Lithium Discontinuation and Reintroduction

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Abstract

Stopping medication in patients who are lithium responders is associated with a high risk of early recurrence of bipolar illness, especially mania, in the following months. A shorter time to recurrence has been shown after rapid versus slow discontinuation. A loss of the preventive effect of lithium on suicidal risk has also been shown after lithium discontinuation. Possible refractoriness to treatment was described more than 20 years ago following lithium discontinuation; however, available data do not provide convincing evidence that lithium is less effective when it is reintroduced after treatment discontinuation.

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Key Points

- Discontinuation of lithium is associated with an increased risk of mood episode recurrence in the following months. Time to recurrence is shorter with rapid, versus slow, discontinuation.
- No data are available on the effectiveness of lithium reintroduction after it has been stopped during pregnancy and/or breastfeeding. The same is true regarding suicide prevention.
- Altogether, available data do not suggest that lithium is less effective when it is restarted after discontinuation, compared to uninterrupted treatment.
- Studies addressing this issue are still limited.

14.1 Introduction

There is general agreement that lithium does not lose its efficacy in patients who are good responders during long-term maintenance treatment. Thus, a tolerance effect has not been shown for long-term lithium treatment (Kleindienst et al. 1999). However, possible refractoriness following lithium discontinuation in nine previously stable patients (Post et al. 1992) was described more than 20 years ago. No similar change in efficacy seems to be described with other mood-stabilizing agent, which merits discussion of the data on lithium discontinuation and reintroduction. This subject has been reviewed by Post (2012). Interestingly, most clinical practice guidelines do not address either the question of maintenance-treatment interruption in bipolar symptom-free patients or the issue of refractoriness.

14.2 Lithium as Maintenance Treatment: Discontinuation and Course of the Disease

Lithium is still the only mood-stabilizing agent whose efficacy is demonstrated in the very long term. As its use can be associated with several side effects, such as weight gain and renal and thyroid dysfunction (Grandjean and Aubry 2009), questions pertaining to the interruption of treatment are of primary importance for the good care of patients. Back in 1970, Baastrup and colleagues described the resurgence of bipolar symptoms upon discontinuation of lithium therapy in 12 % of 50 patients when switched to a placebo, whereas none presented a relapse when lithium was continued. Patients were treated on average for 4 years (12–84 months) with lithium, and resurgence of symptoms occurred within the 5 months following medication cessation. These initial results were later confirmed by Suppes and colleagues (1991), who collected data from 179 bipolar I patients included in nine studies and evaluated the risk of new episodes upon lithium discontinuation in a blind manner. Sixty-three percent of patients switched to placebo presented a relapse the following months, whereas only 10 % presented these symptoms when lithium was continued. Including the data arising from non-blinded studies, the authors

conclude that the time to recurrence of mania was 5.2 times earlier than for depression (2.7 vs 14 months).

Baldessarini and colleagues (1999b) collected data from 28 reports pertaining to the efficacy of lithium, collected in different clinical setting (controlled and not controlled) upon discontinuation. He found that the recurrence rate of symptoms averaged 1.5 ± 2.40 % per month during treatment with lithium versus 26.0 ± 34.0 % per month without lithium. This 17-fold risk difference after discontinuation of lithium was highly significant ($p < 0.001$). After discontinuation, he found that recurrence rates were three times higher in bipolar than in unipolar patients, whereas the number of monthly episodes was identical upon lithium.

Biel and colleagues (2007) followed 213 patients who were stable on lithium monotherapy for 30 months. Lithium was slowly discontinued over a period of 10 weeks in 54 patients, and they were then followed for 6 years. The risk of relapse was three times higher during the first year in the discontinuation group than in the lithium-free cohort. Patients who continued lithium had, on average, a survival time to recurrence of 7.3 years (95 % confidence interval (CI) 5.7–9.7), and for the group of patients who stopped lithium, the survival time was 1.3 years (95 % CI 0.3–2.3). Interestingly, when subgroups were analysed in the lithium continuation cohort, those who were maintained on relatively low lithium levels (<0.80 mM/L) during the 2 years of clinical stability were less likely (relative risk, RR 0.21) to relapse than those maintained at high lithium levels (1.00–1.26 mM/L). The group of patients whose lithium levels were intermediate (0.80–0.99 mM/L) had an RR of 0.54. Even if the discontinuation group did not benefit from a placebo treatment, these results confirm the long-term effectiveness of lithium.

Therefore, there is convincing evidence that stopping lithium medication, even after several years of treatment, is associated with a high risk of early recurrence of mood episodes, especially mania, in the following months.

14.3 Lithium Discontinuation: Rapid Versus Slow Dose Tapering

The reoccurrence of bipolar symptoms following the end of lithium therapy could result, at least partially, from a withdrawal effect, since the mechanism of lithium effectiveness appears to involve biochemical adaptive processes in the central nervous system (Malhi et al. 2012; Schloesser et al. 2012; Alda 2015).

In a study with 64 bipolar I and II patients, Faedda and colleagues (1993) compared rapid (1–14 days) versus more gradual discontinuation (>15 days). Time to 50 % risk of a first recurrence of depression or mania was more than fivefold shorter when lithium was stopped rapidly compared to gradual discontinuation. These results were further confirmed in 78 Sardinian bipolar I and II patients (Baldessarini et al. 1997), as well as in a secondary analysis of data pooled from both studies plus 19 new added cases (Baldessarini et al. 1996). Of note, and as stated by the authors, patients discontinuing lithium while starting an episode of hypomania or depression were not included in these studies. Lithium discontinuation was not part of a study

protocol. The most common reason for stopping lithium (55 % of patients) was the patient's wish to discontinue treatment after several years of stability; pregnancy or significant adverse effects were the reasons for stopping lithium in 21 % of patients (Baldessarini et al. 1999b). The remaining 24 % were patients refusing ongoing treatment with lithium after years of affective stability, but who were open to trying other mood stabilizers in the future if required.

