

Review: lithium reduces relapse rates in people with bipolar disorder

Geddes JR, Burgess S, Hawton K, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004;**161**:217–22.

Q Does lithium reduce relapse rates in people with bipolar disorder?

METHODS

 **Design:** Systematic review with meta-analysis.

 **Data sources:** The Cochrane Collaboration databases, reference lists, textbooks, relevant journals, and conference abstracts were searched. Trial authors were contacted, as were other experts and pharmaceutical companies.

 **Study selection and analysis:** Randomised controlled trials (RCTs) of ≥ 3 months, comparing lithium with placebo for the maintenance of bipolar disorder were included. Trials where one group abruptly discontinued lithium and those with mixed groups of people with bipolar and unipolar disorder were excluded. Study quality was assessed to determine allocation concealment and blinding. STATA software was used to conduct meta-analyses, leading to pooled fixed effects and random effects relative risk (RR) ratios.

 **Outcomes:** Risk of relapse (total, manic, depressive), total withdrawal rates, risk of specific adverse events.

MAIN RESULTS

Five RCTs met inclusion criteria ($n = 770$), with follow up periods of 11 months to four years. Total relapses: lithium prevented significantly more relapses compared with placebo (risk of relapse, lithium *v* placebo: 40% *v* 60%; RR 0.65, 95% CI 0.50 to 0.84). Manic episodes: lithium prevented significantly more manic episodes compared with placebo (risk of relapse, lithium *v* placebo: 14% *v* 24%; RR 0.62, 95% CI 0.40 to 0.95). Depressive relapses: there were no significant differences between groups (risk of relapse lithium *v* placebo: 25% *v* 30%; RR 0.85, 95% CI 0.66 to 1.11). Overall withdrawal from trials was lower with lithium (RR = 0.86, 95% CI 0.80 to 0.93). Adverse effects more common with lithium were somnolence, nausea, and diarrhoea.

CONCLUSIONS

Recent trial evidence shows that lithium reduces the rate of relapse for people with bipolar disorder. A meta-analysis of five trials showed a significant reduction in relapses in the lithium group overall, more pronounced for manic episodes than depressive episodes.

NOTES

Although lithium has been in use for over 50 years, much of the RCT evidence is new, having been published from 2000 onward. In these trials, lithium has been used in a comparison arm when new drug agents are being studied for management of bipolar disorder. Bias in

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favour of lithium is therefore unlikely. In the original paper, there was an error in table 1: the previous lithium use in Kane *et al*'s 1982 study should have been listed as "unclear". Also, in figure 3, the rate of depressive relapse with placebo in Bowden *et al*'s 2003 study should have been 30% ($n = 21$ of 70). The pooled depressive relapse rate with placebo was therefore 30% ($n = 89$ of 297) rather than 32%. The pooled fixed effect relative risk (reported on p 219) was 0.83 (95% CI 0.63 to 1.08) and the random effects relative risk was 0.85 (95% CI 0.66 to 1.11). These changes do not materially change the conclusions of the article.

Commentary

For more than 50 years, lithium has been used for acute and long term treatment of mood disorders. Worldwide, many evidence-based treatment guidelines plus clinicians and researchers consider lithium to be the mood stabiliser of choice for maintenance treatment of bipolar¹ and unipolar² disorder. However, until recently, the number of large controlled studies with sound methodology has been limited. Lithium, being an inexpensive drug, has not been a focus of pharmaceutical companies for obvious reasons for many years. Due to new drug developments this situation has changed. As several recent large scale trials investigating the efficacy of newer compounds for bipolar disorder included lithium as a comparator drug, it seems more than timely to re-examine lithium's efficacy in relapse prevention in bipolar disorder. The number of studies and subjects included in these trials is now sufficiently high to perform a meta-analysis.

The paper by Geddes *et al* is, to the best of my knowledge, the first published, methodologically rigorous meta-analysis of randomised, double blind, placebo controlled trials comparing lithium with placebo in the prevention of relapse in bipolar disorder. The overall results of this meta-analysis give firm evidence that lithium reduces the risk of affective relapse in bipolar disorder. Specifically, there is reasonable evidence that lithium prevents manic relapse, but less evidence that lithium prevents depressive relapses. These results will reassure clinicians that lithium still "works", particularly for the prevention of mania and also for relapse prevention of depression, albeit to a lesser extent compared with mania. The latter result suggests that clinicians may want to consider alternative mood stabilisers³ if lithium fails to prevent depression in individual patients, or a combination of another mood stabiliser with lithium. Unfortunately, the evidence from controlled trials on the efficacy of such combination treatments is very limited to date, but the combination of two or even more mood stabilisers seems clinically reasonable and therefore worth recommending to effectively prevent depressive in bipolar disorder.

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- Müller-Oerlinghausen, Berghöfer A, Bauer M. Bipolar disorder. *Lancet* 2002;**359**:241–7.
- Bauer M, Whybrow PC, Angst J, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP). Guidelines for biological treatment of unipolar depressive disorders, part 2: Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. *World J Biol Psychiatr* 2002;**3**.
- Goodwin GM, Bowden CL, Calabrese JR, *et al.* A pooled analysis of two placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* 2004;**65**:432–41.