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Is There a Lithium Withdrawal Syndrome?
An Examination of the Evidence

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The evidence for abstinence phenomena after discontinuation of lithium is weak and ambiguous. Early manic and depressive recurrences after lithium discontinuation may suggest rebound, but studies carried out with appropriate methodology have failed to confirm its reality. Discontinuation of prophylactic lithium treatment of recurrent manic-depressive illness, whether abrupt or gradual, involves risk of relapse, but the existence of a special lithium withdrawal syndrome remains unproven.

Prophylactic lithium treatment keeps recurrent manic-depressive illness under control but does not cure it; when lithium is discontinued, relapses are likely to occur (Baastrup *et al*, 1970). The frequency of relapses after discontinuation of lithium may be the same as before treatment (Schou *et al*, 1970), or it may be higher (Grof *et al*, 1970) because the disease course tends to deteriorate. A gradual shortening of cycle length with time has been observed in both unipolar and bipolar manic-depressive illness (Angst *et al*, 1979; Zis *et al*, 1980; Goodwin & Jamison, 1990).

It has been suggested that a special lithium withdrawal syndrome may develop after discontinuation of lithium, particularly after abrupt discontinuation, and this has been the subject of many publications. But its nature is unclear, and its existence has not been unequivocally proven. Part of the murkiness in the field comes from lack of precision of the terms used; the following attempt at clarifying matters therefore starts with definitions of relevant terms as they are used here.

Terminology

In some contexts *relapse* and *recurrence* mean different things, but in this review they are used synonymously for the development of mania or depression in a patient who previously has had manic or depressive episodes.

Abstinence symptoms refer to mental or physical distress that may develop shortly after discontinuation of a chemical agent (drug, narcotic, alcohol) on which the organism has become physically dependent.

Rebound is a term used in connection with illnesses with a periodic course, for example epilepsy. When epilepsy is treated with appropriate drugs, the frequency of seizures falls; when the treatment is discontinued, the frequency rises. During the period immediately after discontinuation of treatment the frequency may rise temporarily to a level higher than that encountered before treatment started. This is called rebound. The temporary nature of the rise is important; a permanently higher frequency after treatment than before treatment indicates aggravation of the disease and is not regarded as a rebound phenomenon.

Rebound and abstinence differ. In rebound there is reappearance (with temporarily increased frequency) of something the patients had experienced previously, for example epileptic seizures. In abstinence there is development of signs and symptoms not experienced previously by the patients, for example the nausea, shivering and sweating of morphine abstinence.

The term *withdrawal* has been used with a number of different meanings, sometimes referring merely to discontinuation, sometimes to what followed discontinuation, sometimes to abstinence, sometimes to rebound. The term is here used exclusively in its sense of discontinuation of lithium treatment.

In the following the evidence for and against abstinence is considered first and the evidence for and against rebound thereafter.

Abstinence

The occurrence of abstinence phenomena after abrupt discontinuation of lithium is questionable. Some authors have looked for but failed to find such effects (Schou *et al*, 1968; Rifkin *et al*, 1975; Merry, 1979; Goodnick, 1985; Tondo *et al*, 1990). Two reports about development of acute confusion after discontinuation of lithium (Wilkinson, 1979; Yuce, 1979) have remained the only ones of their kind, and it has been argued that what was seen was manic relapse (Merry, 1979; Rifkin, 1980; Lawrence, 1985).

Some patients may be nervous or anxious after discontinuation of prophylactic lithium treatment because they feel exposed and vulnerable without the support of the treatment situation and the therapeutic team. To distinguish between this and true abstinence,

discontinuation without the patients' knowledge is required, i.e. blind transfer to placebo.

Such studies tell about manic and depressive recurrences developing at various times after the discontinuation, but usually they do not contain observations that indicate abstinence; in some studies this is specifically pointed out (Christodoulou & Lykouras, 1982; Mendlewicz, 1984).

There are, however, exceptions. A group in Munich (Klein *et al*, 1981; Greil *et al*, 1982; Klein *et al*, 1983) discontinued lithium blindly in 21 manic–depressive patients. This resulted in two phenomena. Eleven patients suffered relapses that were symptomatologically similar to the episodes they had experienced before lithium treatment. Among the ten patients who did not relapse, six developed nervousness, irritability, insomnia and labile mood. These symptoms, which disappeared spontaneously within one to two weeks, resemble the transient signs of irritability, anxiety and lability after discontinuation of lithium that were noted by King & Hullin (1983) (only in one of whose patients lithium was discontinued blindly).

