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Editorial

Lithium Revisited

A Re-examination of the Placebo-Controlled Trials of Lithium Prophylaxis in Manic–Depressive Disorder

J. MONCRIEFF

Lithium has been used as a prophylactic or maintenance agent in the treatment of manic–depressive disorder since the 1960s. However, epidemiological studies have shown that, despite its use, there has been no reduction in the number of admissions for affective episodes. Admissions for mania were found to increase or remain the same over 1970–81 (Symonds & Williams, 1981; Dickson & Kendell, 1986). Naturalistic follow-up studies of patients on lithium also fail to show a good outcome and find no difference between patients who are prescribed lithium and those who are not (Marker & Mander, 1989; Harrow *et al*, 1990).

There has been a difficulty interpreting these findings, as the efficacy of lithium is believed to have been established beyond doubt by the placebo-controlled trials undertaken in the 1970s. Some authors have concluded that the explanation must therefore be non-compliance and under-prescribing (Guscott & Taylor, 1994). An alternative explanation is that the original controlled trials of lithium prophylaxis produced spurious results owing to flawed methods. A close re-examination of these studies is now due.

Open trials

The claim that lithium has prophylactic potential was originally based on evidence from studies that compared the course of the illness in an individual patient before and after starting lithium. This method was criticised by Blackwell & Shepherd (1968), who reanalysed the data from the largest and most influential of these studies, that of Baastrup & Schou (1967). Blackwell & Shepherd pointed out that all patients who had discontinued lithium within a year of starting it had been excluded from the analysis. It seems probable that this group contained many patients who relapsed while being prescribed lithium. In addition, of the 88 subjects who were presented in the analysis, a prophylactic effect of lithium was doubtful in 55 cases, including 32 patients who had experienced longer spontaneous remissions before lithium treatment than while on lithium. Blackwell & Shepherd also mention the possibility of observer bias, since the investigators had been such 'enthusiastic advocates' of lithium. Other open studies were small and essentially anecdotal (Hartigan, 1963; Baastrup, 1964).

Placebo-controlled trials

To address the criticisms of the 'before and after' studies, a number of placebo-controlled trials were undertaken in the 1970s. These are the trials that are commonly cited as providing the firmest evidence of the efficacy of lithium (for example, see Goodwin & Jamison, 1990). An outline of their methods is given in Table 1.

Table 2 displays the outcome of each of the studies in terms of relapse rates. Rates of depression appear to be similar for lithium and placebo groups, but the performance of lithium with respect to prevention of manic relapse looks impressive. However, it is likely that certain features of the designs of these trials helped to inflate these differences between lithium and placebo.

Discontinuation studies

In the last two decades evidence has accumulated that withdrawal of lithium precipitates mania. In a review of the evidence, Suppes *et al* (1991) looked at 14 studies involving 257 subjects and found 50% of new illnesses occurred within 10 weeks of stopping lithium treatment. The time to recurrence of mania was much shorter than for depression. They also found that for 16 patients in whom a cycle length before lithium treatment was recorded, the time to a new episode after discontinuation was on average seven times shorter than the previous cycle length. They concluded that the "risk of early recurrence of bipolar illness, especially of mania, evidently is increased following discontinuation of lithium and may exceed that predicted by the course of the untreated illness".

Mander (1986) retrospectively compared 29 patients who had discontinued lithium with 50 patients who had never been on lithium. All had a diagnosis of mania. There was a significantly higher relapse rate

Table 1
Methods used in placebo-controlled trials of lithium prophylaxis

Trial	Subjects	*n*	History	Design	Blindness
Baastrup *et al* (1970)	Stable out-patients	Lithium, 28 Placebo, 22	Mean no. of previous episodes, 8	Discontinuation (subjects previously on lithium 1–7 years)	Relapse rates estimated unblind
Coppen *et al* (1971)	Acute admissions	Lithium, 15 Placebo, 22	Majority had more than 5 previous episodes	Prospective	Double blind
Cundall *et al* (1972)	Stable out-patients	Lithium, 13 Placebo, 13	Mean no. of previous episodes, 10	Discontinuation cross-over design (subjects on lithium 1–3 years)	Double blind
Hullin *et al* (1972)	Stable out-patients	Lithium, 18 Placebo, 18	Not given	Discontinuation (subjects on lithium 2 years)	Double blind
Prien *et al* (1973*a*)	Admissions for mania	Lithium, 101 Placebo, 104	Median no. of previous admission, 3	Prospective	Single blind
Prien *et al* (1973*b*)	Admissions for depression	Lithium, 18 Placebo, 13	Mean no. of admissions in previous 2 years, 1.8	Prospective	Single blind
Stallone *et al* (1973)	Stable out-patients	Lithium, 25 Placebo, 27	At least 3 previous episodes	Discontinuation design in 'some' subjects	Double blind
Dunner *et al* (1976)	Out-patient referrals (bipolar II)[1]	Lithium, 16 Placebo, 24	At least 2 episodes in previous 2 years	Prospective	Double blind
Fieve *et al* (1976)	Stable out-patients	Lithium, 17 Placebo, 18	At least 2 episodes in previous 2 years	Discontinuation design in up to a third of subjects	Double blind

