Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed?

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CRD summary
This review concluded that vortioxetine was an option for the treatment of major depressive disorder, and the most common adverse events were nausea, constipation and vomiting. Due to several concerns about the conduct and reporting of the review, its findings and conclusions may not be reliable.

Authors' objectives
To evaluate the efficacy and safety of vortioxetine for major depressive disorder.

Searching
PubMed was searched up to October 2013, with no date and language restrictions. Two clinical trial registers were checked; abstracts from relevant conferences in 2012 and 2013 were assessed; and the product manufacturer was contacted to provide additional conference posters. The product label was consulted for further information. Search terms were reported.

Study selection
All available reports of clinical trials of vortioxetine for major depressive disorder were eligible for inclusion. Studies focusing on generalised anxiety disorder were excluded.

All the included trials were of adults, and the mean participant age ranged from 42 to 48 years, except in one trial, where the mean age was 70.6 years. Most participants were female and had already received treatment for major depressive disorder. The mean Montgomery and Asberg Depression Rating Scale (MADRS) score at the start ranged from 29 to 34. In most trials, patients with treatment resistance or other potentially confounding, comorbid, psychiatric or somatic conditions were excluded. Vortioxetine dosage varied between 1mg and 20mg per day.

It appears that one reviewer selected the studies.

Assessment of study quality
The author did not state that the quality of the trials was assessed.

Data extraction
The changes observed on the MADRS and the 24-item Hamilton Rating Scale for Depression (HRSD-24) were extracted to calculate least squares mean changes from the start. Data on remission (a MADRS score of 10 or less at the end), and response (reduction of at least 50% in MADRS score) were extracted from the trials. Sheehan Disability Scale (SDS) outcomes were extracted.

The number needed to treat, and the number needed to harm, comparing vortioxetine (and active controls) with placebo, were calculated, where appropriate. Where possible, 95% confidence intervals were calculated for each number needed to treat and harm.

It appears that one reviewer extracted the data.

Methods of synthesis
Where possible, trial data were pooled to calculate the overall numbers needed to treat and harm. The method used to pool the data was not reported. Sensitivity analyses excluding trials that found no significant differences, and those using lower doses, were conducted. The results were also presented in a narrative and in tables.

Results of the review
Twelve randomised placebo-controlled trials of vortioxetine were included; all trials were conducted by the manufacturer of vortioxetine. Participant completion rates ranged from 74% to 90%. Follow-up data at six-to-eight weeks were analysed. Nine trials were of non-elderly patients and reported their changes in MADRS or HRSD-24; one trial was of elderly patients only; and two trials did not report outcome data.

Four of the nine trials on non-elderly patients found no difference between vortioxetine and placebo; two had an active comparator – one found no differences and one found a difference for the active comparator only (negative trial). The other five trials were considered positive for vortioxetine at doses of 1mg per day (one trial), 5mg per day (two trials), 10mg per day (two trials), 15mg per day (one trial), and 20mg per day (three trials). Two of these trials were positive for vortioxetine 20mg, but not for 10mg (one trial) or 15mg (one trial). The trial of elderly patients found a statistically significant difference between vortioxetine and placebo, at eight weeks, on the HRSD-24.

In placebo-controlled trials that also had an active comparator, duloxetine 60mg per day (three trials) and venlafaxine 225mg per day (one trial) had more favourable results, for response and remission, than vortioxetine at any dose. One trial, without placebo, compared vortioxetine with agomelatine and found a statistically significant difference, in MADRS score at 12 weeks, favouring vortioxetine.

The number needed to harm, for discontinuation of vortioxetine due to an adverse event, was 36 (95% CI 24 to 70). Compared with placebo, the most common adverse events (incidence 5% or more, and at least twice the rate of placebo) were nausea (NNH 6, 95% CI 6 to 7), constipation (NNH 64, 95% CI 37 to 240) and vomiting (NNH 28, 95% CI 23 to 38). The author reported that changes in weight were not clinically significant. Further results were reported.

**Authors’ conclusions**

Vortioxetine was an option for the treatment of major depressive disorder. The most common adverse events were nausea, constipation and vomiting.

**CRD commentary**

The review question was clear and supported by broad selection criteria. Sources of both published and unpublished data were consulted. It appears that study selection and data extraction were performed by one reviewer, introducing a risk of reviewer error and bias. The quality of the trials was not assessed, which limits the extent to which the strength of the evidence can be appraised.

The methods used to pool the data were not reported, and it is unclear if they were appropriate. The sensitivity analyses that excluded trials that found no differences are unlikely to have been appropriate, and are at high risk of bias. Analyses of numbers needed to treat and harm are limited, and these results may not be reliable. Some trials included the active comparators venlafaxine and duloxetine; it is unclear why no direct comparisons between these drugs and vortioxetine were reported. This should be considered when interpreting the findings of the review.

Given the limitations, the findings and conclusions of this review are unlikely to be reliable.

The author reported consultancy for, honoraria from, and conducting clinical research for various manufacturers, including Takeda Pharmaceuticals, the manufacturer of vortioxetine.

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

**Practice:** The authors stated that the mechanism of action for vortioxetine might be sufficiently different from other available antidepressants to make it an option when other drugs were inadequate or not tolerated.

**Research:** The authors stated that more information on the time course of response or remission, and for the common adverse event of nausea, would be helpful. Further analyses of relevant data on vortioxetine and active controls were needed to better understand any sexual function side-effects. Pragmatic clinical trials, collecting data that are more generalisable to all patients with major depressive disorder, were recommended.

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