A systematic review of duloxetine and venlafaxine in major depression, including unpublished data


CRD summary
The review concluded that venlafaxine was probably preferred for short-term treatment of major depression compared to duloxetine for efficacy and tolerability and a valid alternative in patients who did not tolerate or respond to selective serotonin reuptake inhibitors and tricyclic/tetracyclic antidepressants. Few studies compared duloxetine and venlafaxine directly. The reliability of the authors' conclusions is not totally clear.

Authors' objectives
To evaluate the efficacy and tolerability of two selective serotonin-norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, in major depression and compare them to other antidepressants.

Searching
MEDLINE, EMBASE, PsycINFO, PSYNDExplus and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to January 2008. PsiTri was searched for primary studies to May 2007. Cochrane Database of Systematic Reviews, HTA database and DARE were searched to January 2008. Clinical trial registries, online study results databases and European Medicines Agency (EMEA) and US Food and Drug Administration websites were screened. Publications in English, German and French were included. Studies in other languages were included if the study was identified as potentially relevant via an English title or abstract. The manufacturers of duloxetine (Lilly) and venlafaxine (Wyeth) and selected manufacturers of comparator drugs were contacted for unpublished studies. Persons and parties who commented on a preliminary HTA report by the German Institute for Quality and Efficiency in Health Care (IQWiG) on the two drugs in a public hearing were contacted for additional studies. Reference lists of secondary publications were handsearched. Search terms were available from the authors and via another IQWiG publication (see Other Publications of Related Interest). Only full-text documents were included.

Study selection
Double-blind randomised controlled trials (RCTs) that evaluated the efficacy and tolerability of two SNRIs (duloxetine and venlafaxine) in adult patients with major depression as the primary diagnosis (according to the International Classification of Diseases, Diagnostic and Statistical Manual of Mental Disorders or Research Diagnostic Criteria) were eligible for inclusion. Eligible studies could compare the two drugs with each other, placebo or any antidepressant (including St John's wort) according to approval status in Germany. Eligible treatments could be short-term (at least six weeks) or long-term treatment for relapse or recurrence prevention (at least 6 months for relapse or 12 months for recurrence) after re-randomisation. Eligible studies needed to have at least one patient-relevant outcome. These included: remission; response; symptomatic improvement according to depression rating scales and rating scales for accompanying symptoms (such as pain, anxiety); relapse; recurrence; mortality; suicidality; health-related quality of life; social functioning and activities of daily living; and adverse events.

This analysis focused on short-term trials alone and only the most commonly reported outcomes (remission and response and discontinuation due to adverse events). Few of the included studies directly compared duloxetine and venlafaxine. About four times as many studies compared venlafaxine to other treatments or placebo than compared duloxetine to other treatments or placebo. Most of the other drugs used for comparison were selective serotonin reuptake inhibitors (SSRIs, which included citalopram, escitalopram, fluoxetine, paroxetine and sertraline) with a smaller number of studies of tricyclic and tetracyclic antidepressants (TCAs, which included amitryptiline, clomipramine, dosulepin, imipramine, maprotiline and nortriptyline). Eighty per cent of studies were of outpatients. Mean patient age ranged from 35 to 54 years in most studies; 9% of studies were in elderly patients with a mean age range of 71 to 78 years. About two-thirds of patients were female. Most patients in the duloxetine studies had moderate depression; those in the venlafaxine studies tended to have more severe disease.

Pairs of authors independently performed the study selection. Disagreements were resolved by consensus.
Assessment of study quality
Criteria included randomisation, allocation concealment, blinding of patients and investigators, sample size estimation, handling and reporting of study discontinuation and use of an intention-to-treat analysis. Studies were categorised as having no deficiencies (all criteria met), minor deficiencies (deficiencies did not challenge the study’s main result) and major deficiencies (deficiencies challenged the study’s main result).

Methodological quality was assessed by one reviewer and checked by a second. Disagreements were resolved by consensus.

Data extraction
The authors used standardised tables developed by IQWiG. Binary effect differences were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Remission and response were defined as reported in the trials. For most studies, response was a 50% reduction from the baseline score on Hamilton (HAM-D) or Montgomery-Asberg (MADRS) depression rating scales and remission was a HAM-D score of seven or less or a MADRS score of 10 or less or 12. Further study details were obtained from study registries and pharmaceutical companies and cross-checked with original study data.

One reviewer performed the data extraction, which was checked by a second reviewer. Disagreements were resolved by consensus.

Methods of synthesis
Where feasible, data were pooled using a random-effects model. Between-study heterogeneity was determined using $I^2$. No pooled analyses were performed where substantial heterogeneity was present ($I^2>50\%$). Results for different drugs in the same class were pooled (SSRIs and TCAs), as were study arms for different doses of the same drugs.