Three interpretations of this latter set of symptoms seem possible. (a) They may have been manic or depressive relapses, only mild and short-lasting. The differences in symptomatology between these phenomena and ordinary manic and depressive relapses speak against this explanation. (b) They may have been abstinence phenomena caused by development of physical dependence on lithium. Abstinence symptoms after withdrawal of other psychotropic drugs such as barbiturates and benzodiazepines include nervousness and insomnia, but usually these are accompanied by tremor, dizziness, and sometimes epileptic seizures. (c) They may have been caused by the abolition of a stabilising action of lithium. Psychometric findings in the Munich study and observations made on healthy volunteers and on lithium-treated patients during intervals between episodes (Schou, 1968; Schou *et al*, 1968; Linnoila *et al*, 1974; Judd, 1979; Müller-Oerlinghausen *et al*, 1979; Folstein *et al*, 1982) show that lithium may have subtle effects on normal mental functions: longer reaction time, lowered alertness and emotional reactivity, increased mood stability. Disappearance of such actions can be expected to lead to irritability, anxiety and labile mood.

When discontinuation of lithium is followed by manic or depressive relapses, this is seen as re-emergence of the manic–depressive illness when it no longer is under the control of the treatment. I have heard a different view aired, namely that manic episodes occurring after discontinuation of lithium treatment may be abstinence phenomena resulting from development of physical dependence on lithium. There is no support for this assumption. Lithium is used for various physical illnesses, for example cluster headache. Discontinuation of lithium given on this indication is often followed by recurrence of headache attacks because the disease no longer is under the control of the treatment. Development of mania or depression after discontinuation of lithium given for cluster headache or, generally, on indications other than affective illness has not been reported.

Conclusion concerning abstinence

The evidence for abstinence symptoms after discontinuation of lithium is weak and ambiguous.

Rebound

Development of relapses soon after discontinuation of lithium has been observed numerous times (Schou *et al*, 1970; Grof *et al*, 1970; Small *et al*, 1971; Fyrö & Petterson, 1977; Lapierre *et al*, 1980; Cordess, 1982; Margo & McMahon, 1982; Sashidharan & McGuire, 1983; Svestka *et al*, 1984; Kakita *et al*, 1985; Mander, 1986; Mander & Loudon, 1988; Strober *et al*, 1990; Klein *et al*, 1992). These observations emphasise that stopping prophylactic treatment may have serious consequences and should be undertaken only after careful consideration. This is the important and clinically significant point.

Of more theoretical interest is whether rebound, i.e. transitory additional increase of the frequency of relapses, occurs after discontinuation of lithium. Many authors have concluded that rebound does occur, but the foundation for these conclusions must be analysed carefully, for in only some studies does data collection meet necessary requirements. A number of considerations are important where documentation of rebound is concerned.

Firstly, if in spite of lithium maintenance treatment a manic–depressive patient develops a slight manic relapse, he or she may feel unusually well, 'on top of the world', and in no need of further lithium. The treatment may then be discontinued, with the result that the impending mania develops into a full-blown one, thus giving an erroneous impression of rebound (Grof, 1985; Kukopulos *et al*, 1985; Strober *et al*, 1990). Studies aimed at proving rebound must fulfil the criterion that lithium is discontinued on the initiative of the physicians and not of the patients. To avoid suggestion, the patients should be blind to the discontinuation.

Secondly, the mere appearance of relapse shortly after discontinuation of lithium cannot be taken as

evidence of rebound. If one assumes that the periodic course of the illness continues underneath the prophylactic action of lithium, then arbitrarily timed discontinuation of lithium must sometimes take place at a time when without lithium the patient would have been in an episode, and rapid relapse then need not indicate rebound.

Thirdly, frequent recurrences soon after discontinuation of lithium cannot in themselves be taken as an indication of rebound. To establish the latter phenomenon one must analyse the course of the disease in such a manner that simple re-emergence of the disease and rebound (i.e. re-emergence with temporarily increased relapse frequency) can be distinguished from each other. This can be accomplished only by following the patients over long periods, most effectively by using survivorship function analyses (life-table methods) with semi-logarithmic plot of the disease course.

Figure 1 shows the outcome of such a study (Schou *et al*, 1970; Schou, 1979). The number of patients not yet having suffered relapse is plotted against time, expressed in months, during a one-year period before lithium treatment, a one-year period under lithium treatment, and a one-year period following discontinuation of lithium. Note that relapses developed exponentially (the straight line of the semi-logarithmic plot). They were frequent before and after lithium treatment and infrequent during the treatment; this illustrates the prophylactic effectiveness of the therapy. If rebound had occurred, the curve after discontinuation of lithium would have had a particularly steep slope immediately after the discontinuation, indicating a temporary rise in the frequency of recurrences. Figure 1 reveals no such phenomenon; the slope (decay constant) is the same throughout the 12 months following discontinuation of lithium.

