

Lithium Treatment of Acute Mania in Adolescents: A Large Open Trial

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ABSTRACT

Objective: To examine initial response to treatment in a large sample of acutely manic bipolar I adolescents and to examine potential predictors of nonresponse, such as the presence of prominent depressive features, psychosis, or psychiatric comorbidity. **Method:** Adolescents, 12 to 18 years of age, with an acute manic episode were treated with open lithium. Response was defined as a decline in Young Mania Rating Scale total score of $\geq 33\%$ and a rating of "much improved" or "very much improved" on the Clinical Global Impressions Improvement item at week 4. Remission of mania was defined as a Young Mania Rating Scale score of ≤ 6 . Axis I diagnoses were assessed using the Lifetime Schedule for Affective Disorders and Schizophrenia for Adolescents. **Results:** Of 100 subjects, 63 met response criteria and 26 achieved remission of manic symptoms at the week 4 assessment. Prominent depressive features, age at first mood episode, severity of mania, and comorbidity with attention-deficit/hyperactivity disorder did not distinguish responders from nonresponders. When treated with adjunctive antipsychotic medication, subjects with psychotic features at baseline responded as well as subjects without psychosis. **Conclusions:** In this largest systematic treatment trial of acutely manic adolescents to date, lithium appears effective for acute stabilization of symptoms. Controlled treatment studies in adolescents with acute mania are needed. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(9):1038–1045. **Key Words:** bipolar, lithium, comorbidity.

Acute mania in adolescents is a psychiatric emergency that is often accompanied by suicidal ideation and psychotic features. Lithium, anticonvulsants, and atypical antipsychotic medications are commonly used to treat acute mania in adolescents. However, the few studies that assess treatment response in acutely manic bipolar adolescents are all open trials (Kowatch et al., 2000; Papatheodorou et al., 1995; Strober et al., 1988; Wagner et al., 2002, West et al., 1994). The only published placebo-controlled treatment study in adolescents with bipolar disorder was a relatively small sample of outpatients with

secondary substance dependency (Geller et al., 1998). Most had been ill for several years before entering that study. They were also heterogeneous in diagnosis (bipolar I, bipolar II, mania or major depression with predictors of bipolarity) and in phase of illness upon presentation (manic, hypomanic, depressed, or mixed phase). Some efficacy for lithium was suggested on a global measure, the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). In that study, a CGAS score of >65 was achieved by 46.2% on lithium versus 8.3% on placebo ($p = .046$, using a one-tailed Fisher's Exact Test). There was no difference between the groups treated with lithium and placebo on measures of mood symptoms.

A randomized comparison of lithium, valproate, and carbamazepine in 41 outpatient children and adolescents (ages 6–18 years) with bipolar I and II disorder found large effect sizes for all three medications (Kowatch et al., 2000). The relatively small sample size and lack of a placebo control arm limited that study's ability to detect differences between the three medications.

An open study with 50 hospitalized adolescents reported generally good response rates to lithium treatment on a global measure (56% after 4 weeks and 68% after 6 weeks;

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Strober et al., 1988). Other smaller open studies suggested some efficacy for valproate in the treatment of acute mania in hospitalized adolescents (Papatheodorou et al., 1995; West et al., 1994). However, all three of these studies of hospitalized, acutely manic adolescents (Papatheodorou et al., 1995; Strober et al., 1988; West et al., 1994) used adjunctive antipsychotic medication throughout the protocol for most subjects. In a recent study, the use of adjunctive treatment with the atypical antipsychotic medication quetiapine improved the response rates to treatment with divalproex in acutely manic hospitalized adolescents with and without psychotic features (DelBello et al., 2002). The necessity for continued treatment with an antipsychotic medication beyond the acute response phase in adolescents with psychotic mania has been suggested (Kafantaris et al., 2001a,b).

Initial clinical presentation of mania may be complicated by other variables that influence response to treatment. For example, comorbid attention-deficit/hyperactivity disorder (ADHD) has been reported to predict poor anti-manic response to lithium (Strober et al., 1988, 1998) in some but not all studies (Kafantaris et al., 1998). Depressive features at baseline in adults (Swann et al., 1997), psychiatric comorbidity, and onset of psychiatric illness before the age of 12 years (Strober et al., 1988) have also been reported to decrease the likelihood of response to lithium treatment.

