Adverse cardiovascular events in antidepressant trials involving high-risk patients: a systematic review of randomized trials

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CRD summary
This review assessed the incidence of cardiovascular adverse events in patients at high risk treated with selective serotonin re-uptake inhibitor (SSRI) antidepressants. The authors concluded that the available evidence was too scarce to clearly establish the risk associated with SSRI administration. There were limitations to this review but, overall, these conclusions are likely to be reliable.

Authors' objectives
To evaluate the risk of cardiovascular adverse events (AEs) in patients treated with selective serotonin re-uptake inhibitor (SSRI) antidepressants.

Searching
MEDLINE (from 1967 to May 2005) and the Cochrane CENTRAL Register (up to November 2004) were searched; the search terms were reported. The bibliographies of reviews and retrieved articles were checked for additional articles. Abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Parallel-group randomised controlled trials (RCTs) were eligible for the review. In only 3 studies did the duration of follow-up exceed 26 weeks.

Specific interventions included in the review
Studies comparing an SSRI antidepressant with either placebo, tricyclic antidepressants (TCAs), or another active treatment were eligible.

Participants included in the review
Studies of patients at high risk for cardiovascular AEs (including patients with cardiac diseases, diabetes mellitus, stroke, geriatric age, Alzheimer's disease, nicotine dependence, alcoholism, human immunodeficiency virus infection, obesity or metabolic syndrome) were eligible. The mean age of the participants in the included studies was 58 years (range: 29.8 to 70.3).

Outcomes assessed in the review
Studies with follow-up periods of at least 1 week, evaluating any cardiovascular AE, were considered for the review. AEs were divided into serious cardiovascular AEs (i.e. death due to a cardiovascular cause, heart failure, transient ischaemic attack, stroke and myocardial infarction) and non-serious cardiovascular AEs (i.e. palpitations, chest pain, angina, arrhythmia, hypertension or hypotension-syncope, and unspecified cardiovascular or neurological events).

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies, with any disagreements resolved through discussion with a third reviewer.

Assessment of study quality
The authors stated that a formal validity assessment was not performed.

Data extraction
Two reviewers independently extracted the data, with any disagreements resolved through discussion with a third reviewer.
Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using Peto's fixed-effect model. Only studies reporting the number of cardiovascular AEs were included in the analysis.

How were differences between studies investigated?
The authors stated that statistical heterogeneity was not assessed because of the rarity of cardiovascular AEs and zero cells. A sensitivity analysis was conducted that excluded longer-term trials. The authors stated that sources of clinical and methodological heterogeneity (including clinical indication, trial duration, gender, age, sample size and drop-outs) were explored.

Results of the review
One hundred and twenty-two studies (n=13,828 patients) were included in the review. Fifty studies reported that cardiovascular events were included in analyses (n=6,588).

There was no significant difference between SSRIs and placebo for both serious and non-serious cardiovascular AEs. Compared with TCAs, the use of SSRIs significantly decreased the odds of non-serious cardiovascular AEs (OR 0.46, 95% CI: 0.24, 0.86, p=0.02) while the rate of serious AEs was similar (OR 0.97, 95% CI: 0.06, 15.58). Comparable incidences of serious and non-serious cardiovascular AEs were found for SSRIs and other active treatments. The results of the sensitivity analysis did not significantly change the overall findings.

Authors' conclusions
There is no definite evidence to clearly establish the risk of cardiovascular AEs associated with SSRI administration, owing to limitations in the clinical trials.

CRD commentary
This review addressed a well-defined question in terms of participants, interventions, study outcomes and study design. One relevant database and a trial register were searched, but no specific attempts to minimise either language or publication bias were reported and some relevant studies might have been missed. The potential influence of publication bias was not considered in the report. The authors carried out the study selection and data extraction process in duplicate, thereby minimising reviewer error and bias. Statistical heterogeneity was not formally assessed, which leaves it unclear whether the authors’ decision to pool the studies was appropriate; however, the authors did justify this. The authors’ conclusions appear appropriate, but the limited search and incomplete reporting of the review process must be taken into consideration.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further trials of antidepressants should improve the quality of reporting cardiovascular AEs.

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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.