Evidence of rebound was lacking also in another discontinuation study with analysis by semi-logarithmic plot of disease courses (Grof *et al*, 1970). One non-blind study (Sashidharan & McGuire, 1983) and two blind studies (Fyrö & Petterson, 1977; Mendlewicz, 1984) provided information about how soon after discontinuation the relapses occurred, and the patients were followed for many months. I have made semi-logarithmic plots of the data to look for rebound, but in none of them was there any sign of it.

An apparently different outcome was obtained in a study with semi-logarithmic plotting of disease courses (Mander, 1986). After discontinuation of lithium, the survivorship curve showed a steep slope during the first three months and thereafter a less steep slope with a decay constant which was the same as that of a group of patients not given lithium. This study may seem to provide evidence of rebound after discontinuation of lithium, but the trial was retrospective and non-blind, and the discontinuations were patient-initiated (cf. the points made above).

The same author group carried out a prospective, randomised, double-blind, placebo-controlled discontinuation study on 14 bipolar patients (Mander & Loudon, 1988). Seven definite and two possible manic relapses occurred during four weeks of placebo administration. The authors felt that the proportion of patients relapsing was too large to be reasonably accounted for by simple re-emergence of the disease and saw the outcome as evidence of what they called "a pharmacologically induced withdrawal syndrome", i.e. rebound as the term is used here. However, no evidence was presented of a larger relapse rate (a steeper slope) immediately after discontinuation of lithium than later, and the conclusion remains unsupported.

A meta-analysis of the literature about recurrence following discontinuation of lithium in bipolar

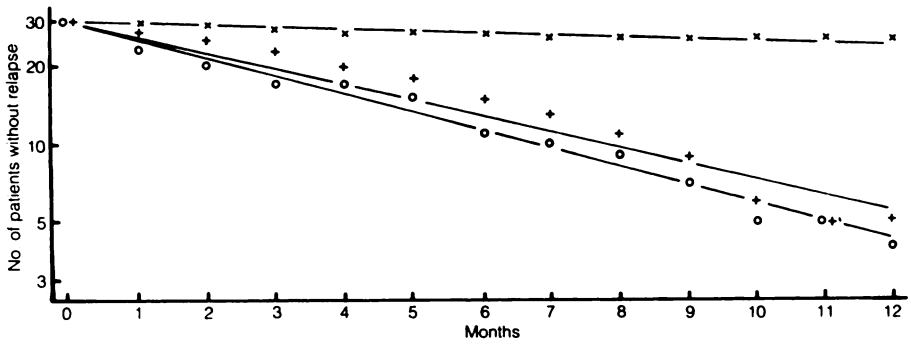

Fig. 1 Comparison of rates of relapse: +, before lithium treatment; ×, during lithium treatment; ○ after discontinuation of lithium. The number of patients not yet having relapsed is plotted semi-logarithmically against time (from Schou, 1979).

disorder (Suppes *et al*, 1991) concluded that risk of early relapse, especially of mania, is increased following discontinuation of lithium and may exceed that predicted by the course of the untreated disorder. This conclusion is supported by the data (although, as pointed out by the authors themselves, assessment of relapse risk in untreated patients was based on a small subset of cases). As far as rebound is concerned, one cannot find evidence of this. Exponential survivorship curves for the time after discontinuation of lithium are presented, but the points shown are too crude to permit reliable semi-logarithmic plotting. Besides, data from blind, physician-initiated, and non-blind, mostly patient-initiated, discontinuations are mixed. This study highlights the risk involved in discontinuing prophylactic lithium treatment, but it does not contribute to the problem of rebound.

Conclusion

The question of rebound after discontinuation of prophylactic lithium treatment of recurrent manic–depressive illness remains without a definitive answer, and there is scope for further trials of appropriate design. Rebound, if it exists, may be associated with particular circumstances and special patient characteristics (Grof, 1985; Mander, 1989).

Overall conclusion

The evidence for abstinence phenomena after discontinuation of lithium is weak and ambiguous. The evidence for rebound after discontinuation of lithium is inconclusive. Further studies are needed.

There is also a need for examination of abrupt versus gradual withdrawal of lithium with respect to both abstinence and rebound. Several authors have suggested that manic and depressive recurrences develop more readily when lithium is discontinued abruptly than when the dose is lowered gradually. If that is so, it is of clinical relevance. However, a retrospective study did not find evidence of such a difference (Kukopulos *et al*, 1985), and no systematic, prospective comparisons of the two procedures have been carried out.

The present review is based on the evidence available in the literature today and on conventional terminology. Paul Grof, whom I asked for comments on this manuscript, suggests that recurrence of unusual intensity may sometimes develop after discontinuation of lithium ('intensity rebound'). No direct reference to such a phenomenon has yet been published.

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