Pharmacogenetics of lithium response in bipolar disorder

Martin Alda, MD

Department of Psychiatry, Dalhousie University, Halifax, N.S.

Lithium is the first-line treatment for bipolar disorder. In the past, genetic studies have attempted to identify factors associated with positive treatment response or side effects. Several research groups have shown that familial factors, family history of primary bipolar disorder, and negative family history of schizophrenia in particular, correlate well with prophylactic lithium response. Conversely, studies of lithium responsive patients and their families can assist genetic research of bipolar disorder. Lithium responders appear to suffer from a form of bipolar disorder that is more genetically based and more homogeneous. In a series of family studies, the author and his colleagues have confirmed the differences in family histories of lithium responders and nonresponders and shown that the mode of inheritance in lithium responders is compatible with a major-gene model. Subsequently, they initiated an international collaborative study to map the gene(s) predisposing to the illness or treatment response, or both, using both linkage and association strategies. To date, a sample of 32 families, 138 unrelated patients and 163 control subjects has been studied. In these studies, they found support for the role of phospholipase C in lithium responsive bipolar disorder.

Le lithium est le traitement de première ligne contre le trouble bipolaire. On a essayé dans le passé, dans le cadre d'études de génétique, d'identifier des facteurs associés à une réaction positive au traitement ou à des effets secondaires. Plusieurs groupes de chercheurs ont montré qu'il est possible d'établir de bons liens entre des facteurs familiaux, des antécédents familiaux de trouble bipolaire primaire et des antécédents familiaux négatifs de schizophrénie en particulier avec une réaction au lithium prophylactique. Par ailleurs, des études réalisées sur des patients qui réagissent au lithium et sur les membres de leur famille peuvent aider la recherche génétique sur le trouble bipolaire. Les sujets qui réagissent au lithium semblent atteints d'une forme de trouble bipolaire fondé davantage sur des éléments génétiques et plus homogène. Dans le contexte d'une série d'études familiales, l'auteur et ses collègues ont confirmé la différence au niveau des antécédents familiaux chez les sujets qui réagissent au lithium et chez ceux qui n'y réagissent pas et montré que l'hérédité de la réaction au lithium est compatible avec un modèle à gène majeur. Par la suite, ils ont lancé une étude internationale en collaboration pour cartographier les gènes qui prédisposent à la maladie ou à la réaction au traitement, ou les deux, en utilisant à la fois des stratégies d'établissement de liens et d'associations. Jusqu'à maintenant, ils ont étudié un échantillon de 32 familles, 138 patients non apparentés et 163 sujets témoins. Dans le cadre de ces études, ils ont constaté que les données appuyaient le rôle de la phospholipase C dans le trouble bipolaire qui réagit au lithium.

Correspondence to: Dr. Martin Alda, Department of Psychiatry, Abbie J. Lane Building, 5909 Jubilee Rd., Halifax NS B3H 2E2; fax 902 473-4596; malda@is.dal.ca

Medical subject headings: association; bipolar disorder; family; genetics; linkage (genetics); lithium; pharmacogenetics

J Psychiatry Neurosci 1999;24(2):154-8.

Submitted Aug. 19, 1998
Revised Sept. 29,1998
Accepted Sept. 30, 1998

Introduction

Lithium is considered the treatment of choice for bipolar disorder. Studies have shown its efficacy in the treatment of mania and in the prophylactic treatment of bipolar illness. Although lithium acts at many biochemical and cellular levels, its effect in bipolar illness is more specific than with all other psychotropic drugs. Genetic factors may be connected with the use of lithium in mood disorders, in that they can influence the effect of the drug and can be used to predict treatment response. Conversely, response to lithium and its mechanism of action can be helpful in the genetic research of bipolar disorder. Bipolar disorder has a strong familial basis. Although the evidence from family, twin and adoption studies points to the genetic origin of familial clustering, the genetic mechanisms remain unknown.

