

Short Report

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Timing of onset of lithium relapse prevention in bipolar disorder: evidence from randomized placebo-controlled trials

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Dr. Taylor reports personal fees from Sunovion, Otsuka, Lundbeck, outside the submitted work.

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Summary

Lithium is widely prescribed, but the timing of key effects remains uncertain. The timing of onset of its relapse prevention effects is clarified by placebo-controlled randomised trials (k=3, n=1120). Lithium reduced relapse into any mood episode over the first two weeks of treatment - hazard ratio 0.40, 95%CI 0.16 to 0.97. Fewer manic relapses were evident within the first four weeks, however early effects on depressive relapse were not demonstrated. There is an early onset of lithium relapse prevention effects in bipolar disorder, particularly against manic relapse. Full effects against depressive relapse may develop over a longer period.

Introduction

Lithium is a key agent in the treatment of bipolar disorder, with well-established actions in relapse prevention [1]. However ongoing uncertainty around its underlying mechanisms [2] complicates efforts to develop improved future treatments.

A clear understanding of the timing of clinical effects provides information not just of clinical relevance, but can also clarify fundamental underlying biological mechanisms - for example through constraining potential models of action. Lithium has a wide variety of biological effects, but none of the hypotheses for its mechanism of action have been conclusively confirmed [2]. The timing of onset of its prophylactic effect was recently highlighted as a key uncertainty [2]. Lithium must have some rapid central effects, given its effectiveness in the acute treatment of manic episodes over a periods of days or weeks, however it is often suggested that beneficial preventative effects may take a long time to become apparent [3,4].

Combining data from multiple clinical trials is an approach that combines the methodological power of experimental intervention with sufficient statistical power to demonstrate potentially subtle early effects. In other areas of psychiatry, such an approach has successfully clarified timing of clinical effects [5]. Here we sought to investigate the early effects of lithium on relapse rates in bipolar disorder through meta-analysis of survival curve data from placebo-controlled randomised controlled trials.

Method

Placebo-controlled randomized clinical trials of lithium for relapse prevention in bipolar disorder were identified from an existing systematic review and meta-analysis [1], original protocol in the Cochrane Library, search updated to May 2018. From these, studies were identified that presented survival curve data on relapse with weekly resolution of data. In studies with more than two treatment arms, outcome data from those not randomized to placebo or lithium were not used in this analysis.

Survival curve data were extracted using a plot digitizer (<http://arohatgi.info/WebPlotDigitizer>, version 3.11). Interval Hazard Ratios (HR) and their variance were estimated as previously described [6,7]. Hazard ratios for those randomized to lithium versus those randomized to placebo in each trial were calculated for relapse into any mood episode. Pooled estimates of HR and 95% Confidence Intervals (CI) were obtained by inverse variance meta-analysis with a random effects model. Heterogeneity was assessed by use of I^2 . Relapses into mania and depression were also assessed separately. Given these pole-specific relapses necessarily involved fewer events, hazard ratios were calculated over longer intervals, providing reduced temporal resolution.

Analyses were performed using *R* (version 3.3.2), with *meta* package (version 4.7).

Results

Three placebo-controlled randomized clinical trials of relapse prevention in bipolar disorder were identified for inclusion [8–10]. The studies had included lithium as an active comparator; two were designed to investigate lamotrigine [8,9] and one quetiapine [10], and are described further elsewhere [1]. A total of 1120 people with DSM-IV bipolar I disorder had been randomised to either lithium or placebo, of whom 40% had an index depressive episode, 60% had an index manic or mixed episode.

Relapse

For relapse into any mood episode, an early reduction in risk of relapse was seen in those randomized to lithium. Between baseline and week 2, those randomized to receive lithium were significantly less likely to relapse than those randomized to placebo (HR 0.40, 95% CI 0.16 to 0.97). Similarly, a significant reduction was seen between week 2 and week 4 (HR 0.62, 95% CI 0.41 to 0.93), and similar effects seen over following intervals (Figure 1A), although the effect over the final time interval assessed did not reach statistical significance (HR 0.50, 95% CI 0.24 to 1.03). Substantial heterogeneity between studies was evident for this final estimate (I^2 87%; Figure 1B).

