Efficacy and safety of selective serotonin reuptake inhibitors in the treatment of depression in children and adolescents: practitioner review

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CRD summary
This review concluded that selective serotonin re-uptake inhibitors may be effective and are generally well tolerated in adolescents and children with major depressive disorder. However, their use must be monitored closely as they may increase risk of suicide. The review was subject to probable publication bias, as well as methodological weaknesses, and therefore these conclusions might not be reliable.

Authors' objectives
To assess the safety and efficacy of selective serotonin re-uptake inhibitors (SSRIs) in treating adolescents and children with major depressive disorder.

Searching
MEDLINE was searched from 1990 to 2004; the search terms were reported. In addition, the bibliographies of relevant articles were also checked, and two unpublished studies available from the website of GlaxoSmithKline were also assessed. The Food and Drug Administration website was reviewed for data relating to their 2004 review of SSRIs.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised, placebo-controlled studies were eligible for inclusion.

Specific interventions included in the review
Studies comparing SSRIs with placebo were eligible for inclusion. The interventions included fluoxetine (10 to 60 mg), paroxetine (10 to 50 mg), sertraline (50 to 200 mg), citalopram (unknown dose) and imipramine (20 to 40 mg), with or without cognitive-behavioural therapy (CBT). These were compared with placebo or CBT for a duration of 8 to 12 weeks. Most studies were conducted in North America.

Participants included in the review
Studies of children with major depression, verified by a reliable and valid screening tool, as the primary disorder were eligible for inclusion. The participants in the included studies were aged between 6 and 18 years and had been recruited from a variety of sources including in-patient and out-patient settings, as well as from newspaper and radio advertisements. The primary studies excluded participants with psychiatric co-morbidity or at high risk of suicide.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the outcomes. The included studies most commonly used the following outcome measures to assess efficacy: the Children's Depression Rating Scale-Revised (CDRS-R), the Clinical Global Impression (CGI) Scale and associated subscales, the Hamilton Rating Scale for Depression (HAM-D), the depression subscale of the Kiddie Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version (K-SADS-L), and the Montgomery and Asberg Depression Rating Scale. Child and parent subjective scales were also used in some studies. Adverse events and tolerability were measured using the Side Effects Checklist. Most of the included studies obtained outcome data either weekly or fortnightly.

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

Assessment of study quality
The authors did not state that they assessed validity, though they evaluated whether the comparison groups in the studies were comparable at baseline.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Efficacy outcomes were reported as numbers in each group meeting the depression score thresholds or as the group's mean improvement in depression score, with p-values for differences between the groups. Safety and tolerability were reported descriptively.

**Methods of synthesis**
**How were the studies combined?**
The studies were presented in a narrative synthesis, structured by outcome and type of intervention.

**How were differences between studies investigated?**
Clinical differences between the studies were discussed briefly in the text.

**Results of the review**
Ten randomised controlled trials (RCTs; n=2,344) were included, of which 7 were published (n=1,619). Five included adolescents only (range: 12 to 18 years; n=1,273)

Eight studies reported baseline patient demographics by treatment group. Five studies reported similar demographics between the treatment groups, 2 studies reported a difference in history of depression or anxiety between the treatment groups, and 1 study reported a difference in the gender distribution of participants between the treatment groups.

**Efficacy.**
Three (n=754) out of 4 RCTs of fluoxetine versus placebo showed statistically significant improvements in depression scores in the intervention group, using the CGI and the CDRS-R scales. There was no statistically significant difference between the groups in the fourth RCT (n=40).

One RCT (n=275) found a statistically significant difference between paroxetine and placebo, measured using the HAM-D, K-SADS-L and CGI scales. There was no difference between imipramine and placebo on any measures in the same study. Two other (unpublished) RCTs of paroxetine versus placebo (n=792) found no statistically significant difference between the groups. One RCT (n=174) of citalopram found a statistically significant benefit for citalopram in remission rates, measured by CDRS-R response. A second (unpublished) study (n=233) found no significant difference in depression scores between the citalopram and placebo groups.

A single study of sertraline (n=376) showed a statistically significant benefit for sertraline compared with placebo, using the CDRS-R and CGI subscale scores.

**Tolerability and safety.**
Where reported, study withdrawal rates due to adverse events ranged from nil to 9.7% and were highest for paroxetine. Seven studies described adverse events, commonly dry mouth, vomiting, nausea, diarrhoea, somnolence, insomnia, dizziness, tremor and agitation. Adverse events were more common in the SSRI group than in the placebo group, though this was rarely reported to reach statistical significance.

Serious adverse events (significant psychiatric symptoms or requirement for hospitalisation) were also more common in the intervention groups. The largest study (n=439) reported a significantly increased risk of harm to self or others associated with fluoxetine, with an apparent protective effect conferred by concurrent CBT.
The authors noted that potentially relevant unpublished data on safety were not available to them for the review, and cited other publications indicating increased risk of suicidal ideation or attempt associated with the use of SSRIs in young people (see Other Publications of Related Interest nos.1-2).

Authors' conclusions
SSRIs may be effective for treating depression in children and adolescents. Overall, they are well tolerated but require close monitoring as they may increase the risk of suicidal ideation and behaviour.

CRD commentary
The review question and inclusion criteria were clear, but the search covered only one database and studies might have been missed. The authors noted that many unpublished data were unavailable, thus publication bias is very likely. There was no description of how the studies were selected for inclusion or how the data were extracted, nor of any steps taken to minimise bias in the review process, such as multiple reviewers making decisions independently. There was also no indication that the validity of the primary studies was systematically assessed. However, the authors drew attention to the limited applicability of the included studies and their short follow-up times.

The results were difficult to interpret because in most cases only statistically significant outcomes were reported in the review. Sometimes it was unclear how many measures had been applied in the individual studies and whether the outcomes reported were predetermined primary outcomes; thus there is a risk that the findings were subject to reporting bias. The abstract and introductory sections of the review were inconsistent with the main text and excluded three unpublished studies. The authors' conclusions and recommendations appear to derive partly from the findings of other systematic reviews and guidelines, rather than from the evidence of the included studies. Given the likelihood of publication bias, as well as methodological weaknesses in the review process, the conclusions of the review might not be reliable.

Implications of the review for practice and research
Practice: The authors stated that SSRIs are a first-line pharmacological intervention for children and adolescents for whom psychological treatments have failed or are not an option. Clinicians should start with low doses and monitor patients closely, and should warn caregivers of the adverse effects and potential safety risks associated with SSRIs. It should be noted that these recommendations derive partly from sources not included in the current review.

Research: The authors stated that controlled long-term studies are needed to assess the safety and efficacy of SSRIs in the paediatric population and to investigate the potential for combined treatment with CBT to help protect against suicidal ideation.

Bibliographic details

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Other publications of related interest
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Subject indexing assigned by NLM

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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.