British Journal of Psychiatry (1994), **164**, 149–152

Editorial

Recurrence of Mania after Lithium Withdrawal

Implications for the use of lithium in the treatment of bipolar affective disorder

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The usual indications for starting lithium treatment are well known: conventional wisdom usually requires two illnesses within two years, or three illnesses in five years in otherwise uncomplicated cases. The usual factors inhibiting the use of lithium are its acknowledged danger in overdose, its side-effects and associated inconveniences to the patient, and uncertainty about the subsequent course of the illness. The established frequency of episodes should dictate how long lithium must be taken in order to produce benefit (Goodwin & Jamison, 1990). Currently, the implications of stopping treatment prematurely and whether this may do harm are not considered. I argue that the risk of a manic recurrence soon after lithium withdrawal in bipolar patients has major implications for how we should employ lithium. While the phenomenon has been described and discussed by others, the clinical implications for how to use lithium, or how not to use it, have not been explored fully so far.

The literature

The existence of early manic relapse following lithium discontinuation is not without controversy. Some authors do not accept that it occurs at all (Schou, 1980, 1993), and some psychiatrists probably regard it as being so obvious, clinically, that it is barely worth discussing. While it is not the purpose of this editorial to review the relatively small amount of literature exhaustively, a few points deserve attention.

There has been some confusion between the possibility of a distinct 'withdrawal syndrome' and early recurrence of illness. For example, there was a report of a confusional state immediately following lithium withdrawal rather than a manic illness (Wilkinson, 1979) and it has been implied also that rebound symptoms can be regarded differently from a true recurrence of illness (Klein *et al*, 1981). However, frank manic symptoms are the defining feature of significant withdrawal effects and appear to be of a comparable severity to those seen in manic illness generally, often requiring hospital admission. Indeed, many of the data supporting the concept of early recurrence have used the criterion of readmission. Whether such recurrences tend to persist for a shorter time or are easier to treat is not established.

Early recurrence of affective illness after lithium discontinuation in stable patients was reviewed in detail by Suppes *et al* (1991). This is an important study because it offers a quantitative analysis of all the existing reports together with additional unpublished data. Such analyses are preferable to selective, qualitative reviews of the research literature, which can be highly misleading and deflect argument away from the evidence and towards differences of opinion. In general medicine, such quantitative methodology has assumed increasing importance, but still attracts controversy because its conclusions sometimes question the evidential basis of cherished beliefs and practices (Mann, 1990). The main advantage is that conclusions can be based on the largest possible number of cases, and it is a fact that only from large aggregate sample sizes can statistical confidence be derived.

To summarise the present evidence in relation to lithium withdrawal, in 14 studies involving 257 patients with first-episode bipolar disorder, more than 50% of new episodes of illness occurred within three months of stopping treatment. The length of treatment preceding discontinuation varied widely, but averaged about 30 months; this represents the time for which patients had been stable. Mania was much more common than depression in the first three months after discontinuation. These rates of recurrence translate into very high risks of illness after discontinuation compared to the risks when on lithium. Indeed, a crude comparison of new episodes per month at risk gives a staggering 28-fold difference for patients on and just off lithium. As Suppes *et al* note, the rates are so high that they appear likely to exceed appreciably those expected from the spontaneous recurrence rate in untreated bipolar illness. This point is related critically to the argument that will be expanded below.

The most authoritative review against any increased risk of withdrawal mania was that of Sashidaran & McGuire (1983). At that time there was less research literature and the size of their series was probably inadequate to provide a definitive answer; the same database in Edinburgh subsequently

has been the source of larger studies, to be described below. Furthermore, influenced by case reports of very early recurrence within days of stopping lithium, Sashidaran & McGuire (1983) perhaps were seeking to exclude too extreme an effect.

There is still a dearth of controlled studies and, as Suppes *et al* suggest, there is a need to understand the phenomenon further and explore ways of minimising risk by slow withdrawal or adjunctive treatment. However, most patients who discontinue lithium may do so at their own initiative, when such measures may not be possible. The finding of withdrawal recurrence in a well controlled study (Mander & Loudon, 1988) paralleled the result found by retrospective examination of the case records of bipolar patients who discontinued lithium in the same population (Mander, 1986).

