Is Response to Prophylactic Lithium a Familial Trait?

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Background: Selecting a drug according to the treatment response in a relative has been widely accepted advice in the management of mood disorders. However, this recommendation has not been adequately substantiated in the literature. We tested the hypothesis that response to long-term lithium treatment is a familial trait.

Method: We compared response to long-term lithium treatment in bipolar relatives of bipolar lithium responders and bipolar controls. Twenty-four relatives with bipolar disorder (as determined using the Schedule for Affective Disorders and Schizophrenia-Lifetime version [SADS-L] and Research Diagnostic Criteria [RDC]) were identified in families of 106 patients with lithium-responsive bipolar disorder. A consecutive series of 40 lithium-treated patients in a bipolar clinic (meeting RDC and DSM-IV criteria for bipolar disorder) served as a comparison group. Lithium response was evaluated on a rating scale reflecting the quality and quantity of available data.

Results: The prevalence of unequivocal response among the relatives was 67%, as compared with the response rate of 35% in the comparison group ($\chi^2 = 6.04$, df = 1, p = .014).

Conclusion: This highly significant difference in response between relatives and the control group supports the view that the response to lithium prophylaxis clusters in families.

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Identifying a treatment likely to be effective in a particular patient is one of the most important clinical tasks. In most psychiatric textbooks and review articles on this subject, there appears a standard recommendation that the response to a given drug in a patient's relative is an important indicator for selecting the optimal treatment.[1–5] While this idea is intuitively appealing, the observations supporting such a recommendation are surprisingly limited.

Angst[6,7] studied treatment responses to imipramine in a case series of 200 patients with depression. He concluded that relatives suffering from endogenous depression tend to respond to imipramine in a similar way. Out of 9 pairs suffering from endogenous depression, 8 responded similarly (5 positively, 3 negatively). On the other hand, in 5 other pairs suffering from endogenous psychoses of different etiology, the responses were irregular.

Pare and collaborators studied responses in pairs of depressed relatives treated with tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants. In the first study,[8] which included 170 patients, information about 8 relatives was found to be sufficient to make an assessment of the response to an antidepressant. In a second study, which included 515 probands,[9,10] the response to an antidepressant drug could be determined in 13 first-degree relatives. In both studies, there was a marked similarity between the response of probands and first-degree relatives when they received an antidepressant from the same group (tricyclics or MAOIs); however, responses differed when the drug belonging to the other group was used.

McKnew and coworkers[11] selected 6 children of bipolar, lithium-responsive patients for treatment with lithium. The children suffered from incapacitating psychopathology, and their age ranged from 6 to 12 years. The treatment was carried out in a double-blind, placebo-controlled manner, with weekly ratings performed over the course of 16 to 18 weeks. Two children who met the diagnostic criteria for a bipolar affective disorder had a clear-cut response to lithium. The authors noted a clear parallel between bipolar affective illness in children and adults from the same family, expressed not only in treatment response but also in physiologic measurements such as augmentation on the evoked potentials. Close resem-

blance between parents and children in their response to lithium treatment was also noted by Annell.[12]

O'Reilly and coworkers[13] reported a pattern of selective response to tranylcypromine in a larger family afflicted by 8 cases of major depression in 2 generations. Four relatives suffered from severe prolonged depressive disorders and did not benefit from therapeutic doses of either tricyclic or newer antidepressants but subsequently responded to tranylcypromine. This observation supported a familial tendency to respond to a specific antidepressant, and O'Reilly and coworkers concluded that a history of response in a relative may be helpful when selecting an effective antidepressant for a patient.

Most recently, Franchini et al.[14] studied 45 relatives of depressed probands treated successfully with fluvoxamine and found the concordance of the treatment response to be 67%. They noted a stronger family history of bipolar disorder in the concordant pairs. In a related study, Serretti et al.[15] found support for a major-gene effect when studying the mode of inheritance of affective illness in 68 families selected for good response to fluvoxamine.