Figure 1 near here

Manic relapse

For risk of manic relapse, risk was lower in those randomized to receive lithium between baseline and week 4, HR 0.41 (95% CI 0.24 to 0.73), with a similar effect between week 4 and week 15, HR 0.47 (95% CI 0.32 to 0.69), and between week 15 and week 76 (HR 0.36, 95% CI 0.21 to 0.63) (Figure 1C).

Depressive relapse

For depressive relapse, there was no significant reduction in relapse rates in those randomized to lithium between baseline and week 4 (HR 0.84, 95% CI 0.51 to 1.38), however rates of depressive relapse were lower in the lithium group between weeks 4 and 15 (HR 0.65, 95% CI 0.44 to 0.96) but not statistically significant between week 15 and week 76 (HR 0.38, 95% CI 0.09 to 1.54) (Figure 1D).

Heterogeneity estimates were lower for manic relapse (I^2 between 0 and 42%) than for depressive relapse (I^2 between 32% and 86%)

Discussion

This analysis combined data from three placebo-controlled randomized clinical trials of lithium for relapse prevention in bipolar disorder. People with bipolar I disorder randomised to lithium rather than placebo have a lower risk of relapse evident within the first two weeks of treatment. Considering poles of illness separately, the full effect to reduce manic relapse appears evident within the first four weeks (HR 0.41, 95% CI 0.24 to 0.73), however early effects on depressive relapse are not clearly demonstrated (HR 0.84, 95% CI 0.51 to 1.38).

The magnitude of the early preventative effects found here are similar to the overall relative risks previously described [1] for both any relapse (RR 0.66, 95% CI 0.53 to 0.82), and manic relapse specifically (RR 0.52, 95% CI 0.38 to 0.71). These data indicate that in future studies of the mechanism of action of lithium in preventing relapse in bipolar disorder, anti-manic mechanisms should be apparent within four weeks of use, however the mechanisms underlying its effects against depressive relapse may take longer to become apparent.

The temporal resolution of this analysis is restricted by the size of underlying studies, and the risk of relapse over time, and the underlying review was not designed specifically to identify timing of onset data. If there were a substantial delay in onset of relapse prevention effects within the first two weeks, one would expect the overall estimate for that period to be lower than for later intervals. This does not on initial inspection seem to be the case for total relapse or manic relapse specifically.

However, the results here are consistent with a slower onset of preventative effects for depressive relapse. These results avoid any bias by enrichment design, as trial participants were not pre-selected for acute episode response to lithium. However,

the conventional approach in reporting relapse in trials in bipolar disorder may tend to underestimate longer-term benefits against depressive relapse due to differential withdrawal from study follow-up [11], and limited numbers of depressive relapses recorded lead to reduced statistical power.

It has been suggested that beneficial preventative effects of lithium may take years to become fully apparent [3]. Very late onset effects may not be well captured by typical clinical trials given their duration, so such effects may need to be investigated by other methods, through the use of large observational datasets such as those becoming available through the use of electronic health records [12].

These data indicate that there is an early onset of lithium relapse prevention effects in bipolar disorder, particularly against manic relapse. These early effects are similar in magnitude to longer-term estimates previously demonstrated. Full effects against depressive relapse may develop over a longer period.

Legends

Figure 1. A. Effect of lithium versus placebo on risk of relapse in bipolar I disorder over time (weeks). Hazard ratios with 95% Confidence Intervals shown for relapse into any mood episode. Vertical dashed lines mark the boundaries of time intervals over which HR estimates were made. Horizontal axis logarithmic for clarity. B. Forest plot of Hazard ratio estimates over consecutive time intervals. C. Effect on risk of relapse into manic episodes D. Effect on risk of relapse into depressive episodes

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