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After completing this CME activity, the psychiatrist should be able to:

- Recognize mania as a legitimate diagnostic consideration in children
- Compare mood stabilizers with antidepressant, antipsychotic, and stimulant medications in the treatment of children with maniclike symptoms
- Assess the effectiveness of mood stabilizers in treating maniclike symptoms in children

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The Naturalistic Course of Pharmacologic Treatment of Children With Maniclike Symptoms: A Systematic Chart Review

Joseph Biederman, M.D.; Eric Mick; Jeff Q. Bostic, M.D.; Jefferson Prince, M.D.; Jeff Daly, M.D.; Timothy E. Wilens, M.D.; Thomas Spencer, M.D.; Jennifer Garcia-Jetton; Ronald Russell; Janet Wozniak, M.D.; and Stephen V. Faraone, Ph.D.

Objective: To assess the effectiveness of mood stabilizers in treating maniclike symptoms in children.

Method: Subjects were consecutively referred pediatric patients who, at initial intake, satisfied DSM-III-R criteria for mania on a structured diagnostic interview. We systematically reviewed their clinical records to assess (1) the course of maniclike symptoms and (2) all medications prescribed at each follow-up visit. Survival analysis was used to determine the effect of mood stabilizers and other medications on the course of maniclike symptoms.

Results: Of the 59 subjects meeting criteria for mania, 44 (75%) exhibited evidence of maniclike symptoms during follow-up. The occurrence of manic symptoms significantly predicted the subsequent prescription of mood stabilizers (rate ratio = 2.9, 95% confidence interval [CI] = 1.6 to 5.5), and use of mood stabilizers predicted decreases in manic symptoms (rate ratio = 4.9, 95% CI = 1.2 to 20.8). However, improvement was slow and associated with a substantial risk for relapse.

Conclusion: Mood stabilizers were frequently used in children with maniclike symptoms, and their use was associated with significant improvement of maniclike symptoms, whereas use of antidepressant, antipsychotic, and stimulant medications was not.

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Received June 7, 1997; accepted March 3, 1998. *From the Pediatric Psychopharmacology Unit of the Child Psychiatry Service, Massachusetts General Hospital (Drs. Biederman, Bostic, Prince, Daly, Wilens, Spencer, Wozniak, and Faraone, Messrs. Mick and Russell, and Ms. Garcia-Jetton), Harvard Medical School (Drs. Biederman, Bostic, Prince, Daly, Wilens, Spencer, Wozniak, and Faraone), the Harvard School of Public Health (Mr. Mick), and the Massachusetts Mental Health Center and the Commonwealth Research Center (Dr. Faraone).*

Reprint requests to: Joseph Biederman, M.D., Pediatric Psychopharmacology Unit, ACC 725, 15 Parkman St., Boston, MA 02114.

The diagnosis of childhood mania continues to be met with skepticism by the clinical and research community.[1] The corresponding reluctance to diagnose or study juvenile mania puts clinicians at risk for underidentifying this pernicious disorder. Because rational pharmacotherapy follows diagnostic hypotheses, this reluctance may hinder the treatment of some severely ill children.[2] Bipolar disorder at any age can be incapacitating; thus, lack of identification and treatment of manic children can have serious consequences. Not treating mania in an affected child may lead to kindling, a chronic course, and treatment resistance.[3]

Although it has been recognized since Kraepelinian times that bipolar disorder can have an onset in childhood,[4] studies of bipolar children are scarce.[5] As a result, little research is available to guide our therapeutic approach to the management of these difficult children. In addition to a few case reports and case series,[2,6–9] DeLong and Aldershof[10] reported on the long-term efficacy of lithium treatment in a heterogeneous sample of children. They found that lithium was most effective for children with bipolar disorder and for children of lithium-responsive parents.[10]

However, because most reports to date on the use of mood stabilizers are anecdotal,[11,12] clear guidelines on how to treat the manic child are not yet available. Results from prospective, randomized clinical trials are clearly needed to provide the field with appropriate answers on this important subject.[2] Initial steps are also needed to begin evaluating the effectiveness of mood stabilizers in the treatment of manic youth.

Although systematic reviews of clinical records have been very useful for generating therapeutic hypotheses,[13,14] prior applications of this methodology have been limited in several ways. One problem is that most chart

review studies are based on the treatment being studied. For example, to address the effectiveness of mood stabilizers, all patients receiving these agents would be selected for review. Although providing useful information about effectiveness in a naturalistic setting, such work makes it difficult to address questions about diagnosis, because patients with the disorder of interest who did not receive the treatment are not selected for study.

Another problem comes from the selection of patients based on chart diagnoses. Clinical diagnoses are sometimes changed after the clinician observes the patient's response to treatment, making it hard to draw inferences about the correspondence between diagnosis and treatment delivery. Also, most clinics employ several clinicians whose threshold for diagnosing juvenile mania may vary considerably.

