Prediction of response to lithium in affective disorders

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Introduction

The rediscovery of lithium and its reintroduction to psychiatry in 1949 has provided one of the most dramatic developments in psychiatric practice. Indeed it has antedated the introduction of chlorpromazine in 1957 and imipramine in 1962. Moreover its established efficacy in the management of manic depressive psychosis has affirmed Kraepelin's distinction between schizophrenia and manic depressive psychosis and later on the distinction between bipolar and unipolar affective disorder. Its efficacy in the management of affective disorders has been established by numerous high quality controlled studies which showed that the use of lithium substantially reduces the morbidity and mortality of recurrent affective disorders Coppen, A (1994). However the impact of Lithium on the naturalistic outcome of affective disorders was challenged by Dickson and Kendell (1986) who reported a threefold increase of admissions for mania to the Royal Edinburgh Hospital between 1970 and 1981, despite a tenfold increase in the use of lithium during that period. Goodwin and Jamison (1990) criticised the study referring to factors that could have contributed to this finding; diagnostic shift from schizophrenia to mania, the increased incidence of drug and alcohol misuse and the increased use of antidepressants resulting in greater risk for mania or lithium-resistant mania. Naturalistic studies reported from the Lithium Clinic in Epsom however consistently reported higher rates of efficacy for lithium in both bipolar and unipolar illness (Abou-Saleh, and Coppen 1990) including studies evaluating lower doses / levels of lithium (Coppen and Abou-Saleh, 1988). My personal interest in the study of lithium developed when I worked with the Medical Research Council, Metabolic unit at the Royal Edinburgh Hospital in 1978. Whilst I was impressed with its dramatic and almost curative effects in bipolar illness, I was also intrigued with its lack of efficacy in some patients. This observation prompted me to study predictors of response in an attempt to identify subgroups of patients in response in an attempt to identify subgroups of patients in relation to response to lithium including those who were lithium resistant who could be spared exposure to it. This review will focus on prediction of response to lithium in the acute treatment of mania, depression and to its prophylactic effects in recurrent affective disorders.

General Considerations

Before reviewing the evidence for the effective use of various predictors of response to lithium it is important to address a number of issues. Firstly there is the issue of definition of response which ranges from complete success when no further episodes are observed to the other extreme of total lack of efficacy. Secondly there are qualitative and quantitative measures of response. In our studies, we have used the affective morbidity index (AMI) which is a composite index of the severity and duration of affective episodes. A recent analysis of the already published data (Abou-Saleh and Coppen 1990) showed that predictors of response were the same whether a qualitative (response/non-response) or quantitative measure of outcome (AMI) was used. Thirdly there is non-compliance in relation to prediction of response. Aagaard and Vestergaard (1990), distinguished between predictors of non-compliance with lithium and true predictors of response in lithium adherent patients. Fourthly there is the issue of consistency of response or nonresponse between episodes of illness which has not been adequately studied.
Jefferson (1995) identified a number of other issues including the specificity of predictors to response to lithium versus other treatments such as anti-convulsants e.g. poor response to lithium in dysphoric mania, co-morbid substance abuse and personality disorder. The selection of patients and its impact on outcome with more recent studies showing less efficacy for lithium than earlier studies Grof et al, (1998).

Predictors of anti-manic response
In a recent review, Jefferson (1995) identified a number of putative predictors of response to lithium in acute mania. Clinical characteristics of mania are poor predictors of response to lithium and the earlier finding that manic patients with paranoid destructive features respond poorly to lithium was not confirmed in later studies. Severity of mania including mania with psychotic features is also not a reliable predictor of poor response. The most important predictor of response however is the presence of depressive symptoms with mania particularly if these symptoms qualify for the diagnosis of major depressive episode. It was noted that mixed affective states occur in 40% of manic episodes Goodwin and Jamison, (1990) with a good response that is half of that in pure mania. The recent placebo-controlled study of lithium, divalproex in mania suggested that even a modest level of pre-treatment depression-related symptoms is a robust predictor of lithium non-response and is associated with better response to divalproex Swann et al, (1997). The search for biological predictors of response has been disappointing. Sullivan et al, (1997) reported that good response to lithium was associated with higher platelet monoamine oxidase activity than poor response. Swann et al, (1987) reported that lithium nonresponders had higher ratios of urinary MHPG excretion. Stoll et al (1991) found that patients with a high RBC choline levels had a poor response to lithium, a finding which may be related to the notion that patients with higher RBC cholina levels were more severely ill than those with lower levels. Goodwin and Jamison (1990) in reviewing the evidence, identified predictors of poor antimanic response to lithium : mixed affective state, substance misuse and a history of rapid cycles which appear to predict a good antimanic response to carbamazepine.