Genetic factors influencing the effects of lithium

The pharmacokinetic properties of lithium are relatively simple. It is not metabolized; it is eliminated unchanged almost exclusively by the kidneys. However, genetic factors appear to influence the distribution of lithium ion between extracellular and intracellular compartments. The so-called lithium ratio is the ratio of extracellular concentration to intracellular concentration. It is determined by passive transport of lithium into the tissues along the concentration gradient and by active transport, which includes sodium–lithium exchange, inversely correlated with the lithium ratio. The ratio itself appears to be under genetic influence.[1] It has even been suggested that a single gene may control it.[2] More recent studies indicate, however, that several genes are involved in the sodium–lithium countertransport alone.[3]

The lithium ratio has been studied since the 1970s as a possible state marker[4] and as a putative factor in predicting lithium prophylactic response.[5] It has been suggested that lithium transport could be the key to the etiology of bipolar illness.[5,6] More recent studies have indicated that neither the lithium ratio nor sodium–lithium countertransport are associated with affective disorders[7] or treatment response.[8–10] The proposition that the lithium ratio correlates with family history has been unchallenged for the most part.[11,12]

Because the lithium ratio reflects the distribution of lithium in extracellular and intracellular compartments, it is conceivable that it can be related to side effects of the treatment.[13–15] Strickland et al[16] found higher tissue concentrations of lithium in African–American people, in whom side effects tend to develop more frequently during lithium treatment. The lithium ratio can also be helpful in establishing that the observed clinical improvement is the result of the treatment and not the natural course of illness;[17] for instance, in patients with a good treatment response on low serum lithium levels and an adequate lithium ratio.

Family history and prediction of lithium response

Genetic information has been used to predict response to lithium treatment. So far, the most reliable predictors have been the clinical characteristics of patients. Typical responders to prophylactic lithium treatment have a nonrapid cycling course of primary bipolar illness. These patients also typically have an episodic course of illness with full remissions, reflected in normal Minnesota Multiphasic Personality Inventory (MMPI) profiles at optimum.[9,18] Family history and the absence of N blood group[19,20] are other factors associated with favourable response. It is of interest that the MN locus has been linked to the sodium–lithium countertransport.[21]

The value of family history in predicting lithium response is based on a number of family and family history studies.[19,22] In particular, family history of bipolar illness is associated with lithium response, whereas family history of schizophrenia is not.

A theoretically interesting, yet unanswered, question is whether affected relatives respond to the same medication. Although considered to be the case for antidepressants, this issue has not been systematically studied. McKnew et al[23] observed that children of parents successfully treated with lithium shared some of their parents' response characteristics and some showed improvement with lithium treatment. Clinical experience also supports the view that relatives of people who respond to lithium often, but not always, stabilize while receiving lithium. However, it will be difficult to demonstrate the familial effects of treatment response in a prospective controlled study. Such a study would require a large sample of affected pairs of relatives treated according to the same protocol.

Using treatment response to study genetic mechanisms of bipolar disorder

The link between genetic factors and lithium response can also be used to answer questions about the inheritance of bipolar disorder. Patients responsive to prophylactic lithium could be used to define more homogeneous populations for genetic studies. Heterogeneity has plagued much of psychiatric genetic research; different ways of reducing clinical and genetic heterogeneity have been proposed with limited success. It has been suggested, for example, that investigations of ethnically homogeneous populations or groups defined by clinical characteristics such as early onset might lead to more conclusive genetic findings.

Because the effects of lithium are relatively specific in comparison with all other treatments used in psychiatry, well-characterized lithium responders could provide clues to the nature of the genetic susceptibility.

It is beyond the scope of this paper to discuss in detail the issues pertaining to the definition of lithium response for research purposes. It is, however, necessary to point to some issues that make this different from assessing treatment response in a clinical setting. The clinical course of affective disorders is highly variable and largely unpredictable. In research, symptom-free periods in the natural course of the illness must be differentiated from those representing the true prophylactic effect of a mood stabilizer. To date, the clinical course of affective disorders in individual patients can be best approximated by previous patterns. This means that patients who have been treated early in the course of their illness may provide less information with respect to their treatment response, whereas those with a high number or frequency of episodes are likely to continue experiencing recurrences of the illness.