To overcome some of these difficulties, we designed a method that incorporates structured diagnostic interviews, no selection biases, and systematic chart review ratings over multiple and variable review points. Using this approach, we reviewed clinical records of all pediatrically referred patients who, at initial intake, satisfied structured interview diagnostic criteria for mania and were subsequently treated at our center. This research method allowed us to test the following hypotheses: (1) mood stabilizers would be effective in treating maniclike symptoms, and (2) other medications would not lead to an improvement in manic symptomatology.

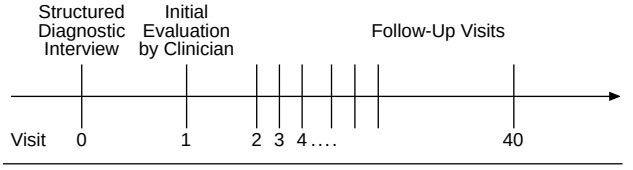
METHOD

Clinical Population and Study Design

The sample comprised all children consecutively referred to our Pediatric Psychopharmacology Clinic from September 1991 through May 1995 (N = 792). Each had been evaluated with a structured diagnostic interview. This clinic sample was nonselected because children were referred for a pediatric psychopharmacology evaluation because of severe psychopathology—not for evaluation of any specific disorder. From this pool of subjects we identified those meeting full criteria for a DSM-III-R diagnosis of mania at a pretreatment baseline assessment (N = 74) using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Epidemiologic Version (K-SADS-E).[15]

Figure 1 describes our study design. First, by defining our cohort by diagnostic status before treatment, the structured interview data could not be influenced by clinician diagnoses or treatment status. Second, by incorporating the sequence of events over time, our analyses

Figure 1. Study Design



afforded inferences for causal relationships between treatment and outcome. Third, by collecting data from all clinic visits, we could take maximal advantage of all the information in the medical records. This allowed us to model the effect of medication changes over time rather than conducting simple "before versus after" treatment comparisons.

Assessment of Lifetime Psychiatric History

All 792 children were evaluated using the K-SADS-E administered to the mother by raters trained and supervised by the senior investigator (J.B.). The raters were blind to the clinical diagnosis but knew that the child had been referred to a pediatric psychopharmacology clinic. Our goal in administering the K-SADS-E was not to establish the clinical diagnosis. Rather, we had 2 goals. First, we sought to describe the sample's lifetime history of psychopathology in a systematic manner. Second, we needed a method to select a subsample of children whose charts should be reviewed for evidence of maniclike symptoms and treatment response during their course of treatment. We decided not to use medical record diagnoses of bipolar disorder in this study because during much of the period of assessment, bipolar disorder was considered to be extremely rare in youth. By focusing on maniclike symptoms, we sought to improve the sensitivity of our assessment by capturing key features of the manic syndrome. Because manic features can arise from a variety of disorders (e.g., bipolar disorder, posttraumatic stress disorder [PTSD]), our results will apply to the broad category of children with maniclike symptoms, but not necessarily to a specific disorder.

Ideally, we would have interviewed both the child and the parent, but that was not possible due to lack of resources. We chose to interview the parent because we chiefly wanted to inquire about the child's lifetime history of psychopathology. Although children may be good reporters of current or recent psychopathology, they are less reliable at recalling signs and symptoms from early childhood.

The interviewers had undergraduate degrees in psychology; they were trained to high levels of interrater reli-

ability. We have assessed our assessment procedures by computing kappa coefficients of agreement by having experienced, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff in our research program. Based on 173 interviews, median kappa value was 0.86 with key disorders attaining kappa values higher than 0.82 (0.99 for ADHD, 0.93 for conduct disorder, 0.83 for major depression, and 0.94 for bipolar disorder).

Before rating independently, interviewers observed interviews by experienced interviewers and clinicians. They subsequently conducted at least 6 practice (nonstudy) interviews and at least 2 study interviews while being observed by senior interviewers. The principal investigator (J.B.) supervised the interviewers throughout the study. Although there are some limitations to using interviewers with bachelor's degrees—and to only interviewing mothers—we emphasize that these assessments were simply used as a means to select a smaller group of subjects whose clinical charts could then be rated for manic symptoms by child psychiatrists.

For every diagnosis, information was gathered regarding the ages at onset and offset of symptoms, number of episodes, and treatment history. Every diagnosis was reviewed by a diagnostic sign-off committee chaired by the service chief (J.B.). The committee reviewed the items endorsed during the interview along with detailed notes taken by the interviewers. Because the anxiety disorders comprise many syndromes that have a wide range of severity, we use 2 or more anxiety disorders to indicate the presence of a clinically meaningful anxiety syndrome and refer to this category as "multiple anxiety disorders" as we have elsewhere.[4]

We rated a diagnosis as positive only if the committee's consensus was that criteria were met to a clinically meaningful degree. By *clinically meaningful* we mean that the data collected from the structured interview indicated that the diagnosis should be a clinical concern owing to the nature of the symptoms, the associated impairment, and the coherence of the clinical picture. A key point is that these diagnoses were made as part of the clinical assessment procedures for our clinic; they were not simply research diagnoses computed by counting symptoms endorsed and applying an algorithm.

