IS LITHIUM STILL A FIRST-LINE TREATMENT IN THE PROPHYLAXIS OF BIPOLAR MOOD DISORDER?

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ABSTRACT

Lithium has been the treatment of choice for the prophylaxis of bipolar affective illness for the past 25 years. Recently, doubts have been expressed about its value for the prevention of affective illness, the acute treatment of mania, and as an adjunctive treatment for resistant depression. This paper reviews the evidence of the value of lithium for these indications, with emphasis on its prophylactic effect. Published material conclusively shows that lithium is effective in reducing further episodes of affective illness in patients with clear bipolar mood disorder with no other associated psychiatric condition and who are compliant with therapy. Lithium should only be prescribed as a prophylactic agent to patients who agree to take the drug long-term and who can be closely supervised during treatment.

Keywords: *Bipolar Mood Disorder; Discontinuation; Human; Lithium; Prevention*

INTRODUCTION

Lithium was reintroduced into psychiatry 50 years ago and has been licensed for the treatment of affective disorder for the past 30 years. It remains the treatment of choice for the prophylaxis of bipolar affective disorder and is also widely used for the prevention of recurrent depression, as an adjunct to drug therapy for resistant depression and for the acute treatment of mania (Jefferson, 1998). It is also valuable for control of aggressive behaviour (Tyrer, 1994) and for certain medical disorders including cluster headache and neutropenia. Lithium is estimated to be used by one in every 1000 to 1300 people in the United Kingdom at any one time (McCreadie & Morrison, 1985).

DOUBTS ABOUT CLINICAL UTILITY

Despite its widespread use, the value of lithium has recently been questioned on stringent evidence-based criteria (Moncrieff, 1997). On review of the published data, Moncrieff finds insufficient evidence to suggest lithium is effective for three of its most commonly recommended uses: prophylaxis of bipolar disorder; treatment of acute mania; and augmentation of treatment in resistant depression.

This paper has provoked advocates of lithium treatment into a vigorous defence of the value of this drug (Cookson, 1997; Baldessarini & Tondo, 1998a; Jefferson, 1998). Why should there still be continuing controversy about the value of lithium after 30 years of regular clinical use? It is instructive to examine Moncrieff's criticisms and relate them to the historical use of lithium.

PROPHYLAXIS OF BIPOLAR DISORDER

Moncrieff's main concerns about the studies that have been carried out to examine the effect of lithium for the prophylaxis of bipolar disorder are related to the fact that a number of these trials used a discontinuation design and numerous studies have now shown that patients with bipolar disorder who are stabilised with lithium are particularly prone to manic relapse on discontinuation of the drug (Mander & Loudon, 1988; Suppes *et al.*, 1991). It has consistently been shown that if lithium treatment is not adequately monitored, the relapse rate is higher than when supervision is carried out in out-patient lithium clinics (Kehoe & Mander, 1992; Guscott & Taylor, 1994). Furthermore, Moncrieff is concerned that the research into the natural history of bipolar disorder raises further doubts about the impact of lithium. Unless it can be shown that administration of lithium reduces the frequency of affective episodes in patients with bipolar affective disorders who have not previously been treated with the drug, its value is clearly not established.

Moncrieff is quite correct in pointing out that studies of patients receiving short-term prophylactic lithium, who subsequently reduce the dose or stop taking the drug can affect interpretation of the effectiveness of lithium. In a study examining 14 patients with bipolar disorder who were maintained effectively by lithium for some years, discontinuation of lithium in a double-blind cross-over design led to half of the patients becoming manic within two weeks (Mander & Loudon, 1988). A larger study by Suppes *et al.* (1991) involving 257 patients revealed that the risk of developing mania after discontinuation was more than five times higher than supervention of a depressive episode and half occurred within five months of

stopping the drug. Reduction in lithium dosage can also lead to relapse (Tyrer *et al.*, 1983) although gradual reduction over one year or more reduces this hazard considerably (Baldessarini & Tondo, 1998b). It is not generally recognised that for patients with bipolar disorder maintained with serum lithium levels below 0.8 mmol/L the relapse rate is 2.6 times that of patients maintained at a higher level (Gelenberg *et al.*, 1989). In a large study of lithium prophylaxis carried out by Prien *et al.* (1984), the patients who relapsed during the two-year study period had lower serum lithium levels than those patients who did not relapse, suggesting non-compliance. A similar phenomenon was found in a later trial (Guscott & Taylor, 1994).

The question of the natural course of bipolar affective disorder was originally raised by Blackwell and Shepherd (1968) 30 years ago when they criticised the design of the study employed by Baastrup and Schou (1967). Blackwell and Shepherd believed that only 33 of the 88 patients involved in this study had an outcome suggestive of a prophylactic action due to lithium, the remainder were doubtfully recurrent, remained ill, or had spontaneous remissions. There was little published data available about the natural history of bipolar affective disorder at that time, although a subsequent paper published three years later showed that, for patients who were not receiving any drug treatment for recurrent affective illness, there was a decreasing interval between episodes of affective illness in patients with bipolar disorder (Grof *et al.*, 1970). Any drug that reduces the frequency of episodes of illness must be having an effect.

