Family History and Symptom Levels during Treatment for Bipolar I Affective Disorder

William Coryell, Hagop Akiskal, Andrew C. Leon, Carolyn Turvey, David Solomon, and Jean Endicott

Background: Studies of family history and lithium response in patients with bipolar affective disorder have produced mixed results, but the majority have shown relationships between the presence of affective disorder among relatives and positive responses to lithium in probands. The analysis presented here sought to confirm and to further characterize such relationships.

Methods: Subjects described here participated in a long-term, prospective follow-up; had a history of Research Diagnostic Criteria manic disorder or schizoaffective disorder, manic type; and took lithium for periods of 26 weeks or longer. The majority participated in a family study in which first-degree relatives were directly interviewed. Morbidity during lithium and during anticonvulsant trials was quantified in alternative ways, as were the risks among first-degree relatives for bipolar I and non-bipolar affective disorders.

Results: Familial loading for bipolar affective disorder was not associated with better outcomes during lithium treatment. Rather, the presence of major depressive disorder (MDD) among relatives was associated with slower improvement during acute treatment and with higher symptom levels during continuing treatment. Findings for morbidity during anticonvulsant treatment were similar. The patients who experienced symptom persistence with lithium did so as well during periods of anticonvulsant treatment and during periods without thymoleptics.

Conclusions: A family history of MDD may have an enduring and negative prognostic significance that manifests across treatment conditions. Though difficult to reconcile with several earlier studies, these findings invite replication and further exploration. Biol Psychiatry 2000;47:1034–1042 © 2000 Society of Biological Psychiatry

Key Words: Bipolar disorder, family history, lithium response, anticonvulsant response, prognosis and follow-up

Introduction

The familial nature of bipolar affective disorder gave rise to the original proposals to separate unipolar and bipolar forms (Leonhard et al 1962; Perris 1966). Many patients with bipolar affective disorder lack a family history of that illness, though, and subgrouping by family history may enhance homogeneity. This, in turn, would speed the identification of replicable, physiologic correlates of bipolar affective disorder. On a practical level, classification by family history may prove useful for treatment selection.

Some studies of this latter possibility have shown that those patients who have relatives with bipolar disorder derive more benefit from lithium prophylaxis than do those whose family history is negative (Grof et al 1994; Maj et al 1985; Mendlewicz et al 1973). Others have found no such relationship (Dunner et al 1976; Shapiro et al 1989; Taylor and Abrams 1981), and at least one described strong trends to the contrary (Engstrom et al 1997).

Most of these authors have determined illness among relatives indirectly, through interviews with probands or with other informants. This approach, the family history method, is known to detect illnesses among relatives with much less sensitivity than specificity because it fails to identify many cases that a direct interview would detect (Andreasen et al 1986). Only three studies have used the more labor-intensive family study method, which derives morbid risks exclusively from directly interviewed relatives. Of these, Zvolcsky et al (1974) described only total psychiatric morbidity in relatives. The two studies by Mendlewicz et al (1973, 1978) provided more diagnostic detail and, though small, produced compelling results. In one (Mendlewicz et al 1973), 15 of 24 (62.5%) lithium responders but only two of 12 (16.7%) lithium non-responders had one or more first-degree relatives with...
bipolar illness. The two groups had similar likelihoods of unipolar illness among relatives. In the other study, 12 of 16 (75.0%) monozygotic twins who responded to lithium had co-twins with bipolar illness, though this was true of only two of nine (22.2%) monozygotic nonresponders (Mendlewicz et al 1978). Rates for unipolar illness were 12.5% and 0% for the co-twins of responders and nonresponders, respectively.

Among studies using the family history method, some have found positive relationships between proband lithium response and the presence among relatives of affective disorder generally (Abou-Saleh and Coppen 1986, 1990; Smeraldi et al 1984). Others have found only family histories of bipolar illness to be important (Grof et al 1994; Maj et al 1985). The literature therefore leaves open the question of whether a family history of unipolar illness is also relevant to outcome during lithium treatment.