To be given a lifetime diagnosis of mania, the child had to meet full DSM-III-R criteria for a manic episode with associated impairment. Thus, a child must have met criterion A for a period of extreme and persistently elevated, expansive, or irritable mood; criterion B, manifested by 3 (4, if the mood is irritable only) of 7 symptoms during the period of mood disturbance; plus criterion C, associated impairment. All diagnoses of mania were reviewed by the diagnostic sign-off committee.

Follow-Up Clinical Assessment of Manic Symptomatology

The NIMH Clinical Global Impressions Scale (CGI)[17] was used to assess the severity and improvement (relative to baseline) of maniclike symptoms. The CGI is a well-known Likert scale in which severity of maniclike symptoms is rated from 1 (not ill at all) to 7 (severely ill) and improvement of specific manic symptoms is coded from 1 (very much improved) to 7 (very much worse). Severity of Illness and Improvement scores focused only on the DSM-III-R manic symptoms described above that take into consideration the presence of severe irritability and dysphoria. This form of the CGI has been used previously by our group to assess changes in the severity and improvement for specific disorders.[18] The Severity of Illness and Improvement scores on the CGI for manic symptoms were determined by consensus of a review team of 3 child and adolescent psychiatrists (J.Q.B., J.D., and J.P.) who systematically evaluated the information recorded in the medical record at each follow-up visit. Although the record reviewing team was not blind to the research diagnoses of subjects included in this study, only a small minority of subjects (7% [N = 3] of the 44 subjects with manic symptoms during the follow-up phase) were treated clinically by any of the physician reviewers.

Because patients were treated clinically, the intervisit interval and the number of visits varied among patients. This sample of children was treated by 12 clinicians, and although the interaction of each individual clinician with his or her patients may be of interest in assessing outcome, sufficient data for testing clinician-specific effects were not available. After reviewing each clinical note, the review team discussed the most appropriate score to be given for that patient for that visit based on the recorded information. Improvement was defined as attaining a CGI-Severity of Illness (CGI-S) score of ≤ 2 (borderline or not at all ill) and a CGI-Improvement (CGI-I) score of ≤ 2 (much or very much improved). Relapse was defined as attaining a CGI-I score of ≥ 6 (much or very much worse) following a period of improvement.

In addition, the type of medication and number of medications prescribed at each follow-up visit were systematically collected from the medical records. Because clinicians used many medications, these were grouped by class as follows: (1) mood-stabilizing agents (lithium carbonate, carbamazepine, and valproic acid), (2) selective

serotonin reuptake inhibitor (SSRI) antidepressants (fluoxetine, sertraline, paroxetine), (3) tricyclic antidepressants (TCAs; desipramine, imipramine, nortriptyline), (4) stimulants (methylphenidate, dextroamphetamine, and pemoline), and (5) antipsychotics (chlorpromazine, haloperidol, perphenazine, thioridazine, trifluoperazine). Total daily dosages for these groups are presented in methylphenidate equivalents for the stimulants (1.0 mg of methylphenidate = 0.5 mg of dextroamphetamine = 3.0 mg of pemoline), fluoxetine equivalents for the SSRIs (1.0 mg of fluoxetine = 10.0 mg of sertraline = 1.0 mg of paroxetine), desipramine equivalents for the TCAs (1.0 mg of desipramine = 0.5 mg of nortriptyline = 1.0 mg of imipramine), and chlorpromazine equivalents for the antipsychotics (1.0 mg of chlorpromazine = 0.01 mg of haloperidol = 0.2 mg of perphenazine = 1.0 mg of thioridazine = 0.1 mg of trifluoperazine). Dosages are reported separately for mood stabilizers.

Statistical Analysis

Categorical data were analyzed with the Fisher exact test; continuous variables were analyzed by t tests. Data are presented as mean ± SD values unless otherwise specified. Cox proportional hazards models estimated the relative rates of improvement associated with each particular class of medication. Rate (hazard) ratios are reported as the measure of effect. These indicate the increased rate of improvement due to the effect of the associated covariate. Covariates were modeled as time-varying to account for the changing configuration of medication combinations from visit to visit. Multivariate analysis was used to estimate the effects of mood stabilizers adjusted by confounding factors such as severity of illness and other medications. The statistical significance of each covariate was determined by the Wald chi-square statistic; likelihood ratio tests were used to assess the significance of interaction terms on the predictive ability of the models.

RESULTS

Seventy-four children and adolescents met diagnostic criteria for mania on a structured diagnostic interview at the pretreatment initial assessment. Of those, 15 (20%) did not return to the clinic at least twice after their initial evaluation; they were dropped from the study. There were no significant demographic or clinical differences between those patients who were followed and those who were not included in this investigation. The mean number of days of follow-up available for analysis was 616.6 ± 391.5 days (range, 43–1605 days).

