Efficacy and tolerability of second-generation antidepressants in social anxiety disorder

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CRD summary
This review found that the evidence supported the efficacy of second-generation antidepressants escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine in patients with social anxiety disorder; the drugs did not differ in efficacy, but differed in their adverse event profiles. The review was generally well-conducted and the authors’ conclusions seem reliable.

Authors' objectives
To determine the efficacy of second-generation antidepressants in patients with social anxiety disorder.

Searching
MEDLINE, EMBASE, the Cochrane Library, PsycLIT and International Pharmaceutical Abstracts (1980 to October 2006) were searched to locate relevant studies. Search terms were not reported. Reference lists of review articles and letters to the editor were also searched. Pharmaceutical companies were asked to submit relevant information. The Center for Drug Evaluation and Research database was search for unpublished research.

Study selection
Randomised controlled trials (RCTs) of at least 12 weeks duration, which rated as fair or good quality and showed no significant differences at baseline between groups that were thought may affect outcomes, and which compared second-generation antidepressants to each other or placebo in outpatients with a Diagnostic and Statistical Manual of Mental Disorders (DSM) defined diagnosis of were eligible for inclusion. Studies assessing relapse prevention or that did not assess outcomes using a pre-specified rating scale were excluded. Studies evaluated: venlafaxine (192 mg or 202 mg) or escitalopram (20 mg) compared to paroxetine (44 mg, 46 mg or 20 mg, respectively); and escitalopram (18 mg), fluoxetine (44 mg), fluvoxamine (174 mg to 209 mg), paroxetine (20 mg to 50 mg), sertraline (126 mg to 159 mg) and venlafaxine (152 mg to 214 mg) compared with placebo.

Outcomes included the Liebowitz Social Anxiety Scale (LSAS), Sheehan Disability Scale (SDS), Clinical Global Impression of Improvement scale (CGI-I) and adverse events. The severity of disease of the patients varied, with LSAS scores ranging from 74 to 97, when reported; some patients had coexisting psychiatric conditions. Only one study enrolled children and adolescents (mean age 13 years); the mean age of the other studies ranged from 35 to 41 years. There were similar numbers of males and females. Two reviewers independently assessed the studies for inclusion in the review. It was not reported how disagreements were resolved.

Assessment of study quality
Study validity was assessed in relative to randomisation, allocation concealment, similarity of comparison groups, use of intention-to-treat analysis and loss to follow-up, rated as good, fair or poor quality. The authors did not state how the validity assessment was performed.

Data extraction
Relative benefit (RB) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes (CGI-I), mean differences and 95% CIs for continuous outcomes (LSAS, SDS), and incidence and 95% CI for adverse events. When standard deviations were not reported, these were estimated from similarly designed trials. Data were extracted by one reviewer and checked by a senior reviewer.

Methods of synthesis
Pooled relative benefits for binary outcomes and weighted mean differences (WMD) for continuous outcomes and 95% confidence intervals were calculated using a random-effects meta-analysis when more than two trials evaluated the same drug were available; where this was not possible a narrative synthesis was presented. Where multiple dosing arms were reported, data from the highest dose approved by the FDA were used. Where two active treatments were
compared to placebo, the placebo arm was divided to avoid double counting. Statistical heterogeneity was assessed using the I\(^2\) statistic. Where heterogeneity was found, possible reasons were explored. It was not reported how pooled mean incidence rates of adverse events were calculated. Indirect comparisons of medications were undertaken using a network meta-analysis for assessment of CGI-I. Publication bias was assessed graphically using funnel plots and statistically using Egger’s regression test and the rank correlation test of Begg and Mazudmar.

**Results of the review**

Eighteen RCTs (n=5,172) were included: three using active comparators (n= 1,334) and 15 using placebo (n= 3,838). Duration of studies ranged from 12 to 28 weeks. One study was rated good quality and the others rated fair. Direct comparisons showed a statistically significant reduction in anxiety with high dose escitalopram compared with paroxetine using LSAS (figures not provided), but no difference was observed either between venlafaxine and paroxetine or between lower dose escitalopram and paroxetine in LSAS, SDS or CGI-I scores.

Compared to placebo, statistically significant improvements in LSAS were seen with escitalopram (WMD 10.3, 95% CI: 5.9, 14.6; two studies), fluvoxamine (WMD 12.3, 95% CI: 8.2, 16.3; three studies), paroxetine (WMD 16.1, 95% CI: 13.1, 19.1; six studies), venlafaxine (WMD 14.8, 95% CI: 10.6, 19.0; three studies) and sertraline (mean difference 9.3, 95% CI: 4.1, 14.5; one study).

Pooled estimates showed active treatment to produce significant improvement in the work (WMD 1.25, 95% CI: 0.9, 1.5), social (WMD 1.16, 95% CI: 0.9, 1.4) and family (WMD 0.86, 95% CI: 0.6, 1.1) domains of SDS; pooled results for individual drugs were not reported for functional impairment. Improved CGI-I was observed for escitalopram (RB 1.31, 95% CI: 1.17, 1.46; two studies), paroxetine (RB 1.85, 95% CI: 1.49, 2.29; eight studies), sertraline (RB 1.78, 95% CI: 1.45, 2.16; three studies) and venlafaxine (RB 1.68, 95% CI: 1.47, 1.93; four studies), but not for fluvoxamine. No statistically significant difference was found for any outcome with fluoxetine. The only meta-analysis to demonstrate significant heterogeneity was the global impression with paroxetine (I\(^2\)=82%).

The network analysis found no differences between any of the treatments in CGI-I. Sensitivity analyses did not significantly alter the results. No publication bias was detected for any of the analyses. The pooled mean incidence with 95% CIs were reported for nausea, asthenia, sweating, somnolence, insomnia, dry mouth, abnormal ejaculation and libido decrease.

**Authors’ conclusions**
The evidence supported the efficacy of escitalopram, fluvoxamine, paroxetine, sertraline and venlafaxine in social anxiety disorder. The drugs did not differ in efficacy, but the adverse event profiles did.

**CRD commentary**

This review had clearly stated inclusion criteria with respect to study design, participants, interventions and outcome measures. The authors searched relevant databases and efforts were made to find further information by reviewing reference lists. Attempts were also made to locate unpublished studies. It was not stated if language restrictions were applied, so language bias can not be ruled out. The study selection was performed independently by two reviewers and the data extraction was checked by a second reviewer, thus minimising the risk of errors and bias in the review process. However, it was not reported how validity assessment was conducted, therefore, error or bias may have been introduced at this stage. The authors were not able to include direct head-to-head comparisons of the drugs due to a lack of evidence, but appropriate methods were used to carry out indirect comparisons between the drugs. The findings from indirect comparisons were subject to limitations and should be interpreted with caution. Statistical heterogeneity was assessed. The authors stated that heterogeneity was observed only for one meta-analysis; reasons for its presence were explored. A thorough assessment of publication bias was conducted and no outcomes showed evidence of this. The review was generally well-conducted, and the authors’ conclusions seemed reliable.

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

Practice: The authors did not state any recommendations for practice.

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