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Lithium response in families can inform the selection of long-term treatment of bipolar disorder

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ABSTRACT

Lithium, recommended as the first-line choice for recurrence prevention in bipolar disorder, is fully effective in only about one-third of patients. It is therefore important to identify early those patients likely to benefit in the long-term. Earlier studies suggested that the response to lithium stabilization runs in families and that family history is an important predictor of treatment outcome. To overcome the limitations of the earlier studies - small sample size in particular - we carried out a multicenter study and used a standardized assessment of treatment response. Collaborating centers in Canada, Italy, and Poland recruited 92 biological relatives of 78 probands assessed for response to long term lithium monotherapy. We compared their data with those from 78 unrelated persons with bipolar disorder. The response to treatment has been quantified on a scale previously described and validated. Among the relatives of lithium responders, 69% were also good responders; in relatives of non-responders, only 22% responded to treatment ($p < 0.0001$). The odds of responding were 7.8 times higher in families of responders compared to non-responders (95% CI 3.0 to 20.1). The response rate in the comparison group was 31%, lower than in the responders' relatives ($p < 0.0001$), but not significantly different from the rate in families of non-responders ($p = 0.31$).

Our findings support the familial nature of the response to lithium. When information about the response in relatives is available, family history of lithium response is a crucial factor to consider when selecting long term treatment.

1. Introduction

The response to pharmacological treatments in psychiatry is varied and heterogeneous. One hypothesized source of this heterogeneity is genetic variability. The first observations in psychiatry suggesting the familial nature of treatment response emerged in the early 1960s with respect to imipramine response (Angst, 1961). This was followed by case series differentiating depression into familial subtypes responsive to tricyclic antidepressants versus inhibitors of monoamine oxidase (Pare et al., 1962; Pare and Mack, 1971). Further support for family-concordant response to antidepressant came from studies of fluvoxamine (Franchini et al., 1998) and a case report of members of a single family with all treated members responding to tranylcypromine (O'Reilly et al., 1994). Compared to antidepressant data, the literature on other medication classes (antipsychotics or mood stabilizers) is even more sparse. In an earlier study of family members treated with lithium,

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we showed that the likelihood of favorable response was 3.7 times higher in relatives of long-term responders compared to unrelated, randomly selected individuals (Grof et al., 2002). In a case series, Duffy et al. (2007) reported concordant response to lithium between parents with bipolar disorder and their affected offspring. Here, we report a follow-up study of the original sample from Grof et al. (2002), expanding the sample substantially and including families of patients who did not respond to treatment. We hypothesized that the response to lithium long term treatment would co-segregate within families.

2. Experimental procedures

The study was conducted in collaborating centers in Canada, Italy, and Poland. We recruited patients with bipolar disorder type I or II, who received long term lithium treatment for a minimum of one year. Included patients had to have one or more biological relatives with bipolar disorder or recurrent major depression treated with lithium for at least a year. Two probands had a diagnosis of recurrent depression but were also included as they had relatives treated for bipolar disorder (see Table 1). As a comparison group, we included unrelated patients with bipolar disorder treated with lithium and selected at random from an outpatient mental health clinic. All patients were diagnosed according to DSM-IV diagnostic criteria using all available information from diagnostic interviews, most commonly SADS-L format (Endicott and Spitzer, 1978), and longitudinal follow-up.

All study participants signed an informed consent. The data come from studies, protocols of which were approved by appropriate local ethics boards, namely those at the Nova Scotia Health Authority, the Royal Ottawa Hospital, University Hospital of Cagliari and former Health Agency 8 – Cagliari (now Health Agency of Sardinia), and Poznan University of Medical Sciences.

The Canadian sample was recruited from specialized mood disorders clinics in Halifax and Ottawa and included 54 relatives of 42 probands. Twenty-four of the relatives were part of the study by Grof et al. (2002). The recruitment took place between 1997 and 2024. The average duration of treatment was 12.5 ± 10.8 years with mean lithium dose of 918 ± 254 mg of lithium carbonate and average plasma levels of 0.67 ± 0.13 mEq/L. In Halifax, we also recruited a comparison group of 78 patients previously described by Garnham et al. (2007) to estimate the overall response rate in a population not selected for family history of response/non-response to treatment. Due to changes in the medical record keeping, we have incomplete information on lithium doses and plasma levels for those Canadian patients currently not followed at the Halifax clinic.

