Chart Review of the Impact of Attention-Deficit/Hyperactivity Disorder Comorbidity on Response to Lithium or Divalproex Sodium in Adolescent Mania

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Purpose: Although adolescent onset of bipolar disorder is common, the optimal treatment approach for mania in this age group remains understudied. Comorbid attention-deficit/hyperactivity disorder (ADHD) has been reported to predict lithium resistance in adolescents with bipolar disorder. Little is known about response to divalproex sodium in adolescents with bipolar disorder comorbid with ADHD. This study was conducted to evaluate comparative response rates to lithium and divalproex sodium in adolescent mania with and without this comorbidity.

Method: Medical records were reviewed for 42 patients (ages 12–19 years) who were hospitalized for acute mania and discharged with a diagnosis of DSM-III-R or DSM-IV bipolar disorder on either lithium (N = 29) or divalproex sodium (N = 13) treatment. A clinician blinded to treatment status rated improvement on the basis of abstracted notes in each case utilizing the Clinical Global Impressions Scale modified for use in bipolar illness (CGI-BP). Response was defined as a discharge CGI-BP overall change score of 1 or 2 (much or very much improved). Data were collected from January 1992 through May 1999.

Results: 36/42 (85.7%) patients presented with mixed mania, and 14/41 (34.1%) patients had a history of ADHD. The overall response rate was 80.9% (34/42). 92.6% (25/27) of patients without ADHD were responders versus 57.1% (8/14) of subjects with comorbid ADHD (p = .007). There were no significant differences in response rates for lithium versus divalproex sodium in subjects with and without ADHD.

Conclusion: These retrospective data suggest overall equivalent response rates for lithium and divalproex sodium in predominantly mixed adolescent mania. However, a history of ADHD was associated with a significantly diminished acute response to both divalproex sodium and lithium as a primary treatment for the manic phase of bipolar disorder.

(J Clin Psychiatry 2004;65:1057–1063)

Received Feb. 7, 2002; accepted Jan. 29, 2004. From the Department of Psychiatry, Harbor-UCLA Medical Center, Torrance, Calif., and the UCLA School of Medicine (Dr. State); the Department of Psychiatry and Biobehavioral Sciences, Neuropsychiatric Institute and Hospital and the UCLA School of Medicine (Drs. Frye, Altshuler, Strober, and DeAntonio); and the Biostatistics Unit, VA West Los Angeles Medical Center (Ms. Hwang and Dr. Mintz), Los Angeles, Calif.

This research was supported in part by an unrestricted educational grant from Abbott Laboratories, Abbott Park, Ill. (Dr. State).

This article was presented in part at the 153rd annual meeting of the American Psychiatric Association, May 13–18, 2000; Chicago, Ill.

Dr. State has received grant/research support from Abbott, Bristol-Myers, and Forest and has received honoraria from Abbott. Dr. Frye serves as a consultant to Abbott, AstraZeneca, Bristol-Myers, Cephalon, Elan, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Novartis, Ortho-McNeil, Otsuka, Pfizer, and UCB Pharma; has received grants from Abbott, American Foundation for Suicide Prevention, GlaxoSmithKline, National Institute of Mental Health, Pfizer, Solvay, and Stanley Medical Research Institute; and serves on the speakers' bureau for Abbott, AstraZeneca, Bristol-Myers, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Novartis, Ortho-McNeil, and Otsuka. Dr. Altshuler serves as a consultant to, has received honoraria from, and serves on the advisory board for Abbott, Bristol-Myers, Eli Lilly, Forest, and Janssen; has received grant/research support from Abbott, Eli Lilly, and Forest; and serves on the speakers' bureau for Abbott.

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The lifetime prevalence of bipolar disorder in a community-based sample of adolescents has been estimated at 1%, a rate similar to that found in the adult population.[1] Despite recognition of the frequency and associated morbidity of bipolar illness in youth, the pharmacologic treatment of the disorder in adolescence remains understudied.[2]

By and large, mainly uncontrolled studies of lithium in child and adolescent bipolar disorder report generally positive results.[3] However, it is well appreciated that adolescents with bipolar disorder frequently present with mixed mania or with a history of a depressive episode immediately preceding an episode of mania, which may predict suboptimal lithium response.

