An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder


Authors' objectives
To examine the effect size from recent controlled trials of serotonin selective re-uptake inhibitors (SSRIs) in treating panic disorder, and to compare these findings with a previous meta-analysis of non-SSRIs for panic disorder (see Other Publications of Related Interest no.1).

Searching
PsycLIT and MEDLINE were searched using the following key terms (alone and in combination): 'panic', 'medication', 'treatment outcome', 'selective serotonin reuptake inhibitor', 'SSRI', 'paroxetine', 'fluoxetine', 'fluvoxamine', 'sertraline' and 'citalopram'. No dates for the searches were reported. The reference sections of related articles were examined and colleagues of the review's authors were consulted.

Study selection
Study designs of evaluations included in the review
Double-blind placebo-controlled randomised controlled trials (RCTs) were eligible for inclusion in the review.
Uncontrolled medication trials, studies examining the effects of SSRIs on biological challenge procedures, case reports, long-term or follow-up studies, and articles reviewing several studies that were published separately, were excluded.

Specific interventions included in the review
Comparisons of SSRIs (paroxetine, fluoxetine, fluvoxamine, sertraline and citalopram) with placebo were included.

Participants included in the review
People with panic disorder, with or without agoraphobia. No further details of the participants were provided.

Outcomes assessed in the review
The effect sizes were calculated for all dependent variables at post-treatment, excluding measures of depression symptoms. A separate panic frequency effect size (for full panic attacks only) was also calculated. The drop-out rates, and the percentage of participants who were free of panic at end point were also reported. No further details of the outcome measures reported in the included studies were provided.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

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

Data extraction
The authors do not report how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted on: intervention; publication date; sample size; drop-out rate; overall effect size; the percentage of panic-free participants (at the end of the study); and the panic frequency effect size. The effect sizes were only calculated for doses identified as effective. If results for a particular measure were reported as proportions (rather than means, standard deviations and t-scores), the effect sizes were determined using a table provided by Glass et al. (see Other Publications of Related Interest no.2).
Methods of synthesis
How were the studies combined?
Both the weighted and unweighted (by sample size) overall effect sizes were calculated.

Potential publication bias was examined using a funnel plot that plotted the effect size against the sample size.

How were differences between studies investigated?
No attempt was made to investigate differences between the studies.

Results of the review
Twelve RCTs (n=1,741) were included. There were 4 RCTs of fluvoxamine, 3 of paroxetine, 3 of sertraline, one of citalopram and one of fluoxetine.

A mean unweighted study effect size of 0.55 and a weighted effect size of 0.47 were obtained. The panic frequency effect size (based on 8 studies) was 0.38 unweighted and 0.37 weighted. Larger studies were significantly associated with lower effect sizes (p<0.009). The mean study drop-out rate was 19.9%. The funnel plot was indicative of a strong negative association between the sample size and effect size, and of publication bias.

The authors compared the overall mean effect sizes from this review with the mean effect sizes for imipramine and antidepressants from the previous review (see Other Publications of Related Interest no.1), using t-tests. The results are not reported here as they are the results of an indirect comparison using selected intervention arms from the RCTs.

Authors' conclusions
An effect-size analysis of controlled studies of treatments for panic disorder revealed no significant differences between SSRIs and older antidepressants in terms of the efficacy or tolerability in short-term trials. An inverse relationship was evident between the sample size and effect size for SSRIs. Early studies of small samples may have led to initial overestimations of the efficacy of SSRIs for panic disorder.

CRD commentary
The review question was stated. Some study selection criteria were also stated, although these were only clear for the intervention and study design. The dates over which the literature search was conducted were not provided, and details of the included studies (participants and outcome measures) were not given. No attempt was made to search for unpublished studies; the results of the funnel plot analysis indicate possible publication bias.

The pooled effect size approach may have been appropriate but it is difficult to tell without seeing what the original outcome measures were. No measures of variance of the pooled effect sizes were given, so it is unclear whether the effect size for SSRIs versus placebo was statistically significant. The review's authors then undertook an indirect comparison with effect sizes from a previous meta-analysis of other drugs versus placebo, and compared the effect sizes using t-tests. This was not an appropriate approach as it uses indirect comparisons rather than direct comparisons from RCTs. Thus, the authors' conclusions, which are drawn from this final comparison, should be treated with great caution.

Implications of the review for practice and research
Practice: The authors state that an implication of their findings is that earlier estimates of the relative efficacy of cognitive behaviour therapy and older antidepressants may well be applicable to SSRIs.

Reviewer's comment: This implication, however, does not follow directly from the results of the review.

Research: The authors state that direct comparison (three arm) outcome studies of SSRIs, older antidepressants and placebo have the potential of further clarifying the efficacy relationship among these agents.
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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.