The methods used to determine lithium responsiveness for individual patients are variable but also critical to the interpretation of the above studies. One method simply designates as nonresponders patients who developed recurrences while they took lithium at presumably adequate doses. This confuses natural history with treatment response. The patient whose illness would entail many episodes without lithium treatment may be more likely to have breakthroughs during treatment than a patient whose natural course tends toward more widely separated episodes. Yet, the former patient may be benefiting from lithium such that recurrences are less likely on the drug than off.

Other authors (Engstrom et al 1997; Grof et al 1994; Maj et al 1985) have classed as lithium responders those who had fewer episodes during lithium treatment than before lithium treatment began. The retrospective mapping of episodes is difficult, however, and these reports did not describe how patients who began lithium during their first episode could be classified by this method. Also, it is typically the occurrence of an episode that determines the onset of lithium treatment, and this is likely to artifactually decrease episode frequency during the subsequent observation period. A more accurate summary of most of the literature, therefore, is that a family history of bipolar illness, or perhaps affective illness generally, is associated with fewer recurrences during lithium treatment.

Is family history relevant only to lithium response or does it predict recurrence rates during treatment with other thymoleptics as well? If so, family history would have prognostic importance but would not be useful in treatment selection. Post et al (1987) associated response to carbamazepine with a negative family history, but very little relevant information exists otherwise. If a family history of bipolar illness is associated with lower morbidity on lithium but not on carbamazepine or valproate, then it is probably lithium response that is being predicted rather than the illness’ natural history.

The following analyses use family study data to pose three questions. Does affective illness among first-degree relatives predict morbidity during lithium treatment among probands with bipolar affective disorder? If so, is this relationship specific to bipolar disease among relatives? Does this relationship hold as well for anticonvulsants? The data presented below derive from a study in which a long-term follow-up of patients with major affective disorders began concurrently with a family study of first-degree relatives. The sample size and length of follow-up provide a unique opportunity to address those questions.

Methods and Materials

Subjects

Between 1978 and 1981, inclusive, the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies (CDS) recruited patients as they sought treatment for affective illness at any of five academic centers: Massachusetts General Hospital and Harvard University in Boston, Rush Presbyterian–St. Luke’s Medical Center in Chicago, University of Iowa College of Medicine in Iowa City, New York State Psychiatric Institute and Columbia University in New York, and Washington University School of Medicine in St. Louis. Inclusion required that the patient meet Research Diagnostic Criteria (RDC; Spitzer et al 1978) for major depressive disorder (MDD), schizoaffective disorder, or manic disorder. They also required that participants be white, English speaking, and knowledgeable of their biological parents. All participants provided informed consent. The analyses presented here describe only probands who, either before the baseline assessment or at some time during follow-up, met RDC for manic disorder or for schizoaffective disorder, manic type. The RDC for schizoaffective depression overlaps substantially with DSM-IV criteria for MDD or mania with mood-incongruent psychotic features. The RDC schizoaffective subtype “mainly schizophrenic” approximates the DSM-IV definition of schizoaffective disorder, but only a few subjects met inclusion criteria for these analyses (Table 1).

Procedures

Baseline assessments included the full Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978). Final diagnoses reflected input from the patient and informants, as well as from medical records. Raters also used the Family History RDC (FH-RDC; Andreasen et al 1977) to systematically question probands about mental disorders in each of their first-degree relatives.

Two thirds of the probands participated in a family study conducted as proband recruitment proceeded (Andreasen et al
Raters who were blind to proband diagnosis used the lifetime version of the SADS to interview all adult, first-degree relatives willing to participate, and of these, 72% were reinterviewed 6 years later (Coryell et al. 1995; Rice et al. 1992). The later interview covered, first, any lifetime psychopathology that had occurred before the first interview, and then any disorder that had developed in the intervening 6 years. The results of both interviews were considered in deriving the final best-estimate diagnosis for that relative. All participants, both probands and relatives, provided informed consent before participating.