1. Bipolar II disorder is defined as severe depressive episodes accompanied by mild manic episodes which have not required admission.

Table 2
Outcome of placebo-controlled trials of lithium prophylaxis

Trial	*n*	Length of follow-up	No. of subjects suffering manic relapse	No. of subjects suffering depressive relapse	No. of subjects relapsing (%)	No. of subjects remaining in remission (%)
Baastrup *et al* (1970)	Lithium, 28 Placebo, 22	Up to 5 months	Lithium, 0 Placebo, 7	Lithium, 0 Placebo, 5	Lithium, 0 (0) Placebo, 12 (55)	Lithium, 28 (100) Placebo, 10 (35)
Coppen *et al* (1971)	Lithium, 15 Placebo, 22	Mean 74 weeks for lithium group. Not given for placebo group	Not given	Not given	Not given	Not given
Cundall *et al* (1972)	Lithium, 13 Placebo, 13	6 months	Lithium, 2 Placebo, 10	Lithium, 2 Placebo, 3	Lithium, 4 (31) Placebo,11 (85)	Not given
Hullin *et al* (1972)	Lithium, 18 Placebo, 18	6 months	Not given	Not given	Lithium, 1 (6) Placebo, 6 (33)	Lithium, 17 (94) Placebo, 12 (67)
Prien *et al* (1973*a*)	Lithium, 101 Placebo, 104	24 months	Lithium, 35 Placebo, 70	Lithium, 8 Placebo, 14	Lithium, 43 (43) Placebo, 84 (80)	Lithium, 58 (57) Placebo, 20 (19)
Prien *et al* (1973*b*)[1]	Lithium, 18 Placebo, 13	1–4 months	Not given	Not given	Lithium, 4 (22) Placebo, 7 (54)	
Prien *et al* (1973*b*)[1]	Lithium, 17 Placebo, 9	5–24 months	Lithium, 2 Placebo, 3	Lithium, 2 Placebo, 5	Lithium, 3 (18) Placebo, 6 (67)	Lithium, 9 Placebo, 1
Stallone *et al* (1973)	Lithium, 25 Placebo, 27	Up to 28 months	Not given	Not given	Lithium, 11 (44) Placebo, 25 (93)	Lithium, 14 (56) Placebo, 2 (7)
Dunner *et al* (1976)	Lithium, 16 Placebo, 24	Up to 36 months, mean 15.5	'Hypomania': Lithium, 1 Placebo, 6	Lithium, 9 Placebo, 12	Not given	Lithium, 9 or 10 (63) Placebo, not given
Fieve *et al* (1976)	Lithium, 17 Placebo, 18	Up to 53 months	Lithium, 10 Placebo, 17	Lithium, 5 Placebo, 8	Admissions: Lithium, 3 (18) Placebo, 9 (50)	Lithium 7 (41) Placebo, 1 (6)

1. Results are presented separately for each follow-up period, with no overall figures given.

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in the group who had discontinued lithium in the first three months after withdrawal.

The trials by Baastrup *et al* (1970), Cundall *et al* (1972) and Hullin *et al* (1972) were entirely discontinuation trials. All subjects had been taking lithium long-term before entering the trial and there was a high rate of manic relapse in all the placebo groups. In the discontinuation study of Cundall *et al* (1972) the ratio of manic to depressive episodes before starting on lithium was 0.67:1. After discontinuation it was 3.5:1. The authors comment that the results may suggest that "attacks of mania are actually provoked by withdrawal".

