Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis

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Authors' objectives
To investigate the relative efficacy and tolerability of venlafaxine compared with other antidepressants.

Searching
Relevant trials were identified from the authors' existing database (see Other Publications of Related interest no.1). In addition, the following databases were searched: MEDLINE, EMBASE, BIOSIS Previews, PsycLIT, the National Research Register, HealthSTAR, SIGLE, the Cochrane Controlled Trials Register and the Current Controlled Trials Register. The keywords were ‘venlafaxine’, ‘efexor’ and ‘effexor’. The reference lists of the included studies were reviewed and unpublished data were sought from authors and study sponsors.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible. The average length of follow-up was 10 weeks (range: 4 to 48).

Specific interventions included in the review
Comparisons of venlafaxine with an alternative antidepressant were eligible. The included studies compared venlafaxine with the following:

- tricyclic antidepressants (TCAs), i.e. clomipramine, imipramine, dothiepin and amitriptyline;
- selective serotonin re-uptake inhibitors (SSRIs), i.e. fluoxetine, fluvoxamine, paroxetine and sertraline; and other drugs, i.e. trazodone and mirtazapine.

The included studies were predominantly conducted in out-patient settings. The mean venlafaxine dose ranged from 75 to 300 (the units were not specified).

Participants included in the review
Studies of patients with depression were eligible. Depression was defined broadly and included explicit clinical or research criteria for major depression, such as DSM-IV (American Psychiatric Association, 1994), or if the clinician considered the patients to be depressed and eligible for antidepressant treatment. Where stated, the mean age of the participants ranged from 39 to 74 years and the proportion of women ranged from 50 to 81%.

Outcomes assessed in the review
The primary outcome in the review was the mean depression severity, as measured by the final Hamilton Rating Scale for Depression, the Montgomery and Asberg Depression Rating Scale or the Clinical Global Impression, with preference in that order where more than one scale was reported. The secondary outcomes were response rate, remission rate and tolerability, including all-cause withdrawal rates and the reason attributed for withdrawal.

How were decisions on the relevance of primary studies made?
Two authors independently assessed each potentially eligible study and any disagreements were resolved by discussion within the review team.

Assessment of study quality
Validity was assessed by considering the adequacy and concealment of randomisation (as reported in the paper). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were extracted: inclusion and exclusion criteria; dose and regimen of venlafaxine and alternative antidepressant; the number of patients randomised; the loss to follow-up; form of analysis (completer analysis or last observation carried forward); relevant clinical outcomes reported; the age and gender of the participants; and the length of follow-up. The authors of the original papers and/or sponsors were contacted for missing data. Data were extracted on an intention-to-treat basis whenever possible. Standardised effect sizes were estimated from the efficacy data for each treatment group. Where study variance was not reported, this was imputed taking the average for the studies using the same outcome. The odds ratios (OR) and absolute risk differences were estimated for the secondary outcomes.

Methods of synthesis
How were the studies combined?
The studies were combined by estimating the pooled treatment effect and 95% confidence intervals (CIs) using Gibbs sampling in BUGS software (see Other Publications of Related Interest nos 2-3). The absolute risk differences and 95% CIs were estimated using the method of DerSimonian and Laird (see Other Publications of Related Interest no.4) and interpreted as the number-needed-to-treat (NNT) and 95% CI. Venlafaxine was compared with all comparators combined, and separately with SSRIs, TCAs, other drugs and individual drugs. Random-effects models were used when venlafaxine was compared with a variety of agents, whereas fixed-effect models were used when venlafaxine was compared with individual agents. Publication bias was assessed using a meta-regression analysis and by visual inspection of funnel plots.

How were differences between studies investigated?
Meta-regression was used to examine the predictive value of the following potentially important explanatory factors on the primary efficacy outcome: size of trial; in-patient versus out-patient status; design, i.e. last observation carried forward versus completer analysis; age and gender; comparator drug class; length of follow-up; rating scale used; dose of venlafaxine; and whether variance was imputed.

Results of the review
Thirty-two RCTs (5,562 patients) were included. There were 20 RCTs (3,844 patients) that compared venlafaxine with SSRIs, 9 RCTs (1,356 patients) that compared venlafaxine with TCAs, and 3 RCTs (418 patients) that compared venlafaxine with other drugs.

The average sample size was 179 patients (range: 28 to 382). Most trials used the last observation carried forward for the primary analysis. None of the RCTs indicated whether the concealment of allocation was conducted properly.

Efficacy.
Venlafaxine significantly reduced the depression score compared with all comparators combined and compared with SSRIs: the pooled effect sizes were -0.14 (29 studies, 95% CI: -0.22, -0.07) and -0.17 (95% CI: -0.27, -0.08), respectively. There was no statistically-significant difference between venlafaxine and either TCAs (pooled effect size -0.13, 95% CI: -0.33, +0.09) or other drugs (pooled effect size -0.09, 95% CI: -0.42, +0.23). The results appeared consistent across the SSRI studies but there were differences among the TCA studies.

Response rates.
Venlafaxine significantly increased the response rates compared with all comparators combined; the OR was 1.27 (95% CI: 1.07, 1.52), the risk difference was 0.05 (95% CI: 0.02, 0.09) and the NNT was 19 (95% CI: 11, 63).

Remission rates (18 RCTs, including 16 RCTs that used SSRIs as the comparator).
Venlafaxine significantly increased the remission rates compared with all comparators combined; the OR was 1.36 (95% CI: 1.14, 1.61) and the NNT was 14 (95% CI: 9, 29).

None of the potentially explanatory factors were significantly predictive in the meta-regression analyses.

No evidence of publication bias was found by the meta-regression or visual inspection of the funnel plots.

Treatment discontinuation.

There was no statistically-significant difference in the discontinuation rates for venlafaxine; the overall risk difference was -0.004 (95% CI: -0.029, +0.020).

**Authors' conclusions**

Venlafaxine has greater efficacy than SSRIs, although there is uncertainty in comparison with other antidepressants. Further studies are required to determine the importance of this finding.

**CRD commentary**

The aims of the review were stated and the inclusion criteria were defined in terms of the intervention, participants and study design. The comprehensive search included several relevant databases and attempts were made to locate unpublished material. The methods used to select the studies were described. Only double-blind RCTs were included in the review and validity was assessed using defined criteria. Relevant data were extracted and tabulated. The data were extracted on an intention-to-treat basis, but the methods used to extract the data and assess validity were not reported. The mean venlafaxine dose was reported whereas the doses of the other antidepressants were not, thus the adequacy of the comparator drug dose cannot be judged. The meta-analyses were undertaken without a prior assessment of statistical heterogeneity. Hence, it is unclear whether a meta-analysis was appropriate for combining the studies. The influence of potentially important explanatory factors on the primary efficacy outcome was explored and publication bias was assessed.

The evidence presented appears to support the authors’ conclusion, but the clinical importance of the effect size difference favouring venlafaxine is unclear. There is, as the authors acknowledged, the potential for a conflict of interest since the review was supported by a pharmaceutical company.

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

Practice: The authors did not report any implications for practice.

Research: The authors state that further randomised trials, including those of naturalistic design, which involve larger numbers of patients in different clinical settings (particularly primary care), are required to find out how generalisable these results are to different settings.

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Other publications of related interest

These additional published commentaries may also be of interest. Simon GE. Review: venlafaxine is more effective than selective serotonin reuptake inhibitors for depression. Evid Based Med 2002;7:177. Simon GE. Review: venlafaxine is moe effective than selective serotonin-reuptake inhibitors for depression. ACP J Club 2002;137:101.

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