Raters recontacted probands at 6-month intervals for the next 5 years and annually thereafter. They used information from the patient interview and from medical records to complete the Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al. 1987) during the first 2 years, the LIFE-II in years 2 to 5, and the Streamlined Longitudinal Interval Continuation Evaluation in year 6 and beyond (all available upon request). These instruments tracked each RDC syndrome on a week-by-week basis. Interviewers identified change points for each syndrome active since the last assessment and then rated symptom levels for the intervals. For MDD; manic disorder; schizoaffective disorder, depressed type; and schizoaffective disorder, manic type, the Psychiatric Status Ratings (PSRs) used six levels. A rating of 1 indicated no symptoms, a 2 indicated the presence of no more than one or two symptoms to a mild degree, a 3 indicated a full syndrome, and a 6, a relatively severe, full syndrome. Other RDC syndromes such as alcoholism and minor depression were rated on 3-point scales, and for these, a 3 indicated the presence of a full syndrome. Eight consecutive weeks with ratings of no more than 1 or 2 indicated recovery from a specified syndrome, and a recurrence required the redevelopment of a full syndrome.

Participation in this study did not determine or influence treatment. Raters carefully quantified all somatic treatment directed at mental disorders, though, and recorded on a week-by-week basis all individual drugs and their doses as well as lithium levels whenever these appeared in the medical records.

### Statistical Analysis

Morbidity indices were determined for all probands who, during follow-up, had at least one period of 26 or more consecutive weeks of lithium therapy. The selection of a minimum 6-month period was intended to encompass both stabilization and at least the beginning of prophylaxis. All follow-up weeks during which lithium was taken without carbamazepine or valproate were considered in quantifying morbidity during lithium treatment. The “total affective morbidity” during lithium treatment was the proportion of weeks with lithium treatment during which PSRs exceeded 2 for MDD, mania, schizoaffective disorder, minor depression, intermittent depression, or hypomania. To show whether a progressive relationship existed between familial loading for illness and proband morbidity during lithium therapy, patients were ranked according to their total affective morbidity score and divided into low, medium, and high morbidity groups.

### Table 1. Baseline Variables

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of probands</td>
<td>62</td>
<td>55</td>
<td>69</td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>39.5 (14.0)</td>
<td>35.8 (14.5)</td>
<td>35.0 (12.4)</td>
</tr>
<tr>
<td>Mean (SD) age at first episode&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.3 (11.0)</td>
<td>26.4 (10.7)</td>
<td>22.0 (9.7)</td>
</tr>
<tr>
<td>No. (%) female</td>
<td>34 (54.8)</td>
<td>30 (54.6)</td>
<td>37 (53.6)</td>
</tr>
<tr>
<td>No. (%) inpatient status</td>
<td>59 (95.2)</td>
<td>51 (92.7)</td>
<td>62 (89.9)</td>
</tr>
<tr>
<td>No. (%) with three or fewer previous episodes</td>
<td>46 (74.2)</td>
<td>42 (76.4)</td>
<td>49 (71.0)</td>
</tr>
<tr>
<td>Diagnosis at intake, # (%) with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar I&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60 (96.8)</td>
<td>44 (80.0)</td>
<td>59 (85.5)</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>1 (1.6)</td>
<td>3 (5.4)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>7 (11.3)</td>
<td>11 (20.0)</td>
<td>13 (18.8)</td>
</tr>
<tr>
<td>Polarity at intake, # (%) with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manic phase only&lt;sup&gt;c&lt;/sup&gt;</td>
<td>29 (46.8)</td>
<td>24 (43.6)</td>
<td>14 (20.3)</td>
</tr>
<tr>
<td>Depressed phase only&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6 (9.7)</td>
<td>15 (27.3)</td>
<td>13 (18.8)</td>
</tr>
<tr>
<td>Cycling, not mixed&lt;sup&gt;e&lt;/sup&gt;</td>
<td>25 (40.3)</td>
<td>15 (27.3)</td>
<td>36 (52.2)</td>
</tr>
<tr>
<td>Mixed</td>
<td>2 (3.2)</td>
<td>1 (1.8)</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>No. (%) schizoaffective disorder, mainly schizophrenia subtype&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>No. (%) with alcoholism at intake</td>
<td>5 (8.1)</td>
<td>3 (5.4)</td>
<td>8 (11.6)</td>
</tr>
<tr>
<td>No. (%) drug dependent at intake</td>
<td>3 (4.8)</td>
<td>1 (1.8)</td>
<td>2 (2.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>χ<sup>2</sup>(2) = 6.3, p = .0023.
<sup>b</sup>χ<sup>2</sup>(2) = 8.0, p = .018.
<sup>c</sup>χ<sup>2</sup>(2) = 11.9, p = .003.
<sup>d</sup>χ<sup>2</sup>(2) = 6.1, p = .048.
<sup>e</sup>χ<sup>2</sup>(2) = 7.9, p = .005.
<sup>f</sup>χ<sup>2</sup>(2) = 6.9, p = .031.
by at least 1 week without lithium and in which a full manic syndrome was present. Survival analyses were then conducted to estimate both times to recovery from all major affective syndromes and times to recovery from manic syndromes per se. Loss to follow-up and the discontinuation of lithium before full recovery were censoring variables.