In addition, in the studies by Stallone *et al* (1973) and Fieve *et al* (1976) some subjects had been taking lithium long term before the trial, and so these were also partly discontinuation studies. Stallone *et al* (1973) found that 21 out of 27 of the placebo-treated patients relapsed in the first six months, mostly into mania, which suggests it may have been predominantly a discontinuation study.

In two of the other studies (Prien *et al*, 1973*a*,*b*) patients were stabilised on lithium before randomisation and so a discontinuation effect may have operated in some subjects.

Prospective studies

The problem with the largest prospective study, that of Prien *et al* (1973*a*), is that it was not double blind. The treating physicians, responsible for diagnosing and managing relapse, were aware of the identity of subjects' medication. They were also instructed to increase the dose of lithium when a patient on lithium started to show symptoms. The importance of this issue is that it means that the treatment conditions of the two groups were not comparable. If lithium is an effective antimanic agent, some of the lithium group were therefore receiving early treatment for mania. It is also probable that this was accompanied by other efforts to prevent relapse in these patients, such as increased social support. Of the 'relapse-free' subjects in the lithium group, 16% had symptoms that were treated in this way and a further 12% had their lithium increased for unspecified reasons; 31% had dose adjustment for low serum levels. Therefore, in the lithium group a further 16% and possibly up to 28% had symptoms that required intervention but were not classified as relapse. This means that only 29% of the lithium-treated group can reliably be classified as remaining in remission, and this is no longer significantly different from the 19% in the placebo group.

The other problem with a single-blind design is the possibility of biased diagnosis of relapse by the investigators. This was probably minimised in the above study, since severe relapse was defined as requiring admission, a fairly objective measure. The other study by this group, however (Prien *et al*, 1973*b*), may well have been subject to this problem.

For these reasons, most investigators prefer a double-blind design. However, Oxtoby *et al* (1989) have pointed out that this design also has its limitations, as patients are often able to guess the identity of their medication because of side-effects, and studies have shown that this is the case with lithium (Marini *et al*, 1976). Thomson (1982) suggested that the experience of side-effects could produce an "amplified placebo response" in relation to treatment for depression. This effect may explain the small trend in favour of lithium in rates of depressive relapse in some of the trials described here.

In the prospective study by Coppen *et al* (1971), relapse rates are not presented. The main index of morbidity given is the proportion of time that a patient spent in an affective episode compared with time in the trial. This figure obviously depends on the size of the denominator, which is likely to be smaller in the placebo group, although no figure is given, because of a large number of drop-outs. This would inflate the difference between the groups. Finally, the paper presents data only on patients who completed at least 16 weeks of the trial. This is likely to be a highly select group of patients and so the results do not reflect the overall performance of either treatment. It is also essential to have information on the relative relapse and drop-out rates from the two groups in the first 16 weeks to obtain a genuine comparison of the treatments.

Dunner *et al*'s (1976) prospective study used a diagnosis of bipolar II disorder, which may include people who do not have classic manic–depressive disorder and indeed only one 'hypomanic' relapse required admission. There was no significant difference in rates of depression.

Natural history of manic–depressive disorder

Relapse rates for lithium-treated patients can be seen in Table 2. Two short-term trials had very low relapse rates (Baastrup *et al*, 1970; Hullin *et al*, 1972). At around two years of follow-up, however, studies in which overall data are presented show relapse rates of over 40% in the lithium group (Prien *et al*, 1973*a*; Stallone *et al*, 1973).

The natural course of manic–depressive illness is poorly documented. Much research predates modern operational diagnostic criteria and does not present outcome in terms of relapse rates or illness episodes. Lundquist (1945), however, presented this kind of

follow-up data 20 years or more after a first admission for affective illness. Those subjects whose index episode was mania had a 30% chance of recurrence in the ensuing three years. Those subjects who had two episodes had a 31% chance of a further episode in the next year and a 57% chance in the next three years.

Two recent studies give similar results. In the retrospective follow-up study by Mander (1986), 21 of 50 patients (42%) who had been admitted for the first time with mania relapsed within two years, and 29 (58%) remained well. Of the relapses, 68% were manic. In a naturalistic follow-up of patients 1.7 years after an admission for mania, Harrow *et al* (1990) found a 40% relapse rate, with no difference between patients who were taking lithium at follow-up and those who were not.

These populations, especially first admissions, are not strictly comparable with those involved in the controlled trials of lithium. However, relapse rates in the lithium-treated groups in most of the trials look remarkably similar to the data on the natural course of the disorder.

