Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials

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CRD summary
This generally well-conducted review concluded that duloxetine and venlafaxine-XR are effective, compared with placebo, for the treatment of major depressive disorder. Venlafaxine tends to have a favourable trend in remission and response rates compared with duloxetine. Conclusions relating to comparisons with placebo seem reliable, but the conclusion regarding the superiority of venlafaxine over duloxetine is not fully supported by the results.

Authors' objectives
To compare indirectly the efficacy and safety of extended-release (XR) venlafaxine and duloxetine for the treatment of major depressive disorder (MDD).

Searching
MEDLINE, EMBASE, and the Cochrane Library were searched from 1996 to January 2005 for published studies; the search terms were reported. The bibliographies of relevant articles were screened. Abstracts and reports in meetings or symposia were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised placebo-controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing venlafaxine-XR (75 to 225 mg/day) or duloxetine (40 to 120 mg/day) administered orally for at least 8 weeks with a placebo were eligible for inclusion. A 1-week placebo lead-in was required prior to the active intervention. In the included studies, the doses of venlafaxine and duloxetine ranged from 75 to 225 mg/day and from 40 to 120 mg/day, respectively. The duration of treatment ranged from 8 to 12 weeks.

Participants included in the review
Studies of out-patients over 18 years of age with MDD, diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (4th edition), were eligible for inclusion. A minimum score of 15 on the Hamilton Rating Scale for Depression (HAM-D), or 18 on the Montgomery-Asberg Depression Rating Scale (MADRS), was required. Studies of participants that used concomitant medication such as antidepressants or drugs that affected the central nervous system (other than low, stable doses of hypnotics or tranquillisers), or that included those with co-morbid conditions (other than those related to MDD), were excluded. Studies of elderly patients only, or people with bipolar disorder, a history of alcohol abuse or dependence, acute suicidal tendencies, a primary axis I disorder other than and unrelated to MDD, or who were therapy resistant were also excluded. Where reported, the mean age ranged from 40 to 45 years, the proportion female from 56 to 75%, the baseline HAM-D score from 17.2 to 27.6, the MADRS score from 21.5 to 29, and the Clinical Global Impression of Severity (CGI-S) score from 4.1 to 4.4.

Outcomes assessed in the review
The studies had to report at least one primary outcome, which were remission (improvement in the HAM-D to 7 or less, or the MADRS to 10 or less) and response (decrease of 50% from baseline on HAM-D or MADRS), to be included in the efficacy analysis. Studies with at least one secondary outcome, which included drop-out rates (due to lack of efficacy or adverse events) and adverse events, could be included in the safety analysis.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed primary studies for relevance, with any disagreements resolved by consensus.
Assessment of study quality
Only double-blind, RCTs were eligible for inclusion. No formal quality assessment of the included RCTs was undertaken.

Data extraction
Two reviewers independently extracted the data, with any disagreements resolved by consensus. The mean HAM-D, MADRS or CGI-S scores were extracted, with standard deviations, from each study. The number and proportion with successful remission or response, and drop-out rates, were also obtained for each study. Where studies had several fixed-dose arms, all within the dosing range specified by the inclusion criteria, these arms were combined.

Methods of synthesis
How were the studies combined?
Pooled weighted clinical rates and mean differences (MDs) from placebo rates, with 95% confidence intervals (CIs), were calculated for each outcome using a random-effects meta-analysis. For active drug comparisons, Bartlett's test was used; a Z-test was used where the test indicated homogeneity, while a Mann-Whitney U-test was used where heterogeneity was indicated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. Sensitivity analyses were conducted to investigate heterogeneity, by removing studies with outlying results. Studies that included patients with co-morbid conditions related to MDD were not included in the main analysis but were included in a sensitivity analysis.

Results of the review
Ten RCTs met the inclusion criteria (n=2,301); six evaluated duloxetine (n=1,481) and four evaluated venlafaxine (n=8,320). Five RCTs evaluating duloxetine (n=1,199) and three evaluating venlafaxine (n=580) were included in the main analyses; the other two were only included in the sensitivity analyses.

Duloxetine (5 RCTs).
Duloxetine resulted in a significantly better rate of remission (MD 0.142, 95% CI: 0.089, 0.195, p<0.001) and response (MD 0.186, 95% CI: 0.130, 0.242, p<0.001), and significantly fewer withdrawals due to lack of efficacy (MD -0.111, 95% CI: -0.159, -0.063, p<0.001) but significantly more withdrawals due to adverse events (MD 0.057, 95% CI: 0.015, 0.100, p=0.008), compared with placebo. No statistical heterogeneity was observed for any of these analyses.

Venlafaxine (3 RCTs).
Venlafaxine resulted in a significantly better rate of remission (MD 0.178, 95% CI: 0.090, 0.265, p<0.001; 2 RCTs) and response (MD 0.244, 95% CI: 0.150, 0.337, p<0.001), and significantly fewer withdrawals due to lack of efficacy (MD -0.107, 95% CI: -0.151, -0.064, p<0.001) but significantly more withdrawals due to adverse events (MD 0.061, 95% CI: 0.025, 0.097, p<0.001), compared with placebo. No statistical heterogeneity was observed for any of these analyses.

Duloxetine versus venlafaxine.
Indirect comparisons of the drugs showed no statistically significant difference in relation to remission rates, response rates or drop-out rates for any reason.

Adverse events were inconsistently reported and were not subjected to meta-analysis. Visual inspection of the data revealed no clinically important differences between the two drugs. Further results of sensitivity analyses were reported, but these did not alter the results of the main analyses.

Authors' conclusions
Duloxetine and venlafaxine-XR are both effective, compared with placebo, for the treatment of MDD. Venlafaxine tends to have a favourable trend in remission and response rates compared with duloxetine; however, adverse events and drop-out rates did not differ between the two drugs. A direct comparison is warranted to confirm this tendency.

**CRD commentary**
The review question was clear with well-defined inclusion criteria. Relevant databases were searched, but it was not clear whether language restrictions were applied and there is a potential for both publication and language bias. The study selection and data extraction processes were conducted in duplicate, thus reducing the potential for error and bias. Although the review was restricted to double-blind RCTs, this is not a guarantee that the included studies used appropriate methods and were of good quality; no formal quality assessment of the included studies was conducted. The analysis seems appropriate and heterogeneity was investigated. This was a generally well-conducted review, the results of which are likely to be reliable in relation to efficacy compared with placebo. However, the conclusion regarding the superiority of venlafaxine over duloxetine was based on indirect comparisons which showed no statistically significant difference between the two drugs.

**Implications of the review for practice and research**
Practice: The authors recommended caution in the use of venlafaxine or duloxetine where cardiac problems could occur.

Research: The authors stated that future research should directly compare venlafaxine and duloxetine.

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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.