In Italy, one group of participants, 15 relatives of 15 probands, were recruited in the lithium clinic in the Department of Clinical Pharmacology at University of Cagliari and followed from 1973 to 2025, for 16.7 ± 11.1 years. Their average lithium dose was 685 ± 240 mg of lithium carbonate with plasma levels of 0.60 ± 0.10 mEq/L. The second sample of 17 relatives of 16 probands was followed at the Centro Bini in Cagliari. These participants were followed between 1978 and 2025 and treated with lithium for 12.0 ± 9.7 years on average. Their lithium dose of 767 ± 272 mg and plasma level 0.60 ± 0.12 mEq/L.

In Poland, the patients were followed at the specialty lithium clinic at Poznan University of Medical Sciences. The data was collected between 2017 and 2018. There were 6 relatives of 5 probands, treated with lithium for 11.6 ± 8.0 years, on 750 ± 228 mg of lithium carbonate with average plasma levels of 0.62 ± 0.21 mEq/L.

At all sites, the response to lithium was rated on a scale previously described and validated (Grof et al., 2002). In brief, the scale considers the change of frequency, duration and severity of mood episodes in the course of treatment (score A) and adjusts it with respect to the pre-treatment number and frequency of episodes, duration of treatment as well as compliance and need for adjunct medication during periods of stability (scores B1 – B5). The scores on the scale range from 0 to 10. As in earlier studies, we considered total scores of 7 or higher as a good response and scores of 6 or lower as an incomplete or poor response. All centers participated in inter-rater reliability training and evaluation in the context of the ConLiGen study (Manchia et al., 2013). The study investigators achieved good concordance of ratings with a weighted kappa of 0.75 for a dichotomous measure of response and intraclass correlation of 0.96 for a continuous measure (total score).

We described the demographic (age, sex) and basic clinical data (age at onset, rates of comorbid substance use and anxiety disorders) in the three groups (probands, relatives, comparison patients) using the chi-square test and analysis of variance with *post hoc* pairwise *t*-tests.

The hypothesis of differential response rates in relatives of proband responders and non-responders, and in the comparison group was analyzed using chi-square tests. To quantify the degree of association between probands' and relatives' response, we used tetrachoric correlation and odds ratios. Finally, to adjust for effects of potential confounders, we performed sensitivity analyses using logistic regression and log-linear model analyses.

Most of the families consisted of one proband-relative pair, but there were 7 families with 3 members and 1 family each with 4 and 5 members assessed. The probands were defined as usual in family studies (the person through whom the family is ascertained). To test if proband selection in families influenced our results, we performed sensitivity analysis. Using a permutation test with 10,000 repetitions we selected the probands at random and calculated the measures of association (chi-squared test and odds ratios). The analysis was done using an in-house R script.

Table 1
Demographic and clinical data.

Variable	Probands	Relatives	Control BD patients
N	78	92	78
Men: Women (Men %)	33: 45 (42.3%)	39: 53 (42.4%)	28: 50 (35.9%)
Diagnosis, N (%)			
Bipolar disorder type I	63 (80.8)	64 (69.6)	62 (79.5)
Bipolar disorder type II	13 (16.7)	24 (26.1)	16 (20.5)
Recurrent depression	2 (2.6)	4 (4.3)	0
Age (years ±SD)	52.5 ± 16.2*	49.0 ± 16.1	45.7 ± 12.9
Age at onset (years ± SD)	25.1 ± 10.8	27.2 ± 12.1	31.3 ± 10.2**
Age at onset of Li treatment (years ± SD)	36.9 ± 13.5	36.6 ± 15.0	36.0 ± 10.7
Comorbid anxiety	14/75 (18.7%)	17/83 (20.5%)	24/78 (30.8%)
Comorbid substance abuse	12/75 (16.0%)	14/83 (16.9%)	27/78 (34.6%)***

* significantly different from the unselected control group ($F = 3.82$; d.f. = 2, 236; $p = 0.02$).
** significantly different from the probands and relatives ($F = 6.20$; d.f. = 2, 242; $p = 0.002$).
*** significantly different from the probands and relatives ($\chi^2 = 9.91$; d.f. = 2; $p = 0.007$).