The atypical presentations characteristic of adolescent mania account for the increasing use of anticonvulsants in this age group. At least 8 uncontrolled trials and case reports[4–11] note the potential utility of this class of

Table 1. Characteristics According to Chart Review of 42 Hospitalized Adolescents With Mania Treated With Lithium or Divalproex Sodium

Variable	Lithium (N = 29)	Divalproex Sodium (N = 13)	Total (N = 42)
Age, mean ± SD, y	16.1 ± 1.8	16.9 ± 2.2	16.3 ± 1.9
Age at first manic episode, mean ± SD, y	15.1 ± 2.0	14.3 ± 3	16.0 ± 2.3
Male, N (%)	20 (68.9)	8 (61.5)	28 (66.6)
History of prior hospitalization, N (%)	5 (17.2)	5 (38.4)	10 (23.8)
No. of psychotropics at admission, mean ± SD	0.68 ± 0.96	1.0 ± 1.29	0.78 ± 1.0
CGI-S score at admission, mean ± SD	4.8 ± 0.58	4.9 ± 0.75	4.8 ± 0.6
Cycling, N (%)[a]	2 (6.9)	4 (30.7)	6 (14.2)
Mixed mania, N (%)	25 (86.2)	11 (84.6)	36 (85.7)
History of alcohol abuse, N (%)[b]	6/20 (30.0)	4/9 (44.4)	10/29 (34.4)
History of substance abuse, N (%)[b]	11/23 (47.8)	8/11 (72.7)	19/34 (55.8)
ADHD, N (%)[b]	10/28 (35.7)	4/13 (30.7)	14/41 (34.1)
Psychotic, N (%)	18 (62.0)	8 (61.5)	26 (61.9)
Time from hospital admission to start of mood stabilizer treatment, mean ± SD, d[c]	4.7 ± 4.8	1.5 ± 0.6	3.7 ± 4.2
Length of stay, mean ± SD, d[d]	21.2 ± 14	13.3 ± 4.44	18.8 ± 12.6

[a]Depressive episode immediately preceding the index episode of mania; $\chi^2 = 4.177$, df = 1, p = .041.
[b]Data not available for all patients.
[c]t = 2.37, df = 39, p = .022.
[d]t = 2.68, df = 37.3, p = .010.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions-Severity of Illness scale.

agent in teens with bipolar illness. No placebo-controlled, double-blind trial of lithium or divalproex sodium in the treatment of acute adolescent mania has been published thus far.

Given the frequency with which attention-deficit/hyperactivity disorder (ADHD) antedates the onset of bipolar illness in adolescents and reports suggesting poorer response to mood stabilizers in bipolar teens with comorbid ADHD,[12–15] we sought to retrospectively evaluate comparative response rates to lithium and divalproex sodium in adolescent mania with and without comorbid ADHD.

METHOD

The UCLA Institutional Review Board approved this retrospective study, and informed consent was waived due to the retrospective design. We identified 101 patients, ages 12 to 19 years, hospitalized at the UCLA Neuropsychiatric Hospital between January 1992 and May 1999 with a discharge diagnosis of DSM-III-R or DSM-IV bipolar disorder in which the index episode was mania. Only patients who received either lithium or divalproex sodium mood stabilizers as their index treatment were considered for the study. No patient in this cohort started taking one mood stabilizer and then switched over due to initial drug failure to a second mood-stabilizing agent during the index hospitalization. In each case, the choice of mood stabilizer and the use of concomitant antipsychotics and/or benzodiazepines was made on the judgment of the treating clinician.

Patients were excluded from the study for: (1) a diagnosis of substance-induced mood disorder, (2) significant medical or neurologic illness proximal to the index episode, (3) concurrent electroconvulsive therapy, (4) discharge to another acute inpatient facility or against medical advice before treatment could be instituted or readmission within 1 week following discharge, (5) medication refusal of ≥ 25% of the doses, (6) an IQ of < 70, or (7) concomitant use of another mood stabilizer.

The final study group consisted of patients (N = 42) taking mood stabilizers—29 treated with lithium and 13 treated with divalproex sodium. A portion of these patients (N = 3) were reported on previously by Strober and colleagues.[15] Discharge diagnoses in subjects were based on clinical psychiatric interviews and observations conducted or supervised by 1 of 2 authors (M.S., R.C.S.), both highly experienced in the assessment of adolescents.