Indirect support for the familial clustering of response may be derived from studies demonstrating an aggregation of the same mood disorder in the families of treatment responders. For response to lithium prophylaxis, such observations have been made by Mendlewicz et al.,[16,17] Zvolsky et al.,[18] Smeraldi et al.,[19,20] Sautter and Garver,[21] and Grof et al.[22]

Thus, over the past 40 years, the literature on the pharmacogenetics of mood disorders is sparse, based mainly on published clinical impressions, and data for bipolar disorder on long-term treatment are nonexistent. Small sample sizes make statistical analysis difficult. Some observations reported in support of familial response are open to alternative interpretations such as, for example, a similarity of clinical course in the families rather than of treatment response.

It is not difficult to understand why the important question of whether relatives respond to the same drug has not been rigorously investigated in a suitable plan. From a methodologic point of view, a study of this nature poses major challenges for design and feasibility. The probands and the relatives should be treated with the same drug in a research manner allowing the evaluation of the treatment outcome. They all should be diagnosed according to the same criteria and treated with monotherapy in an adequate dose and for a sufficient duration. The appropriate design would enable the investigator to evaluate the response in each participating individual, and the interpretation would have to take into account the probability of a spontaneous improvement. To make an adequate statistical analysis possible, a large number of probands and relatives would be needed.

To complicate the feasibility further, for a variety of reasons including psychodynamic ones, there has been a tradition not to treat more than one member of a family. While such a caution remains valid for intensive psychotherapy, it further complicates pharmacogenetic research.

Table 1. Demographic and Clinical Data for Bipolar Relatives of Bipolar Probands Responsive to Lithium and the Comparison Group of Bipolar Patients

Variable	Relatives (N = 24)	Comparison Group (N = 40)	p Value
Age, mean ± SD, y	46.1 ± 18.3	41.3 ± 13.2	.36*
Males, N (%)	7 (29)	11 (28)	.89†
Age at onset of bipolar disorder, mean ± SD, y	26.3 ± 12.7	25.7 ± 11.5	.83*
Bipolar I, N (%)	13 (54)	24 (60)	.65†

*Kruskal-Wallis test.
†Chi-square test.

METHOD

Subjects

The subjects for this study were 24 relatives of 21 probands from our ongoing genetic study of 106 patients with bipolar disorder responsive to lithium, and 40 subjects in a comparison group.

Probands. Probands were selected prospectively on the basis of the diagnosis of bipolar disorder and on strict criteria of the response to long-term lithium treatment proposed earlier.[22,23] All probands were interviewed using Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) semi-structured interviews[24] and diagnosed according to Research Diagnostic Criteria (RDC).[25] They had a mean of 8.7 ± 5.0 episodes of mania and/or depression before the treatment with lithium and had 12.6 ± 7.9 years of full stability on lithium monotherapy.

Relatives. We identified 17 first- and 7 second-degree relatives, all diagnosed with bipolar disorder and treated with an adequate dosage of lithium for more than 12 months. Their demographic and diagnostic data are presented in Table 1. Since there were no differences between the first- and second-degree relatives with respect to age, age at onset, diagnosis, and the response to lithium, we pooled their data for all analyses. Three additional relatives with recurrent unipolar disorder received lithium treatment, but they were not included in the analysis.

As with the probands, diagnoses in relatives were also based on SADS-L interviews and RDC criteria. Final diagnoses were made by a consensus panel of research psychiatrists who were using, in a blind fashion, all available data including the comprehensive interview and collateral information.

Comparison group. The comparison group consisted of a consecutive series of 40 patients with bipolar disorder who were followed in a specialized clinic and treated with lithium for a minimum of 12 months. Patients referred for treatment refractoriness and/or with evidence of sig-

Table 2. Retrospective Criteria of Lithium Response in Research Subjects[a]

Criterion A is used to determine an association between clinical improvement and lithium treatment. Criteria B1–B5 establish whether there is a causal relationship between the improvement and the treatment.