3. Results

We included 78 probands and their 92 relatives in the study. The families included 30 parent-child pairs, 46 sib pairs, 9 pairs with second-degree and 7 with third-degree relatives. The demographic and basic clinical data are summarized in Table 1.

Forty probands (51.3% of the total) were responders to long term lithium. Out of their 51 relatives, 35 (68.6%) were also responders, while out of 41 relatives of non-responders only 9 (22.0%) were responders. The association between the probands' and relatives' response rates was significant ($\chi^2 = 19.8$, df = 1, $p < 0.0001$; tetrachoric correlation $r = 0.67$) with an odds ratio of 7.8 (95% CI 3.0; 20.1). Excluding any family members with unipolar depression did not change the results ($\chi^2 = 19.0$, df = 1, $p < 0.0001$; tetrachoric correlation $r = 0.68$) with an

odds ratio of 7.9 (95% CI 3.0; 20.8).

When we restricted the analysis to the first-degree relatives only, we saw a very similar pattern (27 out of 40 relatives of responders had a good response compared to 7 out of 36 relatives of non-responders ($\chi^2 = 17.7$, df = 1, $p < 0.0001$; OR = 8.6 (95% CI 3.0; 24.8). Controlling for the type of relationship did not change the results (log-linear analysis: $\chi^2 = 8.7$, df = 9, $p = 0.46$). Similarly, comorbid anxiety or substance abuse did not have a significant effect on the observed association between probands and relatives (in log-linear analysis: $\chi^2 = 6.4$, df = 3, $p = 0.09$ and $\chi^2 = 3.5$, df = 3, $p = 0.32$, respectively). In the sensitivity analysis, the mean chi-square value out of 10,000 permutations for the association of the probands' and relatives' responses was 15.8 ± 2.3 (median 16.4, $p < 0.0001$) and mean odds ratio 6.3 ± 1.1 (median 6.3).

In the comparison group, 24 patients (30.8%) were responders. This figure is significantly lower (OR = 0.2, 95% CI 0.1; 0.4), than the rate in responders' relatives ($\chi^2 = 17.8$, df = 1, $p < 0.0001$); but not different from the relatives of non-responders ($\chi^2 = 1.0$, df = 1, $p = 0.31$), and it is close to the rates of lithium response reported in the literature (Baldessarini and Tondo, 2000; Rybakowski et al., 2001). For the rates of response in all three groups, see the Fig. 1.

The online Supplement provides further details of the results with the comparison group included: predictors of lithium response based on logistic regression (Supplementary Table 1), sensitivity analysis excluding particpants with unipolar depression (Supplementary Table 2), and 3-way tables of response by group and comorbid substance abuse (Supplementary Table 3) and anxiety (Supplementary Table 4).

4. Discussion

Our study is the largest investigation of the familial nature of long-term response to lithium in bipolar disorder. Similar to previous reports (Duffy et al., 2007; Grof et al., 2002), we confirmed that the response is familial – that is relatives of responders are more likely to be responders themselves and vice versa. These observations add evidence to the clinically applicable data that can help in selecting effective long-term treatment for people with bipolar disorder.

The findings support the hypothesis of the genetic nature of response to lithium. One might consider an alternative familial interpretation - an effect of shared environment akin to psychological modelling. Admittedly, the data do not allow differentiation between the two possibilities. However, it seems less likely. given the long-term stability of the treatment response in our data with patients in all centers followed for >10 years on average.