Genetic studies of lithium response to date can be divided into family studies comparing the rates of various illnesses in the relatives of responders and nonresponders, studies examining the mode of inheritance, and molecular genetic studies searching for specific susceptibility genes. Family studies suggest that lithium responders are genetically distinct from nonresponders and that their illness appears to have a stronger genetic basis.[19]

Although accepted by most researchers, the association of family history and favourable treatment response has not been supported uniformly. For instance, Dunner et al[24] did not find any differences in family histories, and Misra and Burns[25] found positive family history in nonresponders to lithium. Engström et al[26] found better response in patients with less familial loading for affective disorders and interpreted this as a sign of anticipation — that is, a more severe form of illness and earlier onset in subsequent generations of affected family members.

In studies exploring the mode of inheritance, the genetic transmission of the illness was compatible with a single-gene effect.[27] Although segregation analyses should be considered hypothesis-generating rather than testing, such results are promising for molecular genetic investigations.

In a research group at the University of Ottawa in Ottawa, Ontario, I and colleagues have investigated the issue of genetics and lithium response in a systematic fashion for a number of years. In a series of family studies, we have confirmed that responders' relatives are at higher risk for bipolar disorder, whereas nonresponders had more relatives with schizophrenia.[19] In the families of responders, we observed clustering of bipolar, unipolar and schizoaffective disorders. Alcoholism did not appear to be genetically associated with affective disorders in either responders' or nonresponders' families.[28] In 2 separate studies,[29,30] we found that the most likely mode of transmission involves a gene with a major effect, and the data were not compatible with a polygenic model with sex-specific thresholds. In a study of high-risk people, we observed that it may be the nature of the clinical course rather than any specific symptoms that best differentiate the affectively ill offspring of lithium responsive and nonresponsive parents.[31]

Molecular genetic studies of lithium responsive bipolar illness are rare, and most have had negative results.

In collaboration with other centres of the International Group for the Study of Lithium (IGSLI) — namely, lithium clinics in Århus, Berlin, Göteborg, Prague and Vienna — we initiated a collection of excellent lithium responders, their families and unrelated control subjects. The sample consisted of 32 families, 138 unrelated patients and 163 controls. In association studies of lithium responders and controls, we observed no differences with respect to the tyrosine hydroxylase marker[32] or a set of markers on chromosome 18 including the gene for G_{OLF} protein.[33] Similarly, no linkage to chromosome 18 markers was found in 25 families of lithium responders.[34] These initial investigations focused on genes implicated by other research groups. Tyrosine hydroxylase is a rate-limiting enzyme in catecholamine synthesis and has

been suggested as a candidate gene in several linkage and association studies.[32] Similarly, chromosome 18 has been a subject of intensive analyses since 1994 when Berrettini et al[35] suggested a linkage of bipolar disorder to markers in the pericentromeric region.

Thus far, the most promising result has been obtained with the gene for phospholipase C.[36] Phospholipase C is an enzyme in the phosphoinositol cycle that is assumed to be a target of lithium. In an association study we observed a difference in distributions of alleles of *PLCG1* polymorphism, an untranslated $(CA)_n$ repeat, between patients and controls, namely higher frequency of longer alleles among patients ($p = 0.012$). Furthermore, in a linkage study with the same polymorphism, we found modestly positive lod score (lod = 1.45, empirical $p = 0.004$) in 13 families characterized by unilineal transmission. Although this research strategy is promising, a number of questions remain unanswered.

Studies and clinical experience support the view that patients who respond to lithium suffer from a typical, Kraepelinean, episodic form of bipolar illness. It is not clear, however, whether this is a distinct subtype or whether this is a core subgroup not complicated by other conditions such as personality disorders or substance abuse. The family studies, however, favour the former possibility. Alternatively, response to treatment could be influenced by a separate genetic factor independent of the predisposition to the illness itself. Clarification of these questions and will depend on the availability of a large number of families whose affected members are treated in a way allowing accurate determination of treatment response; this will not be easy. Molecular-genetic studies could, for example, use affected sib pairs discordant for the treatment response to search for genes not shared (identical-by-descent) that could affect treatment responsiveness.