The final sample consisted of 49 (83%) boys and 10 (17%) girls who ranged in age from 3.5 to 17.0 years (10.8 ± 3.7 years). Twenty-three (39%) were adolescents (≥ 12 years) and 36 (61%) were children. The mean duration of mania identified by the structured diagnostic interview prior to treatment at our center was 3.0 ± 3.0 years, the mean age at onset of maniclike symptoms was 6.3 ± 4.6 years, and the mean number of maniclike symptoms was 5.2 ± 1.2. Forty-three (73%) of the manic subjects presented with mixed mania, 9 (15%) presented with biphasic cycles of mania and depression, and 7 (12%) exhibited only manic psychopathology.

Correspondence Between Structured Interview Diagnosis of Mania and Clinician-Based Impressions

Subjects were considered to have maniclike symptoms if the CGI rating for mania, coded from the clinical record, indicated symptoms of at least mild severity (CGI-S score ≥ 3) at some point during the follow up period. Using this criterion, 75% (N = 44) of the youth with a structured interview diagnosis of mania had evidence from the clinical record of maniclike symptoms during the follow-up period (Table 1). Although information in the clinical record incorporated both maternal and patient self-reported information, caution should be used in making inferences regarding agreement between these methods of assessment because the clinical chart reviewers were not blind to the structured interview diagnosis. There were no meaningful differences in any sociodemographic or structured interview diagnoses between those with and without evidence of maniclike symptoms (see Table 1).

Prescriptions for mood stabilizers were more frequently given to subjects with evidence of maniclike symptoms than to those without maniclike symptoms (59% vs. 7%, $p < .01$; Table 2). Subjects who were prescribed mood stabilizers were more likely to have had maniclike symptoms at their first clinic visit (80% versus 33%; $p = .001$) and at subsequent follow-up visits (65% vs. 25% of visits, $p < .001$) than subjects who were not prescribed mood stabilizers. In addition, subjects who were prescribed mood stabilizers had a significantly higher percentage of visits with severe manic symptomatology (22% vs. 3% of visits, $p < .001$). Using a time-varying Cox regression model, we found that the presence of maniclike symptoms from visit to visit significantly predicted the administration of mood stabilizers (rate ratio = 2.9; 95% confidence interval [CI] = 1.6 to 5.5; $p < .001$). This result was mainly accounted for by lithium carbonate and valproic acid, as they were the most prevalent medications prescribed at evaluation and during treat-

Table 1. Demographics and Baseline Characteristics[a]

Characteristic	Maniclike Symptoms in PPPC Follow-Up: Present (N = 44)		Absent (N = 15)	
Sex, N (%)	35	80%	14	93%
Socioeconomic status, mean ± SD	2.4 ± 1.3		2.5 ± 1.4	
Age at evaluation, mean ± SD	10.5 ± 3.8		11.7 ± 3.3	
Baseline bipolar severity (CGI-S for mania ≥ 3), N (%)	27	61%	0	0%
Psychiatric comorbidity,[b] N (%)				
Lifetime				
ADHD	38	86%	14	93%
Psychosis	10	23%	1	7%
Conduct disorder	16	36%	3	20%
Oppositional defiant disorder	39	91%	14	93%
Major depression	39	89%	13	87%
Multiple (> 2) anxiety disorder	22	50%	9	60%
Posttraumatic stress disorder[c]	7	19%	2	15%
Current Month				
ADHD	33	75%	14	93%
Psychosis	6	14%	1	7%
Conduct disorder	12	27%	1	7%
Oppositional defiant disorder	35	80%	14	93%
Major depression	29	66%	9	60%
Multiple (> 2) anxiety disorder	18	41%	8	53%
Duration of follow-up				
Days, mean ± SD	485.0 ± 333.2		353.8 ± 343.7	
Visits, mean ± SD	10.7 ± 7.7		6.6 ± 4.1	

[a]There were no statistically significant differences between the 2 groups for any of the variables. Abbreviations: ADHD = Attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions-Severity of Illness scale, PPPC = Pediatric Psychopharmacology Clinic.
[b]Assessed using the CGI and the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS-E).
[c]Posttraumatic stress disorder information was missing for 7 "present" and 2 "absent" subjects.

ment in our center. Sufficient data on specific mood stabilizers were not available for an analysis of switching of mood stabilizers over the course of treatment. Neither the number nor the type of concurrent medications of other classes differed between subjects with and without maniclike symptoms.

Improvement of Manic Symptoms

To define improvement of maniclike symptoms, we required subjects to attain a severity score on the CGI for mania of ≤ 2 (not ill, or borderline) and an improvement score of ≤ 2 (much or very much improved). Analysis of Cox proportional hazards models indicated that mood stabilizers significantly predicted improvement of maniclike symptoms independently of other medications prescribed at each visit (rate ratio = 4.9; 95% CI = 1.2 to 20.8; p = .031). In contrast, treatment with TCAs, SSRIs, stimulants, or antipsychotics was not associated with improvement of maniclike symptoms when adjusted for treatment with mood stabilizers (Figure 2). Furthermore, interaction terms between mood stabilizers and other medications did not significantly improve the predictive ability of the model, indicating that the positive effect of mood stabilizers was not dependent upon the concurrent prescription of other medications.

