlined dosing, lack of requisite blood monitoring, and the profile of safety and efficaciousness of this agent in youths suffering from acute manic symptoms of BPD made it easy for the patients to be compli-

ant and make olanzapine a potentially attractive agent for pediatric use. The significant weight gain that occurred during treatment with olanzapine warrants further studies to investigate interventions that either prevent or reduce weight gain in this population. Further research comparing olanzapine to mood stabilizers is indicated in controlled trials to assess fully the short- and long-term safety and efficacy of olanzapine and of mood stabilizers in the treatment of youths with BPD.

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