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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

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of patients across many centres prevented the observer bias of a single clinical team and many of the clinicians involved were actually motivated by scepticism rather than conviction to enter patients into the trial. The drop-out rates were greater in the placebo group, and independent clinical and social work ratings of symptoms all favoured the interpretation of a benefit from lithium. Failure to blind the physicians actually treating the patients, difficult when blood levels required assessment, is the only real criticism of the study. The use of a flexible-dose regime in patients showing symptoms likewise does not invalidate the study. To employ this strategy with an inactive drug would have been ineffective, as appears to have been the case in the placebo group. Increasing the dose for other reasons, especially low plasma levels, seems simply to follow good practice. The good outcome figures for treated and control groups can be massaged down to 29% *v.* 19% by including subjects who failed to complete the two years of the study (so particularly favouring the placebo group) and excluding all patients whose lithium levels were adjusted for reasons other than low plasma levels (28%). It is concluded that this would then not have been statistically significant. While true, it misses the point that this would still be a worthwhile effect (50% improvement in outcome), but it would require a larger study to give statistical confidence. However, such a partial reading of the data must be giving a worst-case interpretation of the findings in any case.

The second important trial which was taken to prove the efficacy of long-term lithium in bipolar illness showed the same major advantage for lithium treatment (Coppen *et al*, 1971). The outcome measure was general morbidity rather than recurrence and readmission, and the assessment by a psychiatric social worker was made completely independent of all medical treatment. It may as well be argued that this is both more sensitive and more relevant than raw rates of relapse than the converse. The difference between lithium and placebo groups was very large (82% *v.* 0% of bipolar patients showed no psychiatric morbidity during the trial). The only specific criticism is that the higher drop-out rate from the placebo group invalidates the measure. Actually it would tend to inflate positive effects in the placebo group with shorter observation periods (as occurred when the author herself adjusted comparisons in the Prien study above). There seems nothing exceptional in not including patients who failed to complete 16 weeks of a trial of prophylaxis, and no obvious bias appears likely to have been introduced to favour lithium. I can, accordingly, see no grounds for disregarding Coppen's trial, which was, remarkably, conducted double blind. The most important component of any clinical trial is randomisation, and both trials satisfied this criterion. It may be preferable to have a double-blind design where the results are largely based on self-report, but relapse of mania is likely to be observable and both trials had blind observers.

What then does this criticism of the classic prospective trials of lithium amount to? In essence it raises a series of small points, none smaller than the discussion of an amplified placebo response, none larger than the failure of the Prien group to maintain the treating doctors double blind. These criticisms are then taken to be grounds for rejecting the trials entirely, in anticipation, perhaps, of a more perfect trial to come. In practice all trials are imperfect, though rarely more so than clinical experience. They offer us estimates of the probability that a particular treatment works. When many imperfect trials tell us the same thing, meta-analysis may leave no real room for doubt, even in psychiatry (e.g. Davis *et al*, 1993). It could well be argued that we need more patients in randomised studies of lithium prophylaxis to increase our confidence in its efficacy; let future doubts be founded upon more such data, not on the splitting of hairs.

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