Conclusion

The link between genetic factors and various aspects of lithium treatment has been a subject of investigation for almost 3 decades. It has provided clinicians with practically useful information and researchers with important questions that can contribute to a better understanding of bipolar disorder.

Acknowledgements

Dr. Martin Alda has been supported by the Ontario Mental Health Foundation and by the Medical Research Council of Canada. Dr. Paul Grof provided valuable comments on the manuscript and Ms. Carrie Robertson assisted with preparation of this paper.

References

1. Dorus E, Pandey GN, Davis JM. Genetic determinant of lithium ion distribution: an in vitro and in vivo monozygotic-dyzygotic twin study. *Arch Gen Psychiatry* 1975;32:1097-102.

2. Dorus E, Cox NJ, Gibbons RD, Shaughnessy R, Ghanshyam NP, Cloninger R. Lithium ion transport and affective disorders within families of bipolar patients: identification of a major gene locus. *Arch Gen Psychiatry* 1983;40:545-52.

3. Hasstedt SJ, Hunt SC, Wu LL, Williams RR. Evidence for multiple genes determining sodium transport. *Genet Epidemiol* 1994;11:553-68.

4. Elizur A, Shopsin B, Gershon S, Ehlenberger A. Intra:extra cellular lithium ratios and clinical course in affective states. *Clin Pharmacol Ther* 1972;13:947-52.

5. Mendels J, Frazer A. Intracellular lithium concentration and clinical responses: towards a membrane theory of depression. *J Psychiatr Res* 1973;10:9-18.

6. Dorus E, Pandey GN, Schaughnessy R, Gaviria M, Val E, Ericksen S, et al. Lithium transport across red cell membrane: a cell membrane abnormality in manic-depressive illness. *Science* 1979;205:932.

7. Richelson E, Snyder K, Carlson J, Johnson M, Turner S, Lumry A, et al. Lithium ion transport by erythrocytes of randomly selected blood donors and manic-depressive patients: lack of association with affective illness. *Am J Psychiatry* 1986;143:457-62.

8. Rybakowski J, Strzyzewski W. Red blood cell lithium index and long term maintenance treatment. *Lancet* 1976;2:1408.

9. Grof P, Lane J, MacCrimmon D, Werstuik E, Blajchman M, Daigle L, et al. Clinical and laboratory correlates of the response to long-term lithium treatment. In: Schou M, Stromgren E, editors. *Origin, prevention and treatment of affective disorders.* London: Academic Press; 1979. p. 27-40.

10. Kocsis JH, Kantor JS, Lieberman KW, Stokes PE. Lithium ratio and maintenance treatment response. *J Affect Disord* 1982;4:213-8.

11. Rihmer Z, Arato M, Szentistvanyi I, Banki CM. The red blood cell/plasma lithium ratio: marker of biological heterogeneity within bipolar affective illness? *Psychiatry Res* 1982;6:197-201.

12. Yassa R, Nair V. Prophylaxis and the lithium ratio in bipolar patients. *Prog Neuropsychopharmacol Biol Psychiatry* 1985;9:423-28.

13. Hewick DS, Murray N. Red-blood-cell levels and lithium toxicity. *Lancet* 1976;1(7982):473.

14. Foster JR, Silver M, Boksay IJE. Lithium in the elderly: a review with special focus on the use of intra-erythrocyte (RBC) levels in detecting serious impending neurotoxicity. *Int J Geriatr Psychiatry* 1990;5:1-7.

15. De Maio D, Buffa G, Riva M, Laviani M, Levi-Minzi A. Lithium ratio, phospholipids and the incidence of side effects. *Prog Neuropsychopharmacol Biol Psychiatry* 1994;18:285-93.

16. Strickland TL, Lin K, Fu P, Anderson D, Zheng Y. Comparison of lithium ratio between African-American and Caucasian bipolar patients. *Biol Psychiatry* 1995;37:325-30.

17. Yassa R, Nair V, Kraus DJ. A possible indication for red cell lithium determinations: a case report. *Can J Psychiatry* 1984;29: 44-5.