Dose-Response Relationship

Total daily doses of lithium carbonate, carbamazepine, and valproic acid were modeled separately controlling for the dosages of other medications and the severity of maniclike symptoms. Whereas total daily doses of lithium carbonate (p = .006) and carbamazepine (p = .01) significantly predicted improvement of maniclike symptoms, the dose of valproic acid did not (p = .9). Using the median dose of lithium carbonate and carbamazepine as the cut-off point, we were able to show that higher daily doses of lithium carbonate and carbamazepine led to increased rates of improvement (Figure 3).

Rates of Improvement and Relapse

Figure 4 depicts the Kaplan-Meier survival curves for (A) improvement after being placed on treatment with mood stabilizers and (B) relapse after initial improvement with mood stabilizers. As depicted in Figure 4A, 17% of subjects improved by 6 months, 30% by 1 year, and 65% by 2 years, indicating a slow rate of improvement. Using a definition of relapse as a score of much or very much worse on the CGI-I for mania, Figure 4B shows that 40% of previously improved subjects relapsed within 2 months, whereas the remaining subjects did not relapse for 1 year. This definition of relapse indicates unequivocal clinical evidence for worsening of maniclike symptoms.

Psychiatric Hospitalization

Of the 59 subjects meeting criteria for mania on the structured diagnostic interview, 13 (22%) had been psychiatrically hospitalized before receiving treatment at our center and 9 (15%) during their treatment. The strongest predictor of psychiatric hospitalization during the follow-up period was a prior history of hospitalization (rate ratio = 3.8; 95% CI = 1.5 to 9.5; p = .004): 56% (5/9) of children requiring hospitalization during the follow-up had a prior history of hospitalization.

DISCUSSION

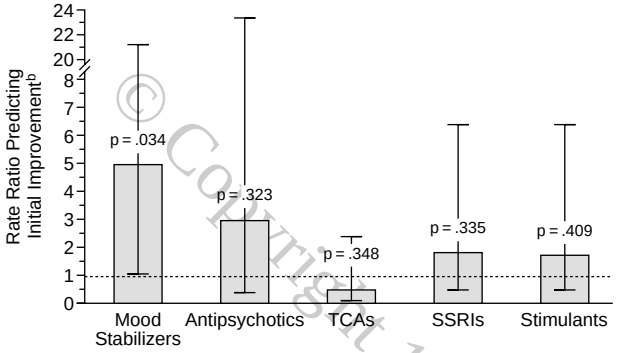
We systematically reviewed the clinical records of all referred pediatric patients who, at initial intake, satisfied

Table 2. Distribution of Medications[a]

Medication	Maniclike Symptoms in PPPC Follow-Up: Present (N = 44)		Absent (N = 15)	
Mood stabilizer trials, N (%)				
None	18	41%	14	93%
Any	26	59%[b]	1	7%
One	15	34%[b]	1	7%
Two[b]	10	23%[b]	0	0%
Three	1	2%	0	0%
Lithium carbonate				
At evaluation, N (%)	10	23%	1	7%
Ever during follow-up, N (%)	21	48%[b]	1	7%
Duration of treatment, d (mean ± SD)	255.1 ± 216.9		240.0 ± 0	
Maximum dosage, mg/d (mean ± SD)	932.1 ± 441.5		900.0 ± 0	
Valproic acid				
At evaluation, N (%)	1	2%	0	0%
Ever during follow-up, N (%)	10	23%[b]	0	0%
Duration of treatment, d (mean ± SD)	164.9 ± 188.9		0 ± 0	
Maximum dosage, mg/d (mean ± SD)	682.5 ± 314.7		0 ± 0	
Carbamazepine				
At evaluation, N (%)	0	0%	0	0%
Ever during follow-up, N (%)	7	16%	0	0%
Duration of treatment, d (mean ± SD)	238.6 ± 205.9		0 ± 0	
Maximum dosage, mg/d (mean ± SD)	571.4 ± 188.9		0 ± 0	
TCAs				
At evaluation, N (%)	5	12%	4	27%
Ever during follow-up, N (%)	25	56%	10	67%
Duration of treatment, d (mean ± SD)	288.8 ± 245.7		245.4 ± 200.4	
Maximum dosage, mg/d (mean ± SD)	95.4 ± 94.5		106.3 ± 70.0	
Stimulants				
At evaluation, N (%)	6	14%	5	33%
Ever during follow-up, N (%)	19	43%	11	73%
Duration of treatment, d (mean ± SD)	274.3 ± 280.0		219.9 ± 287.8	
Maximum dosage, mg/d (mean ± SD)	29.6 ± 22.7		46.1 ± 23.5	
SSRIs				
At evaluation, N (%)	2	5%	0	0%
Ever during follow-up, N (%)	17	39%	3	20%
Duration of treatment, d (mean ± SD)	216.6 ± 205.9		196.0 ± 215.6	
Maximum dosage, mg/d (mean ± SD)	16.9 ± 10.6		35 ± 39.7	
Antipsychotics				
At evaluation, N (%)	3	7%	0	0%
Ever during follow-up, N (%)	9	20%	0	0%
Duration of treatment, d (mean ± SD)	202.1 ± 240.3		…	…
Maximum dosage, mg/d (mean ± SD)	120.5 ± 100.5		…	…
Other medications, N (%)				
Other antidepressants[c]	6	14%	1	7%
Antihypertensives[d]	18	41%	6	40%
Anxiolytics[e]	9	20%	1	7%
Overlap between mood stabilizers (N = 26) and other classes of medication, N (%)				
Plus SSRI	11	42%	…	…
Plus stimulant	11	42%	…	…
Plus TCA	13	50%	…	…
No other	3	12%	…	…
Number of concurrent medications,[f] N (%)				
No medication	3	7%	0	0%
One medication at a time	8	18%	6	40%
Two concurrent medications	13	29%	4	27%
Three concurrent medications	10	23%	5	33%
Four concurrent medications	6	14%	0	0%
Five concurrent medications	4	9%	0	0%

