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Withdrawal Symptoms from Lithium

Four Case Reports and a Questionnaire Study

J. R. KING and R. P. HULLIN

Summary: Evidence from four case reports of heightened anxiety, irritability and emotional lability following withdrawal of lithium was confirmed by a questionnaire survey of 110 defaulters from a lithium clinic: 19 per cent of respondents retrospectively reported these temporary symptoms following withdrawal. The possible mechanisms of such a withdrawal effect are discussed, and a phased withdrawal is advocated in situations where continued clinical benefit from lithium is being evaluated. The questionnaire results also confirm anecdotal evidence that lithium reduces emotional responsiveness. The significance of these findings in terms of the current models of lithium's action is discussed.

Until recently it was widely assumed that lithium withdrawal produced no symptoms (Schou, 1980). The absence of such symptoms was taken as confirmatory evidence for lithium's status as a unique treatment, essentially different from other psychotropic drugs, having little effect on the mind other than as a specific life-long prophylactic agent against manic-depressive psychosis (Baastrup and Schou, 1967; Rifkin *et al*, 1975). This model of a life-long treatment, however, has meant that investigators have not been alert to the possibility of withdrawal effects occurring, and have not designed studies with the specific intention of revealing them (Johnson, 1979). This situation is now changing as lithium is increasingly prescribed for recurrent depression and other diagnostically less homogenous conditions whose recurrence is by no means predictable. It is important therefore to determine the existence of any withdrawal syndrome, so that this is not confused with relapse in patients who are withdrawn after a limited period on the drug.

At the time our study was carried out, the only report of a lithium withdrawal reaction in the literature was that of Wilkinson (1979). Below, we give four further case reports of patients who, in 1981, experienced withdrawal symptoms after stopping lithium.

Case 1: Mrs P.H. was aged 44. She was a capable professional woman who had been emotionally labile since the age of 13, and experienced short periods of euphoria or depression which lasted for hours or days. She had beome more severely depressed following an unhappy love affair and had been started on lithium carbonate, which she took reliably for eight years. The blood levels of lithium were within the target range of 0.5–0.8 mmol/l. During this time her emotional lability disappeared and she remained stable. She progressed in her career, successfully negotiated a potentially traumatic divorce, and subsequently re-married. The possibility was considered that her original illness had been reactive in nature and that she could now manage without lithium. The patient herself was keen on a trial discontinuation; but in order to eliminate possible psychological effects due to stopping the tablets, it was arranged that a placebo be substituted at a date unknown to her and the supervising physician. Four days after the placebo was substituted she developed emotional lability. Tearfulness and irritability (for no discernible reason) were interspersed with sudden short-lived euphorias. These lasted for three weeks, at the end of which time she was recommenced on lithium. She then stabilized rapidly. Four days after restarting lithium she was again well, and she has remained so since. Her husband independently remarked on her personality change during the time on placebo.

Case 2: Miss D.S. was aged 21. She had been taking lithium carbonate for seven months following a hypomanic illness and had remained well, but she always appeared somewhat distant and aloof. This had been the only illness in an otherwise stable girl, and had been associated with external stresses at work. Two to three days after a trial discontinuation of lithium she developed symptoms of anxiety. She was apprehensive, worried over trivia, and complained of light-headedness, insomnia, and disturbing dreams.

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She felt emotionally off balance and was easily moved to tears. She worried that these symptoms might herald a major relapse. However, over the course of approximately three weeks these anxiety symptoms faded, and she spontaneously remarked that her emotions felt more natural than when she was on lithium. Objectively, she appeared less distant and aloof. She has subsequently remained well without lithium.

Case 3: Mrs E.H. was aged 62. Lithium had been started nine years previously to treat her severe atypical psychosis, which had a strong affective component. She responded well to lithium. Two or three days after a reduction in dose, from 1000 mg to 800 mg, she developed a condition of irritability which lasted for two weeks. Her husband, who was a reliable witness, reported this change. No external precipitating factors appeared to account for it.