18. Grof P, Alda M, Grof E, Fox D, Cameron P. The challenge of predicting response to stabilising lithium treatment. The importance of patient selection. *Br J Psychiatry* 1993;(Suppl 21): 16-9.

19. Grof P, Alda M, Grof E, Zvolsky P, Walsh M. Lithium response and genetics of affective disorders. *J Affect Disord* 1994;32:85-95.

20. Alda M, Grof P, Grof E. MN blood groups and bipolar disorder: evidence of genotypic association and Hardy-Weinberg disequilibrium. *Biol Psychiatry* 1998;44:361-3.

21. Weder AB, Schork NJ, Julius S. Linkage of MN locus and erythrocyte lithium-sodium countertransport in Tecumseh, Michigan. *Hypertension* 1991;17:977-81.

22. Mendlewicz J, Fieve RR, Stallone F. Relationship between the effectiveness of lithium therapy and family history. *Am J Psychiatry* 1973;130:1011-3.

23. McKnew DH, Cytryn L, Buchsbaum MS, Hamovit J, Lamour M, Rapoport JL, et al. Lithium in children of lithium-responding parents. *Psychiatry Res* 1981;4:171-80.

24. Dunner DL, Fleiss JL, Fieve RR. Lithium carbonate prophylaxis failure. *Br J Psychiatry* 1976;129:40-4.

25. Misra PC, Burns BH. "Lithium nonresponders" in a lithium clinic. *Acta Psychiatr Scand* 1977;55:32-40.

26. Engström C, Åström M, Nordqvist-Karlsson B, Adolfsson R, Nylander P. Relationship between prophylactic effect of lithium therapy and family history of affective disorders. *Biol Psychiatry* 1997;42:425-33.

27. Smeraldi E, Petroccione A, Gasperini M, Macciardi F, Orsini A, Kidd KK. Outcomes on lithium treatment as a tool for genetic studies in affective disorders. *J Affect Disord* 1984;6:139-51.

28. Duffy A, Grof P, Grof E, Zvolsky P, Alda M. Evidence supporting the independent inheritance of primary affective disorders and primary alcoholism in the families of bipolar patients. *J Affect Disord* 1998;50:91-6.

29. Alda M, Grof P, Grof E, Zvolsky P, Walsh M. Mode of inheritance in families of patients with lithium-responsive affective disorders. *Acta Psychiatr Scand* 1994;90:304-10.

30. Alda M, Grof E, Cavazzoni P, Duffy A, Martin R, Ravindran L, et al. Autosomal recessive inheritance of affective disorders in families of responders to lithium prophylaxis? *J Affect Disord* 1997;44:153-57.

31. Duffy A, Alda M, Kutcher S, Fusee C, Grof P. Psychiatric symptoms and syndromes among adolescent children of parents with lithium-responsive or lithium-nonresponsive bipolar disorder. *Am J Psychiatry* 1998;155(3):431-3.

32. Cavazzoni P, Alda M, Turecki G, Rouleau G, Grof E, Martin R, et al. Lithium-responsive affective disorders: no association with the tyrosine hydroxylase gene. *Psychiatry Res* 1996;64:91-6.

33. Turecki G, Alda M, Grof P, Grof E, Martin R, Cavazzoni PA, et al. No association between chromosome-18 markers and lithium responsive affective disorders. *Psychiatry Res* 1996;63:17-23.

34. Turecki G, Martin RB, Cavazzoni P, Duffy A, Grof E, Grof P, et al. Lithium-responsive bipolar disorder and chromosome 18 [abstract]. *Am J Med Genet (Neuropsychiatr Genet)* 1997;74(6):676.

35. Berrettini WH, Ferraro TN, Goldin LR, Weeks DE, Detera-Wadleigh S, Nurnberger JI, et al. Chromosome 18 DNA markers and manic-depressive illness: evidence for a susceptibility gene. *Proc Natl Acad Sci U S A* 1994;91:5918-21.

36. Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Ahrens B, et al. Preliminary evidence for a role of phospholipase C-γ1 in the pathogenesis of bipolar disorder. *Mol Psychiatry* 1998;3:534-8.