Patients were categorized as having comorbid ADHD if records reviewed by a trained child and adolescent psychiatrist (R.C.S.) yielded unequivocal evidence of DSM-IV ADHD on the basis of reports provided by parents and teens. The following information was extracted from the inpatient records: past psychiatric history, age at onset of mood disorder, history of substance abuse, use of antipsychotics and benzodiazepines during acute hospitalization, length of hospitalization, mood stabilizer serum levels, and presence of psychotic features and suicidality at admission. Serum levels drawn within 3 days of discharge were considered "discharge" serum levels. Additional demographic and admission data from the sample are shown in Table 1.

Admission and progress notes were abstracted and given to 1 investigator (M.A.F.) who was blinded to medication assignment, serum levels, and comorbid diagnoses. Each case was then classified as either classic or mixed

mania based on extensive review of clinician notes that detailed mood symptomatology.

Mixed mania was categorized according to DSM-IV criteria minus time duration for depression (as this was never reliably noted in chart). In addition, it was noted and recorded when admission data revealed that a teen had a depressive episode immediately preceding the index episode of mania ("cycling"). The investigator rated improvement in each case utilizing the Clinical Global Impressions scale modified for use in bipolar illness (CGI-BP)[16] on the day of admission, day 5, day 10, and the day of discharge. Day 5 and day 10 were chosen as time points to assess response after adequate serum mood-stabilizer levels had been achieved. A patient with a CGI score of 1 (very much improved) or 2 (much improved) was considered to be a responder in dichotomous analyses. Several outcome variables were used, including rates of response, length of stay, and serum drug levels in relationship to outcome.

Statistical analyses were performed using SAS software.[17] Comparisons of the medication groups on a number of descriptive characteristics were performed using t test (continuous variables) or χ^2 analyses (frequencies) as appropriate. Regression analysis was used to determine relationships between serum levels and improvement in order to evaluate evidence for a therapeutic range for each drug and improvement. Response rates with respect to histories of ADHD were also compared using χ^2 analyses. Due to a skewed distribution for length of stay, a log transformation of length of stay was done to stabilize the variance.

RESULTS

Demographic and clinical features by treatment group are presented in Table 1. As noted, some patients received concurrent antipsychotics or benzodiazepines for mood stabilization or treatment of psychosis while hospitalized. The distribution of these medications, however, was similar across lithium and divalproex sodium groups.

Forty-one subjects had adequate histories to assess for ADHD. Of those 41 adolescents, 14 (34.1%) were categorized as having a comorbid diagnosis of ADHD: 10 were in the lithium group and 4 were in the divalproex sodium group. Within the lithium and divalproex sodium treatment groups, there were comparable percentages of adolescent patients with comorbid ADHD (lithium = 35.7% [10/28] vs. divalproex sodium = 30.7% [4/13]; $\chi^2 = 0.0965$, df = 1, p = .756). However, only 3 adolescents were treated with concurrent stimulants at the time of discharge; all 3 were treated with dextroamphetamine extended release, 10 to 15 mg/day.

There were no significant differences between lithium or divalproex sodium groups in age, gender composition, CGI-severity of illness (CGI-S) score for the index (admission) episode, number of prior hospitalizations, percentage of patients with mixed episodes or psychoses, number of psychotropics at admission, or use of adjunctive antipsychotics or benzodiazepines. The divalproex group contained a higher percentage of patients who were classified as "cycling" at the time of admission (lithium = 6.9% [2/29] vs. divalproex = 30.7% [4/13]; $\chi^2 = 4.17$, df = 1, p = .041).

The number of days after admission to the hospital that a mood stabilizer was started was significantly later for patients taking lithium compared with patients taking divalproex sodium (lithium = 4.7 days vs. divalproex = 1.5 days; t = 2.37, df = 39, p = .022). While the reason for this is not clear, further analysis revealed a subgroup of lithium-treated patients who were started on lithium treatment within 72 hours of admission (lithium-early group, N = 16), and a subgroup for whom lithium was initiated beyond 72 hours of admission (lithium-late group, N = 13). These groups were combined after statistical analysis revealed no significant demographic or illness variable differences between them.