Sensitivity analyses were performed to assess possible sources of heterogeneity (such as variations in study quality).

Results of the review
Seventy RCTs were identified (18,180 participants, range 31 to 1,096). Thirteen studies had no quality deficiencies, 43 studies had minor deficiencies and 14 studies had major deficiencies. Twenty-three studies were previously unpublished. None of the studies compared duloxetine with TCAs. The full review reported in German included 78 studies (see Other Publications of Related Interest).

Antidepressant efficacy, response/remission: Duloxetine showed a significantly higher response rate (OR 1.99, 95% CI 1.65 to 2.39, $I^2=30.7\%$; 12 studies) and remission rate (OR 1.91, 95% CI 1.56 to 2.34, $I^2=33.8\%$; 12 studies) than placebo. There were no significant differences between duloxetine and SSRIs for response ($I^2=22.7\%$; nine studies) or remission rates ($I^2=18.4\%$; nine studies).

Venlafaxine showed a significantly higher response rate (OR 2.04, 95% CI 1.74 to 2.38, $I^2=33.8\%$; 20 studies) and remission rate (OR 1.97, 95% CI 1.64 to 2.35, $I^2=2.3\%$; nine studies) than placebo. Venlafaxine had a significantly higher response rate than SSRIs (OR 1.20, 95% CI 1.07 to 1.35, $I^2=12.5\%$; 25 studies) and no significant difference in remission rates ($I^2=15.7\%$; 18 studies). There were no significant differences between venlafaxine and TCAs for response ($I^2=36.3\%$; 10 studies) and remission rates ($I^2=0\%$; three studies).

Direct comparison between duloxetine and venlafaxine showed no significant difference in response rate ($I^2=29.1\%$; two studies). Heterogeneity was too high ($I^2=54.3\%$; two studies) for a definite conclusion for remission rate.

Tolerability, discontinuation due to adverse events: There was a significantly higher discontinuation rate for duloxetine versus placebo (OR 2.22, 95% CI 1.55 to 3.19, $I^2=24.8\%$; 12 studies) and for duloxetine versus SSRIs (OR 1.53, 95% CI 1.10 to 2.13, $I^2=0\%$; nine studies). Heterogeneity was too high to allow a definite conclusion for discontinuation rate for venlafaxine versus placebo ($I^2=53.7\%$; 23 studies). Sensitivity analysis that removed studies with major deficiencies reduced heterogeneity and found a significantly higher discontinuation rate for venlafaxine versus placebo (OR 2.47, 95% CI 1.81 to 3.37, $I^2=38.1\%$). Discontinuation rates were significantly higher for venlafaxine versus SSRIs (OR 1.38, 95% CI 1.15 to 1.66, $I^2=18.6\%$; 29 studies). There was no significant difference for venlafaxine versus TCAs ($I^2=0\%$; 11 studies). Direct comparison showed a significantly higher discontinuation rate for duloxetine than venlafaxine (OR 1.79, 95% CI 1.16 to 2.78, $I^2=0\%$; two studies).
No conclusions were made for dose-response relationships.

**Authors' conclusions**
In the short-term treatment of major depression, venlafaxine appeared to be a preferential option compared to duloxetine and a valid alternative in patients who did not tolerate or respond to SSRIs or TCAs, rather than being a first-line option. Duloxetine offered no advantages in antidepressant efficacy and tolerability compared to venlafaxine, TCAs or SSRIs and did not seem to be indicated as a first-line treatment.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched for publications in any language, but the authors reported that eight studies in languages other than English, German and French were excluded. One third of the studies were unpublished. Efforts were made to reduce error and bias throughout the review process.

Study quality was assessed using suitable criteria and most studies had no or only minor deficiencies in quality. Some relevant study details were reported, but there were few details of individual studies. Statistical heterogeneity was assessed and the authors found evidence for heterogeneity with some outcomes. Few studies were identified that compared duloxetine and venlafaxine directly. There were differences in disease severity between patients in the duloxetine and venlafaxine studies. The analyses performed seemed appropriate. Some relevant sensitivity analyses were performed, but not all the results were reported.

One author had received unrestricted research grants for trials, including investigator-initiated trials, from AstraZeneca, GlaxoSmithKlein and AFFECTIS Pharmaceuticals.

Although the review was performed well, few studies compared duloxetine and venlafaxine directly, which implies that the reliability of the authors' conclusions may not be totally clear.

**Implications of the review for practice and research**
**Practice:** The authors stated that duloxetine could still be used where there was therapy resistance or contraindications to the use of venlafaxine.

**Research:** The authors identified a need for pragmatic RCTs in diverse populations in heterogeneous settings to find out which agents should be first line treatment for major depression and thus inform clinical practice. Such studies should have a broad range of outcomes. Studies that compared TCAs with duloxetine were needed particularly.

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