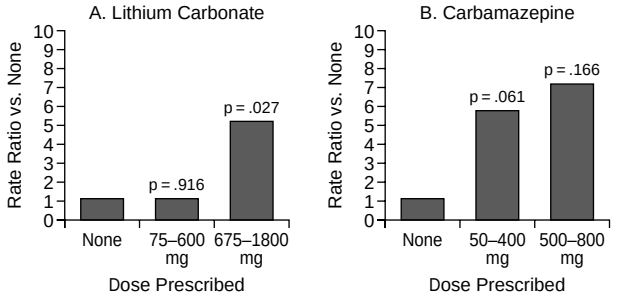
[a]Abbreviations: SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants. Symbol: … = not applicable.
[b]Indicates $p \leq .05$ using the Fisher exact test.
[c]Bupropion, trazodone, doxepin.
[d]Clonidine, propranolol, guanfacine.
[e]Clonazepam, tranxene, lorazepam.
[f]The maximum number of medications prescribed at a single visit during any point during the follow-up in the PPPC.

Figure 2. Adjusted Effects of Medication on the Rate of Improvement From Maniclike Symptoms[a]



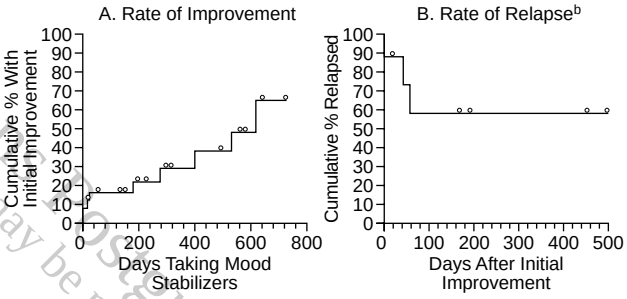
[a]Adjustments made using Cox proportional hazards model including time-varying covariates for each class of medication and bipolar severity (to control for confounding by indication). The dotted line represents the null hypothesis of a hazards ratio = 1.0.
[b]Bracketed section for each drug group indicates 95% confidence interval (CI).

Figure 3. Association Between Dose and Response to Mood Stabilizers[a]



[a]Test for trend for lithium carbonate: rate ratio = 2.25, 95% CI = 1.05 to 4.8, p = .035; for carbamazepine: rate ratio = 3.4, 95% CI = 1.03 to 11.3, p = .044.

Figure 4. Kaplan-Meier Curves Depicting Mood Stabilizer–Specific Outcome[a]



[a]Circles indicate censored observations.
[b]Among those who improved with mood stabilizers.

diagnostic criteria for mania based on a structured diagnostic interview with the mother. Mood stabilizers were frequently used in these children, and their use was associated with significant improvement of maniclike symptoms that their psychiatrists had recorded in the medical record. In contrast, antidepressants, antipsychotics, and stimulants were not associated with improvement of maniclike symptoms. Although these preliminary findings require confirmation from controlled clinical trials, they suggest that mood stabilizers may be effective in the treatment of manic children.

For lithium carbonate and for carbamazepine, we found that higher and more therapeutic doses predicted greater decreases in the maniclike symptoms recorded by the treating clinician in the medical record. In contrast, we failed to find any association between valproic acid dose and response. This finding may have been due to low statistical power, given the relatively small number of subjects treated with valproic acid.