This report describes the response to open lithium treatment in terms of reduction in mania, depression, and suicidal ideation in a large sample of acutely manic bipolar I adolescents. Exploratory analyses were also conducted to assess whether response rates were associated with (1) psychotic features at baseline, (2) prominent depressive symptoms, (3) comorbid diagnoses, (4) early onset of mood disorders, (5) severity of mania at initial presentation, and (6) hospitalization.

METHOD

This is a report of data from the open phase of our investigation of lithium in the treatment of acute mania in adolescents. Data were collected over a 4-year period from 1995 to 1999. The Institutional Review Board of our medical center approved and monitored the implementation of this protocol. Eligible participants were between the ages of 12 and 18 years and met *DSM-IV* criteria for a current manic or mixed episode based on a clinical interview by consensus of two board-certified child and adolescent psychiatrists. In addition, a score of at least 16 points on the Young Mania Rating Scale (YMRS) (Young et al., 1978) at baseline was required, representing at least a moderate severity of mania. Exclusionary criteria for study participation were mental retardation, a neurological or other medical impair-

ment, current substance dependence (but not substance abuse), and adolescents whose parents did not give permission to discontinue stimulant treatment. Patients receiving antidepressants just prior to study entry were included only if their symptoms of hypomania or mania preceded the initiation of antidepressant therapy and did not improve after discontinuation of the antidepressant.

Potential subjects were referred by their treating clinicians from consecutive admissions to the adolescent psychiatry inpatient unit, the Child and Adolescent Psychiatry Crisis Service, and the pediatric emergency department of our medical center. Written consent was obtained from at least one parent or guardian, and each adolescent gave written assent to participate.

The diagnosis of bipolar I disorder was confirmed by structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia-Lifetime version; K-SADS-L) (Klein, 1993) with a parent or guardian and with the adolescent, when stable enough to cooperate. Premorbid and comorbid *DSM-IV* Axis I diagnoses, including a full assessment of disruptive behavior disorders, substance use disorders, and depressive symptoms with and without concomitant mania, were also obtained with the K-SADS-L. The diagnostic interviewers were highly trained clinicians (board-certified child psychiatrist or licensed child psychologist). However, the interviewers were not blinded to the results of the clinical interview or to study status. Family histories of first- and second-degree relatives were obtained from at least one parent of nonadopted subjects using a semi-structured interview based on the Family History-Research Diagnostic Criteria method (Andreasen et al., 1977).

Level of suicidality was assessed at baseline and at week 4 using the Suicide item of the Hamilton Depression Rating Scale (Ham-D, 17-item) (Williams, 1988), in which anchors ranged from 0 (absence of any signs of suicidality) to 4 (an actual suicide attempt). A cutoff of 3 or higher was used to identify patients with clear suicidal ideation.

Treatment Procedures

All participants received treatment with immediate-release lithium carbonate capsules. Rapid titration of lithium to therapeutic levels ranging from 0.6 to 1.2 mEq/L was facilitated by the use of the pharmacokinetic method of predicting therapeutic dose (Cooper et al., 1973). In this method, a lithium serum level is drawn exactly 24 hours following an initial dose of 600 mg lithium. The serum was sent by overnight mail to Mr. Cooper's laboratory for analysis. The resulting lithium level for that participant was used to predict the total daily dose of lithium that would produce therapeutic serum levels in that individual (Cooper et al., 1973). To minimize the risk of acute adverse effects such as nausea and vomiting, we modified the lithium titration schedule as follows: subjects received the 600-mg "test dose" of lithium on day 1 and 900 mg on day 2, after the 24-hour serum level was drawn. For predicted therapeutic doses >900 mg/day, the lithium dose was increased by 300 mg/day until the predicted target dose was reached. Weekly lithium levels were obtained as a measure of treatment adherence.

So as not to withhold potentially beneficial treatment, our protocol required that patients who had psychosis or severe aggression without psychosis be treated with an antipsychotic medication concurrently with lithium. The first-line adjunctive antipsychotic medication was changed from haloperidol to risperidone in 1998. Subjects unable to tolerate the first-line medication were placed on an alternative antipsychotic agent by their primary clinicians. Lorazepam up to 6 mg/day for up to 3 consecutive days was permitted for severe agitation or insomnia. No lorazepam was administered within 12 hours prior to a research rating. No other concurrent psychoactive medications were allowed.