Overall, 36 of 42 (85.7%) bipolar adolescent patients in this sample presented with mixed mania. Comparable percentages of patients in each treatment group—86.2% (25/29) of lithium-treated patients and 84.6% (11/13) of divalproex sodium–treated patients—presented with mixed mania. No significant differences were observed in rates of mixed mania between teens with and without ADHD (ADHD = 78.5% [11/14] vs.non-ADHD = 88.8% [24/27], $\chi^2 = 0.785$, df = 1, p = .375).

The overall response rate was 80.9% (34/42). Equivalent response rates at discharge were observed for patients treated with lithium (82.7%) and divalproex sodium (76.9%) ($\chi^2 = 0.198$, df = 1, p = .656).

In 41 patients for whom there was information on concurrent medications at the time of discharge, benzodiazepines and/or antipsychotics were prescribed for 6 (14.6%) and 24 (58.5%) patients, respectively. Similar percentages of lithium and divalproex sodium-treated patients were discharged on concomitant benzodiazepine (lithium 17.8% vs. divalproex 7.6%; $\chi^2 = 0.734$, df = 1, p = .391) and/or antipsychotics (lithium 57.1% vs. divalproex 69.2%; $\chi^2 = 0.545$, df = 1, p = .460) treatment.

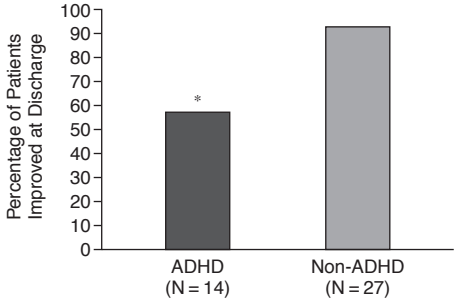
Comparable percentages of patients had discharge serum levels obtained: 23/29 (79.3%) patients taking lithium and 11/13 (84.6%) taking divalproex sodium. For the divalproex sodium group, all discharge serum levels (11/11; 100%) were within the therapeutic range of 50 to 150 μg/mL (divalproex observed range, 58–144 μg/mL; mean ± SD = 101.1 ± 21.0 μg/mL). For the lithium group, 16/23 (69.5%) had discharge serum levels within the therapeutic range of 0.8 to 1.5 mmol/L (lithium observed range, 0.5–1.6 mmol/L; mean ± SD = 0.9 ± 0.3 mmol/L). Within the observed lithium range, analyses were conducted for patients with levels less than 0.8 mmol/L

Table 2. Response to Lithium Versus Divalproex Sodium in Adolescent Mania With and Without Comorbid Attention-Deficit/Hyperactivity Disorder (ADHD)

Variable	Lithium	Divalproex Sodium	Total
Responders, N/N (%)	24/29 (82.7)	10/13 (76.9)	34/42 (80.9)
ADHD responders, N/N (%)[a]	6/10 (60.0)	2/4 (50.0)	8/14 (57.1)
Non-ADHD responders, N/N (%)[b]	17/18 (94.4)	8/9 (88.8)	25/27 (92.6)

[a]Data not available for all patients.
[b]Non-ADHD responders vs. ADHD responders: $\chi^2 = 7.37$, df = 1, p = .007.

Figure 1. Overall Treatment Response in Mania (N = 41): Comorbid ADHD Versus Non-ADHD Patients



*OR = 9.4, p = .007.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

and for patients with levels greater than or equal to 0.8 mmol/L. In neither group was a correlation found between serum level and response.

There was sufficient information to assess for a history of substance abuse in 34 patients (see Table 1). Of those, 19 (55.8%) had a positive history of substance abuse. There were no significant differences in overall response rates for patients with a history of substance abuse ($\chi^2 = 0.006$, df = 1, p = .940). Further, no significant differences were observed in response rates for patients with a history of prior psychiatric hospitalization ($\chi^2 = 2.22$, df = 1, p = .136), suicidality at admission ($\chi^2 = 2.22$, df = 1, p = .134), or psychotic features ($\chi^2 = 2.22$, df = 1, p = .780).