Because this was not a controlled trial, our results cannot be considered definitive. Nevertheless, our methodology provides some assurance that the decrease in maniclike symptoms was due to mood stabilizers. If we had simply shown that patients treated with mood stabilizers eventually got better, that result could have been attributed to the normal waxing and waning of maniclike symptoms. Instead, the Cox model showed that mood stabilizers—but not other medications—predicted decreases in maniclike symptoms from one visit to the next. Moreover, by collecting data from all clinic visits, we used all the information in the medical records. This design allowed us to model the effect of medication changes over time rather than conduct simple "before versus after" treatment comparisons. If decreases in maniclike symptoms were simply spontaneous remissions, then our evidence for effectiveness should not have been limited to time periods when mood stabilizers were used. Moreover, a spontaneous remission hypothesis would not predict a differential effectiveness of mood stabilizers and other drugs, and we should not have found any dose-response effects, as we did for lithium carbonate and for carbamazepine. Also unlikely is the hypothesis that the benefits observed were due to improvement of ADHD symptoms, since evidence supporting the usefulness of mood stabilizers in ADHD is weak.[19]

Although treatment with mood stabilizers was associated with a statistically significant decrease in maniclike symptoms, this improvement was slow to develop and

was associated with frequent relapses. Although somewhat discouraging, these findings are consistent with outcome data from naturalistic follow-up studies of bipolar children and adults.[20,21] For example, the survival analysis from our study indicates that 65% of the children would improve if treated with lithium carbonate for 2 years. This finding is remarkably consistent with results from DeLong and Aldershof,[10] who reported a 66% response rate for bipolar children treated with lithium carbonate over a 10- to 70-month treatment period and with findings reported by Strober et al.[21] showing that multiple relapses were most often seen in subjects with mixed mania.

Similarly, much research shows that adult bipolar disorder is marked by a slow response to treatment, multiple relapses, and significant interepisode psychopathology, despite adequate pharmacotherapy.[22] For example, Gitlin et al.[23] and Goldberg et al.[24] reported the outcome of a naturalistic study of bipolar adults in the context of long-term maintenance pharmacotherapy. The bipolar adults had a high (73%) rate of relapse and considerable morbidity, irrespective of adequate pharmacotherapy. Goldberg et al.[25] reported that bipolar disorder in adults was associated with a gradual improvement of symptoms over several years. In a 5-year follow-up study of bipolar adults, Keller et al.[26] reported that mixed bipolarity had a lower probability of recovery and a substantially faster time to relapse following recovery compared with nondysphoric mania. In a review article, Solomon et al.[27] reported that bipolar adults who failed lithium prophylaxis were characterized by many prior episodes, mixed (dysphoric) mania, comorbid psychopathology, and rapid cycling. Because these clinical characteristics are commonly observed in juvenile mania,[28] it is not surprising to find that our juveniles with manic psychopathology had a chronic course, high level of relapse, and limited response to pharmacotherapy.

Twenty percent of our children with maniclike symptoms received antipsychotic medications. This is consistent with the common use of antipsychotics in adult mania[22,27] and the frequent co-occurrence of psychotic symptoms in manic children. For example, Wozniak et al.[28] reported that 16% of preadolescent manic children had psychotic symptoms. An analysis of Child Behavior Checklist findings from the same sample found the Psychotic Symptoms scale scores to be elevated in these children.[29] Because psychotic symptoms, at any age, are associated with severe dysfunction, they may account for our finding that, despite aggressive pharmacotherapy, the manic children had a high rate of hospitalization. Similarly, naturalistic follow-up studies of bipolar adults have found high rates of rehospitalization despite adequate pharmacotherapy.[24]

The children with maniclike symptoms also received treatment with stimulants and antidepressants for ADHD and depression. Although we cannot rule out the possibility that these concomitant treatments inhibited or delayed the response to mood stabilizers, maniclike symptoms improved despite these additional treatments. Clearly, controlled studies are needed to fully examine the effects of combined pharmacotherapy. Until such data become available, our findings suggest the cautious use of combined pharmacotherapy to address clinical instability and comorbidity in children with maniclike symptoms.

A small minority of children with structured interview diagnoses of mania at baseline assessment did not have subsequent evidence of maniclike symptoms in the information collected from the clinical record. This raises the question of misdiagnosis after the structured interview with the mother, but could also suggest that the bipolar condition was persistent but expressed as depression instead of mania. It is also possible that for these cases, maniclike symptoms were in remission during the follow-up period. These diagnostic issues underscore a key limitation of our work: neither the structured interview diagnoses nor the clinical chart ratings can be accepted as unequivocal evidence for the diagnosis of bipolar disorder. For example, some of our patients met criteria for PTSD, and we did not assess for other disorders such as reactive attachment disorders that might present with manic symptoms. Thus, although our results demonstrate a link between mood stabilizer treatment and maniclike symptoms, they are not definitive as regards the treatment of bipolarity.

It is possible that our results could reflect the selective use of mood stabilizers by astute psychopharmacologists. However, patients were assigned to many different clinicians during a period of time that the diagnosis of childhood mania was rarely considered even by experienced pediatric psychopharmacologists. Moreover, although mood stabilizers were selectively helpful in controlling the manic symptoms affecting these children, they were not the most commonly prescribed psychotropics in our sample. Children were randomly assigned to 12 different clinicians depending on availability at the time of the referral. Moreover, since our program does not preselect subjects, all clinicians are expected to treat all subjects irrespective of their diagnostic status. Because patients were treated clinically, the intervisit interval and the number of visits varied among patients. Since children were treated by different clinicians, we do not know the impact

of individual clinicians on patient outcomes. Clinicians evaluating and treating these children exercised their best clinical judgment using pharmacologic and nonpharmacologic options as they saw fit. Treatment choices were clinically driven to best serve the affected child and his or her family and were not dictated by the service chief. Although the interaction of each individual clinician with his or her patients may be of interest in assessing outcome, sufficient data for testing clinician-specific effects were not available.

