Lithium augmentation in treatment-resistant-depression: meta-analysis of placebo-controlled studies

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Authors' objectives
To determine whether evidence exists to support the clinical efficacy of lithium augmentation in refractory depression.

Searching
MEDLINE (1980 to June 1997) was searched using the keywords 'lithium augmentation', 'lithium addition', 'lithium with augmentation', and 'lithium with depression'. The Cochrane Library (no dates given) was searched using the keywords 'lithium augmentation' and 'lithium addition'. An intensive search by hand using the references of published reviews on lithium augmentation and standard textbooks on refractory depression was undertaken. No language constraints were applied.

Study selection
Study designs of evaluations included in the review
Placebo-controlled, double-blind studies. Preliminary reports of placebo-controlled trials were excluded if the final version was published in the meantime.

Specific interventions included in the review
Lithium (lithium, lithium carbonate) at daily doses of 250-1,200mg (in five studies lithium dose was adjusted according to serum levels (range 0.5-1.1 mEq/L)), for a duration of 2-42 days, was added to pre-study treatment regimens (duration of 3-6 weeks) of conventional antidepressants (amitriptyline or equivalent (150-300 mg/day), desipramine (150-300 mg/day), mianserin (90-120 mg/day), imipramine or equivalent (greater than or equal to 150 mg/day or minimum dose of 2.5 mg/kg of body weight), phenelzine (greater than or equal to 60 mg/day), maprotiline (150-200 mg/day), fluvoxamine (greater than or equal to 150 mg/day), dibenzepine (greater than or equal to 480 mg/day), fluoxetine (20 mg/day), lofepramine (140-210 mg/day) and citalopram (40-60 mg/day)). All studies compared placebo addition in place of lithium.

Participants included in the review
Persons who satisfied accepted operationalised diagnostic criteria for depression (American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, DSM-III; International Classification of Diseases, ICD-9; or Research Diagnostic Criteria, RDC) and had not responded to treatment with conventional antidepressants. Mean ages ranged from 37-54 years and the male to female ratio was approximately 4:7.

Outcomes assessed in the review
The primary outcome measure was response to lithium (response or no response) defined as a greater than or equal to 40% decrease in Hamilton Rating Scale for Depression (HAM-D) score, final HAM-D score less than 7, greater or equal to 50% decrease in HAM-D score, greater or equal to 50% decrease in HAM-D score and final HAM-D score less than 10, or decrease of 2 or more points on Short Clinical Rating Scale (SCRS). For inclusion, response criteria based on the acceptable measurement of depression as an outcome variable had to be specified.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The quality of each study was assessed according to a quality assessment scale (see Other Publications of Related Interest no.1). Because not every question on the scale was applicable to every study, quality was expressed as a percentage of achievable scores. The quality of each study was assessed independently by two investigators. Results
were compared and differences were discussed and settled by consensus.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on: patient characteristics, initial antidepressant therapy, study design, study therapy, response criteria, number of lithium responders/non-responders, number of placebo responders/non-responders and quality score. The odds ratio together with its 95% CI was calculated for every study (see Other Publications of Related Interest no.2).

**Methods of synthesis**
How were the studies combined?
Odds ratios and 95% CIs were combined using the Mantel-Haenszel method (see Other Publications of Related Interest no.2). Additionally, a pooled risk ratio, a pooled risk difference (see Other Publications Of Related Interest no.3) and number needed to treat were calculated. The variance of the studies' effect sizes was not taken in account when calculating CIs.

Pooling of all studies was undertaken only for exploratory purposes. For confirmatory purposes, only those studies that used a minimum dose of 800 mg/day, or a dose sufficient to reach lithium serum levels greater than or equal to 0.5 mEq/L and a minimum duration of treatment of 2 weeks were combined.

How were differences between studies investigated?
The variance of the pooled estimate was calculated (see Other Publications of Related Interest no.4). Although no statistically significant heterogeneity was found, clinically relevant heterogeneity was investigated. Cumulative meta-analyses (see Other Publications of Related Interest no.5) were performed with respect to lithium dosage (in increasing order) and duration of lithium therapy (in increasing order).