As seen in Table 2, a highly significant difference in overall response rate, regardless of drug given, was observed for patients with and without comorbid ADHD; 57.1% of subjects (8/14) with ADHD were responders versus 92.6% of subjects (25/27) without ADHD ($\chi^2 = 7.37$, df = 1, p = .007). Teens with bipolar disorder comorbid with ADHD were 9.4 times less likely to be categorized as responders than their non-ADHD counterparts (Figure 1). There were no significant differences between response rates for lithium (60%) versus divalproex sodium (50%) in subjects with ADHD ($\chi^2 = 0.117$, df = 1, p = .733). Similarly, there were no significant differences in response rates for lithium (94.4%) versus divalproex sodium (88.8%) in subjects without ADHD ($\chi^2 = 0.270$, df = 1, p = .603).

Table 3. Characteristics of Patients Started on Lithium (Li-early) or Divalproex Sodium Treatment Within 72 Hours of Hospital Admission Versus Patients Started on Lithium After 72 Hours (Li-late)

Variable	Li-Late (N = 13)	Li-Early (N = 16)	Divalproex Sodium (N = 13)
CGI-S score at admission, mean ± SD	4.84 ± 0.55	4.87 ± 0.61	4.92 ± 0.75
Mixed mania, N (%)	11 (84.6)	14 (87.5)	11 (84.6)
ADHD, N (%)[a]	5/12 (41.6)	5/16 (31.2)	4/13 (30.7)
Psychotic, N (%)	11 (84.6)	7 (43.7)	8 (61.5)
ADHD responders, N (%)[a]	3/5 (60.0)	3/5 (60.0)	2/4 (50.0)
Non-ADHD responders, N (%)[a]	6/7 (85.7)	11/11 (100.0)	8/9 (88.8)
Overall responders, N (%)	10 (76.9)	14 (87.5)	10 (76.9)
Year of admission, mean ± SD	1993 ± 1.8[b]	1995 ± 1.9	1996 ± 1.3
Length of stay, mean ± SD, d	29.7 ± 17.1[c]	14.3 ± 5.7	13.3 ± 4.4

[a]Data not available for all patients.
[b]F = 10.36, df = 2.39, p = .0002.
[c]t = 2.68, df = 37.3, p = .010.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions-Severity of Illness scale.

The possibility that the inclusion of the lithium-late subgroup in the analysis of lithium response may have biased these results was considered. Therefore, the data were reanalyzed to compare the lithium-early, lithium-late, and divalproex groups separately. A longer length of stay and earlier year of admission for the lithium-late group were observed; however, there were no significant differences in overall response rates between lithium-late, lithium-early, and divalproex subgroups at discharge (lithium-late = 76.9% vs. lithium-early = 87.5% vs. divalproex = 76.9%; $\chi^2 = 0.7186$, df = 2, p = .698). As seen in Table 3, a comparably reduced response rate to mood stabilizers in patients with ADHD compared with patients without ADHD was observed in all 3 groups. Five of 12 subjects (41.6%) in the lithium-late subgroup, 5 of 16 subjects (31.2%) in the lithium-early subgroup, and 4 of 13 subjects (30.7%) in the divalproex group had comorbid ADHD. The response rate for patients with comorbid ADHD was 60% (3/5) in the lithium-late group, 60% (3/5) in the lithium-early group, and 50% (2/4) in the divalproex group ($\chi^2 = 0.1167$, df = 2, p = .943). The response rate for patients without comorbid ADHD was 85.7% (6/7) in the lithium-late group, 100% (11/11) in the lithium-early group, and 88.8% (8/9) in the divalproex group ($\chi^2 = 1.5428$, df = 2, p = .462).

DISCUSSION

In the absence of a placebo-controlled design with random assignment to parallel groups, this retrospective

study does not allow for definitive conclusions regarding the efficacy of lithium and divalproex sodium in adolescent mania. However, within the context of this limitation we present data on adolescent patients with clearly defined manic states examined by an investigator blinded to comorbid diagnoses and treatment rendered that suggest that both lithium and divalproex sodium are effective mood stabilizing agents in teens hospitalized for acute mania. Most subjects (80.9%) studied herein were significantly improved at the time of discharge.

