Efficacy, tolerability and side-effect profile of fluvoxamine for major depression: meta-analysis


CRD summary
The authors concluded that there were no large differences between fluvoxamine and any other antidepressant in efficacy or tolerability during the acute phase of treatment of depression, but that side-effects differed between drugs. Overall, this was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To compare the efficacy of fluvoxamine with other active antidepressant agents in adults with major depression.

Searching
The Cochrane Depression, Anxiety and Neurosis Group’s Controlled Trials Register, MEDLINE, EMBASE, PsycINFO, PSYNDEX and LILACS were searched in June 2006. Search terms were reported. Searches were not restricted to the English language. Major psychiatric and medical journals and conference proceedings, databases of trials and ongoing trial registries from North America, Europe, Japan and Australia were handsearched for unpublished and ongoing randomised controlled trials. In addition, pharmaceutical companies and experts in the field were contacted, and reference lists of included studies, previous systematic reviews and major textbooks were screened.

Study selection
Randomised controlled trials (RCTs) that compared fluvoxamine with any other active antidepressants in the acute phase treatment of adults (aged 18 years or over) with major depression were eligible for inclusion. Patients had to be diagnosed using established diagnostic criteria. Trials of depressive patients with psychotic features, a primary diagnosis of other Axis I or Axis II disorders, or a serious co-existing medical condition, trials in which more than 20% of patients had bipolar depression, and trials that used fluvoxamine as an augmentation strategy were excluded.

The primary review outcome was response at the end of the acute phase of treatment (between six and 12 weeks). Response was defined as a reduction of at least 50% on the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression rating Scale (MADRS). Secondary outcomes were remission (defined as a score of 7 or less on the 17-item HAM-D and 8 or less on longer version of the HAM-D), tolerability evaluated using the number of drop-outs for any reason or because of side effects. The original authors’ definitions of response and remission were not used in this review. The review also assessed outcomes for early phase treatment (between one and four weeks).

The included trials compared fluvoxamine with the following: tricyclic antidepressants; heterocycles; selective serotonin re-uptake inhibitors; serotonin-noradrenaline re-uptake inhibitors; other new agents and other antidepressants (sulpiride). Participants included inpatients, outpatients, a mix of the two with a minority of patients from general practice. Some trials included elderly patients. Most studies used the HAM-D to measure outcomes. The duration of included interventions ranged from two to 10 weeks (mean 5.5 weeks). Most trials were funded by industry.

Two reviewers independently selected studies and resolved disagreements on inclusions by discussion.

Assessment of study quality
Two reviewers independently assessed validity using published criteria that included allocation concealment and blinding. Disagreements were resolved by discussion.

Data extraction
Response and remission rates reported as dichotomous data were extracted as relative risks (RR) and 99% confidence intervals (CI). Where they were reported as continuous data with means and standard deviations (SD), these were transformed into dichotomous data using the validated imputation methods; where standard deviations were not reported, values used in other studies were substituted.
Two reviewers independently extracted data and resolved disagreements by discussion.

**Methods of synthesis**
The review compared fluvoxamine with all comparator antidepressants combined and with each individual class of antidepressant; p values <0.01 and 99% CI were considered to be statistically significant for remission and response comparisons and p<0.05 and 95% confidence intervals were used for tolerability comparisons. Pooled relative risks and 99% confidence intervals were calculated for response and remission using a random-effects model. Heterogeneity was assessed using the Q and the I^2 statistics; I^2 of 50% or more, and p <0.1 were taken to indicate heterogeneity.

The number needed to treat (NNT) was calculated where significant differences between treatments were found. Data were analysed on an intention-to-treat (ITT) basis, assuming drop-outs to have had an unfavourable response; last observation carried forward data were used where reported.

Subgroup analysis was used to examine the influence of treatment setting on response. A priori sensitivity analysis was undertaken by: excluding trials funded by or with authors associated with pharmaceutical companies marketing fluvoxamine; comparing trials in which fluvoxamine was the investigational drug with trials in which it was the comparator drug; and excluding trials in which response and remission rates were obtained using imputation methods. Side effects were grouped according to the affected organ and pooled relative risks with 95% confidence intervals calculated. Publication bias was assessed using a funnel plot.

**Results of the review**
Fifty-three RCTs (with 59 comparisons) were included in the review (n=at least 4,421 patients).

Forty-eight RCTs (50 comparisons) were included in efficacy analyses and 49 RCTs (53 comparisons) included in tolerability analyses; 29 trials compared fluvoxamine with tricyclic antidepressants, five trials compared fluvoxamine with heterocyclics, 10 trials compared fluvoxamine with selective serotonin reuptake inhibitors, three trials compared fluvoxamine with serotonin-noradrenaline reuptake inhibitors, four trials compared fluvoxamine with newer antidepressants, one trial compared fluvoxamine with sulpiride, and one trial compared fluvoxamine with amitriptyline, doxepin and paroxetine. None of the studies clearly reported allocation concealment. Forty-two trials were double-blind.

At the end of acute phase of treatment (primary outcome, 31 comparisons, n=2,663 patients): There was no statistically significant difference in response or remission rates between fluvoxamine and other antidepressants combined or between fluvoxamine and each class of antidepressant. Results were similar for sensitivity analyses. No significant heterogeneity or evidence of publication bias was found.

Results for early phase treatment were also reported.

**Tolerability:** There was no statistically significant difference in drop-outs for any reason, or for drop-outs due to side-effects between fluvoxamine and other antidepressants combined or between fluvoxamine and each class of antidepressant.

**Side effects profile:** The authors stated that few of the trials used standardised methods to record side-effects. Side-effect profiles differed. In particular, fluvoxamine was associated with significantly more nausea or vomiting than tricyclic antidepressants (RR 1.94, 95% CI 1.52 to 2.47).

**Authors’ conclusions**
There were no large differences between fluvoxamine and any other antidepressant in efficacy or tolerability during the acute phase of treatment of depression. There was evidence of differing side-effects, especially for gastrointestinal side-effects with fluvoxamine compared with tricyclic antidepressants.

**CRD commentary**
The review question was clearly stated and inclusion criteria appropriately defined. Several relevant sources were
searched and attempts were made to minimise publication and language bias. Appropriate methods were used to minimise reviewer error and bias during the review process. Only RCTs were included and a validity assessment limited to two criteria was performed and results were reported. Trials were generally short-term, as the authors pointed out. Appropriate methods were used for the meta-analyses; heterogeneity was assessed and various predefined sensitivity analyses conducted. Overall, this was a well-conducted review and the authors’ conclusions are likely to be reliable.

Three of the authors disclosed links to pharmaceutical companies.

Implications of the review for practice and research
Practice: The authors stated that clinicians should take differing side-effects profiles of antidepressant drugs into account when selecting a drug to treat major depression.

Research: The authors did not state any implications for research.

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