Bayesian meta-analyses of the tolerability of selective serotonin reuptake inhibitors and tricyclic antidepressants for treating patients with depression

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CRD summary
This review compared the tolerability of selective serotonin re-uptake inhibitors (SSRIs) with tricyclic antidepressants (TCAs) for treating depression in primary care. The authors concluded there was no clear evidence that SSRIs were better tolerated than TCAs. Poor reporting of the review methods and the lack of a quality assessment make it difficult to confirm the robustness of the conclusions.

Authors' objectives
To use Bayesian meta-analyses to compare the tolerability of selective serotonin re-uptake inhibitors (SSRIs) with tricyclic antidepressants (TCAs) for the treatment of patients with depression in primary care.

The review also compared the tolerability of SSRIs with TCAs for the treatment of patients in a general setting. However, this second meta-analysis was a meta-analysis of another review, and hence did not meet eligibility criteria for inclusion in DARE. Thus, this abstract only refers to the review of primary care patients.

Searching
MEDLINE and the Cochrane Library were searched without language restriction up to May 2004. Previous meta-analyses and reviews were also screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion if they provided sufficient information on study design, treatments, tolerability and other unspecified study characteristics.

Specific interventions included in the review
Studies that compared SSRIs with TCAs or any other antidepressant with the same mechanism of action were eligible for inclusion. The included studies compared the SSRIs fluoxetine, paroxetine, citalopram and sertraline with the TCAs dothiepin, amitriptyline, lofepramine and clomipramine. Treatment lasted from 6 to 22 weeks.

Participants included in the review
Studies of patients with depressive disorders in primary care were eligible for inclusion. Subsequently, a decision was made to exclude two studies in elderly patients (65 years and over). The included studies were in patients meeting various criteria for depression: Research Diagnostic Criteria; Diagnostic Systems (DSM-III); Hamilton Anxiety Scale (HAM-D), at least 14 to at least 17; Montgomery-Asberg Depression Rating Scale, at least 16 to at least 22; Clinical Global Impression Scale, at least 4; and Clinical Anxiety Scale, at least 11. The mean age of the participants ranged from 41.7 to 47.1 years (five studies) and the majority were female (range: 66.5 to 73.5%).

Outcomes assessed in the review
Studies that assessed efficacy and tolerability were sought. It was clear that the outcome of interest was the premature discontinuation of treatment due to drug-related side-effects.

How were decisions on the relevance of primary studies made?
The authors did not state how studies 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.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the number of patients who discontinued treatment due to side-effects was extracted for each treatment group and the odds ratio (OR), with 95% confidence interval (CI), was calculated.

Methods of synthesis
How were the studies combined?
The studies were initially pooled using a fixed-effect classical meta-analysis. Pooled ORs with 95% posterior intervals (PIs) were then calculated using Bayesian meta-analysis models that incorporated different values for the prior distribution, reflecting the following beliefs about the relative tolerability of SSRIs and TCAs: SSRIs were significantly better tolerated than TCAs; SSRIs were better tolerated than TCAs; SSRIs were identical in tolerability to TCAs (indifferent prior); and TCAs were better tolerated than SSRIs (non-informative prior). Detailed methods for Bayesian analysis were reported.

How were differences between studies investigated?
Statistical heterogeneity was assessed and a forest plot was presented. The classical fixed-effect meta-analysis was repeated after excluding one study that strongly favoured SSRIs.

Results of the review
Seven double-blind RCTs (n=2,524) were included.

Classical model.
The meta-analysis suggested that SSRIs were significantly better tolerated than TCAs (OR 1.35, 95% CI: 1.06, 1.73); significant statistical heterogeneity was found (P=0.09). After excluding one study that strongly favoured SSRIs, the difference between treatments was no longer statistically significant (OR 1.15, 95% CI: 0.83, 1.60).

Bayesian meta-analysis.
The posterior distributions varied according to the respective prior distributions.
The meta-analysis using priors reflecting the belief that SSRIs were significantly better tolerated than TCAs found that SSRIs were significantly better tolerated than TCAs (OR 1.47, 95% PI: 1.21, 1.77).
The meta-analysis using priors reflecting the belief that SSRIs were better tolerated than TCAs found that SSRIs were significantly better tolerated than TCAs (OR 1.23, 95% PI: 1.02, 1.48).
The meta-analysis using priors reflecting the belief that SSRIs were identical in tolerability to TCAs or that TCAs were better tolerated than SSRIs found no statistically significant difference between treatment for tolerability (for both priors, OR 0.53, 95% PI: 0.11, 2.52).

Authors' conclusions
There was no clear evidence that SSRIs were better tolerated in primary care patients than TCAs.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. However, the decision to exclude studies of elderly patients was made post hoc and could have led to selection bias. Limiting the search to studies identified in two databases plus references might have resulted in the omission of other relevant studies. No details of the search strategy were reported, so it was not possible to assess whether it was appropriate. No language restrictions were applied to the search, thus minimising the possibility of language bias, but no attempts were made to minimise publication bias. The methods used to select studies and extract the data were not
described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Study validity was not assessed, thus the results from these studies and any synthesis may not be reliable. Drug doses were not reported, so it was not possible to determine the comparability of treatment doses.

The studies were pooled using meta-analysis and statistical heterogeneity was assessed, although the methods used were not reported. From inspection of the forest plot one study appeared to be an outlier; the influence of this study was examined. However, potential reasons for differences between the studies were not discussed in detail. In addition, most studies were short-term (only one lasted more than 12 weeks) and this too limits the evidence. The lack of reporting of review methods and lack of a quality assessment make it difficult to confirm the robustness of the conclusions.

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

**Practice:** The authors stated that primary care physicians must carefully monitor patients receiving SSRIs (fluoxetine, paroxetine, citalopram and sertraline in particular).

**Research:** The authors stated that future research could consider undertaking meta-analyses of other newer antidepressants and in other populations such as the elderly.

**Bibliographic details**


**Indexing Status**

Subject indexing assigned by CRD

**MeSH**

Antidepressive Agents, Tricyclic / adverse effects / therapeutic use; Bayes Theorem; Data Interpretation, Statistical; Depressive Disorder / drug therapy; Models, Statistical; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors / adverse effects / therapeutic use; Treatment Outcome

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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.