

**SYSTEMATIC REVIEW AND META-ANALYSIS ON LITHIUM
FOR SUICIDE PREVENTION IN AFFECTIVE DISORDERS**

PROTOCOL

Andrea Cipriani, Keith Hawton, Sarah Stockton and John R. Geddes

VERSION 1.2 – OCTOBER 2011

BACKGROUND

In our previous study (Cipriani et al., 2005), the evidence seemed unequivocal that patients treated with lithium were much less likely to die from suicide or from any cause than patients given an alternative to lithium, whether the alternative was placebo or another compound. However, some issues remain to be addressed. First, even though it is true that observational and randomised studies suggest that long-term lithium treatment has a significant antisuicidal effect in mood disorders, it is still uncertain whether this association is a genuine therapeutic effect for both unipolar and bipolar disorders. Second, in our review the low numbers of events led to substantial random error and, consequently, unstable estimates of the treatment effect with wide confidence intervals. Thus, because of the small numbers of events and small size of the trials, only one or two moderately sized trials with neutral or negative results could materially affect the estimates. Since our last update on the matter, new evidence has emerged and it is important to include this new studies because the debate about the potential effect of lithium on suicide prevention is still debated in the scientific literature (Perlis 2011).

METHODS

Types of studies and types of participants

RCTs (either double-blind, single-blind or open) comparing lithium with another active drug (antipsychotic, mood stabiliser or antidepressant) or placebo as oral therapy in the long term treatment of mood disorders (unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling, diagnosed according to DSM and ICD criteria) will be included. We arbitrarily defined long-term treatment as treatment with a minimum duration of 3 months (more than 12 weeks). A concurrent Axis I diagnosis of another psychiatric disorder will be considered as exclusion criteria. A concurrent Axis II diagnosis of psychiatric disorder will not be considered as exclusion criteria. No restrictions in terms of age will be applied (children, adolescents, adult and elderly will be included). Studies with patients with a serious concomitant medical illness as an inclusion criterion will be excluded. All add-on studies will be included as well. We therefore will investigate heterogeneity between these different types of studies. Quasi-randomized trials (such as those allocating by using alternate days of the week) will be excluded.

Outcome measures

To compare lithium with all other active treatments (or placebo) in terms of:

- number of people who committed suicide
- number of people who committed suicide and deliberate self harm (suicidal ideation only was not considered an outcome)
- number of people who died due to any cause

Search strategy

All published and unpublished randomized controlled, trials will be identified (search date: October 2011). We will identify relevant trials from systematic searches in the following electronic databases, MEDLINE, EMBASE, CINAHL, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also consult trial databases of the following drug-approving agencies - (the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) in the EU. Web-based clinical trial registries will be hand-searched for published, unpublished and ongoing controlled trials. No language restrictions will be applied. The terms used will be as follows: (lithium or lithium carbonate or calith or camcolit* or carbolit* or ceglution or duralith or durolith or eskalith or hypnorex or hynorex or hyponrex or lentolith or licab or licarb or licarbium or lidin or lilipin or li?liquid or li-liquid or lilitin or limas or liskonum or litarex or lithan or lithane or litheum or lithicarb or lithionate or lithizine or lithobid or lithocarb or lithocap or lithonate or lithosun or lithotabs or litheril or lilitent or manialit* or maniprex or phanate or phasal or plenur or priadel or quilonium or quilonorm or quilonum or teralithe or theralite) AND (mood disorders or affective disorders, psychotic or bipolar disorder or cyclothymic disorder or depressive disorder or depression, involuntional or dysthymic disorder or seasonal affective disorder or affective disorders or depression, reactive or dysthymic disorder or seasonal affective disorder or affective disorders, psychotic or bipolar disorder or affective disorders or bipolar disorder or cyclothymic personality or major depression or dysthymic disorder or endogenous depression or involuntional depression or reactive depression or recurrent depression or treatment resistant depression or seasonal affective disorder or schizoaffective disorder or affective neurosis or depression or dysthymia or involuntional depression or manic depressive psychosis or bipolar depression or schizoaffective psychosis or depress* or bipolar or schizoaffective). In addition, other relevant articles and major textbooks that cover mood disorders will be checked. The authors of significant papers, other experts in the field, and pharmaceutical companies that manufacture lithium or the comparator drugs will be contacted to identify other relevant published or unpublished randomized, controlled trials and to supplement the incomplete report of the original papers. We will also check the websites of these manufacturers for further studies.

