



# Decreased responsiveness following lithium discontinuation in bipolar disorder: A naturalistic observation study



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## ARTICLE INFO

### Keywords:

Bipolar disorders  
Lithium  
Discontinuation  
Long term treatment  
Unresponsiveness  
Response  
Treatment resistance

## ABSTRACT

Lithium is a cornerstone in treatment of bipolar disorder. Findings are conflicting as to whether acquired unresponsiveness occurs following the discontinuation. Retrospective life chart data were evaluated to investigate the incidence of loss of response. Sixty-five patients chosen from a larger cohort, followed with prospective life charts, who discontinued lithium and had a second lithium treatment. Patients who had at least 2 mood episodes when they were drug naïve to describe the natural frequency of illness and 3 mood episodes before the discontinuation were included. The type of response was defined as excellent, partial, or poor according to mirror design method. Eighteen of 65 patients (27.6%) had a decreased response to lithium following its discontinuation. Nine of these patients (13.8%) were unresponsive and nine patients (13.8%) had attenuated response to second lithium treatment. The mean time of discontinuation was longer in the patients who show decreased response (245.8+268.2 vs. 117.9+149.8 days,  $p=.01$ ). Those who had episode recurrences during the discontinuation were more likely to show reduced responsiveness upon re-treatment. After discontinuation of lithium treatment, more than a quarter of the patients showed an attenuated response or unresponsiveness, and initial partial responders more likely to show unresponsiveness than excellent responders.

## 1. Introduction

Lithium is the first and cornerstone mood stabilizer in the treatment of bipolar disorder (BP) (Cade, 1949; Geddes et al., 2004; Yatham et al., 2013). Even among the other mood stabilizers that have since become available, the efficacy of lithium remains superior (Geddes et al., 2010). The findings of decreasing suicide rates with lithium also imply its essential position in the long-term treatment of BP (Baldessarini et al., 2006; Tondo et al., 1997b). Patients who are lithium responsive are accepted as a core phenotype of BP and responsiveness is thought to be determined by genetic components (Alda et al., 2005; Cruceanu et al., 2011).

Although some reports indicate the stability of effectiveness of lithium maintenance (Rybakowski et al., 2001; Tondo et al., 1997a), other observations suggest that lithium response may dissipate by a tolerance process or that temporary discontinuation in responsive patients may lead to refractoriness when lithium is reinstated (Koukopoulos et al., 1995; Maj et al., 1995; Post, 2012; Post et al., 1992). These conflicting results require further examination and study. Furthermore, because only one third of patients with BP reach full

remission with lithium (Baldessarini and Tondo, 2000; Maj et al., 1998), it is important to examine possible reasons for loss of responsiveness and whether any patients with BD who have poor or moderate response to lithium could have an improved response after a period of lithium discontinuation.

The aim of this study was to investigate any change in responsiveness to lithium after a period off drug in patients who had a previous full or partial response to lithium in long-term prophylaxis.

## 2. Method

### 2.1. Study subjects

The study patients were chosen from a cohort of 350 patients who were diagnosed as having BP and were prospectively followed up at a specialized mood disorders unit. The follow-up details of the cohort are described elsewhere (Cakir et al., in press; Yazıcı et al., 2004, 2002). In brief, the patients and their accompanying caregivers assisted in the completion of life charts during a structured schedule of visits. Data on clinical course, the severity of manic and depressive episodes, medica-

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tions received, relapse and recurrence, and degree of response to lithium before and after its discontinuation was retrospectively gathered from the life charts and hospital records. The frequency of follow-up visits was similar in both first and second treatment durations. Written informed consent was obtained from patients for the evaluation of their records and life charts.

## 2.2. Inclusion Criteria

1. Patients diagnosed as having BP type I or II according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and having at least 2 mood episodes before the first lithium treatment in order to describe the natural course of illness. The time on lithium would have to be sufficient for the occurrence of as many as 3 mood episodes on lithium before it was discontinued based on the cycle length observed at the baseline before lithium treatment. Consequently the initial response type could be estimated.
2. The patients must have complete life charts and must have been followed up regularly according to the program of the Unit (once a month in the first 6 months following relapse, once every 2 months for the second 6 months, and once every 3 months for the rest of the maintenance period)
3. Having at least two years' lithium maintenance treatment (1st treatment) and also having longer treatment duration than the natural intervals.
4. No evidence of non-adherence to treatment during the first and second treatment phases.
5. At least a four-week long discontinuation period during the lithium treatment phase.
6. The duration of the second lithium treatment phase following discontinuation had to be at least two years and treatment duration longer than natural intervals.
7. The lithium plasma levels had to be within the therapeutic level (0.6–1.00 mEq/L) during the follow-up.
8. The maintenance treatment of the patients should be lithium mono-therapy with adjunctive treatment allowed for only acute episodes (see #9).
9. Thyroid function should be within the normal range.
10. Concomitant antipsychotics, antidepressants or hypnotics allowed only for acute treatment of mood episodes and restricted for three months after recurrence.

