Comparative efficacy and acceptability of pharmacotherapeutic agents for anxiety disorders in children and adolescents: a mixed treatment comparison meta-analysis

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CRD summary
The authors concluded that clinically important differences existed among commonly prescribed pharmacotherapeutic agents for anxiety disorders in children and adolescents in terms of efficacy and acceptability in favour of fluvoxamine. Given the lack of data provided on the included studies, limitations with the review process and the use of indirect comparisons, the authors’ conclusions should be interpreted with caution.

Authors' objectives
To compare the efficacy and safety of different pharmacotherapy treatments for anxiety disorders in children and adolescents.

Searching
A Cochrane Review (see Other Publications of Related Interest) was used and updated by searching Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and PsycINFO between September 2008 and August 2009. Search terms were reported in the previous Cochrane Review. ClinicalStudyResults.org and Dissertation Abstracts International were searched and relevant pharmaceutical companies were scanned for unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared any pharmacotherapy agents in children and/or adolescents diagnosed with anxiety disorders according to Diagnostic and Statistical Manual of Mental Disorders (DSM) codes DSM-III, DSM-III-R and DSM-IV were eligible for inclusion if they reported both efficacy and safety data. Efficacy was defined as improvement according to the seven-item Clinical Global Impressions scale (CGI-I). Safety/acceptability was defined as the proportion of participants who withdrew due to treatment adverse events.

Most of the included RCTs were conducted in USA. Participants had a mean age range of 8.5 to 13.6 years. The proportion of female participants ranged from 23% to 60%. RCTs directly compared selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline) or serotonin norepinephrine reuptake inhibitors (venlafaxine) versus placebo. Most RCTs were sponsored by pharmaceutical companies.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Efficacy (defined as treatment response of one (very much improved) or two (much improved) on the CGI-I) and safety data were extracted for treatment and placebo groups to calculate risk ratios (RRs). It was unclear how missing data were handled.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
A Bayesian model was used to estimate risk ratios and 95% credible intervals (CrI) for both direct and indirect comparisons. Treatments and placebo were ranked for efficacy and acceptability and the cumulative probabilities (%) of each treatment being the best were reported.

Results of the review
Sixteen RCTs (number of patients not reported) were included in the review. Six RCTs assessed fluoxetine, two fluvoxamine, two paroxetine, four sertraline and two venlafaxine. It was unclear how many RCTs were included in the meta-analyses as some RCTs did not provide data on efficacy or safety/acceptability.

**Efficacy:**

Direct comparisons showed that all treatments were more effective than placebo: fluoxetine (RR 3.35, 95% CrI 2.11 to 5.07); fluvoxamine (RR 3.61, 95% CrI 2.25 to 5.47); paroxetine (RR 3.23, 95% CrI 2.40 to 4.26); sertraline (RR 2.79, 95% CrI 1.95 to 3.88); and venlafaxine (RR 2.06, 95% CrI 1.54 to 2.69).

Indirect comparisons indicated that venlafaxine was statistically significantly less effective than fluvoxamine (RR 0.60, 95% CrI 0.35 to 0.95) and paroxetine (RR 0.65, 95% CrI 0.44 to 0.93). Other indirect comparisons showed no significant differences between treatments.

**Acceptability:**

Direct comparisons showed that fluvoxamine (RR 14.36, 95% CrI 1.50 to 69.13), paroxetine (RR 5.24, 95% CrI 1.72 to 13.41) and sertraline (RR 3.43, 95% CrI 1.26 to 8.22) were statistically significantly better tolerated than placebo; fluoxetine and venlafaxine showed no statistically significant difference.

Indirect comparisons indicated that venlafaxine was statistically significantly less well tolerated than fluvoxamine (RR 0.16, 95% CrI 0.01 to 0.64), paroxetine (RR 0.21, 95% CrI 0.05 to 0.59) and sertraline (RR 0.31, 95% CrI 0.08 to 0.83). No other indirect treatment comparisons were significantly different.

Cumulative probabilities showed that fluvoxamine was the most effective treatment (ranked as 47.5%) and the most acceptable (ranked as 50.6%). Venlafaxine and placebo were both ranked as 0% for efficacy and acceptability.

**Authors’ conclusions**

Clinically important differences existed among commonly prescribed pharmacotherapeutic agents for anxiety disorders in children and adolescents in terms of efficacy and acceptability in favour of fluvoxamine.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search included attempts to locate published and unpublished data, which reduced potential for publication bias. Only a proportion of the RCTs used in the Cochrane Review (see Other Publications of Related Interest) were included in this review; it was unclear why the remaining studies were not mentioned. The authors did not state whether study selection and data extraction were undertaken in duplicate, so reviewer error and bias could not be ruled out. The authors did not state that they assessed study quality and so the reliability of the RCTs was unclear. Participant characteristics and study details were lacking. There was no formal assessment of statistical heterogeneity for the head-to-head comparisons. Most results were based on indirect comparisons, which meant that uncertainties associated with indirect comparisons needed to be taken into consideration when interpreting the findings. Credible intervals were wide for some comparisons, which reduced the reliability of the findings.

Given the lack of data provided on the included studies, limitations with the review process and the use of indirect comparisons, the authors’ conclusions should be interpreted with caution.

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

**Practice:** The authors stated that fluvoxamine appeared to be the most beneficial and acceptable pharmacotherapeutic treatment and may qualify as the best choice for treating children and adolescents with anxiety disorders.

**Research:** The authors stated that large observational studies were needed to further investigate adverse events.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract 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.