Response to treatment was assessed weekly using the following battery of rating instruments: (1) YMRS, (2) Ham-D, (3) Brief Psychiatric

Rating Scale (Woerner et al., 1988), (4) the Clinical Global Impressions scales (CGI) (Guy, 1976), and (5) CGAS (Shaffer et al., 1983). Three board-certified child psychiatrists and one licensed child psychologist were trained to administer these weekly ratings. Training prior to study implementation yielded good to excellent interrater reliability indices for each rating measure, with intraclass correlations ranging from 0.97 for the YMRS to 0.75 for the CGAS. Acceptable levels of reliability were maintained during study implementation as assessed by a random sample of 10 baseline ratings, in which reliability coefficients remained between 0.85 to 0.95 for the primary raters. Two of these raters (R.D. and G.P.) were the attending child psychiatrists on the adolescent inpatient unit. At least two raters (one clinical attending and one from the research team) independently rated the same live interview for each patient. In addition, treating clinicians were asked to attend the rating sessions to relate relevant clinical information to the rating team and thus enhance the validity of weekly assessments as a true reflection of patient functioning. Immediately following each patient assessment, a consensus score on each rating scale item was reached during a conference between the trained raters. This consensus method was chosen to help improve the accuracy of the ratings and to help maintain excellent interrater reliability.

Subjects were rated as responders to the open phase of the protocol if they met both of the following criteria: (1) a reduction of $\geq 33\%$ from their baseline Y-MRS score and (2) a rating on the CGI Global Improvement Item of 1 (very much improved) or 2 (much improved). The CGI criterion was included to ensure that subjects whose YMRS scores declined by $>33\%$ had clinically significant improvements in manic symptoms and/or had not cycled into a depressed phase of their illness. To allow our results to be consistent with studies that use a 50% decline, our results are also reported using a 50% reduction in YMRS score and an improvement rating of 1 or 2.

Data Analysis

Tests of association between groups used χ^2 analyses with a Yates correction for continuity (Yates, 1934). Paired *t* tests were used to assess for patterns of response at baseline and at week 4 of treatment. Last observation carried forward procedures were used for intent-to-treat analyses in subjects who completed at least one post-baseline assessment but dropped out prior to completing all 4 weeks. Lithium response rates were compared based on the presence or absence of depressive symptoms, psychotic features, comorbid diagnosis, and specifically ADHD, mood disorder prior to the age of 12 years, and clinical severity assessed as baseline YMRS score. A series of χ^2 analyses were used to test the significance of the associations. All statistical tests were two-tailed with α set at .05.

RESULTS

Clinicians referred 154 eligible patients as potential subjects for this study. Forty-six eligible patients and/or their guardians did not wish to participate in this research project. They received standard clinical care at our medical center. Of the 108 subjects enrolled (70.1% of patients referred), six participants dropped out before the week 1 assessment. Two additional subjects were dropped when the patients' reports on the K-SADS-L indicated that psychotic features had been present without mood symptoms for longer than 2 weeks; therefore, a more appropriate

diagnosis was schizoaffective disorder. The eight subjects dropped from analyses did not differ significantly from the remaining subjects in gender distribution, age, socioeconomic status, or clinical characteristics at baseline.

This intent-to-treat sample of 100 patients was equally distributed between the genders (50% male), and the mean age was 15.23 years (SD 1.85 years; Table 1). Only seven of these participants did not complete all 4 weeks of the treatment protocol: two dropped out prior to week 2, three prior to week 3, and two prior to the week 4 assessment. All of these patients withdrew consent for participation in the protocol. More than three fourths (77%) were hospitalized at the time of their enrollment. The mean length of stay for these hospitalized adolescents was 35.10 days (SD 31.64 days) with some remaining in the hospital while awaiting residential placement or transfer to a long-term hospital. The remaining subjects were judged not to require hospitalization at the time of their initial clinical assessment. The sample was 65% white, 16% African-American, 7% Hispanic, 6% Asian American, and 6% of mixed ethnic background. Subjects came from a broad socioeconomic spectrum, reflective of the medical center's catchment area. The mean Hollingshead two-factor scale score (Hollingshead, 1957) of 36.20 (SD 16.46) was generally consistent with a middle class socioeconomic designation. Almost half (48%) of the sample were residing with both biological parents at the time of study enrollment, and almost two thirds (65%) of the sample resided in two-parent households with biological parents, stepparents, or legal guardians.

