Escitalopram in the treatment of major depressive disorder: a meta-analysis
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CRD summary
This individual patient data review concluded that escitalopram was superior to other selected antidepressants for the treatment of major depressive disorder, largely explained by differences between escitalopram and citalopram. There were several potential methodological limitations in the review, including the search strategy, validity assessment, reporting of results, and the general review process. The reliability of the authors' conclusions is unclear.

Authors' objectives
To compare the efficacy of escitalopram and comparator antidepressants in the treatment of major depressive disorder.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from 1966 to 2007. Search terms were reported. Reference lists of retrieved articles were scanned for additional studies in any language. Unpublished studies were located through the Controlled Trials database and the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service (1972 to 2005). One manufacturer provided unpublished results for one study. Four clinical trial registration sites were searched.

Study selection
Double-blind randomised controlled trials of escitalopram compared with another antidepressant (with or without placebo), in patients aged at least 18 years, were eligible for inclusion in the review. Patients had to satisfy Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for major depressive disorder, and have a baseline score of at least 16 on the Hamilton Rating Scale for Depression (HAM-D) or at least 18 on the Montgomery-Asberg Depression Rating Scale (MADRS). The eligible primary outcome measures were HAMD or MADRS scores after at least eight weeks of treatment.

The included comparators were serotonin/noradrenaline reuptake inhibitors (SNRIs: venlafaxine, duloxetine) and selective serotonin reuptake inhibitors (SSRIs: citalopram, fluoxetine, paroxetine, sertraline) at various doses. The majority of included trials reported the MADRS total score after eight week’s treatment as the primary outcome. The mean MADRS total score at baseline was 30. Secondary outcome measures were the response to treatment (50% or more reduction in baseline MADRS or HAMD score) and remission rate (MADRS total score of 12 or below; HAMD of 7 or below) at eight weeks. The mean age of included patients was 45 years, and a higher proportion was female. The majority of included trials were industry-sponsored.

The authors did not state how papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Individual patient data were collected from the majority of included trials. Data were collected in order to calculated mean treatment differences from baseline using an all-patient-treated data set (those receiving at least one dose of study medication), rather than all randomised patients. Odds ratios (OR), with 95% confidence intervals (CIs), were calculated for response and remission rates. Where data were only provided on patients completing trials for remission rates, it was assumed that patients who had not completed trials had not responded or achieved remission. Adverse events and withdrawal rates were reported. Authors were contacted for missing data, where necessary.

The authors did not state how data were extracted, or how many reviewers performed the data extraction.

Methods of synthesis
A meta-analysis was conducted using individual patient data where available, or published values and weighted means from individual estimates. A fixed-effect model was applied. Pooled estimated treatment differences at eight weeks were calculated for the MADRS total score (all patients) and in severely depressed patients (baseline MADRS score of 30 or above).

Subgroup analyses were conducted comparing escitalopram with SNRIs and SSRIs. Sensitivity analysis was carried out using trials: which were non-randomised; had less than eight weeks duration; did not use MADRS as an outcome measure; used a fixed dose of escitalopram (20mg); according to differences in pre-treatment severity. Heterogeneity was assessed (method not reported).

Results of the review
Sixteen trials (n=4,602 patients) were included in the review (individual patient data were available for 4,549 patients).

Escitalopram versus all comparators: For all patients, escitalopram was associated with a statistically significant reduction of 1.1 points on the Montgomery-Asberg Depression Rating Scale (MADRS; 95% CI 0.6 to 1.6; 16 trials). When compared with placebo, this was 2.3 points (95% CI 1.4 to 3.1; five trials). Significantly higher response (OR 1.33, 95% CI: 1.15 to 1.53) and remission rates (OR 1.22, 95% CI 1.06 to 1.40) were reported for patients receiving escitalopram. In severely depressed patients, the mean reduction on the MADRS was 1.8 points (95% CI 1.1 to 2.5). Again, significantly higher response (OR 1.60, 95% CI 1.33 to 1.94) and remission rates (OR 1.39, 95% CI 1.15 to 1.68) were reported in this sub-group.

Escitalopram versus selective serotonin reuptake inhibitors (SSRIs): For all patients, escitalopram was associated with a statistically significant reduction of 0.9 points on the MADRS (95% CI 0.3 to 1.5). Response rates were significantly greater in the escitalopram group. For specific SSRIs, statistical significance remained only for the comparison with citalopram (mean treatment difference 1.2 points, 95% CI 0.3 to 2.1; five trials), with response and remission rates significantly greater in the escitalopram group. In severely depressed patients, the mean treatment difference compared with all SSRIs on the MADRS was 1.4 points (95% CI 0.6 to 2.2), and statistical significance remained in the comparison with citalopram. Response rates were significantly greater in the escitalopram groups.

Escitalopram versus serotonin/noradrenaline reuptake inhibitors (SNRIs): For all patients, escitalopram was associated with a statistically significant reduction of 1.7 points on the MADRS (95% CI 0.5 to 2.8). In severely depressed patients, this was 2.9 points (95% CI 1.4 to 4.4). Response and remission rates for both groups were significantly higher in favour of escitalopram. Further results are presented in the paper for analyses of escitalopram versus individual SNRIs.

Sensitivity analyses did not materially influence the main findings. Higher incidences of adverse events were reported for SSRIs and SNRIs compared to escitalopram. Higher withdrawal rates at eight weeks were noted for patients receiving comparator drugs (16 trials).

Authors' conclusions
The superior efficacy of escitalopram compared to SSRIs and SNRIs for the treatment of major depressive disorder was confirmed, although the superiority over SSRIs was largely explained by differences between escitalopram and citalopram.

CRD commentary
The question for this individual patient data review was clear, and this was supported by detailed and reproducible inclusion criteria. However, the justification for exclusion of four trials using the HAMD score from the meta-analysis was unclear, and may mean that important evidence was filtered out. The search strategy included some relevant sources, but there was very limited evidence to suggest that trialists or manufacturers were contacted to identify further studies or unpublished data. It was not clear to what extent the review process was conducted with attempts to minimise errors and bias. There was no reported validity assessment. In particular, there was no apparent attempt to perform any data checking or to verify the completeness of data with individual trialists, which are essential components of individual patient data analysis.
There was limited reporting of details and results from individual trials (including the number of randomised patients and reporting of heterogeneity). Intention-to-treat analysis was not conducted, and the general lack of clarity regarding the methods of individual patient data analysis made it difficult to assess the suitability of the assumptions made. The clinical significance of findings was questionable, and there were potential conflicts of interest arising from industry sponsorship for the review and from financial connections between two of the authors and various drug manufacturers (listed in the paper).

Given the potential methodological limitations outlined above, the extent to which the authors' conclusions are reliable is unclear.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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