The timing of recurrence

The implications can be summarised best diagrammatically. Fig. 1 illustrates the effects of using lithium for 6 or 18 months, with an estimated recurrence rate of 50% in the three months after discontinuation. It is assumed that there is no recurrence while patients are taking lithium, and that there is a reversal to the control rate of recurrence after three months of lithium. The control rate of recurrence is a linear extrapolation taken from the figures of Mander (1986) for a group of 50 patients with first-episode bipolar disorder admitted to the Royal Edinburgh Hospital and not treated with lithium. Its precise course was established only roughly beyond 24 months, but is not important for this argument. The origin of the graph is taken from the time of clinical recovery from the first episode (three months after discharge from hospital). It will be evident from Fig. 1 that if the withdrawal rate of recurrence in three months is 50%, the cumulative risk is *increased* appreciably by treatment with lithium for 6 to 18 months compared with the untreated case. As shown by the left-pointing arrow in Fig. 1, discontinuation after 6 months, with a 50% withdrawal recurrence, brings forward the time at which cumulative risk is 50% by about 20 months. As illustrated below, even treatment for two years remains marginally disadvantageous! These estimates would be made even less favourable if there was a finite risk of recurrence (as is likely) while patients were taking lithium.

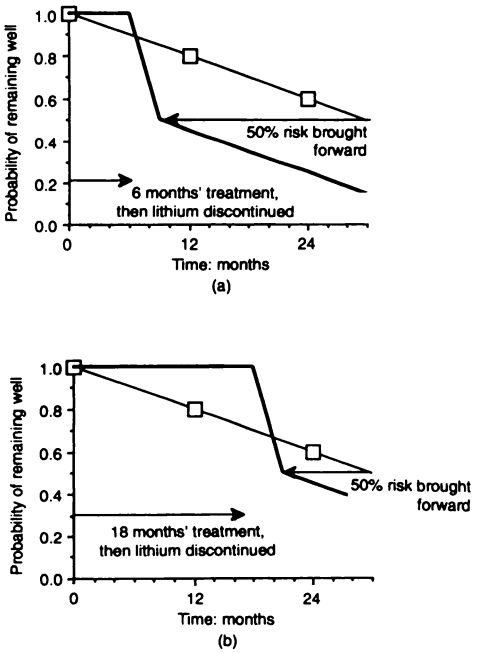

Fig. 1 The graphs show the effects of lithium discontinuation assuming a 50% risk or recurrence within the subsequent three months. The time of discontinuation is after (a) 6 months or (b) 18 months. Lines without symbols show the effect of stopping. The control risk in first episode bipolar patients not treated with lithium is taken from Mander (1986) (□). The left-directed horizontal arrows show how discontinuation brings forward the time of 50% recurrence in either case.

The proportion of patients experiencing early recurrence

The figure of 50% recurrence at three months after discontinuation is an average value and remains subject to considerable uncertainty. Indeed, Mander & Loudon (1988) had an apparently higher rate of recurrence in their placebo-controlled withdrawal. However, lower rates of early recurrence will still bring forward the risk that patients become ill prematurely on stopping short-term lithium treatment. The relationship between duration of lithium treatment and the increase or decrease in time to 50% recurrence compared to no treatment is shown for several withdrawal risks in Fig. 2. An increase obviously represents an advantage and a decrease a disadvantage from lithium treatment (emphasised by the shading in Fig. 2). The relationship has been estimated for 20, 30, 40, and 50% recurrence rates in the three months after stopping lithium. Even if it is assumed that the relapse rate is only 30%, the use of lithium for 6 or 12 months has a negative impact on the probability of recurrence. These findings imply that treatment with lithium for less than two years is almost certainly either of negligible benefit or actually harmful to bipolar patients.

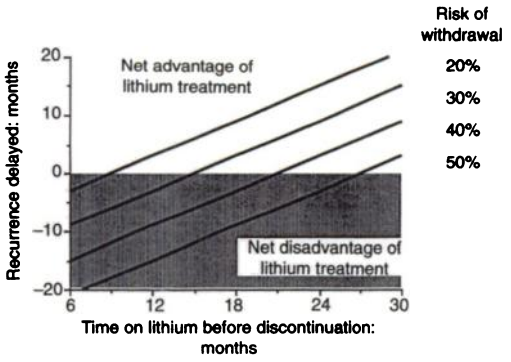

Fig. 2 The relation between time on treatment before discontinuation and the time of 50% recurrence relative to time of equivalent control risk, calculated by assuming relationships illustrated in Fig. 1 and for different risks of relapse in the three months after lithium discontinuation.

