The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis

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CRD summary
This review concluded that lamotrigine augmentation may be an effective treatment for patients with clozapine-resistant schizophrenia. The conclusions were appropriately cautious, but there were some limitations in the reporting of review methods and study details.

Authors’ objectives
To assess the efficacy and safety of lamotrigine for the treatment of clozapine-resistant schizophrenia.

Searching
The database of the Cochrane schizophrenia group was searched without year or language limits. This includes searches of journals and conference proceedings and the following databases: BIOSIS Inside, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, EMBASE, MEDLINE and PsycINFO. Clinical trials registers and a trial register of the drug manufacturer were searched. Some details of search terms were reported. Reference lists were searched and authors were contacted.

Study selection
Double-blind randomised controlled trials (RCTs) of lamotrigine augmentation to clozapine in patients with schizophrenia who were resistant to clozapine were eligible for inclusion. The primary outcome was the total symptom score for Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS). Secondary outcomes were scores for positive and negative symptoms and adverse events.

The included studies all compared lamotrigine to placebo with doses that ranged from 100mg/day to 400mg/day taken for between 10 and 24 weeks.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Double-blinding was a requirement of the inclusion criteria. Two authors independently assessed allocation concealment as low, medium or high risk of bias (using criteria of the Cochrane Collaboration Handbook). Studies classed as high risk of bias were excluded from the meta-analysis.

Data extraction
Means and standard deviations of the symptom score at baseline and follow-up (on an intention-to-treat basis using last observation carried forward) were extracted and used to calculate standardised mean differences (SMD) (using Hedge's g) of the change from baseline. A cut-off of 20% or greater reduction in their total global score was used to classify patients as responders or non-responders; these binary data were used to calculate odds ratios (OR). For cross-over trials, data were used from the first period only.

Data were extracted by two reviewers independently. Disagreements were resolved by discussion.

Methods of synthesis
Data were pooled in either a fixed-effect or random-effects model depending on the amount of heterogeneity. Heterogeneity was assessed with a $\chi^2$ test and the I$^2$ statistic.

Results of the review
Five trials (n=161) were included. Sample size ranged from four to 60. All studies were rated as low risk of bias for allocation concealment. Two studies were funded by industry. No statistically significant heterogeneity was observed and so all results were from fixed-effect models.
Lamotrigine augmentation was superior to placebo for total symptom scores (SMD 0.57, 95% CI 0.25 to 0.89, I² = 37%), positive symptoms (SMD 0.34, 95% CI 0.02 to 0.65) and negative symptoms (SMD 0.43, 95% CI 0.11 to 0.76). Lamotrigine was associated with a higher proportion of patients who responded (OR 0.19, 95% CI 0.09 to 0.43; number needed to treat=4, 95% CI 3 to 6). There were three reports of severe adverse events that involved psychiatric symptoms after lamotrigine (with facial pain and gingival infection in one case) and two cases that involved psychiatric symptoms for placebo. Rash was reported in four lamotrigine and two placebo patients. There was no difference in drop-out rate.

Authors' conclusions
Lamotrigine augmentation may be an effective treatment for patients with clozapine-resistant schizophrenia.

CRD commentary
This review had a clear question and stated inclusion criteria for study design, interventions and setting. The search was extensive and covered a range of sources without language restrictions. Inclusion criteria were restrictive on use of double-blinding, but the quality assessment was inadequate as it covered only one aspect of trial conduct. Data extraction and assessment of allocation concealment were performed in duplicate, but it was unclear whether study selection was performed in the same way. The methods of meta-analysis were appropriate. It appeared that no studies were excluded based on risk of bias, although (as the authors stated) the results were conservative as larger variance estimates were used. No details of participants were presented and there was no consideration of clinical heterogeneity, which seemed important as the baseline total symptom scores varied widely between studies. The conclusions of this review seem appropriately cautious, but a lack of reporting of methods and study details limited the reliability of the review.

Implications of the review for practice and research
Practice: The authors stated that augmentation treatments should only be tried in patients who had an insufficient response to clozapine.

Research: The authors stated that larger trials of longer than 12 weeks duration were needed.

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