TABLE 1
Characteristics at Baseline of the Sample
of Adolescents With Mania (*N* = 100)

Mean age (SD) (yr)	15.23 (1.85)
Male	50%
Delusions and/or hallucinations (psychosis)	35%
Severe aggression or agitation without psychosis	11%
Neither psychosis nor aggression	54%
Onset of mood disorder before age 12	39.6% ^a
Any Axis I diagnosis before age 12	63.5% ^a
First-degree relative with bipolar I disorder	42.9% ^b
At least one additional psychiatric diagnosis	71.9% ^a
History of ADHD diagnosis	32.3% ^a
History of substance use disorder	20.8% ^a
Prominent depressive symptoms (Ham-D) (≥ 18)	35%
Suicidal ideation	23%

Note: ADHD = attention-deficit/hyperactivity disorder; K-SADS = Lifetime Schedule for Affective Disorders and Schizophrenia for Adolescents; Ham-D = Hamilton Depression Rating Scale.

^a *n* = 96 who completed K-SADS interviews.

^b *n* = 91 nonadopted subjects with completed family psychiatric history interviews.

Approximately half ($n = 54$) of our subjects had neither psychosis nor severe aggression and were treated with lithium monotherapy throughout the study. Approximately one third ($n = 35$) of the sample presented with prominent, mood-congruent delusions or hallucinations. An additional 11 patients without delusions or hallucinations had severe aggression and/or agitation that was unresponsive to other forms of treatment, including lorazepam. Most subjects with psychosis or aggression tolerated the first-line antipsychotic agent: 5 mg haloperidol (56.5%), or after 1998, up to 2.25 mg/day risperidone (21.7%). Alternative medications included up to 10 mg olanzapine (15.2%), quetiapine 300 mg, thiothixene 8 mg, or chlorpromazine 100 mg, in one subject each, respectively.

K-SADS diagnostic interviews were completed on 96 of the 100 patients and a parent or guardian. At least one comorbid psychiatric diagnosis was identified in 69 patients (71.9%). ADHD was the most frequent comorbid diagnosis, present in 31 subjects, primarily younger males (32.3%; 27 males, 4 females, mean age 14.38 years, SD 1.90 years). Early onset of a major mood disorder was evident in 25 subjects: 15 had at least one episode of mania and an additional 10 had at least one major depressive episode prior to the age of 12 years. Substance use disorder in the 2-week prior to study enrollment was present in 20 patients (20.8%). No one met criteria for a substance dependence disorder. Family history interviews revealed that mood disorders were extremely prevalent in the relatives of the 91 nonadopted subjects, with 39 patients (42.9%) having at least one first-degree relative (nearly always a parent) with bipolar I disorder (Table 1).

Response to Open Treatment

The mean lithium level at the end of week 1 was well within the therapeutic range at 0.90 mEq/L (SD 0.25

mEq/L). At the end of week 4, the mean dose of lithium was 1,355 mg/day (SD 389 mg/day) with a corresponding mean lithium serum level of 0.93 mEq/L (SD 0.21 mEq/L). There were highly significant improvements across all measures from baseline to the end of week 4 (Table 2). These included ratings of depressive symptoms on the Ham-D as well as mania. Of note was a very large effect size for change in manic symptoms ($d = 1.48$). Indeed, 63 patients met the protocol response criteria (reduction in YMRS scores of $\geq 33\%$ and a CGI of 1 or 2) by week 4. Using the criterion of a 50% reduction in YMRS score, 55 (55%) patients met response criteria. Moreover, remission of manic symptoms (defined as YMRS scores ≤ 6) was achieved in 26 patients by week 4. Only four of the 23 subjects who had suicidal ideation at baseline had persistent thoughts of self-injury by week 4.

Adverse Effects

The rapid titration to therapeutic levels was well tolerated, possibly because the pharmacokinetic dose prediction method individualized dose based on physiological parameters. Adverse effects were assessed weekly by asking subjects if they had experienced any of a list of common adverse effects of lithium during the previous week. Three patients dropped out prior to study completion due to severe gastrointestinal side effects ($n = 2$) and intermittent diplopia ($n = 1$). As can be seen from Table 3, weight gain of 1 to 12 lb was experienced in more than half of the sample. However, it is likely that at least some of this weight gain represents a return of weight that had been lost during the acute manic episode. No clinically significant changes in thyroid-stimulating hormone were observed. Cognitive impairment was not formally assessed. Degree of functional impairment related to side effects was assessed by an examination of the CGI Effectiveness item. Adverse effects

TABLE 2
Weekly Rating Scale Total Scores ($N = 100$)