Morbidity index scores were also determined for an anticonvulsant treatment condition. Patients who underwent 26 or more consecutive weeks of treatment with carbamazepine or valproate, with or without supplemental lithium, were included in this analysis. As with the morbidity indices for lithium treatment, the proportion of weeks of anticonvulsant treatment during which any PSR for MDD, schizoaffective depression, minor depression, manic disorder, hypomania, or schizoaffective mania exceeded 2 was determined for each patient. Because fewer patients had had anticonvulsant trials than had had lithium trials, two groups rather than three were formed. Patients were divided by the median score into high and low morbidity groups.

Illness among relatives was quantified in several ways. The first considered only directly interviewed relatives and included information from the second, 6-year follow-up interview, if this was available. Product-limit survival estimates (Kalbfleisch and Prentice 1980; Kaplan and Meier 1958) of time to first illness onset were used to compare the relatives of probands grouped by affective morbidity on lithium. This was done separately for onsets of RDC MDD or schizoaffective disorder, depressed type, and for onsets of manic disorder or schizoaffective disorder, manic type. The RDC categories of MDD and schizoaffective depression and of manic disorder and schizoaffective mania were combined to better approximate the DSM-IV definitions of MDD and manic disorders. The remaining text refers to these combined groups simply as MDD and manic disorders, respectively. Also, unlike DMS-IV, the RDC definition of MDD includes patients with a history of mania, hypomania, or schizoaffective mania.

Family history data was also treated categorically because many other studies on this topic have quantified familial morbidity in this way and because this is the more clinically applicable approach. These analyses also included uninterviewed relatives for whom FH-RDC information was available. A proband’s family history was considered positive for mania if he or she had any first-degree relative with mania or schizoaffective mania. They were considered family history positive for nonbipolar MDD only if one or more relatives had MDD or schizoaffective depression and no first-degree relative had manic disorder or schizoaffective disorder, manic type. The two proband groups were therefore mutually exclusive.

The Wilcoxon χ² statistic was used to compare product-limit survival estimates of morbid risks. Categoric comparisons used standard χ² tests and other comparisons of continuous variables used analyses of variance with Duncan multiple range tests for follow-up analyses. Regression analyses used a general linear model procedure.

Results

Family Study Analysis

The total of 186 probands participated in the family study, took lithium without carbamazepine or valproate for 26 or more weeks during follow-up, and exhibited RDC manic disorder or schizoaffective disorder, manic type, either before or after study intake. According to morbidity scores for all major affective disorders, 62, 55, and 69 had low, medium, and high levels, respectively, during lithium treatment. Comparisons of baseline variables (Table 1) revealed that low, medium, and high morbidity groups had progressively earlier ages of onset of major affective disorder (Table 1). The three groups also differed significantly by polarity at intake and by the proportions who began the study with a bipolar I diagnosis. Those who were to show the least morbidity on lithium were most likely at intake to be in a purely manic episode, and were least likely to be in a purely depressed episode. Cycling in the index episode was also associated with higher subsequent morbidity on lithium.