Study selection and data extraction

Two reviewers will independently extract data (AC and JRG or KH); disagreements will be resolved by discussion and consensus with a third member of the team (JRG or KH). We will assess the methodological quality of studies according to the criteria of the Cochrane Reviewers' Handbook (Higgins & Green, 2011). Where inadequate details of allocation concealment and other characteristics of trials are provided, the trial authors will be contacted in order to obtain further information. If the raters disagree, the final rating will be made by consensus with the involvement (if necessary) of another member of the review group. For trials in which our outcomes of interest is not reported, we will attempt to obtain the required data from the original authors. As for our previous systematic reviews, we will design and use a structured data abstraction form to ensure consistency of appraisal for each study. Information extracted will include study characteristics (such as lead author, publication year, journal, study setting, sponsorship), participant characteristics (such as diagnostic criteria, mean baseline score, age), intervention details (such as dose ranges, mean doses of study drugs, concomitant and/or rescue medications) and outcome measures.

Comparability of dosages

We will include only studies randomizing patients to drugs within the therapeutic dose (both fixed-dose and flexible-dose designs will be allowed). There is the possibility that some trials compare one agent at the upper limit of its therapeutic range with another agent at the lower limit of its therapeutic range within the same study. We may look at heterogeneity and then add a variable (yes/no) that report if dosages are comparable and use this information for analysis.

STATISTICAL ANALYSIS

Data from intention-to-treat analyses will be used where possible; otherwise endpoint data for trial completers will be used. Deaths and self-harm are comparatively rare in clinical trials, and data will likely be sparse. Several trials will have no such events in one or more arms. Meta-analysis of sparse data can be problematic, because some methods add continuity corrections to trial arms with zero events, and these corrections may exert a substantial effect on the overall results (Sweeting et al., 2004). Peto's method will be used to calculate odds ratios and 95% confidence intervals (CIs) because this method does not apply continuity corrections and has been shown to be the most reliable method when applied to data on sparse events from studies without extreme imbalances (Sweeting et al., 2004). Trials with no events in any treatment arm will be excluded from the analyses because they are uninformative. Statistical heterogeneity, in which variation between the results of the

individual trials is greater than can be explained by chance alone, will be investigated with chi-square tests. Data will be analyzed by using RevMan 5. Sensitivity analyses using other meta-analytic methods will be done to assess the robustness of the results. For trials with more than two arms, we will consider each pairwise comparison as if it is separate two-arm trials. For example, if a trial compares lithium with another active drug and with placebo, we will include the lithium versus placebo arm and the lithium versus active drug arm as separate trials. This approach will include the single lithium group twice in the meta-analysis. We therefore will investigate the effect of this double counting by sensitivity analyses that exclude each of the two trials from the pooled analysis.

Sensitivity analyses

To investigate the effect of lithium on unipolar depression only and to focus on lithium effect on children and adolescents, two sensitivity analyses were performed according to the following variables:

- including only studies recruiting patients with unipolar disorder (studies with at least two thirds of patients with unipolar depression were eligible);
- including studies recruiting only patients aged less than 18 years.

REFERENCES

Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry*. 2005;162(10):1805-19

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.1 [updated March 2011

Perlis RH. Hard outcomes: clinical trials to reduce suicide. *Am J Psychiatry*. 2011;168(10):1009-11

Sweeting MJ, Sutton AJ, Lambert PC: What to add to nothing? use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004; 23:1351–1375