Predictors of anti-depressant response
Overall, bipolar depression responds better to lithium than unipolar depression.Goodwin and Jamison, (1990) in a review of placebo controlled studies, found good response to lithium in 79% of bipolar patients and in 36% of unipolar patients. Studies of personality factors showed distinguishing characteristics of patients on the MMPI who respond well to lithium. Goodwin and Jamison (1990) also reviewed the evidence for personality predictors of lithium response. They noted that, lithium compliance was not adequately controlled for as well as the affective state at the time of personality testing, diagnostic criteria and measures of outcome. Biological variables have not been shown to have predictive value for lithium. Studies of lithium augmentation for refractory depression did not identify any predictors of response (Johnson, 1991).

Predictors of prophylatic response
For both the patient and the clinican, prediction of response for prophylactic lithium is more important than prediction of its antimanic and antidepressants effects : it spares those who are poor responders to lithium, a long term trial of a potentially hazardous treatment and identifies optimal alternative treatment, Reviews of the evidence identified the following predictors (Goodwin and Jamison, 1990; Abou-Saleh, 1993 ; Jefferson 1995)

Diagnosis and clinical features
Bipolar illness responds better to lithium than unipolar illness and 'pure' bipolar illness responds better than schizo-affective illness. Within bipolar illness, bipolar I responds better than bipolar II illness. This is probably related to the higher occurrence of personality disorder and substance misuse in bipolar II than bipolar I illness. Mania with psychotic symptoms responds better than mania without such symptoms, whilst mania with depressive symptoms responds less well than 'pure' mania. Bipolar illness starting with a manic episode responds better than if the first
episode was depression.

Frequency and sequence of episodes
Among bipolar patients, those with frequent (rapid cycling patients) show a greater incidence of prophylaxis failure than those with non-rapid cycling illness. Similarly patients with a higher frequency of recent hospital admissions had a higher incidence of treatment failure on lithium. Depressive episodes of patients with rapid cycling illness are more resistant to lithium than manic episodes. The occurrence of rapid cycling is strongly related to the use of antidepressants in the treatment of bipolar depression. Episode sequence has an impact on prophylactic response. Kukopulos et al (1980) showed that patients with the classic mania-depression-normal interval had more favourable response than those with depression-mania-normal interval whilst those with a continuous circadian course particularly short cycles had a poor response. These findings were confirmed by other investigators (Grof et al, 1987). Maj and colleagues (1984) reported similar findings in a prospective study in which the course of illness was evaluated independently of lithium efficacy.

Early and acute response
Early response (within 6-12 month) strongly predicts long-term response to lithium. Dunner and colleagues (1976) studies clinical predictors of prophylaxis failure in non-rapid cycling bipolar patients. Although none of the clinical variables studied predicted outcome, they observed that patients who received lithium had a failure rate similar to those on placebo in the first six months of treatment. A fourth of their patients had early failure of treatment (within three month), and that tended to predict failure during their continued lithium treatment. Studies, by the author of long term outcome of recurrent affective disorder with lithium treatment showed that the most powerful predictor was impirical: outcome over the first six months and first year predicted long-term outcome over 2-14 years (Abou-Saleh and Coppen 1986; Abou-Saleh and Coppen 1990). The few open studies that evaluated the relationship of acute antimanic or antidepressant response to lithium and prophylactic response reported an association (Svetska and Nahumeck, 1975).

