Is escitalopram really relevantly superior to citalopram in treatment of major depressive disorder? A meta-analysis of head-to-head randomized trials

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CRD summary
This review compared the efficacy of equimolar doses of escitalopram and citalopram in patients with major depressive disorder. The author concluded that claims to the clinically relevant superiority of escitalopram over citalopram in the short-to-medium term were not supported. This conclusion reflected the variable evidence presented, but its reliability is unclear due to potential methodological shortcomings in the review process.

Authors' objectives
To compare the efficacy of equimolar escitalopram and citalopram in patients with major depressive disorder.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus were searched to 2009. Search terms were reported. A Cochrane review and reference lists from other reviews were also used to identify studies. One unpublished source of data was retrieved.

Study selection
Randomised controlled trials (RCTs) that directly compared escitalopram and citalopram in patients with depression were eligible for inclusion in the review. Eligible outcomes of interest were mean change in symptom score using the Montgomery-Asberg depression rating scale (MADRS) or the Hamilton depression rating scale (HAM-D), response rate (proportion of patients who achieved ≥50% reduction from baseline in MADRS or HAM-D) and mean change from baseline in the Changes in Clinical Global Impression of Disease Severity (CGI-S) score.

Most of the included trials were conducted in the European Union or USA and comprised mostly young adult, otherwise healthy outpatients with major depressive disorder without other psychopathology. Superiority and non-inferiority trials were included. Trials varied in terms of control group, primary objective and dosing regimen. Treatment ranged from four weeks to 24 weeks. Some studies reported a placebo run-in period. Two trials were considered to deliver average doses that could be judged as equimolar. Safety outcomes were expressed as discontinuation rates due to adverse events and/or lack of efficacy in patients who received at least one dose of a study drug.

The author did not state how many reviewers selected the studies.

Assessment of study quality
Trial quality assessment was conducted using Cochrane criteria.

The author did not state how many reviewers carried out the quality assessment.

Data extraction
Intention-to-treat data were extracted on the outcomes of interest using the last observation carried forward method. Relative risks, mean differences and 95% confidence intervals (CI) were calculated. Clinical relevance was defined as a reduction of two scale points on MADRS and at least 0.33 scale points on CGI-S. Small effect size was defined as 0.32 or less. Missing data were recovered or imputed using other available data as appropriate.

The author did not state how many reviewers carried out data extraction.

Methods of synthesis
Where data from more than one trial were available, relative risks, weighted mean differences and standard mean differences, with corresponding 95% CIs, were pooled in a random-effects meta-analysis. Statistical heterogeneity was assessed using Cochran Q and $I^2$. Subgroup analyses were planned at different time points (from week one to week 24) and for patients classified with severe depression at baseline (MADRS≥30). The number needed to treat to benefit (NNTB) was calculated (clinically relevant if <10).

**Results of the review**

Seven trials were included in the review (n=2,476 patients and 2,522 in the safety analysis). For six trials, an interpretation of fair quality was adopted from a previous Cochrane review. The additional trial was judged by the present authors to be of limited quality. All trials were double-blind. Three trials were placebo-controlled. Trial duration ranged from one week to 24 weeks.

Compared with citalopram, escitalopram was associated with greater reductions in MADRS symptom score and CGI-S score and a higher response rate at week eight, but none of the results were clinically relevant. Escitalopram was superior to citalopram in patients with severe depression (one trial), but this was not considered to be clinically relevant.

Discontinuation rates due to adverse events or inefficacy were comparable between the drugs up to eight weeks of treatment, beyond which data were inconclusive.

**Authors’ conclusions**

Claims about the clinically relevant superiority of escitalopram over citalopram as a treatment for major depressive disorder in the short-to-medium term were not supported by the evidence.

**CRD commentary**

The review question was clear and supported by potentially reproducible inclusion criteria. The search strategy contained relevant sources, although central reliance for study retrieval was on a Cochrane review. Attempts were made to retrieve unpublished data. Quality assessment was carried out using an appropriate tool, although the absence of independent assessment of the included studies presented a potential threat to the reliability of findings. It was unclear whether methods to minimise error and bias in the review process were used. Study details were presented. The chosen method of synthesis appeared to be appropriate given the reported clinical heterogeneity among the studies. The extent to which the primary objective of the review was addressed by most of the included studies that did not demonstrate equimolar status of the drugs was unclear.

The author’s conclusion reflected the variable evidence presented, but the reliability unclear in light of potential methodological shortcomings.

**Implications of the review for practice and research**

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**Research**: The author did not state any implications for research.

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