A recent randomised, double-blind trial of lithium *versus* carbamazepine in the prophylaxis of bipolar disorder showed that 28% of patients maintained on lithium for two and a half years relapsed, as opposed to 47% of patients receiving carbamazepine (Greil *et al.*, 1997). If those patients who had taken additional medication during the two and a half-year period were included as failures, lithium was significantly better than carbamazepine. A subsequent re-analysis of the data by these authors showed that those patients who suffered from bipolar I illness, who had no mood-incongruent delusions, and who were free of other comorbid psychiatric conditions had a highly significant chance of improving with lithium treatment compared with carbamazepine (Greil *et al.*, 1998). Further support for the value of lithium in the maintenance treatment of bipolar disorder is provided by a Canadian systematic review which found that lithium was more effective than both sodium valproate and carbamazepine in the prevention of episodes of affective illness in bipolar patients (Kusumakar *et al.*, 1997).

TREATMENT OF ACUTE MANIA

The early trials of lithium in acute mania were performed before recognition of the value of randomised controlled trials was established. It must also be noted that double-blind trials with manic patients are technically difficult to carry out and mania itself is not a common diagnosis. When more recent studies are included, the value of lithium in the treatment of acute mania becomes more apparent (Tyrer, 1985). Certainly, these criticisms cannot be applied to a recent study by Bowden *et al.* (1994). This was a large randomised controlled trial comparing the effects of lithium, sodium valproate, and placebo in the treatment of mania. This study clearly showed that 10 days of treatment with lithium was superior to treatment with placebo, and lithium was comparable with sodium valproate in efficacy.

AUGMENTATION OF TREATMENT IN RESISTANT DEPRESSION

Lithium has been used for the past 15 years as an adjunctive treatment for patients with resistant depression and a meta-analysis of five randomised controlled trials of lithium augmentation in this condition showed that there was a significant value of lithium compared with placebo in this condition (Austin *et al.*, 1991). Moncreiff criticises these trials on the basis that they were small and the treatment was not carried out for a long period of time. It may well be that a number of patients with resistant depression may not have a severe affective illness but have dysthymia or a non-affective condition. However, recent studies have shown that lithium is most effective for patients with resistant depression who have high Hamilton rating scores and pronounced vegetative signs of depression (Alvarez *et al.*, 1997), suggesting that it is the more severely ill patients with traditional core symptoms of depression who respond when lithium is used as an augmenting drug. The differential response to lithium in this group of patients mirrors the better response observed in patients with classical bipolar disorders (Greil *et al.*, 1998).

DISCUSSION

It is notoriously difficult to establish evidence for the prophylactic effect of any drug that is effective in a condition manifest by irregular cycles occurring at an interval of six months to five years. It is for this reason that it took many years for the value of lithium as a prophylactic agent to be recognised. It is noteworthy that once the efficacy of this drug became established, the diagnosis of affective disorder increased considerably in the United States of America (Kendell, 1975) because it was thought that lithium was an effective treatment for this condition.

Lithium has now become a victim of its own popularity. It is not being given simply to patients with acute mania or to those with evident bipolar affective illness, but to patients with less well-defined affective conditions, which may be complicated by illicit drug use or other psychiatric disorders. Almost 30 years ago, Blackwell (1969), one of the authors of *Prophylactic Lithium: Another Therapeutic Myth?* (1968) wrote that "*to transform 'just plain old lithium' into the elixir of life on the evidence available is an achievement second only to converting a pumpkin into a stagecoach*". Blackwell's letter was in response to an editorial by Kline (1969) who responded that "*Lithium is more like the lost slipper than the pumpkin-stagecoach. It isn't meant for everyone, but when it does fit, there actually is a fairy story quality about it*". This correspondence exemplifies the point made earlier in this article: lithium can be extraordinarily effective in some patients with a severe psychiatric condition — bipolar affective illness — but is of much less value in patients who do not suffer the classical symptoms of this illness.

CONCLUSIONS

The debate about the value of lithium for acute mania and for the augmentation of resistant depression is of much less importance than its use for the prophylaxis of bipolar affective disorder. The vast majority of people taking lithium at any one time are taking it for prophylactic purposes.

Treatment with lithium for patients with bipolar affective disorder should not be started lightly. There should be evidence of at least two and, more usually three, distinct episodes of affective illness. Although there is unequivocal evidence of the value of lithium for preventing depressive episodes in unipolar affective illness (Souza & Goodwin, 1991), there are equivalent alternatives for this condition that are not yet established in bipolar disease. No patient should start lithium for prophylactic purposes unless the individual is motivated to continue treatment for several years. Factors which might lead to non-compliance, including drug and alcohol abuse, personality disorder, and unstable personal relationships, are relative contraindications for this treatment. It has been shown that unless lithium treatment is continued for at least two years, the drug is less effective than if no drug had been given at all (Goodwin, 1994). Only those patients with unequivocal evidence of affective episodes are likely to respond to lithium treatment. If a patient fails to respond and compliance is assured the original diagnosis should be reviewed.

Despite periodic calls announcing the demise of lithium it is still the treatment of choice for the prophylaxis of bipolar affective disorder. Until it is shown that alternative treatments are as effective, lithium should be a first-line treatment for this condition. We do not need to continue asking whether lithium has proved itself (Tyrer, 1986).

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