	Baseline	Week 1	Week 2	Week 3	Week 4	<i>p</i> Value	Effect Size (<i>d</i>) ^a
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
YMRS	25.70 (6.89)	16.11 (6.91)	14.35 (7.01)	13.16 (7.93)	11.12 (6.85)	<.001	1.48
Ham-D	12.63 (7.75)	9.64 (6.36)	8.18 (5.37)	7.76 (5.94)	6.74 (5.76)	<.001	0.69
BPRS	37.66 (10.36)	30.81 (8.37)	29.54 (7.41)	28.40 (7.74)	27.13 (6.20)	<.001	0.88
CGI-severity	5.02 (0.84)	3.88 (0.98)	3.61 (0.95)	3.39 (0.94)	3.12 (1.05)	<.001	1.40
CGAS	36.31 (9.05)	47.14 (9.72)	49.37 (9.48)	50.60 (8.81)	53.09 (10.11)	<.001	1.21

Note: YMRS = Young Mania Rating Scale; Ham-D = Hamilton Depression Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; CGAS = Children's Global Assessment Scale.

^a Effect size was calculated using baseline and week 4 means.

TABLE 3
Adverse Effects of Immediate-Release Lithium
Carbonate Monotherapy^a

Adverse Effect	%
Weight gain (1–12 lb from baseline)	55.3
Polydipsia	33.3
Polyuria	25.5
Headache	23.5
Tremor	19.6
Gastrointestinal pain	17.6
Nausea	15.7
Vomiting	13.7
Anorexia	13.7
Diarrhea	13.7

^a Elicited from > 10% of the sample at week 4.

caused no functional impairment in 14%, minimal functional impairment in 81%, and moderate impairment in only 2%. The three subjects who had severe functional impairment did not continue lithium treatment.

Predictors of Treatment Response

We explored whether response rates were associated with (1) psychotic features at baseline, (2) prominent depressive symptoms, (3) comorbid diagnoses, (4) early onset of mood disorders, (5) severity of mania at initial presentation, and (6) hospitalization. When treated with an adjunctive antipsychotic agent, subjects with psychosis had virtually identical response rates (65.7%) to the 4-week open treatment when compared with subjects without psychotic features (61.5%, $\chi^2 = 0.010$, $df = 1$, $p = .921$). Contrary to expectations, the presence of prominent depressive symptoms during the protocol was not associated with poorer response. Subjects with prominent depressive features were equally likely to respond to lithium (23 of 35 or 65.7%) as those without depressive features (40 of 65 or 61.5%, $\chi^2 = 0.04$, $df = 1$, $p = .845$).

Also contrary to expectations, comorbid diagnoses did not discriminate responders from nonresponders. It was particularly interesting to note the relatively high response rate of 58.1% in the 31 subjects with comorbid ADHD who were not receiving treatment with a psychostimulant during the protocol. Likewise, the presence of a mood or other Axis I diagnosis prior to the age of 12 years was not associated with response at week 4.

To see if greater initial severity at study entry was associated with week 4 response, we examined baseline total YMRS scores in responders (mean 26.60, SD 7.47) and nonresponders (mean 24.15, SD 5.54). Greater severity

at baseline was not significantly associated with response at week 4 ($t = 1.74$, $df = 98$, $p = .09$).

Finally, to help assess the role of hospitalization in initial response, we compared the mean YMRS scores at baseline and at the end of week 1 in hospitalized ($n = 77$) versus nonhospitalized ($n = 23$) subjects. Although as expected, subjects who were hospitalized tended to have somewhat higher mean total YMRS scores at baseline (mean 26.38) than subjects who were outpatients (mean 23.11) ($t = 1.85$, $df = 97$, $p = .067$), by week 1 this difference had virtually disappeared (means 16.18 versus 15.89, respectively; $t = 1.53$, $df = 98$, $p = 0.86$) (Fig. 1). Also contrary to expectations, hospitalization during the initial phase of treatment did not significantly impact response at any assessment point. The proportions of subjects who met response criteria in both inpatient (63.6%) and outpatient groups (60.9%) at week 4 were almost identical ($\chi^2 = 0.00$, $df = 1$, $p = 1.000$).

