Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis

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CRD summary
This review evaluated the efficacy of selective serotonin reuptake inhibitors (SSRIs) in depressed children and adolescents. The authors concluded that limited evidence suggests some benefit from SSRI treatments, especially fluoxetine, when compared to placebo. Despite some limitations in the reporting of review methods, the authors' cautious conclusions are likely to be reliable. Research recommendations are made.

Authors' objectives
To assess the efficacy of SSRIs in children and adolescents with depression.

Searching
Cochrane CENTRAL Register, EMBASE, PsycINFO and MEDLINE were searched to January 2007. Search terms were reported. The websites of pharmaceutical companies and selected regulatory agencies were searched to retrieve unpublished material. Reference lists of retrieved articles and relevant reviews, books and guidelines were also searched.

Study selection
Randomised controlled trials (RCTs) of SSRI therapy compared with other active treatment or placebo were eligible for inclusion. Participants were required to be children or adolescents with depressive disorder or depressive symptoms diagnosed with standardised criteria. The primary review outcome was efficacy, using the primary outcome measure from each individual study. The secondary review outcome was treatment response, defined as a Clinical Global Impression Improvement score of two or less.

The included studies varied widely in their clinical and methodological characteristics. SSRIs used were: fluoxetine, paroxetine, imipramine, citalopram, sertraline and escitalopram. One study included psychotherapy as well as drug therapy. Comparison interventions comprised placebo and (in a single study) imipramine and clomipramine. The duration of treatment ranged from six to 12 weeks. There were wide variations in the psychometric properties of the tools used to measure outcomes and the thresholds used, but all studies showing SSRI efficacy used the Children's Depression Rating Scale-Revised (CDRS-R). Follow up times ranged from six to 14 weeks. There were similar numbers of male and female participants, comprising in-patients and out-patients aged from six to 20 years, mostly with moderate to severe depression. Some studies excluded participants with comorbidities such as: mental retardation; alcohol or substance misuse; and bipolar, eating, psychotic and/or anxiety disorders. Depression was diagnosed based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 3rd or 4th edition. A variety of methods was used to diagnose severity.

All authors screened abstracts for potential eligibility, with retrieval of the full article in case of disagreement. The authors did not state how the final selection of papers for the review was conducted.

Assessment of study quality
The following components of study quality were assessed: allocation concealment, blinding (of participant, care provider and outcome assessor), intention to treat analysis and follow-up rate (>90%, 80-90%, <80% or unclear). One to three points were awarded for each item, for a maximum possible score of 12. Each study was also evaluated using the Jadad scale, which measures adequacy of randomisation, blinding, and management of withdrawals and dropouts. Two reviewers conducted the validity assessment independently.

Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each study. The authors do not state how the data were extracted for the review or how many reviewers performed the data extraction. Outcomes were reported in...
the review for all SSRIs combined and for individual SSRIs.

**Methods of synthesis**
A meta-analysis was performed using a random-effects model to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs). The number needed to treat in order for one participant to benefit (NNT) and the raw proportion of responders in each group were calculated. The Q and the $I^2$ statistics were used to assess statistical heterogeneity. The rank r test was used to investigate any association between study quality, study duration and treatment effect.

**Results of the review**
Thirteen RCTs were included (n=2,530). Approximately 1,276 participants were randomised to SSRIs, 1,105 to placebo and 153 to imipramine and clomipramine. Quality scores for the included studies ranged from six to 11 out of a maximum of 12 points. Overall, 26.3 per cent of participants failed to complete the studies (range 18.5% to 39.6%).

Pooling of 11 RCTs (n=2,274) showed a significantly higher response rate in the SSRI group than in the placebo group, with low heterogeneity OR 1.57 (95% CI: 1.29, 1.91, p<0.00001; $I^2$=24%). The NNT for treatment benefit was nine (95% CI: 7, 15). No statistically significant association was found between the study quality rating or study duration and the effect estimate. The only individual SSRI to demonstrate significantly greater efficacy than placebo was fluoxetine OR 2.39 (95% CI: 1.69, 3.39, p<0.00001; $I^2$=0%; three studies, n=536). The NNT for treatment benefit with fluoxetine was five (95% CI: 3, 8). Nine RCTs (n=2,030) reported response rates (improved or very much improved) based on the Clinical Global Impression Improvement score (CGI-I). Pooling of these studies resulted in an OR significantly favouring SSRIs over placebo, with low heterogeneity OR 1.68 (95% CI: 1.38, 2.03, p<0.00001; $I^2$=12.2%).

The study with a combined fluoxetine and CBT arm (n=439) found that the response rate in the group receiving fluoxetine and cognitive behavioural therapy (CBT) was not superior to the rate in the group receiving fluoxetine only, although the combined therapy was more effective than either monotherapy or placebo in achieving remission.

**Authors' conclusions**
Data are scarce but SSRI treatments, especially fluoxetine, may be significantly more effective than placebo for children and adolescents with depression.

**CRD commentary**
The review question and inclusion criteria were clear in most respects, though eligible comparators were not clearly specified and not all comparisons used in the included studies were reported in the results (for example, SSRIs versus imipramine/clomipramine). A number of relevant sources were searched for eligible studies and efforts were made to minimise the risk of publication bias. Steps were taken to reduce the potential for error and bias in assessment of study validity by having more than one reviewer make decisions independently. However, it was unclear to what extent this also applied to the processes of study selection and data extraction, thus the potential for reviewer bias and error cannot be determined. The meta-analysis of results appears justified. Appropriate methods were used to assess for statistical heterogeneity. Clinical and methodological heterogeneity between the studies was well-addressed in the text, as were potential sources of bias. Despite some limitations in reporting of review methods, the authors' cautious conclusions are likely to be reliable.

**Implications of the review for practice and research**
Practice: the authors stated that the poor quality of the evidence and safety concerns about SSRIs make it impossible to determine whether SSRIs alone or combined with psychological therapy are appropriate as first-line treatment for children and adolescents with depression.

Research: the authors stated that adequately powered RCTs are required to determine the optimum treatment for children and adolescents with depression. Such studies should use validated tools with demonstrated sensitivity to change and should include the following outcomes: time to response; optimal treatment duration; effects of antidepressants; and objective and validated effectiveness scales including quality of life. A psycho-educational run-in phase should be included to identify resistant cases. The control arm should receive care as usual rather than placebo.
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