Case 4: Mr A.T. was aged 67. Since the age of 35 he had shown clear-cut features of a bipolar manic-depressive psychosis which manifested itself at three-yearly intervals. At first, the episodes were depressive and usually required ECT. But later, he suffered a manic illness, as a result of which lithium was started. He then remained free of symptoms for eleven years. Lithium levels were maintained within the range 0.4–0.9 mmol/l. In May 1981 he omitted to take his lithium for the first time, and in less than a week he developed manic symptoms. He was overactive by day and night, emotionally labile, elated and irritable, had pressure of speech and was, as his wife confirmed, just like he was before starting lithium. Unfortunately, at the height of his overactivity he suffered a myocardial infarction which prevented his recommencement on lithium for three weeks. When he was seen again he was calmer, although rapid speech was still noticeable. Lithium was restarted, and rapidly brought about his complete stabilization.

As a result of these observations, a questionnaire survey was undertaken of all patients who, either, had defaulted from a lithium clinic since its inception, or, had stopped taking lithium for other reasons. The questionnaire was designed to elucidate both temporary and permanent changes in emotional responsiveness after stopping the drug; and also, to find out how far these changes were associated with other more well recognized changes in subjective thirst and concentration.

Method

Details were obtained from the case notes of all patients who had discontinued attending the lithium clinic at the Metabolic Research Unit, High Royds Hospital, since its inception. All patients were included in the study, provided there was clear evidence that they had taken lithium for at least two months. No attempt was made to select out those patients who had stated their intention to discontinue lithium or who had discontinued it on medical advice, although these factors were noted.

Questionnaires enquiring into temporary and permanent changes in emotional responsiveness and changes in concentration and thirst were mailed to the patients' last recorded addresses, with covering explanatory letters. Non-respondents were re-mailed two months later. Particular care was taken in the design of both letters and questionnaire to avoid suggesting that any specific type of emotional response was expected. The letters emphasized the equal importance of negative replies. Responses were rated on a five-point scale according to severity (+ = increased, − = decreased). Any amplifying details given by the patients were noted.

Results

Of the 110 patients who were sent questionnaires, the first mailing resulted in 68 responses. This was increased to 79 after the second mailing. The 79 responses were of several types (Table I). The Table shows that the majority (25) of completed question-

TABLE I

Responses to questionnaire

	First mailing		Second mailing		Total	
	No.	%	No.	%	No.	%
Died	14	20	0	0	14	18
Moved away to unknown destination: returned by GPO	21	31	6	55	27	34
Had never stopped taking lithium	8	12	3	27	11	14
Completed questionnaire returned	25	37	2	18	27	34
Total	68	100	11	100	79	100

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naires were returned after the first mailing. The second mailing produced a relatively larger number of moved away notifications, and replies from patients still on lithium. The number of non-respondents after the second mailing was 31. Compared to those who completed the questionnaire, these non-respondents were significantly older (mean age 60, SEM±2.51 years, $P < .01$) and had defaulted from the clinic a longer time ago (mean time 7, SEM±0.6 years, $P < .01$). The case notes indicated that this group contained a larger proportion of inadequate personalities, who may have been less motivated to reply. The response rate, in terms of the responders as a percentage of those able to respond (not known to have died, moved away, etc), can be stated as 47 per cent ($\frac{27}{27+31} \times 100$).

The 27 questionnaires included a group of seven in which respondents stated frankly that they were unable to recall whether or not there had been any changes. These patients tended to be older (mean age 56 years) and to have stopped attending a longer time ago. The results from the remaining 20 questionnaires are set out in Table II. Examination of Table II shows that the majority of responses fall into three main groups: *Group A*—temporary anxiety symptoms present; *Group B*—permanently increased emotional responsiveness but no temporary symptoms; *Group C*—negative responses to all questions.