DISCUSSION

These data describe response to open lithium in the treatment of acute adolescent mania and represent the largest sample of protocol-driven treatment reported to date. All subjects were adolescents diagnosed with a bipolar I disorder. The strengths of this study include our relatively large sample of adolescents who were all acutely manic and met criteria for bipolar I disorder, the use of the pharmacokinetic dose prediction method to achieve well-tolerated therapeutic lithium levels within a few days of initiating treatment, and estimating medication adherence by obtaining weekly lithium levels. In this largely inpatient sample, 4 weeks of treatment was associated with improvements in manic symptoms and overall functioning in 63% of participants on an intent-to-treat basis. Using a response criterion of a 50% decline in YMRS scores, the response rate was 55%. These response rates to lithium are comparable with those found in a similar population of hospitalized manic adolescents (56% on a global improvement measure after 4 weeks [Strober et al., 1988] and 46% in an outpatient sample on a global measure of functioning [Geller et al., 1998]). A large effect size (1.06) for lithium was also found by Kowatch et al. (2000) when using the change in total YMRS score from baseline to endpoint. Our finding of an effect size for lithium of 1.48 on the total YMRS score is comparable.

The treatment protocol also significantly reduced the proportion of subjects with suicidal ideation. Suicidal

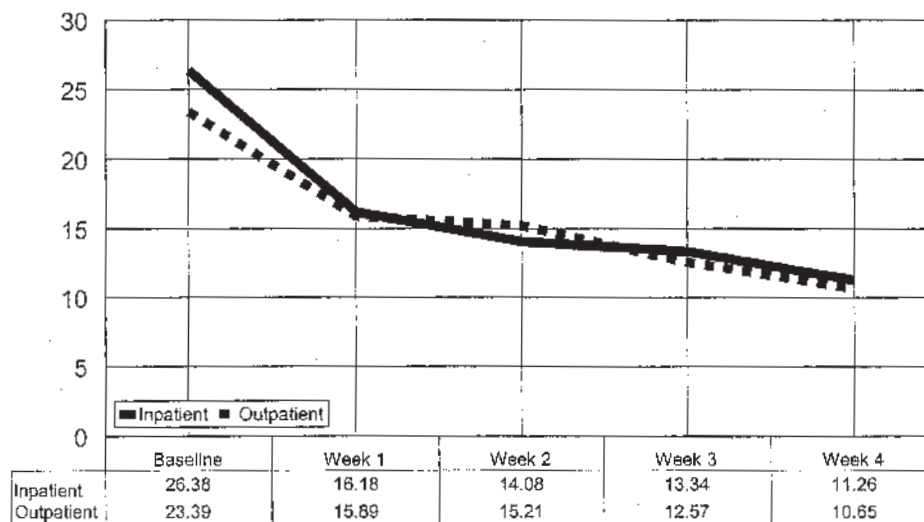


Fig. 1 Average change in Young Mania Rating Scale scores from baseline to week 4 in inpatients ($n = 77$) versus outpatients ($n = 23$).

thoughts were no longer reported by 19 of 23 patients (82.6%) over the 4-week open treatment period. The beneficial effects of lithium on suicidality have been documented in studies of adults (Baldessarini et al., 1999; Thies-Flechtner et al., 1996), and our results are consistent with these findings.

A relatively high proportion (42.9%) of our nonadopted subjects were identified as having a first-degree relative with bipolar I disorder on the Family History-Research Diagnostic Criteria (Andreasen et al., 1977). We have considered several possible explanations for this finding. There may be a higher frequency of ill family members in bipolar youth who have an early age of onset (Strober et al., 1988). This finding could also be related to ascertainment bias, in that referring clinicians were more sensitive to identifying presenting symptoms as related to mania, when they had knowledge that a parent or sibling also had the disorder. In addition, parents of our subjects may have been more accepting of the diagnosis and treatment when they had already experienced the illness themselves or in other family members. It is also possible that the stress of living with a bipolar I relative could precipitate an earlier age of onset.

The rate of comorbid ADHD in our sample (32.3%) is lower than that reported in studies where younger, predominantly male outpatients comprise the vast majority of the sample (Faraone et al., 1997, Geller et al., 2000). Our patients with comorbid ADHD were younger at study ascertainment (mean age 14.38 years, SD 1.90

years) than subjects without ADHD (mean age 15.68 years, SD 1.65 years, $t = 3.43$, $df = 94$, $p = .001$). Our relatively low rate of ADHD is likely due in large part to the equal gender distribution of our sample, in contrast to other samples that are predominantly male (e.g., West et al., 1994). Examination of the breakdown of ADHD diagnosis by gender in our sample confirmed that males enrolled in the study were far more likely to have ADHD (27 of 47 or 57.4%) than females (4 of 49 or 8.2%, $\chi^2 = 25.31$, $df = 1$, $p < .001$).