Several authors have proposed that response to lithium identifies a distinct form of bipolar disorder (Alda, 2017; Scott et al., 2024). Yet, the relative pairs in our study are not completely concordant implying that the boundary between responders and non-responders is not completely sharp. This could be due to the assumed polygenic nature of both bipolar disorder and the response to lithium itself. To wit, molecular genetic investigations found associations of lithium response with low polygenic scores for schizophrenia (Amare et al., 2018), major depression (Amare et al., 2021), and attention deficit disorder with hyperactivity (Coombes et al., 2021) as well as cholinergic and glutamatergic pathways (Amare et al., 2023), and G-protein-coupled receptor family of genes (Cruceanu et al., 2018; Nunes et al., 2021), suggesting multiple loci and gene families. An additional factor contributing to the incomplete concordance of the response might be the complex nature of bipolar disorder. Lithium has multiple clinical effects, and it is conceivable that both the responder and non-responder groups themselves are heterogeneous. Yet, the assessments of the treatment outcome are based on the usual assumption that different bipolar disorder subtypes have the same recurrence risk. As this may not be correct (Angst, 1978), the calculations may underestimate the strength of the familial association.

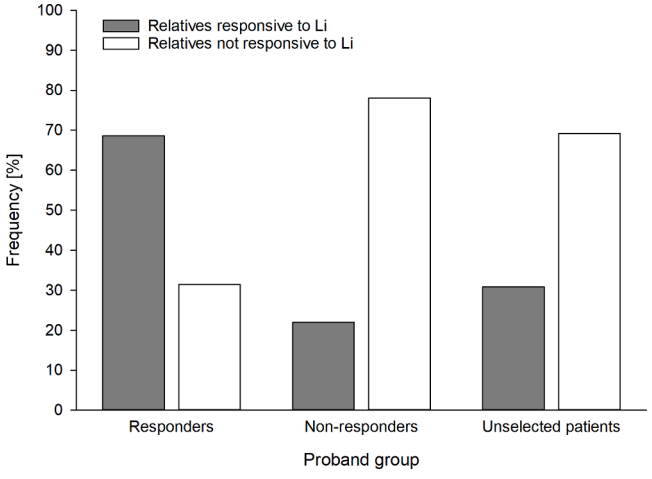

Fig. 1. Rates of lithium response (total score of 7 and higher) and non-response among the relatives of lithium responders, non-responders, and the comparison group of unselected patients with bipolar disorder.

The results need to be interpreted with several limitations in mind. While we expanded our original sample almost four-fold, the number of participants remains limited, and our study is observational, carried out in specialty clinics. The participating sites follow similar clinical practice, minimizing polypharmacy and monitoring treatment compliance.

While a randomized trial would provide a more rigorous design, it would be impractical and hard to justify on ethical grounds. Furthermore, as families are becoming smaller and lithium use is in decline, prospective study of a newly recruited sample might not be feasible. As well, we are unable to assess an impact of the treatment order in those patients who might have received other treatment before lithium. Recent data from Denmark indicate that lithium is prescribed increasingly later in the course of the illness (Jorgensen et al., 2025) but might be chosen earlier if there is evidence of positive response among relatives.

Lastly, the comparison group was not fully matched to the relatives with respect to age at onset and comorbid substance use. However, sensitivity analyses did not find an impact of these confounders on the results; family history of lithium responsiveness was the single factor explaining the between-group difference.

The results indicate that the response to lithium in relatives may be one of the strongest factors to consider when selecting long term treatment of bipolar disorder. This recommendation comes with several caveats. While bipolar disorder is familial, not all patients have affected relatives. Furthermore, those with the illness may be treated in such a way that makes a proper evaluation of treatment response to a single agent difficult – for instance, they may be treated with drug combinations or may not be adherent to treatment. Proper evaluation of treatment response will usually require a detailed assessment - an in-person interview and/or review of medical records. As reported previously, routinely obtained family history is often inaccurate and not clinically useful when considering relatives' diagnoses alone (Baker et al., 1987; Roy et al., 1996). This becomes even more challenging when evaluating finer clinical details such as the long-term clinical course and effects of medication.

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Contributors

MA designed the study, analysed the data, and wrote the first draft of the paper. All authors contributed to data collection and text revisions.

Declaration of competing interest

None of the authors declare conflict of interest with respect to this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2026.112831.

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