Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies
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CRD summary
This review concluded that use of selective serotonin reuptake inhibitors (SSRIs) may be associated with a reduced risk of suicide in adults with depression. Use of SSRIs may increase suicidality among adolescents. These conclusions are likely to be reliable.

Authors' objectives
To review the association between exposure to selective serotonin reuptake inhibitors (SSRIs) and risk of suicide completion or attempt in different age groups.

Searching
MEDLINE and EMBASE were searched between January 1990 and June 2008. Search terms were reported. No language restrictions were applied. References of relevant articles were handsearched.

Study selection
Observational cohort and case-control studies that reported on people exposed to SSRIs and those who were not exposed to antidepressants were eligible for inclusion. Studies needed to report on completed or attempted suicide according to ICD (International Classification of Diseases) criteria in the patient's records. Studies were required to report relative risk estimates suitable for re-analysis. Participants could be of either sex and were required to either have a diagnosis of major depression or have been identified as such via a proxy measure. Suicide-related events such as preparatory acts, suicidal ideation and self-injurious behaviour were excluded.

Most of the included studies were cohort in design. Five studies used patients identified from Medicaid databases and the rest used national registries. Five studies reported completed suicide as an outcome and three used attempted suicide. All studies used ICD-9 or ICD-10 codes to define completed and attempted suicide. Included populations covered adolescents, adults and elderly. Five studies were based in USA or Canada and the rest took place in Denmark or Finland.

Studies were selected by two independent reviewers. Disagreements were resolved by discussion and consensus.

Assessment of study quality
Study quality was assessed using a 10-point scale (adapted from a published scale) intended for observational studies (details reported in appendix). A score of 7 or more indicated high quality and 6 or less indicated low quality; thresholds were based on use of the scale by another review group.

Quality assessment was carried out independently by two reviewers.

Data extraction
Data were extracted in duplicate by two independent reviewers using a standardised form. The most adjusted relative risk (RR), odds ratio (OR) or hazard ratio (HR) from each study was extracted, with corresponding 95% confidence intervals (CI).

Methods of synthesis
Studies were pooled using fixed-effect and random-effects models; random-effects results were presented in the article. Statistical heterogeneity was explored visually via graphs and the I^2 statistic. Unrestricted maximum likelihood random-effects meta-regression was used to explore any association between age and risk of completed or attempted suicide.
Publication bias was examined using funnel plots. Quality scores were used in sensitivity analyses, but not as weights in the primary analysis. Further sensitivity analyses explored: impact of completed suicide only; formal diagnosis of depression; external control group; study quality; population (adults and children); and study design. A meta-analysis influence test eliminated each study in turn to test for excessive influence of individual studies.

**Results of the review**

Eight studies (n=over 200,000) were included: six cohort and two case control designs.

Among adolescents, exposure to SSRIs significantly increased the risk of completed or attempted suicide (OR 1.92, 95% CI 1.51 to 2.44). SSRI exposure in adults significantly decreased the risk of completed or attempted suicide (OR 0.57, 95% CI 0.47 to 0.70). Among those aged 65 years or older exposure to SSRIs had a significantly protective effect against risk of completed or attempted suicide (OR 0.46, 95% CI 0.27 to 0.79).

Meta-regression using age as moderator and risk of completed or attempted suicide as the dependent variable suggested a promoting effect of SSRI exposure on risk of suicide among adolescents and a protective effect among adults and the elderly.

Two studies reported data on the association of suicide risk with particular antidepressant agents. No specific associations were found among adults. Exposure to paroxetine and venlafaxine were significantly associated with increased risk among adolescents.

There was no significant statistical heterogeneity. No statistically significant asymmetry was found in the funnel plot. However, visual inspection suggested there may have been a lack of small studies that failed to show an excess risk associated with SSRI exposure.

Sensitivity analyses did not change any findings. Elimination of studies from the analysis had little or no effect on the results.

**Authors’ conclusions**

Use of SSRIs may be associated with a reduced risk of suicide in adults with depression; among adolescents use of SSRIs may increase suicidality. Differences in long-term efficacy and safety should be confirmed in trials of head-to-head comparisons.

**CRD commentary**

This review addressed a clear question with detailed inclusion criteria. Searches covered the main databases of relevance without language restriction. It appeared that no attempt was made to access grey literature, which may have introduced publication bias. The review processes were clearly described and carried out by two independent reviewers, which reduced the likelihood of reviewer error and bias affecting results. Appropriate quality assessment and synthesis were carried out taking into account variations in data, although it would have been useful had the authors reported the number of people on which each analysis was based. Overall the conclusions of this review are likely to be reliable.

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

**Practice:** Observational study data suggested that it was safe to prescribe SSRIs to patients with major depression. However, children and adolescents should be followed very closely due to a possibility of increased risk in suicidal thoughts and suicide. Paroxetine and venlafaxine may be best avoided as evidence suggested risks may outweigh benefits for most adolescents.

**Research:** Differences in long-term efficacy and safety of SSRIs should be confirmed in trials of head-to-head comparisons.

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