Stimulant treatment was discontinued from participants at the time that lithium treatment was initiated in the hope that the ADHD symptoms may have simply been a *forme fruste* of mania. Lithium treatment appeared to address the increased hyperactivity and impulsivity associated with the onset of the manic episode. However, symptoms of inattention persisted and stimulant treatment, albeit at a lower dose, was re-instituted in most patients at the end of the treatment study. Therefore, it is our hypothesis that these children may have had a "true" ADHD (rather than a *forme fruste* of mania) but later developed an additional disorder (bipolar I disorder).

Adverse effects experienced by our subjects were similar to those previously reported for children and adolescents in other short-term studies (Campbell et al., 1984, 1995; Malone et al., 2000). Our method of directly questioning subjects about whether they had experienced any of a list of adverse effects in the previous week usually results in a higher rate of adverse effect reporting than the method

of recording only those adverse effects volunteered by the patients in answer to an open-ended question (Levine and Schooler, 1986, 1992). Certain adverse effects such as vomiting are typically reported less frequently by patients who take sustained or delayed release formulations (Grof et al., 1976), but only an immediate release formulation of lithium was used in this study. It should also be noted that the lack of a placebo arm makes it difficult to assess the true rate of adverse effects attributable to medication rather than, for example, an intercurrent illness.

Contrary to expectations, the presence of comorbid ADHD, prominent depressive symptoms, and substance use disorders was not associated with poorer response to the treatment protocol. Particularly interesting was the almost equivalent response rate in adolescents with and without comorbid ADHD, a clinical subgroup that has been reported in two previous studies as at-risk for poorer response to lithium (Strober et al., 1988, 1998). We also observed similar rates of response in both inpatients and outpatients (Fig. 1), suggesting that the additional treatments available in the hospital were not an essential component for response.

We observed similar rates of response in patients with and without psychotic features when adjunctive antipsychotic medication was used. Stabilization of both manic and psychotic symptoms using combination treatment was achieved in almost two thirds (65.7%) of patients who presented with prominent delusions or hallucinations at baseline assessment. As previously reported, however, the vast majority of patients who subsequently had their adjunctive antipsychotic medication discontinued after 1 month of combination therapy with lithium experienced an exacerbation of symptoms that resolved only when antipsychotic treatment was resumed (Kafantaris et al., 2001a). The optimal duration of adjunctive antipsychotic treatment of mania in youth remains to be determined.

Limitations

The lack of a concurrent placebo control group in the current investigation leaves unresolved how much of the initial high rate of response in subjects was due to the passage of time in this disorder with time-limited episodes. Adjunctive antipsychotic medication was used in 46% of the sample: therefore, it cannot be known if the response in this subgroup was due to lithium, the antipsychotic medication, or the combination of both. The high exacerbation rate following discontinuation of the antipsychotic medication (Kafantaris et al., 2001a,b) suggests

that the antipsychotic medication was a necessary component of the treatment for subjects with psychosis or severe aggression. Diagnostic interviewers were not blinded to the results of the clinical interview or to study status, nor were raters blinded to the previous treatment course. The pharmacokinetic dose prediction method cannot be easily reproduced by commercial laboratories because they generally do not report serum lithium levels below 0.2 mEq/L, nor do they report lithium levels to the nearest hundredth. Therefore, if rapid attainment of therapeutic levels accelerated response in this sample, this would not be reproduced in clinical samples.

Clinical Implications

A synthesis of the results described above suggests that lithium may be an effective treatment of moderate to severe acute mania in adolescents. Prominent depressive symptoms, substance use, and longstanding histories of ADHD did not diminish response. Although acutely manic adolescents have a greater response rate when adjunctive antipsychotic medication is used (DelBello et al., 2002; Kafantaris et al. 2001a,b), the necessary duration of such treatment is unknown. The potential risks associated with long-term treatment that includes atypical antipsychotic medication is highlighted by a recent report of three adolescents who developed diabetes mellitus while treated with the combination of divalproex sodium and an atypical antipsychotic (Saito and Kafantaris, 2002). Studies examining the relative risks and benefits of maintenance treatment with lithium monotherapy versus combination treatment with an atypical antipsychotic agent are essential so that patients and their families can make informed treatment decisions.

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