The findings reported in this study should be viewed against methodological limitations. We collected data from clinical records that did not always yield complete or detailed information. Because of the large variability in treatment approaches, we were forced to group data from various drug classes to gain statistical power. Thus, we could not evaluate the differential response to individual treatment approaches.

Although we believe that the information provided in this article has implications for clinical practice, these implications must be weighed against the inherent limitations of chart review methodology. A key point is that this was not a randomized controlled trial. Thus, treatment assignments were based on clinical decisions. Given the complexity of clinical decision making, we cannot infer to what degree patient characteristics affected treatment assignment or whether such features affected response to treatment. Moreover, although the chart information was rated and subsequently extracted by child psychiatrists, the psychiatrist recording information was not blind to the treatment status of the child. Thus, these data do not unequivocally show that mood stabilizers are efficacious in treating maniclike symptoms, but they do provide some support of their effectiveness, compared with other medications, when administered by child psychiatrists in clinical practice. Furthermore, although information in the clinical record incorporated both maternal and patient self-reported information, caution should be used when making inferences regarding agreement between these methods of assessment because the clinical chart reviewers were not blind to the structured interview diagnosis.

These limitations are compounded by the slow rate of improvement that may suggest spontaneous remission. However, our finding that beneficial effects were associated specifically with mood stabilizers argues against spontaneous remission. Obviously, these findings should be viewed as hypothesis generating; more definitive conclusions await randomized, placebo-controlled, clinical trials.

Despite these limitations, our systematic chart review study of all referred children satisfying diagnostic criteria from mania shows that children with maniclike symptoms respond selectively to mood stabilizers. Yet, this response was slow and associated with substantial risk for relapse. More work is needed to better define the role of individual mood stabilizers as single or combined treatments for juvenile mania.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin), clonidine (Catapres), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), doxepin (Sinequan and others), fluoxetine (Prozac), guanfacine (Tenex and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lorazepam (Ativan and others), methylphenidate (Ritalin), nortriptyline (Pamelor and others), paroxetine (Paxil), pemoline (Cylert), perphenazine (Etrafon, Triavil), propranolol (Inderal and others), sertraline (Zoloft), thioridazine (Mellaril and others), trazodone (Desyrel and others), trifluoperazine (Stelazine), valproic acid (Depakene and others).

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DISCLOSURE OF OFF-LABEL USAGE

None of the agents specified in this article for treatment of juvenile mania are indicated for that use by the FDA.

Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 628 and correctly answering at least 70% of the questions in the posttest that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
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1. The reluctance to diagnose or study which of the following puts clinicians at risk for underidentifying this pernicious disorder?
   a. Personality disorder
   b. Juvenile depression
   c. ADHD
   d. Juvenile mania
   e. Obsessive-compulsive disorder

2. Which of the following is not one of the possible results of failing to treat mania in an affected child?
   a. Kindling
   b. Dyskinesia
   c. A chronic course
   d. Treatment resistance
   e. None of the above

3. In this study, which of the following medications was compared with mood stabilizers in the treatment of maniclike symptoms in children?
   a. SSRI antidepressants
   b. Tricyclic antidepressants
   c. Stimulants
   d. Antipsychotics
   e. All of the above

4. Which of the following medications was associated with significant improvement of maniclike symptoms in pediatric patients?
   a. Mood stabilizers
   b. SSRI antidepressants
   c. Tricyclic antidepressants
   d. Stimulants
   e. Antipsychotics

5. Which of the following medications predicted greater decreases in maniclike symptoms in children when higher and more therapeutic doses were used?
   a. Valproic acid
   b. Lithium carbonate
   c. Carbamazepine
   d. Answers b and c
   e. Answers a and b

6. Which of the following medications was not associated with improvement of maniclike symptoms in children?
   a. SSRI antidepressants
   b. Tricyclic antidepressants
   c. Stimulants
   d. Antipsychotics
   e. All of the above

7. Although treatment with mood stabilizers was associated with a statistically significant decrease in maniclike symptoms, this improvement was slow to develop and was associated with frequent:
   a. Depressive episodes
   b. Relapses
   c. Rapid cycling
   d. Comorbid psychopathology
   e. None of the above

8. Until data are available from controlled studies on concomitant treatments, the findings from this study suggest the cautious use of combined pharmacotherapy to address clinical instability and comorbidity in children with maniclike symptoms.
   a. True
   b. False

Answers to the May 1998 CME posttest
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Circle the one correct answer for each question.

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   B. Enabled me to compare mood stabilizers with antidepressant, antipsychotic, and stimulant medications in the treatment of children with maniclike symptoms. ❑ Yes ❑ No
   C. Enabled me to assess the effectiveness of mood stabilizers in treating maniclike symptoms in children. ❑ Yes ❑ No
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