Temporary effects

Temporary anxiety, coming on within a week of stopping lithium, was a feature in five cases (Group A, 19 per cent), (in one case there was associated irritability). There was no significant difference in age or length of time on lithium in this group, compared with the rest of the questionnaire respondents. In the most severe case (Group A, case 1) the questionnaire was accompanied by a reliably described account of how the patient had developed acute anxiety symptoms three days after discontinuing lithium. Heightened emotional instability had been a problem until he was eventually recommenced on lithium. A possible reduction in anxiety symptoms was described in only one case (18), in which it was associated with increased capacity for enjoyment. Capacity for enjoyment was negatively correlated with anxiety in those patients experiencing temporary effects (Spearman's rank order correlation, $r = 0.97$, $P < .05$).

All three of the more severe cases of temporary anxiety (rating ≥ 3) were associated with the development of permanently increased emotional responsiveness, whereas only 5 of 17 low-anxiety patients exhibited increased emotional responsiveness. This gives a significant association between these variables (Fisher's exact probability test, $P < .05$).

Permanent effects

Emotional responsiveness

Heightened emotional responsiveness was a feature in eight (30 per cent) replies. Only in one case (19) was the reverse reported, and this patient's lithium levels had often been at the lower limit of the therapeutic range. There was no significant difference in age or length of time on lithium in this group, compared with the rest of the questionnaire respondents. Nine respondents reported no permanent change in emotional responsiveness. The majority of these (Group C) denied other changes, either temporary or permanent.

Concentration and thirst

Seven (26 per cent) patients reported increased concentration, and six (22 per cent) reported decreased thirst, as a consequence of stopping lithium. In both cases, there were solitary examples of patients reporting the opposite effect. There is a trend (not reaching significance) for a decrease in thirst to be associated with increased concentration. No relationship is evident between thirst or concentration changes and emotional responsiveness in those patients reporting side effects (Fisher's exact probability test).

Discussion

The 27 respondents who returned questionnaires were a selected sample of the 110 surveyed, but the results indicate that most of the non-response was due to the unavailability or death of the non-respondents. An additional factor, which may have lead to non-response, is suggested by the older age and greater length of time since lithium was discontinued in that group. They may have had difficulty in recalling and comparing their state of mind years before.

Significance of temporary effects following withdrawal

There are three possible explanations which could account for the high proportion of patients reporting temporary anxiety.

Psychogenesis: An anxiety reaction might be expected in patients who are advised to discontinue a treatment of considerable duration, on which they have become emotionally dependent. This could be an explanation in some cases, e.g. case II. But on the other hand, the questionnaire respondents were often drop-outs from the clinic who had presumably, therefore, never developed such emotional dependence. Furthermore this explanation cannot apply to case I, where a placebo-substitution technique was used.

Rebound psychosis: Recent reports (Lapierre *et al*, 1980; Klein *et al*, 1981; Margo and McMahon, 1982)

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TABLE II

Questionnaire responses from patients who discontinued lithium therapy

					Temporary effects			Permanent effects			
Case	Age	Sex	Years on lithium	Years discontinued	Capacity for enjoyment	Anxiety	Duration	Emotional responsiveness	Concentration	Thirst	Group
1	43	M	2	9	−3	5	weeks	2	0	−3	A
2*	51	M	1	8		4	weeks to months	3	−2	0	
3	39	F	4	2	−2	3	months	3	2	3	
4*	31	M	5	2	0	2	months	0	0		
5	51	F	4	1	1	1	days	0	3	−5	
6	53	M	7	1	0	0		3	2	−3	B
7	31	F	1	9	0	0		3	2	0	
8	36	F	3	8	0	0		3	0	2	
9	35	F	6	3	0	0		3	0	−3	
10	52	F	5	1	0	0		1	2	0	
11	53	F	7	2	0	0		0	0	0	C
12	45	F	3	7	0	0		0	0	0	
13*	47	F	2	6	0	0		0	0	0	
14	32	F	2	3	0	0		0	0	0	
15	25	F	2	5	0	0		0	0	0	
16*	40	M	4	6	0	0		0	0	0	
17*		M	0.25	5	1	0		0		0	
18*	65	M	4	0.08	2	−1		0	2	−5	
19		F	6	4	0	0		−2	0	0	
20	39	F	0.66	7		0		0	2	−3	
Mean	42.6		3.40	4.45							
SEM	2.57		0.47	0.65							

* Planned discontinuation after previous discussion with physician.

have highlighted the possibility that lithium withdrawal can trigger a rapid relapse of psychotic (mainly manic) symptoms, especially in bipolar patients who are particularly susceptible to such switch processes. Such a possibility is applicable to our cases I and IV. But in contrast to the tendency for patients in other studies to continue to deteriorate and need hospitalization, many of our cases improved whether or not lithium was recommenced.