After increasing the total number to 227 bipolar I and II patients, Baldessarini and colleagues (1998, 1999b) carried out a pooled analysis on the effects of rapid (1–14 days) versus gradual (15–30 days) discontinuation. Before discontinuation, patients were treated on average for 4.2 ± 3.3 years. Average lithium level was of 0.60 ± 0.13 mM/L. Time to 50 % risk of a first recurrence was three times shorter after rapid versus gradual discontinuation (6 versus 24 months). Without alternative maintenance treatment, the chances of affective stability for up to 3 years after lithium discontinuation were nearly three times greater after gradual versus rapid discontinuation in these patients (Baldessarini et al. 1999b). The consequences of the interruption of treatment were mostly observed during the first few months after discontinuation, and no clinical predictor allows us to identify which patients will relapse.

In line with these observations, it has been reported that abrupt reduction of serum lithium concentration by about 50 % may also have a clinical impact (Gelenberg et al. 1989; Waters et al. 1982; Rosenbaum et al. 1992).

14.4 Lithium Discontinuation/Reintroduction and Suicide Rate

Several long-term studies and meta-analyses including large samples of bipolar subjects have shown a preventive effect of lithium on suicide risk (Cipriani et al. 2005; Lewitzka et al. 2012; Baldessarini et al. 2006; Goodwin et al. 2003).

The effects of lithium discontinuation/reintroduction on completed and attempted suicide were evaluated in a sample of 300 bipolar I and II patients (Baldessarini et al. 1999a, b; Tondo et al. 1998). Before lithium prescription, the rate was 2.3/100 patient-years. It diminished to 0.36 during lithium maintenance, corresponding to 6.5-fold decrease. After lithium discontinuation, the rate rose to 4.9/100 patient-years, corresponding to a nearly 14-fold increase. The risk of completed suicide rose 13-fold (Baldessarini et al. 1999a; Tondo et al. 1998). Interestingly, suicide risk rose 20-fold during the 12 months after discontinuation and then decreased at a rate approaching pre-lithium treatment. To our knowledge, there are no available data on lithium's effect on suicide attempts/fatalities after reintroduction.

14.5 Lithium Discontinuation and Pregnancy

For women taking lithium as maintenance treatment, anticipation or occurrence of pregnancy is a reason to discontinue the drug. Several studies suggest that pregnancy does not have a protective effect on mood instability and that about 50 % of women

with bipolar disorder are symptomatic during pregnancy and carry a risk of recurrence up to 70 %, particularly in the post-partum period (Viguera et al. 2011, 2007).

In a prospective observational study, Viguera and colleagues showed that discontinuation of lithium or other mood stabilizer during pregnancy, particularly abruptly, is associated with a high risk of mood episode recurrence (Viguera et al. 2007).

In a recent retrospective case series, Deiana and colleagues (2014) compared five women off lithium with seven women on lithium during pregnancy. Of note, all the off-lithium pregnancies were unplanned, and none of them was taking concomitant medication, except one, who was on T4. Lithium was discontinued 24–48 h before caesarean delivery, as suggested by the ISBD guideline (Ng et al. 2009) and was reintroduced when patients were medically stable. Four out of five patients who were off lithium presented an episode during pregnancy and during the post-partum period, whereas two occurred (one possibly due to low lithium dosage) in the post-partum in the seven women on lithium and none during pregnancy.

Even though the number was small, these data suggest a higher rate of recurrence among women who discontinued lithium and a greater risk in the post-partum period (Deiana et al. 2014). Although lithium is frequently reintroduced in previous responders after treatment cessation during pregnancy, there are no published data on the effectiveness of its reintroduction in women who stopped treatment during pregnancy and/or breastfeeding.

14.6 Lithium Reintroduction in Patients Who Were Lithium Good Responders

The phenomenon of lithium refractoriness, that is, a loss of effectiveness when lithium is reintroduced, was proposed by Post and colleagues and subsequently by other authors (Appleby et al. 2006; Bauer 1994; Maj et al. 1995; Oostervink et al. 2000; Post et al. 1992). Other studies have not confirmed these observations (Coryell et al. 1998; Tondo et al. 1997; Baldessarini et al. 1999b).

Two studies included in a meta-analysis suggest that lithium is less effective after discontinuation and reintroduction, and three found no change in effectiveness (de Vries et al. 2013), which allows the authors to conclude that their results do not rule out the possibility of refractoriness in selected subgroups of patients. However, available data do not provide convincing evidence that lithium is less effective when treatment is restarted after discontinuation (de Vries et al. 2013). Since the mechanism of lithium action remains largely unknown, it is difficult to suggest a pharmacological explanation for this possible observation.

14.7 Summary

It is now clearly established that lithium discontinuation is associated with an increased risk of mood episode recurrence in the following months. Moreover, abrupt or rapid discontinuation has been shown to decrease time to recurrence.

Discontinuation of lithium during pregnancy has also been shown to be associated with a high risk of recurrence. Similarly, suicide risk increases markedly during the 12 months after discontinuation.

The phenomenon of lithium refractoriness, or loss of effectiveness, when lithium is reintroduced, described by some authors, is not confirmed by available data. Therefore, reintroduction of lithium treatment for patients who were good responders until lithium was discontinued is justified.

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