A: Rate the degree of response (activity of the illness while on adequate lithium treatment) on the following 10-point scale:
- 10 Complete response; no recurrences during the course of adequate treatment; full functional recovery at work and at home, no residual symptoms
- 9 Very good response; no recurrences, but there may be minimal residual symptoms that could include transient anxiety, sleep disturbance, dysphoria, irritability; these symptoms have not required intervention
- 8 Very good response; illness activity reduced by more than 90%
- 7 Good response; illness activity reduced by 80%–90%
- 6 Good response; reduction in the activity of illness by 65%–80%
- 5 Moderate response; greater than 50% reduction (50%–65%) in illness activity
- 4 Moderate (35%–50%) improvement, i.e., more than one third reduction of illness activity
- 3 Mild improvement, reduction of illness activity by 20%–35%
- 2 Mild improvement (10%–20%)
- 1 Minimal improvement (0%–10%)
- 0 Nonresponse; the frequency, duration, and severity of episodes are unchanged or increased in the course of prophylactic treatment

B: Rate the degree of confidence about the response—subtract 0, 1, or 2 points for each of the following items:

B1: Number of episodes before lithium treatment
- 0 4 or more
- 1 2 or 3
- 2 1

B2: Frequency of episodes before lithium
- 0 Average to high, including rapid cycling
- 1 Low, spontaneous remissions of 3 or more years on average
- 2 1 episode only; risk of recurrence cannot be established

B3: Duration of lithium treatment
- 0 2 or more years
- 1 1–2 years
- 2 Less than 1 year

B4: Compliance during period(s) of stability
- 0 Excellent; documented by serum lithium levels in the therapeutic range
- 1 Good; more than 80% of serum lithium levels in the therapeutic range
- 2 Poor; repeated periods of more than 1 week off lithium treatment; fewer than 80% of serum lithium levels in the therapeutic range

B5: Use of additional medication during the period of stability
- 0 None except infrequent sleep medication (1 dose per week or less); no other mood stabilizers, antidepressants, or antipsychotics for control of mood disorder
- 1 Low-dose antidepressants or antipsychotics as an "insurance" or prolonged use of sleep medication
- 2 Systematic use of antidepressant or antipsychotic medications or additional mood stabilizers

C: Ascertain diagnosis of a mood disorder

[a]This scale should be applied to the period of treatment closest to optimal, i.e., adequate dosage and least use of medications interfering with the effect of lithium. © Martin Alda, M.D.

nificant comorbidity including substance abuse were excluded to avoid a bias against the null hypothesis.

All subjects in the control group met both RDC and DSM-IV criteria for bipolar disorder. The clinical data are presented in Table 1. There were no significant differences between the relatives and the comparison group with respect to age, sex, and age at onset distributions.

Since this study involved a chart review in retrospect, the respective Research Ethics Committees did not require informed consent.

Assessment of Treatment Response

To evaluate the lithium response in the relative and comparison groups retrospectively, we used a rating scale that measures the degree of improvement in the course of treatment (Criterion A) and weighs clinical factors considered relevant for determining whether or not the observed improvement is due to the treatment (Criteria B1–B5; see Table 2). The scale was developed to evaluate the response to long-term treatment in subjects not treated according to a research protocol. The combined maximum score is 10 and the minimum score is 0.

Criterion A is determined as a change in frequency of affective episodes in the course of treatment on a scale from 0 to 10. The Criteria B1–B5 are rated as 0, 1, or 2 points, which then are subtracted from the Criterion A score. The first 2 items specify the recurrence risk (number [B1] and frequency [B2] of episodes before treatment). The higher the risk, the more likely it is that the patient would continue experiencing affective morbidity in absence of effective treatment. The third criterion (B3) is based on the length of treatment, to account for the variable clinical course of bipolar disorder and for the possibility that the observed remission is spontaneous and unrelated to the treatment. The last 2 B Criteria deal with compliance (B4) and concomitant medication (B5) during periods of stability. In noncompliant subjects or in those who use additional medications, the link between improvement and specific treatment is less certain.

For the purpose of the analysis, we used both actual scores and response defined as a score of 7 or higher. The interrater reliability of the scale is very good, with concordance of ratings of 90% and the kappa value of 0.80.