The mean length of follow-up in each morbidity group exceeded 11 years (Table 2). Those with the least morbidity on lithium took the drug for nearly three fourths of their follow-up periods, whereas those in the two higher morbidity groups took lithium for only half of their follow-up. The three groups had similar lithium levels, all within the ranges thought appropriate for prophylaxis. Low, medium, and high lithium morbidity groups were also without thymoleptics for progressively larger proportions of their follow-up periods and, during weeks without thymoleptics, more likely to be symptomatic.

The estimated morbid risks for bipolar I disorder among interviewed relatives did not differ significantly across proband groups with low, medium, and high levels of overall major affective morbidity during lithium treatment, nor did risks for alcoholism or schizophrenia differ significantly (Table 3). In contrast, increasing levels of proband morbidity during lithium therapy were associated with increasing likelihoods of MDD among relatives. Similar patterns emerged when probands were grouped according to levels of mania morbidity during lithium therapy and, again, according to levels of depressive morbidity during lithium, but in neither of these two analyses were the differences statistically significant. The estimated morbidity rate (SE) for MDD among relatives of probands with the least manic and hypomanic morbidity was 38.1 (0.05); for those with the most weeks with manic or hypomanic syndromes, the estimated morbid risk for MDD was 53.6 (0.07). Corresponding figures for the relatives of probands with high and low depressive morbidity on lithium were 38.5 (0.04) and 45.6 (0.06), respectively.

These results were not appreciably altered by the exclusion of comorbid probands, those with current diagnoses at intake of schizoaffective disorder, alcoholism, drug dependence, panic disorder, obsessive-compulsive disorder, drug use disorder, somatization disorder, or antisocial personality disorder. Among these noncomorbid
probands, the 179 relatives of those with low morbidity and the 158 relatives of those with high morbidity had estimated morbid risks (SE) for MDD of 37.7 (4.9) and 49.1 (5.4), respectively. Morbid risks (SE) for manic disorder were 12.9 (2.6) and 16.6 (3.3), respectively. Neither difference was statistically significant, but the degree and direction of differences in morbid risk for MDD were similar to those of the more inclusive groups.

Because of the well-known associations between age of onset and family history (Rice et al. 1987; Weissman et al. 1986), we conducted a linear regression analysis with proband morbidity index as the dependent variable. Independent variables were proband age at first major affective episode and the proportion of interviewed relatives with MDD. The proband morbidity index was associated both with a lower age at onset \((F(1) = 9.24, p = .0027)\) and with a higher proportion of relatives with MDD \((F(1) = 4.09, p = .0447)\).

To determine whether the transmission of an early-onset diathesis per se accounted for higher morbidity levels in probands, we next limited the analysis to probands who had at least one interviewed relative with MDD. Ages at onset did not differ by relative group. Mean (SD) ages at first MDD were 30.7 (12.3) for the 55 affected relatives of the low morbidity probands, 30.4 (10.8) for the 54 affected relatives of the medium morbidity probands, and 28.0 (13.7) for the 75 affected relatives of the high morbidity probands. Proband ages at first MDD, however, did correlate significantly with the onset ages of the first-degree relatives with MDD \((r = .263, p = .0005)\).

To determine whether certain types of depressive illness among relatives were associated with greater proband morbidity during lithium treatment, the low, medium, and high groups were compared by the proportions with family histories positive for the following conditions: any episode of MDD or schizoaffective depression lasting 2 years or longer, multiple recurrences (more than two episodes lifetime), psychotic features during depressive episodes, primary MDD, secondary MDD, or intermittent depressive disorder. Each of these disorders was as likely in the families of the high morbidity probands as in the families of low morbidity probands.