As lithium is, without doubt, often used for less than two years, the theoretical risks should be expressed as poor apparent efficacy. Actually, we are remarkably ignorant of what happens on average in clinical practice. However, such retrospective data as do exist support the view that the measurable benefits of lithium are appreciably less than might be expected. Using all the data from the Royal Edinburgh Hospital, Dickson & Kendell (1986) showed that in the years following the introduction of lithium the rate of admission with manic episodes actually increased rather than decreased. This finding has been described for other populations as well (Symonds & Williams, 1981). Interpretation of this increase cannot be unambiguous, but it could be explained entirely by the frequent use of lithium for under two years (see Fig. 2). Of course, other factors, such as changes in diagnostic practice or the age structure of the population served by the hospitals, could have contributed but these were discounted convincingly by Dickson & Kendell (1986).

Lithium's lack of efficacy

What reason other than excess recurrence after lithium withdrawal could account adequately for the failure to translate the undoubted advantages of lithium treatment shown from short-term trials into a clinical advantage? Quite apart from the research evidence, this failure contradicts clinical experience, because most psychiatrists will have been impressed by patients who do unusually well on lithium treatment. As well as the evidence from total numbers of admissions, the clinical course of individual patients drawn from the Edinburgh population supports the view that, overall, lithium confers only marginal benefit. This was the finding of a retrospective survey by Markar & Mander (1989), who compared the probability of a further admission for patients with recurrent bipolar illness after the introduction of lithium with clinically similar controls not treated with lithium. They showed that there was no advantage of the intention to treat with lithium in the first two years, but that some advantage did appear 2–10 years after starting lithium. By this time, however, the majority of patients in the original sample from both groups had had recurrences.

The simplest explanation is that many patients discontinue lithium within two years, suffer recurrences on withdrawal, and negate the advantages otherwise conferred on those who do persevere in the long term with adequate treatment. The failure to demonstrate any benefit in the two years after the initiation of treatment with lithium is otherwise highly paradoxical because controlled trials usually focus on just this interval and show highly significant differences in favour of lithium prophylaxis (Goodwin & Jamison, 1990).

Given the numbers of patients who start lithium treatment, it may appear surprising that a more comprehensive picture of their clinical course does not exist to confirm or refute the present argument. An audit of this sort is certainly needed. It is a major difficulty that although a decision to start treatment is commonly recorded clearly, the decision to discontinue treatment is rarely so well documented, frequently occurs at the patient's rather than the doctor's initiative, and may be confused with recurrence of illness rather than being seen as its cause. This makes any form of audit difficult even for an out-patient-based hospital follow-up; the more hit and miss arrangements are for follow-up in the community, the worse the situation is likely to be.

The present argument may not apply so forcefully to the use of lithium in recurrent unipolar depression, where there is no comparable evidence for a withdrawal syndrome (Souza *et al*, 1990; Suppes *et al*, 1991), or indeed in patients not selected to have bipolar I illness with clear-cut, clinically significant manic episodes (Sashidaran & McGuire, 1983). However, for bipolar I disorder it is likely that the risk of recurrence is described broadly by the theoretical curves in Fig. 1.

Length of treatment

It is not surprising that most patients will not take lithium for long enough to reap any benefit from it. At present, patients are frequently started on lithium in the recovery phase of a manic illness. This

may be a far from propitious moment. Their views about the desirability of the treatment frequently change on full recovery. Their understanding of how long it may be necessary to take the tablets may be very limited. In addition, doctors are likely themselves to be quite uncertain about how long to recommend a patient stays on lithium. This would not matter if lithium did not have the potential for a negative effect on recurrence. The lesson from Fig. 2 is that lithium does have such an effect, and that, accordingly, it should not be used for less than two years. Three years is probably the minimum length of time worth aiming for. Discontinuation after that time will depend on the usual balance of clinical judgements.

Even where bipolar patients are treated successfully for long periods of time, are definitely compliant with treatment, and enjoy unusual mood stability, withdrawal is still very likely to precipitate a manic recurrence (Mander & Loudon, 1988). In addition, withdrawal in stable patients may carry the more sinister additional risk of subsequent lithium refractoriness (Post *et al*, 1992). It is understandable that doctors are ambivalent about persuading patients to accept lithium treatment indefinitely. Unfortunately, to compromise with a treatment strategy that is also short term may be worse than useless.

Conclusion

Lithium should not be introduced for the prophylactic treatment of bipolar illness unless or until the doctor and patient understand that it must be used for a minimum of two years. If there is no such agreement, then no worthwhile benefit is likely to accrue to the individual patient treated for a shorter time and, instead, it appears rather likely from the present evidence that harm, in the form of a premature recurrence of mania, will be done. A more conservative policy for the use of lithium may have the unusual virtue of greater health for patients and greater economy for the National Health Service. It should be adopted while the balance of the evidence remains what it is. Further work bearing on the question should, however, be welcomed.

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(First received March 1993, final revision June 1993, accepted July 1993)