Conclusion

Nine placebo-controlled trials of lithium prophylaxis have been considered. Differences between lithium and placebo treatment in several of the trials were probably attributable to discontinuation of lithium increasing the likelihood of manic relapse in placebo-treated subjects. In the largest prospective trial, treatment conditions for the two groups were not comparable (Prien *et al*, 1973*a*), and in another prospective trial only a select group of subjects were considered and results were presented in a way which impedes a proper understanding of the data. Finally, in most of the trials, the outcome for the lithium groups was not better than the outcome for untreated cases of manic–depressive illness.

Despite the conclusion of Guscott & Taylor (1994) that the placebo-controlled trials "overwhelmingly supported the efficacy of lithium", it appears that, in fact, this has never been satisfactorily demonstrated. This would explain why lithium has failed to make an impact on the epidemiology of bipolar affective disorder.

It has been suggested that lithium starts to have a beneficial effect only after two years of treatment and should not be used for less than this period (Goodwin, 1994). There is little evidence, however, on which to judge the efficacy and value of lithium treatment after two years. Of the studies described here, only three lasted longer than two years, and then only for a few subjects.

Marker & Mander (1989) retrospectively compared a group of lithium-treated patients and a control group for up to six years. There was no significant difference in relapse rates over the entire study period. Lithium-treated patients did slightly better between years 2 and 6, but even at the point of maximum divergence between the two groups, the difference failed to reach statistical significance. Therefore, the evidence that exists, which was not subjected to the rigours of the randomised controlled design, suggests at best a minimal effect after two years of continuous treatment.

Blackwell & Shepherd (1968) described the 'widely felt need' of psychiatrists to provide some effective treatment for sufferers of a potentially devastating condition such as manic–depressive illness. Unfortunately, after scrutinising the evidence, it seems that lithium might not be the successful prophylactic that was hoped for. Psychiatrists should therefore reappraise the current consensus on the long-term treatment of manic–depressive disorder.

References

BAASTRUP, P. C. (1964) The use of lithium in manic depressive psychosis. *Comprehensive Psychiatry*, **5**, 396–408.

—— & SCHOU, M. (1967) Lithium as a prophylactic agent. *Archives of General Psychiatry*, **16**, 162–172.

——, POULSON, J. C., SCHOU, M., *et al* (1970) Prophylactic lithium: double blind discontinuation in manic depressive disorders. *Lancet*, *ii*, 326–330.

BLACKWELL, B. & SHEPHERD, M. (1968) Prophylactic lithium: another therapeutic myth? *Lancet*, *i*, 968–971.

COPPEN, A., NOGUERA, R. & BAILEY, J. (1971) Prophylactic lithium in affective disorders. *Lancet*, *ii*, 275–279.

CUNDALL, R. L., BROOKS, P. W. & MURRAY, L. G. (1972) Controlled evaluation of lithium prophylaxis in affective disorders. *Psychological Medicine*, **2**, 308–311.

DICKSON, W. E. & KENDELL, R. E. (1986) Does maintenance lithium therapy prevent recurrences of mania under ordinary clinical conditions? *Psychological Medicine*, **16**, 521–530.

DUNNER, D. L., STALLONE, F. & FIEVE, R. R. (1976) A double blind study of prophylaxis of depression in bipolar illness. *Archives of General Psychiatry*, **33**, 117–121.

FIEVE, R. R., KUMBARACI, T. & DUNNER, D. L. (1976) Lithium prophylaxis of depression in bipolar I, bipolar II and unipolar patients. *American Journal of Psychiatry*, **133**, 925–929.

GOODWIN, F. K. & JAMISON, K. R. (1990) *Manic–depressive illness*. New York: Oxford University Press.

GOODWIN, G. M. (1994) Recurrence of mania after lithium withdrawal. *British Journal of Psychiatry*, **164**, 149–152.

GUSCOTT, R. & TAYLOR, L. (1994) Lithium prophylaxis in recurrent affective illness. Efficacy, effectiveness and efficiency. *British Journal of Psychiatry*, **164**, 741–746.

HARROW, M., GOLDBERG, J. F., GROSSMAN, L. S., *et al* (1990) Outcome in manic disorders. A naturalistic follow-up study. *Archives of General Psychiatry*, **47**, 665–671.