### Table 2. Treatment Conditions during Follow-Up Mean (SD)

<table>
<thead>
<tr>
<th>Morbidity on lithium</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of probands</td>
<td>62</td>
<td>55</td>
<td>69</td>
</tr>
<tr>
<td>Weeks of follow-up</td>
<td>579.1 (274.0)</td>
<td>604.1 (240.7)</td>
<td>612.7 (229.1)</td>
</tr>
<tr>
<td>Weeks on lithium(a)</td>
<td>408.1 (300.2)</td>
<td>297.0 (214.5)</td>
<td>286.6 (233.5)</td>
</tr>
<tr>
<td>Serum lithium levels</td>
<td>0.73 (0.30)</td>
<td>0.70 (0.38)</td>
<td>0.72 (0.35)</td>
</tr>
<tr>
<td>Weeks on lithium/weeks of follow-up(b)</td>
<td>0.714 (.343)</td>
<td>0.548 (.327)</td>
<td>0.470 (.323)</td>
</tr>
<tr>
<td>Weeks ill on lithium/weeks on lithium(c)</td>
<td>.047 (.027)</td>
<td>.221 (.077)</td>
<td>.805 (.199)</td>
</tr>
<tr>
<td>Weeks without thymoleptic(d)</td>
<td>136.9 (231.8)</td>
<td>316.4 (238.3)</td>
<td>246.6 (239.4)</td>
</tr>
<tr>
<td>Weeks without thymoleptic/weeks of follow-up(e)</td>
<td>.240 (.338)</td>
<td>.330 (.325)</td>
<td>.419 (.335)</td>
</tr>
<tr>
<td>Weeks ill without thymoleptic/weeks without thymoleptic(f)</td>
<td>.157 (.286)</td>
<td>.254 (.317)</td>
<td>.584 (.375)</td>
</tr>
</tbody>
</table>

\(a\) F(2) = 4.44, \(p = .0130\). Low > medium, high.
\(b\) F(2) = 9.07, \(p = .0002\). Low < medium < high.
\(c\) F(2) = 61.94, \(p = .0001\). Low < medium < high.
\(d\) F(2) = 3.68, \(p = .0271\). Low < high.
\(e\) F(2) = 4.67, \(p = .0155\). Low < high.
\(f\) F(2) = 30.32, \(p = .0001\). Low < high; medium < high.

### Table 3. Morbid Risks among Interviewed Relatives

<table>
<thead>
<tr>
<th>Proband morbidity on lithium</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of relatives interviewed</td>
<td>194</td>
<td>177</td>
<td>205</td>
</tr>
<tr>
<td>Morbid risks (SE) for Mania/hypomania</td>
<td>13.3 (2.6)</td>
<td>9.5 (2.8)</td>
<td>14.2 (2.8)</td>
</tr>
<tr>
<td>MDD(a)</td>
<td>38.2 (4.7)</td>
<td>42.8 (5.4)</td>
<td>52.3 (5.7)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>17.4 (3.1)</td>
<td>15.1 (3.4)</td>
<td>21.0 (3.3)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0</td>
<td>1.3 (.92)</td>
<td>1.4 (1.0)</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder.
\(\chi^2(2) = 6.1, p = .0481\).
exclusively, though, increased significantly from low to medium to high morbidity groups.

Ages of onset decreased from low to medium to high morbidity groupings; mean (SD) values were 28.0 (10.4), 24.7 (10.0), and 22.7 (9.6), respectively \(F(2) = 5.63, p = .0041\). As before, we conducted a linear regression analysis with morbidity groupings as the dependent variable. Independent variables were family history grouping (positive vs. negative for MDD) and proband age at onset. Both proband age at onset \(F(1) = 9.64, p = .0022\) and a family history of MDD \(F(1) = 5.97, p = .0155\) were significantly associated with proband morbidity on lithium.

Figure 1 shows that the association between low morbidity levels in probands and the absence of major affective disorder among relatives was stable over time. The proportions of weeks with major affective syndromes present varied across these time periods, and in none of the years were the group differences statistically significant. In each, however, morbidity was lowest for those who lacked a family history of major affective disorder and highest for those with a family history of only MDD.

Family history groupings were also compared by the times to recovery during lithium treatment for acute mania (Table 5). Those without family histories of affective disorder reached full recovery much more rapidly than did those with family histories positive for MDD. Times to recovery from manic syndromes per se showed the same pattern, but differences did not reach statistical significance.