The lithium response rate in this adolescent cohort is similar to that reported in uncontrolled studies in teens[18,19] but higher than the 49% response rate reported by Bowden et al.[20] in a large, controlled trial of adult patients or the 46% response rate that Geller and colleagues[21] reported in the first placebo-controlled lithium trial in adolescents with bipolar disorder. It is to be noted, however, that the Geller et al. study[21] involved a sample of 25 teens with bipolar I (N = 12), bipolar II (N = 5), or major depressive disorder with purported predictors of latent bipolar disorder (N = 8) comorbid with substance dependence, principally to cannabis and alcohol. The relatively low rate of response observed in that controlled adolescent study is not inconsistent with data in adults that suggest an association between poor lithium response and substance use in bipolar illness.[22]

Response to divalproex sodium in this adolescent sample similarly exceeds the 48% response rate in adults reported in the study by Bowden et al.,[20] but is consistent with open trials of divalproex sodium that have reported response rates of roughly 60% to 80% in the adolescent age group.[4–8] More than 80% of the teenage patients in our study presented with mixed mania, a higher rate than the 40% seen on average in adult samples.[23] Due to the high rate of mixed mania in our sample, it was not possible to compare response rates to lithium and divalproex sodium for mixed versus euphoric mania. Whereas in adults mixed mania has been shown to be a robust predictor of lithium nonresponse,[22,24,25] lithium and divalproex sodium were equally effective acute treatments in this predominantly mixed adolescent sample. It is problematic at best to attempt comparisons in rates of response in controlled versus uncontrolled trials. However, given the very limited literature available in the field, we state those findings together here.

Limited empirical data are available with regard to therapeutic blood levels of lithium and divalproex sodium in adolescent mania. In our study, the response rates for divalproex sodium and lithium were 76.9% and 82.7%, respectively. All divalproex sodium blood levels in this adolescent sample were consistent with the therapeutic range in adults of 50 to 150 μg/mL (divalproex observed range, 58–144 μg/mL; mean = 101.1 ± 21.0 μg/mL). Therefore, while no clear therapeutic range has been established for divalproex sodium in adolescent mania, this range was therapeutic for most of the divalproex-treated adolescents in our study. Among lithium-treated subjects, serum lithium levels ranged from 0.5 to 1.6 mmol/L, which is outside the lithium range of 0.8 to 1.2 mmol/L commonly recommended for the acute treatment of mania in adults. However, almost all lithium-treated subjects had a good response, and no statistically significant differences were observed in response rates for patients with lithium levels of < 0.8 mmol/L versus lithium levels of > 0.8 mmol/L. Therefore, for lithium, the "therapeutic window" for adolescents with mania may be different from adults. More studies are needed.

Comparable response rates were observed for lithium versus divalproex sodium in this sample, in line with published results of the first direct prospective comparison of lithium, divalproex sodium, and carbamazepine in early-onset bipolar illness.[26] In that study, 42 outpatient children and adolescents, aged 8 to 18 years, meeting DSM-IV criteria for bipolar I (N = 20) or bipolar II (N = 22) disorder (mixed or manic) were treated openly for 6 weeks, titrating serum mood stabilizer levels for lithium to 0.8 to 1.2 mmol/L, for divalproex sodium to 85 to 110 μg/L, and for carbamazepine to 7 to 10 μg/L. At the completion of the study, response rates to divalproex sodium, lithium, and carbamazepine were 53%, 38%, and 38%, respectively. There were no statistically significant differences in response rates between agents, and effect sizes were comparable for all 3 mood stabilizers. Seventy-one percent (30/42) in that study also met criteria for ADHD. However, separate response rates for subjects with ADHD versus those without ADHD were not reported.

We find a reduced response rate to either drug in adolescents with comorbid ADHD compared with adolescents without this comorbidity. The role of psychiatric comorbidity in treatment response is an important area that currently remains understudied. High rates of comorbidity, in general, have been reported in children and adolescents with bipolar disorder, particularly with ADHD.[27–29] Suboptimal lithium response in bipolar disorder comorbid with ADHD has been reported in some,[14,15] but not all,[30] lithium trials in acute adolescent mania. These data further suggest that ADHD comorbidity may predict diminished responsivity to divalproex sodium as well. Thus, adolescent-onset bipolar disorder complicated by a history of ADHD may delimit a subgroup that is broadly more difficult to treat rather than specifically lithium resistant.