As a further sensitivity analysis, the pooling of the odds ratios was also performed using other methods (see Other Publications Of Related Interest no.6 and no.7).

**Results of the review**
Nine RCTs (n=234) were included in the meta-analysis. A study by Cournoyer et al was not included in the meta-analysis because no response criteria were given. In this study, 12 patients with major depressive disorder (RDC and DSM-III) were considered tricyclic antidepressant-resistant after 21 days of treatment with amitriptyline or trimipramine (200 mg/day) and entered a 48-hour double-blind cross-over study. Significant improvement occurred with lithium, but not with placebo.

The trials included in the meta-analysis achieved quality scores ranging from 39 to 93%.

Combining three studies (n=110) that used a minimum dose of 800mg/day, or a dose sufficient to reach lithium serum levels greater than or equal to 0.5 mEq/L, and a minimum treatment duration of 2 weeks indicated that the response rate during lithium administration was greater than during placebo treatment, pooled odds ratio (OR) 3.31 (95% CI: 1.46, 7.53). No significant heterogeneity was found (p=0.851). The corresponding relative risk was 2.14 (95% CI: 1.23, 3.70), the risk difference was 27% (95% CI: 9.8%, 44.2%), and the number needed to treat was 3.7 (95% CI: 2.3, 10.2).

Combining all studies (n=234) included in the review resulted in higher estimates, OR 3.89 (95% CI: 2.14, 7.08). No significant heterogeneity was found (p=0.119). The relative risk was 2.25 (95% CI: 1.45, 3.51), the risk difference was 29% (95% CI: 18.6, 39.4) and the number needed to treat was 3.4 (95% CI: 2.6, 5.4).

Two cumulative meta-analyses were performed. The first showed that there is a significant lithium effect from a dose of 600 to 800 mg/day onward. The second demonstrated a significant lithium effect from the point of including studies of at least 7 days duration.
Authors' conclusions
With respect to efficacy, lithium augmentation is the first-choice treatment procedure for depressed patients who fail to respond to antidepressant monotherapy. Study results indicate that lithium augmentation should be applied for a minimum of 7 days at doses that are sufficient to reach lithium serum levels of greater than or equal to 0.5 mEq/L.

CRD commentary
Overall, the methodology of the review was fairly good. It addressed a well-defined review question and included appropriate, clear inclusion/exclusion criteria. The literature search could have been more extensive and publication bias explored using a funnel plot. Quality of the individual studies was formally judged but no detail was given regarding the extraction of data. Heterogeneity was assessed and did not appear to be statistically significant. However due to evidence of clinically relevant heterogeneity, heterogeneity was explored in two cumulative meta-analyses.

The authors' conclusions should be approached with caution due to the small number of studies included in the 'confirmatory' meta-analysis. However, findings from the cumulative meta-analyses appear to support the conclusions regarding dose and duration of treatment.

Implications of the review for practice and research
Practice: The authors state that lithium augmentation with respect to efficacy is recommended for depressed patients who do not respond to therapy with conventional antidepressants. Study results indicate that lithium augmentation should be applied for a minimum of 7 days at doses that are sufficient to reach lithium serum levels of greater than or equal to 0.5 mEq/L.

Research: The authors do not state any recommendations for further research.

Bibliographic details

PubMedID
10505584

Other publications of related interest
Correction by authors to "Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies". J Clin Psychopharmacol 2000;20:287.


These additional published commentaries may also be of interest. Lam RW. Review: lithium augmentation increases treatment response in refractory depression. Evid Based Med 2000;5:88. Lithium augmentation for treatment-resistant depression. Bandolier 2000;77:4-5.
MeSH
Antidepressive Agents /therapeutic use; Depressive Disorder /drug therapy /psychology; Double-Blind Method; Drug Therapy, Combination; Humans; Lithium /therapeutic use; MEDLINE; Psychiatric Status Rating Scales; Randomized Controlled Trials as Topic; Research Design; United States

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.