### Anticonvulsant Analysis

Only 31 bipolar probands had taken either carbamazepine or valproate without lithium for at least 26 consecutive weeks during follow-up. For the 15 probands in the low morbidity group, 57 relatives were directly interviewed, as were 58 relatives of the 16 probands in the high morbidity group.

The relatives of probands with higher affective morbidity on anticonvulsants had somewhat higher rates of MDD than did the relatives of probands who experienced less morbidity on anticonvulsants, but differences were not statistically significant. Estimated risks for MDD were 39.5 (SE = 8.1) and 27.0 (SE = 7.7), respectively. Risks for bipolar I disorder were 10.8 (SE = 4.6) and 8.9 (SE = 3.8), respectively.

Of the 39 probands who took an anticonvulsant for 26 or more weeks during follow-up, 36 (92.3%) also took lithium for 26 or more weeks at some other time during follow-up. As shown in Table 6, nearly all who experi-

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**Table 4. Proportions with Any III Relative (Family Study + Family History [FH] Methods)**

<table>
<thead>
<tr>
<th>Proband morbidity on lithium</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, probands</td>
<td>76</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>No. (%) FH + for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>manic disorder</td>
<td>18  (23.7)</td>
<td>19 (23.8)</td>
<td>16 (19.3)</td>
</tr>
<tr>
<td>MDD only*</td>
<td>26  (44.8)</td>
<td>35 (57.4)</td>
<td>45 (67.2)</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder.

* \(\chi^2(2) = 6.3, p = .042\).

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Figure 1. Proportion of weeks with major affective disorder by family history status and year of follow-up. *Family history negative for both major depressive disorder (MDD) and mania. **At least one first-degree family member with manic disorder. ***At least one first-degree relative with MDD and none with manic or hypomanic disorder.
Table 5. Acute Response to Lithium in Prospectively Observed Manic Episodes

<table>
<thead>
<tr>
<th>Proband family history</th>
<th>Negative for MDD or mania</th>
<th>Positive for MDD only</th>
<th>Positive for mania</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Time to recovery from mania and MDD, mean (SD) weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.1 (3.2)</td>
<td>24.2 (8.4)</td>
<td>11.1 (2.3)</td>
</tr>
<tr>
<td>Time to recovery from mania only</td>
<td>6.4 (2.4)</td>
<td>10.4 (3.3)</td>
<td>6.2 (1.4)</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder. Family history (FH) negative vs. FH positive for MDD only: χ²(1) = 6.5, p = .0108. FH negative vs. FH positive for mania: χ²(1) = 3.5, p = .0601. χ²(2) = 7.5, p = .0237.

Discussion

Contrary to expectations, bipolar affective disorder among relatives was not associated with better outcomes for probands given lithium. Better long-term outcomes were, instead, associated with the absence of MDD in family members. This relationship persisted across all years of follow-up and appeared whether illness in relatives was treated categorically with the family history method or as a continuum with the family study method. Higher morbidity levels on lithium did not seem to reflect noncompliance in that mean lithium levels were as high among probands with the most morbidity as they were among those with the least. Moreover, those with the highest morbidity on lithium also experienced high morbidity during periods without thymoleptics. It appears then that the poorer prognosis associated with a family history of MDD manifests with or without pharmacotherapy.

Regression analyses suggested that proband age at onset was an important correlate of proband morbidity levels during lithium therapy; however, the relatives of probands with high morbidity did not themselves develop MDD at earlier ages, though ages at onset for relatives and probands were highly correlated. Thus, it does not appear that the transmission of an early-onset subtype accounted for the association between lithium resistance and family history. It seems, instead, that the presence of MDD in family members predisposed probands with bipolar I disorder to both an early onset and to high morbidity over time.

