Systematic review of lamotrigine augmentation of treatment resistant unipolar depression (TRD)

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CRD summary
This review found there was little evidence on the use of lamotrigine for adults with depression who had not responded to a course of anti-depressants. The authors' conclusions appeared to reflect the lack of evidence available, but their reliability is unclear given the small number of included studies with small sample sizes and lack of reporting on study quality.

Authors' objectives
To assess the effectiveness of lamotrigine for patients with treatment-resistant depression.

Searching
The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, Cochrane Central Clinical trials Register (CENTRAL), PubMed, EMBASE, CINAHL and PsycINFO were searched from inception; search terms were reported. Reference lists of the retrieved articles and major books were searched. Pharmaceutical companies were contacted to identify additional trials.

Study selection
Trials that assessed the effectiveness of lamotrigine in adults (aged 18 to 65 years) diagnosed with a major depressive disorder were eligible for inclusion. In eligible trials, lamotrigine had to be given at minimum doses of 50 mg daily for four weeks. Eligible patients were required to have previously received at least one anti-depressant, at recognised therapeutic doses, for a minimum of four weeks. Patients with bipolar I depression, previous prescription of lithium, co-morbid schizophrenia or drug and alcohol dependence were excluded.

The primary outcomes were response and remission rates. Outcomes measures were quantified in scores on the Hamilton Depression rating scale (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impression (CGI) scale and the Global Assessment of Functioning (GAF) scale.

The patients in the included randomised controlled trial (RCT) began treatment with a fixed dose of fluoxetine of 20mg/day and were assigned to receive either lamotrigine or placebo. The commencing dose of lamotrigine was 25mg/day for two weeks, which was increased to 50mg/day for two weeks and to a maximum dose of 100mg/day thereafter. The patients enrolled also had co-morbid personality disorders, borderline personality disorder and anti-social personality disorder.

Other included studies compared lamotrigine with lithium, or lamotrigine as augmentation to venlafaxine, mirtazepine or sertraline or other drug therapy.

Three reviewers independently performed the study selection.

Assessment of study quality
The methodological quality of the included studies was assessed using an A to C scale: A (adequate), B (uncertain), or C (inadequate). Studies were assessed for internal validity items (allocation concealment, blinding, baseline characteristics, and use of intention-to-treat analyses) and external validity items (definition of inclusion and exclusion criteria, outcome measures, and appropriate measurement of outcomes). Each item was rated A (clearly yes), B (not sure), or C (clearly no).

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data appeared to be extracted on the outcomes and reported as presented in the studies.

The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
The results were presented as a narrative summary grouped by study design.

**Results of the review**
Ten studies were included in the review (n=289 patients), including one randomised controlled trial (RCT), two randomised comparative open-label studies, two comparative open-label studies, two open-label studies and three retrospective chart reviews. The sample sizes ranged between 14 and 42 patients.

One RCT (n=23) was included in the review including 15 patients diagnosed with unipolar depression. The duration of the trial was 42 days. Four patients dropped out of the lamotrigine-treatment arm. The patients were randomly assigned to treatment and the trial used double-blinding. The analyses performed in the trial were conducted on a last-observation-carried-forward basis. There were statistically significant benefits observed in the RCT with lamotrigine compared to placebo on the CGI scale for severity (2.15 ± 1.28 for lamotrigine compared with 3.40 ± 1.17 for placebo; p=0.0308) and improvement (1.46 ± 0.66 for lamotrigine compared with 2.22 ± 0.83 for placebo, p=0.0341). There were no differences between the groups for mean HAM-D scores, MADRS scores or GAF scores.

The results of three comparative open-label studies showed lamotrigine and lithium were equally effective in lowering depressive symptoms on the HAM-D scale or HADRS. One single group study also reported improvements in outcomes with adjunctive lamotrigine. Two studies reported better tolerability in the lamotrigine groups. One single group study reported a decrease in HAM-D scores for lamotrigine augmentation to venlafaxine, mirtazepine or sertaline. One comparative open-label study found that the addition of lamotrigine to sertraline was associated with improvements on CGI scores after six weeks, but not on HAM-D scores. The three retrospective chart reviews showed response rates with lamotrigine ranging from 40.5 to 76%.

**Authors' conclusions**
A small number of retrospective studies and open label studies provided preliminary evidence for lamotrigine as an augmentation therapy in adults with treatment-resistant depression. There was little evidence to guide the use of lamotrigine for depression that had not responded to a course of anti-depressants.

**CRD commentary**
The review addressed a clear question and appropriate criteria were defined for intervention, outcomes and participants, but the inclusion criteria for study design lacked clarity. Appropriate databases were searched and attempts were made to identify unpublished literature. However, the end search dates were not reported and it was unclear whether any language restrictions were applied, so there was potential for language and publication biases. Steps were taken to minimise errors and bias for the study selection, but not for data extraction or the assessment of methodological quality.

Although study quality was assessed, the results were not reported, so adequate verification of the results of the review was not possible. A narrative synthesis of the results was appropriate given the differences between the study designs, interventions and outcomes. A number of single-group design studies were included together with some studies which were retrospective in design; these are subject to multiple biases. Few study details were reported and very little information on the participants was provided.

The authors' conclusions appeared to reflect the relative lack of evidence on the review question. However, the reliability of these conclusions is uncertain given the lack of reporting of study validity and the small number of studies with small sample sizes.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.
Research: The authors stated that further studies, particularly large randomised controlled trials, are required to confirm the efficacy of lamotrigine as augmentation therapy for treatment resistant depression.

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