Statistical Analysis

Nonparametric methods (Kruskal-Wallis test and chi-square test) were the principal methods used.

RESULTS

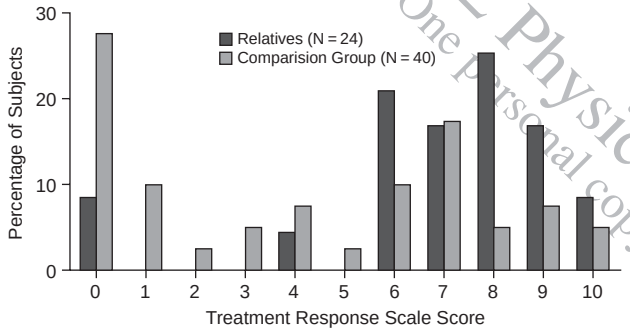
The results of the study are presented in Table 3. The mean ± SD total score on the treatment response scale in

Table 3. Total and Individual Criterion Scores on the Treatment Response Scale and Percentages of Responders[a]

Variable	Relatives (N = 24)	Comparison Group (N = 40)	p Value
Total score	6.9 ± 2.6	4.1 ± 3.5	.002*
Criterion score			
A	8.5 ± 2.2	6.1 ± 3.3	.001*
B1	0.29 ± 0.55	0.55 ± 0.64	.08*
B2	0.29 ± 0.55	0.43 ± 0.59	.32*
B3	0.21 ± 0.51	0.35 ± 0.62	.32*
B4	0.42 ± 0.72	0.30 ± 0.52	.71*
B5	0.33 ± 0.64	1.03 ± 0.89	.002*
Responders (total score ≥ 7), N (%)	16 (66.7)	14 (35.0)	.014†
Responders (Criterion A score ≥ 5), N (%)	22 (91.7)	25 (62.5)	.01†

[a]For explanation of Criterion A and Criteria B1–B5, see Table 2. Unless stated otherwise, the results are given as mean ± SD.
*Kruskal-Wallis test.
†Chi-square test.

Figure 1. Distribution of Treatment Response Scores in the Relatives of Lithium Responders and in the Comparison Sample



the relative group was 6.9 ± 2.6 compared with 4.1 ± 3.5 in the comparison group. The distribution of values is presented in Figure 1. The difference between the groups is statistically significant (p = .002), indicating a better response in the relative group. Similarly, the response rate (response defined as a score of 7 or higher on the treatment response scale) in the group of relatives was 67% compared with 35% in the comparison group ($\chi^2 = 6.04$, df = 1, p = .014).

When we compared the individual items of the response scale, differences emerged only for Criterion A (degree of improvement on lithium) and Criterion B5 (use of additional medication). Thus, the groups were comparable with respect to the number of pretreatment episodes and their frequency, as well as duration of lithium treatment and compliance with the medication.

The response scores (both the Criterion A score alone and the total score) correlated neither with age (r = –0.16 and r = –0.02, respectively) nor age at onset (r = –0.15 and r = –0.10, respectively) in the 2 groups. There was no difference in the response scores between bipolar I and bipolar II subjects (total score: p = .30; Criterion A score: p = .67; Kruskall-Wallis test).

Finally, to make our results comparable to other studies of prophylactic treatment, we have also compared the response rates defined as a 50% improvement in the course of lithium prophylaxis irrespective of other intervening factors (Criterion A only). The response rates defined this way were 92% in the relative group and 63% in the comparison group. This difference is also statistically significant ($\chi^2 = 6.54$, df = 1, p = .01). However, this finding also indicates a good effect of lithium in unselected bipolar patients and argues against a bias toward a high nonresponse rate in this group.

DISCUSSION

There is a widespread assumption that lithium response in a patient selectively predicts the same response in other affected relatives, but satisfactory statistical evidence to support this assumption has not been available. In this investigation, we have confirmed that the response to long-term lithium treatment indeed clusters in families of responders to a large degree. This finding should be discussed at 2 levels: first, as it relates specifically to the responsiveness to lithium; second, as it relates to the drug response in relatives in general.