Surprisingly few probands had undergone trials of anticonvulsants without concomitant lithium. The statistical power to identify the effects of family history on symptom levels was correspondingly limited. Strong trends did emerge, though, and the patterns resembled those seen for lithium treatment. In fact, those with the highest symptom persistence on anticonvulsants also experienced the most symptoms on lithium. Thus, though familial loading has some predictive value for treatment response, it would not serve to recommend one thymoleptic over another.

Can these findings be reconciled with those studies that found higher rates of bipolar illness among the relatives of lithium responders? Among these, Grof et al (1994) described a diagnostically mixed group of probands and findings for the subgroup with bipolar disorder were, strictly speaking, negative. Of the 343 relatives of lithium responders, only nine (2.6%) had bipolar illness themselves. Though bipolar illness was absent among the 37 relatives of bipolar probands who did not respond to lithium, the difference was far from statistically significant.

Studies by Maj et al (1985) and Mendlewicz et al (1973) included only patients who had been compliant with lithium treatment for periods of 2 and 3 years, respectively, and may therefore have selected for a particularly motivated, good-prognosis sample. The high proportion considered lithium responders suggested this was so. Even though the definition of response required the absence of relapse throughout the observation period, two thirds of the patients in both studies achieved this. These patients were also particularly likely to have relatives with bipolar disorder. In the current study, only 24% of the patients with the lowest morbidity on lithium had one or more relatives with bipolar affective disorder, but this was true of 42% of the responders described by Maj et al (1985) and 62% of the responders described by Mendlewicz et al (1973). It is possible that patients in the settings accessed by Maj et al and Mendlewicz et al were more likely to have typical, uncomplicated bipolar illness than those recruited by the CDS. It is also possible that diagnostic criteria were applied more strictly by Maj et al and Mendlewicz et al. It may be that it is within such groups that a family history of bipolar illness is more prognostically favorable.

These possibilities led us to consider whether some depressive illness may be characterized by high likelihoods of comorbidity, poor prognosis, and a high familial loading for depressive disorders. Because comorbidity

Table 6. Within-Subject Affective Morbidity on Lithium and on Anticonvulsants

<table>
<thead>
<tr>
<th>Morbidity during lithium therapy</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>n. (%) with high morbidity on anticonvulsants&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>3 (25.0)</td>
<td>5 (41.7)</td>
<td>10 (83.3)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>χ²(2) = 8.7, p = .013.
Family History and Lithium Response

makes the accurate diagnosis of bipolar affective disorder more difficult, the diagnosis is relatively less certain when other illnesses are present. Such individuals may have been excluded using narrower, more traditional definitions of bipolar affective disorder and would have been less likely to faithfully attend clinic regimens. The exclusion of patients with comorbidity, though, did not substantially lessen the relationship between MDD among relatives and morbidity in probands, nor did bipolar illness among relatives emerge as a predictor of lithium response in this purified subgroup.

The findings described here, though difficult to reconcile with Maj et al (1985) and with Mendlewicz et al (1973), do concur with another study described by Engstrom et al (1997) and by Nylander et al (1999). These authors found a significantly higher proportion of lithium responders among probands who lacked family histories of bipolar or unipolar disorders. In comparing their study with earlier ones, they emphasize their use of relatively long observation periods. In this respect their study resembles the one described here. Our mean prospective observation period exceeded 10 years, far longer than the 2- and 3-year periods described by Maj et al (1985) and Mendlewicz et al (1973), respectively.

In our study, though, some advantage to family history—negative probands, as compared with probands with family history of MDD, was apparent in the first year. Moreover, the existence of a variable that is prognostically favorable in the short term but unfavorable in the long term seems counterintuitive and lacks precedence.

It is more likely that the differing results across studies reflect elusive but important cohort differences. In the context of earlier findings, those presented here weigh against the use of family history in the selection of treatment for bipolar disorder. These findings are potentially important for other reasons, though, and certainly raise a number of questions. Will similar patterns emerge in nonbipolar probands? Would a differently focused analysis suggest the presence of genetic anticipation as suggested by Nylander et al (1994)? Does a familial loading for MDD predict other features of long-term course or of phenomenology? Answers to these questions will be sought in this cohort and should be addressed in other existing data sets as well.

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