## 2.3. Discontinuation

The patients who discontinued lithium treatment for at least four weeks either because of non-adherence or any other reason, such as physician's decision, intolerance, adverse events, and pregnancy were included. Discontinuation was categorized as rapid (< 2 weeks) or gradual (2–12 weeks). Mood episodes that occurred in the off-lithium period were not considered in the evaluation of lithium response types.

## 2.4. Definition of response types to lithium maintenance

Treatment response was categorized in accordance with the mirror design method. Two senior psychiatrists evaluated the patient's life charts to achieve consensus in the definition of the response type. Three response types for phase-1 and phase-2 treatment periods were assessed by comparing the natural (pre-lithium) course to both the first and the second lithium treatment periods:

- i) Excellent response; no minor or major mood episodes during treatment,
- ii) Partial (moderate) response; reduction in frequency, duration or severity of mood episodes compared with the pre-lithium period,
- iii) Poor response (non-response); lack of reduction in frequency,

duration, or severity of mood episodes.

A *change in responsiveness* was defined in three categories comparing the Phase-1 to Phase-2 treatment response types.

1. *Attenuated response*: The transitions from excellent response to partial response
2. *Unresponsiveness*: The transitions from excellent or partial to a poor response
3. *Positive change*: The transition from partial response to excellent or from poor response to partial or excellent response

## 2.5. Statistical analysis

The two patient groups, one with decreased responsiveness and the other with no change in responsiveness to lithium in Phase-2, were compared using Student's *t*-test, Chi-square analysis (Yates's correction was used when appropriate) or Fisher's exact test.

## 3. Results

We evaluated 81 patients who had lithium treatment, discontinued, and reinstated lithium. Sixty-five patients (47 BP type I and 18 type II) met the inclusion criteria of the study (Fig. 1).

Phase-1 treatment: The mean duration of the first lithium treatment was 55.2 months (SD 27.9; range, 24–156 months). Nineteen of the 65 patients (29.2%) had excellent lithium response and 46 patients (70.8%) had a partial response in the first treatment phase (Table 1).

Phase-2 treatment: The mean duration of the second lithium treatment was 47.9 months (SD 12.74; range, 28–90 months) (Table 2). Seven patients (10.8%) had an excellent response, 49 patients (75.4%) had a partial response, and 9 patients (13.8%) had a poor response in the second treatment phase.

Loss of response: 18 of the 65 patients (27.7%) had a change in response in the direction of worse response to lithium after lithium discontinuation. This included:

*Attenuated response*: 9 patients with an excellent response in Phase-1 had a partial response in Phase-2 treatment. Thus, 13.8% showed an attenuated response.

*Unresponsiveness*: 9 patients (13.8%) converted to a poor response in Phase-2. Three of these patients had been excellent responders in Phase-1. In addition, six partial responders in Phase-1 converted to poor response in Phase-2.

We observed no changes in lithium response in 47 patients (72.30%), and no patients showed an improved response in the second phase compared with the first phase.

Fifteen of 65 patients (23.07%) had a relapse during the off-lithium period. These episodes included: 6 manic, 4 mixed, 3 hypomanic, and 2 depressive episodes. Eleven of these 15 patients (73.3%) had a decreased response in the second lithium phase. Five patients showed unresponsiveness (poor response), and 6 showed a partial response (attenuated response) during the second lithium treatment. Eleven of these 15 relapsed patients were in the decreased lithium response group, and only 4 of the 15 maintained their same degree of responsiveness ( $P < .001$ ) (Table 3). Also seen in Table 3 is the finding that the duration of time-off lithium was significantly longer in those who showed a decreased response to lithium in Phase-2 than in those who showed no change. Other clinical variables were not significantly different between the two groups, notably including the rapidity of the rate of lithium discontinuation.

## 4. Discussion

The most important finding of this study is that more than a quarter of patients had a poorer or deficient response to lithium in the second treatment phase following discontinuation compared with the first

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