Co-morbidity
Patients with recurrent affective disorders and co-morbid medical and psychiatric disorders respond less well than those without co-morbidity. The common co-morbid psychiatric disorders are substance misuse, anxiety disorders and personality disorders. Among the clinical features of affective states investigated, marked psychomotor retardation was found to be associated with better response (Dunner et al, 1976). There is inconsistent evidence for an association between the presence of family history of bipolar illness and favourable response to lithium (Carroll, 1979). A family history of non-bipolar affective disorder was not, however, associated with a more favourable response (Dunner et al 1976). Studying a combined group of bipolar and unipolar patients, Svetska and Nahumek (1975) noted a family history of endogenous psychosis or suicide in first-degree relatives to be significantly associated with good prophylactic response. The most convincing evidence that genetic heterogeneity affects response to lithium was presented by Mendlewicz (1979) in a study of twins. A high concordance rate was found in bipolar monozygotic and dizygotic twin pairs in which one twin experienced a good long-term response to lithium. Prophylactic response was better in concordant than in discordant twins. In both bipolar and unipolar patients, those with greater disturbance in their personality characteristics, including neuroticism, introversion, low drive, and low self-confidence, responded less well than those with less or no personality disturbance Abou-Saleh and Coppen, (1990). Patients with substance misuse co-morbidity are at a particularly high risk of relapse of lithium failure which is probaly mediated by the associated mixed affective states and/or poor compliance. It has been claimed that responders show premorbid mood liability, whereas nonresponders have premorbid traits of chronic anxiety and obsessiveness. Social support is strongly associated with good treatment outcome, as
demonstrated in a study of 60 bipolar patients by O’Connel and co-workers (1991). Aagaard and Vestergaard (1990), in their two year prospective study, showed nonadherence to treatment was mainly predicted by substance abuse and many earlier admissions. Nonresponse in those who adhered to treatment was mainly predicted by female sex, younger age, and a previous chronic course. A third of the population of patients studied, however, had a chronic illness and half showed social deterioration prior to starting lithium. Life events in the 12 months prior to starting lithium had no influence on outcome on lithium. They also found that those who relapsed had no more life events prior to their relapse than at other times.

**Biological predictors**

Suboptimal thyroid function and hypothyroidism have been related to prophylaxis failure: thyrod hypofunction was shown to occur in patients who suffered recurrences, including those who developed rapid cycling bipolar disorder. Moreover, Coppen and Swade (1986) showed that patients with high TSH levels without hypothyroidism suffered greater affective morbidity during prophylaxis. A study of biological predictors of response Abou-Saleh and Coppen (1989) showed no association between the dexamethasone suppression test and response. Serotonin transport into the platelet, however, predicted response: patients who had an increase in Vmax had lower long-term morbidity than those with decreased Vmax (Abou-Saleh et al, 1992). Platelet monoamine oxidase (MAO) activity in bipolar patients was not associated with response to prophylactic lithium Abou-Saleh, (1983). Good response was, however, observed in those with increased calcium binding to red blood cells Abou-Saleh (1980). An increase in the red blood cell/plasma lithium ratio and a low frequency of HLA-A3 antigen were shown to predict good response over two years in a study of 100 bipolar and unipolar patients (Maj et al, 1984).

**Conclusion**

The search for predictors of outcome has not been particularly rewarding, and the use of lithium remains empirical: a trial of lithium is the most powerful predictor of outcome. Multivariate analysis of predictors of response showed that most of the variation in prophylactic response was accounted for by 3 factors: the diagnosis, the quality of the symptoms-free interval and the recent frequency of episodes Grof et al, (1993). In our own studies in a series of 116 bipolar and unipolar patients who received prophylactic lithium for a mean of 5.9 years, we identified 3 predictors of outcome: diagnosis, personality factors and early response over the first year Abou-Saleh and Coppen, (1990). Clinical and psychological variables examined may be general correlates or predictors of outcome rather than specific to lithium. However, lithium remains a highly specific treatment for bipolar disorder. Clinical, psychological, and biological correlates of nonbipolar affective disorder: mood-congruent phychotic features, retarded-endogenous profile, cyclothymic personality, positive family history of bipolar illness, periodicity, and normality between episodes of illness.

**References**

8. Abou-Sleh, M.T. Swade, C. and Coppen,