True withdrawal syndrome: The symptoms which patients describe, of anxiety, irritability, and emotional hyper-reactivity, are compatible with a withdrawal syndrome coloured by personality factors, but based on a common core of heightened arousal. The delay of two or three days before the onset of symptoms, shown in two of our case reports, is characteristic of the typical latency expected in a drug withdrawal reaction. The studies of Müller-Oerlinghausen (1977) on cognitive changes following lithium withdrawal, also lend support to this mechanism.

It is noteworthy that in the Klein *et al* (1981) study, most of the patients who did not become psychotic reported a delayed onset of temporary anxiety and irritability. This mixture of reactions to lithium withdrawal closely parallels our own observations and suggests that both mechanisms, rebound psychosis and a withdrawal syndrome, may operate.

Whatever the mechanism, these results confirm that phased withdrawal from lithium is a wise policy in order to minimize withdrawal effects. They also raise the question of whether some of the morbidity in patients maintained on lithium is a consequence of their failing to take the drug regularly.

Significance of permanent effects

The increased emotional responsiveness reported as a long term consequence of stopping lithium is unlikely to be explainable in terms of recurrence of the illness (very few relapsed), but might be partly a reflection of patient's expectations ("no longer on drugs"). However, if the patients' reports of increased emotional responsiveness had been based solely on the rationalization that they were better for having decided not to take lithium, one would have expected this mechanism to apply at least as much to improvements in other more well-recognized side effects, such as thirst and concentration. In fact, however, changes in thirst and concentration are reported rather less often than increased emotional responsiveness.

There is much anecdotal evidence that lithium reduces emotional responsiveness. Schou *et al* (1967), when they took lithium carbonate experimentally, reported the experience as like being separated from environmental stimuli by a glass wall. Case II draws attention to the more natural quality of experience on stopping lithium. Although this is seen as an advantage by some of our patients, e.g. in allowing a normal grief reaction under appropriate circumstances, others appreciate and prefer the emotional stability induced by lithium. A common view is that it helps them feel more confident and assertive. Clearly these differences in attitude are important in determining whether or not patients comply with treatment.

Controlled trials (Judd, 1979; Müller-Oerlinghausen *et al*, 1979) have also indicated that lithium induces feelings of withdrawal from interpersonal and environmental demands, providing a possible explanation for its action in reducing aggression. All these observations add weight to the correlation shown in the present study between withdrawal symptoms and long-term changes in emotional responsiveness. They sustain the general concept of a separate and non-specific action of lithium, applicable where lithium is used for indications wider than manic-depressive psychosis.

This is not to suggest that lithium has no specific action on manic-depressive disorder. On the contrary, the possible inverse correlation between changes in thirst and concentration, indicated by the questionnaire study, sheds an interesting light on the possible mechanism of such a specific action. If confirmed, such a relationship would tie together the cognitive theories of lithium's specific antimanic action (Judd, 1979) with those involving anti-diuretic hormone (Gold and Goodwin, 1978). This will be considered further in another study to be reported separately.

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*J. R. King, B.Sc., L.R.S.C., M.B., Ch.B., M.R.C.Psych., *Research Fellow, Departments of Biochemistry and Psychiatry, University of Leeds, 15 Hyde Terrace, Leeds LS2 9LT*

R. P. Hullin, Ph.D., F.R.S.C., J.P., *Reader in Biochemistry, University of Leeds; Director, Regional Metabolic Research Unit, High Royds Hospital, nr. Ilkley, West Yorkshire*

* Present address: Senior Registrar, The Middlesex Hospital, Mortimer Street, London, W1

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