Reduced responsivity to treatment with lithium or divalproex sodium as mood stabilizers in bipolar adolescents with ADHD could be associated with the longer duration of psychiatric illness in these adolescent-onset cases or to greater lifetime exposure to stimulants and/or antidepressants. DelBello and colleagues[31] have reported that, in bipolar adolescents, a history of stimulant treatment prior to the onset of bipolar disorder was correlated

with an earlier age at onset of bipolar disorder, independent of comorbid ADHD. Earlier onset of bipolar illness may, in turn, be associated with less robust response to treatment.[32]

Further, some investigators have suggested that the "ADHD" seen in adolescent-onset bipolar illness represents a genetically loaded, virulent subtype of affective illness that is inherently treatment resistant.[14,33] Alternatively, given significant symptom overlap between mania and ADHD, the finding of poorer "antimanic" response in these patients may be due to persistent ADHD symptoms that are unresponsive to mood stabilizers alone.[19] It was observed in our study that most adolescents with mania comorbid with ADHD were not treated concurrently with stimulants. This probably reflects a common clinical practice. It is possible that this practice may adversely impact the speed and degree of response in adolescents with both disorders.

Carlson et al.[34] have reported that the combination of lithium (serum level = 0.7–1.1 mEq/L) and methylphenidate (5–10 mg b.i.d.) was superior to either agent alone and to placebo on behavioral measures of attention in a double-blind, crossover trial of children (N = 7) who presented with disruptive behavioral disorders and either bipolar or major depressive disorder. Three of the 7 children had first- and second-degree relatives with bipolar disorder. While this pilot report is limited by its small sample size (N = 7), crossover design, and the diagnostic heterogeneity of the children studied, it does suggest the need for further prospective studies of combination treatments in children and adolescents with bipolar disorder comorbid with ADHD.

In the present sample, 3 of the 14 (21%) adolescents with bipolar disorder comorbid with ADHD were discharged on stimulant treatment concurrent with either lithium (N = 2) or divalproex sodium (N = 1). Two of the 3 adolescents were rated as very much improved at discharge; the third subject was minimally improved. No subject on combination treatment worsened. Due to the small sample size, no statistical comparisons could be made between comorbid patients treated with combination mood stabilizers and stimulants versus mood stabilizers alone. Clearly, the mechanism of treatment resistance—and the development of psychopharmacologic strategies to optimize outcome—in adolescents with bipolar disorder complicated by comorbid ADHD deserves further exploration.

This study is methodologically limited by its retrospective, naturalistic design, which limits interpretation of the results. Pharmacologic intervention was determined by the treating clinician in an uncontrolled fashion. Prior medication response may have influenced selection of, and response to, a particular mood stabilizer, data that could not be reliably evaluated in this study. Further, the study sample was small, thereby limiting the statistical power available for analysis, and many patients were receiving concomitant antipsychotic or benzodiazepine medication. As the study was uncontrolled, a placebo response rate across groups cannot be ruled out.

In addition, a subgroup of lithium-treated patients (N = 13) were started on treatment with this agent more than 72 hours following hospital admission (lithium-late). The remaining patients treated with lithium (lithium-early; N = 16) and all patients treated with divalproex sodium (N = 13) were started on treatment within 72 hours of admission. The possibility that the inclusion of the lithium-late subgroup in the analysis of lithium response may have biased these results was considered. However, there were no significant differences in overall response rates between lithium-late, lithium-early, and divalproex subgroups at discharge. In addition, a comparably reduced response rate to mood stabilizers in patients with ADHD compared with patients without ADHD was observed in all 3 groups.

This naturalistic study provides additional data on the effectiveness of both lithium and divalproex sodium pharmacotherapy in predominantly mixed adolescent mania. Similar to the findings of Kowatch and colleagues,[26] our study suggests overall equivalent response rates to lithium and divalproex sodium in the acute-phase treatment of mania in bipolar adolescents. In addition, we addressed the comparative utility of lithium and divalproex sodium in adolescent mania comorbid with ADHD, an area of considerable clinical relevance for which there is little empirical data. In this study, a history of ADHD was associated with an attenuated response to both divalproex sodium and lithium as a primary treatment for bipolar disorder. Further pharmacotherapy studies aimed at identifying treatment strategies that maximize response in adolescent mania with and without comorbid ADHD are warranted.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), dextroamphetamine extended release (Dexedrine and others), divalproex sodium (Depakote), lithium (Eskalith, Lithobid, and others), methylphenidate (Metadate, Ritalin, and others).

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