The findings show that most, but not all, relatives benefited from long-term administration of lithium. Several factors may have influenced our findings of responsiveness in relatives. In comparison with the probands, relatives usually had fewer recurrences, were treated for shorter periods of time, and often received a combination of drugs. The new rating scale made it possible to evaluate the probability of response to lithium in each treated relative. However, the 67% response rate must be viewed only as an estimate under the circumstances. A more precise value might be obtained if a prospective study with an ideal design were feasible. The absence of similar studies in the literature illustrates the enormous difficulties of such an investigation.

While the response in the control group was evaluated in the same way as in the probands' relatives, the finding of 30% must be also considered as an estimate only, since no randomization or matching was feasible. Similar response rates in unselected bipolar disorders have, however, been reported in the literature, e.g., Baldessarini and Tondo.[26]

The number of relatives with unipolar depressive disorder was too small for statistical analysis, but the findings are of interest. Of the 3 relatives suffering from a frequently recurring unipolar depressive disorder and treated adequately with lithium, 2 responded, making the responsiveness more similar to that of their bipolar relatives than to that of the control group.

When interpreting the findings, one must keep in mind some limitations resulting from our design, which was

determined by feasibility considerations. Under ideal circumstances, one would want to compare blindly, in a prospective study, lithium-treated relatives of a consecutive series of responders to lithium prophylaxis with 2 control groups: lithium-treated relatives of a consecutive series of bipolar patients and lithium-treated relatives of a consecutive series of lithium nonresponders. Results of such a study would be more definitive and could help to differentiate whether familial clustering is due to lithium response, bipolar illness, or perhaps another factor.

Unfortunately, such an ambitious project has not been feasible. It is important to note that the idea that treatment response runs in families was raised nearly 40 years ago and has been quoted many times in numerous textbooks, yet no fully satisfactory study has been completed so far. Treatment assigned to relatives by design has remained a major obstacle.

We believe that we obtained a satisfactory approximation of the correct answer to the question of whether lithium response does cluster in families. However, the accuracy of the findings may have been influenced by the fact that the treatment response in both groups was evaluated retrospectively, the response scale has not yet been fully validated, and the study was nonrandomized. Because of the design employed, we cannot clearly differentiate whether the familiality reflects lithium responsiveness, a subtype of bipolar disorder, or possibly some third factor.

To address this specific question, we have attempted to evaluate lithium response in relatives of lithium-nonresponding bipolar patients, but as one would anticipate, we have not been able to gather a sample that would be suitable for statistical evaluation. After all, it is not often that relatives are placed on lithium after a proband failed to benefit. For similar reasons, we were not able to carry out a study in which affected relatives of clinic attendees, rather than a consecutive series of clinic patients, would be investigated. It is also possible that some bias may have emerged from the fact that the reviewer had some idea as to which group the relative actually belonged. We do believe, however, that this factor has not significantly affected our evaluation. Blindness is critical when evaluating symptoms and severity of illness but is less important when counting the number of recurrences. In 1970, Schou[27] compared the studies of lithium prophylaxis that were carried out under double-blind conditions and open studies and concluded that there was no significant difference in the outcomes.

While randomized, parallel-controlled, double-blind designs are optimal for most clinical experiments, there are also important clinical issues that must be addressed with only limited use of these principles. Besides issues such as the treatment-induced changes of mortality and the optimal management of pregnancy, the question of familial clustering of treatment response may be another example of an issue requiring an adjusted strategy.

This study also relates to a general issue of whether drug responses "breed true" in families. Although studies systematically addressing this question are not available, useful observations may be feasible under special circumstances. A methodology similar to our study could be used with drugs other than lithium. We are currently evaluating the response to other mood stabilizers using the same approach. Because of tremendous interest in family studies of mood disorders and in the collection of family data for molecular genetic investigations, observations on relatives treated with other drugs may soon become available.

Drug names: fluvoxamine (Luvox and others), tranylcypromine (Parnate).

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