HARTIGAN, G. P. (1963) The use of lithium salts in affective disorders. *British Journal of Psychiatry*, **109**, 810–814.

HULLIN, R. P., MCDONALD, R. & ALLSOPP, M. N. E. (1972) Prophylactic lithium in recurrent affective disorders. *Lancet*, *i*, 1044–1046.

LUNDQUIST, G. (1945) Prognosis and course in manic depressive psychosis. *Acta Psychiatrica Scandinavica* (suppl. 35).
MANDER, A. J. (1986) Is there a lithium withdrawal syndrome? *British Journal of Psychiatry*, **149**, 498–501.
MARINI, J. L., SHEARD, M. H., BRODGES, C. I., *et al* (1976) An evaluation of the double-blind design in a study comparing lithium carbonate with placebo. *Acta Psychiatrica Scandinavica*, **53**, 343–354.
MARKER, H. R. & MANDER, A. J. (1989) Efficacy of lithium prophylaxis in clinical practice. *British Journal of Psychiatry*, **155**, 496–500.
OXTOBY, A., JONES, A. & ROBINSON, M. (1989) Is your "double-blind" design truly double-blind? *British Journal of Psychiatry*, **155**, 700–701.
PRIEN, R. F., CAFFEY, E. M. & KLETT, C. J. (1973*a*) Prophylactic efficacy of lithium in manic–depressive illness. *Archives of General Psychiatry*, **28**, 337–341.
——, KLETT, C. J. & CAFFEY, E. M., Jr (1973*b*) Lithium carbonate and imipramine in prevention of affective episodes. *Archives of General Psychiatry*, **29**, 420–425.
STALLONE, F., SHELLEY, E., MENDLEWICZ, J., *et al* (1973) The use of lithium in affective disorders, 3: a double-blind study of prophylaxis in bipolar illness. *American Journal of Psychiatry*, **130**, 1006–1010.
SUPPES, T., BALDESSARINI, R. J., FAEDDA, G. L., *et al* (1991) Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Archives of General Psychiatry*, **48**, 1082–1088.
SYMONDS, R. L. & WILLIAMS, P. (1981) Lithium and the changing incidence of mania. *Psychological Medicine*, **11**, 193–196.
THOMSON, R. (1982) Side effects and placebo amplification. *British Journal of Psychiatry*, **140**, 64–68.

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Commentary

Lithium Revisited
A Reply

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We should never be afraid to re-examine the evidence on which extensive clinical practice has been based. The editorial concludes that lithium has not proved to be the effective drug for the prophylaxis of manic–depressive disorder that early trials suggested it was. In explanation, the author suggests that the positive findings from these trials were actually much less conclusive than is commonly believed. It is possible to sympathise with the first of these propositions without accepting the second.

The failure to translate the advantages demonstrated in clinical trials to real clinical situations has many potential explanations. In the case of lithium, the resolve of clinicians to treat and follow up patients long term is not always what it might be, and patient compliance is the major single factor which limits the intentions of clinicians. The precipitating of manic relapse on the withdrawal of lithium is an additional confounding factor (Goodwin, 1994). Nevertheless, naturalistic studies of compliant subjects suggest that they display much lower rates of suicide than might be expected (Muller-Oerlinghausen *et al*, 1992; Coppen, 1994).

It is a serious matter to claim that the accepted evidence for lithium's efficacy is spurious and the methods that produced it were flawed. Placebo-controlled trials employing a discontinuation design certainly inflated the size of lithium's advantage because of the probability of withdrawal mania. Nevertheless, this very effect strongly suggests an important pharmacological modification of the course of illness by lithium which would be hard to explain if lithium's actions were irrelevant. Indeed, effective acute treatment of manic illness with lithium is also evidence of this.

I strongly dispute that the detailed criticism of the prospective trials by Prien *et al* (1973) and Coppen *et al* (1971) justifies ignoring their findings. Prien *et al*'s findings were based on readmission rates of 205 bipolar patients treated for two years in 18 centres. Although all patients were briefly started on lithium before discharge, withdrawal effects played no part in determining the overall effect. Severe relapses occurred in 67% of the placebo group and in 31% of the lithium group: the major effect was on relapses with mania. The placebo rate was the same as the rate in both groups in the two years before the trial. Relapse-free patients represented 41% of the lithium-treated group and only 11% of the placebo group over the full two years of the trial. The distribution