Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis


CRD summary
This well conducted review concluded that evidence on the relative efficacy of tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) for depression in primary care is sparse and of variable quality. In the short term, no significant differences exist in efficacy between SSRIs and TCAs, but that SSRIs had significantly lower drop-out rates. The authors' conclusions are reliable.

Authors' objectives
To compare the efficacy and tolerability of tricyclic antidepressants (TCAs) with selective serotonin re-uptake inhibitors (SSRIs) in depression in primary care.

Searching
The Cochrane Collaboration Depression, Anxiety and Neurosis Group's Specialised Register was searched up to April 2002. The reference lists of initial studies and other relevant review papers were consulted. Selected authors and experts in the field were also contacted.

Study selection
Study designs of evaluations included in the review
To be eligible, the studies needed to be randomised controlled trials (RCTs).

Specific interventions included in the review
The trials needed to compare a SSRI with a TCA. Both high (at least 125 mg/day) and low doses of TCA were included. Many studies were of short duration, typically 6 to 8 weeks.

Participants included in the review
The studies needed to be concerned with the treatment of (predominantly adult) primary care patients with a depressive disorder. Studies with predominantly children or elderly patients were excluded. Most of the studies in the review included patients aged 18 to 70 years (mean age reported to be 40 to 45). Approximately three quarters of the participants were female. Most participants were white Europeans being treated by their general practitioner.

Outcomes assessed in the review
The main outcome measures were the final mean depression scores and response when using the clinical global impression score. The secondary outcomes were the number of patients withdrawing from treatment at any time and the number withdrawing due to side-effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies.

Assessment of study quality
Methodological quality was assessed according to the recommendations of the Cochrane Collaboration Handbook. Studies were assessed as being of a low methodological quality if they did not meet the minimum requirements on the following aspects: sample size; allocation concealment; clear description of treatment; representative source of participants; use of diagnostic criteria or clear specification of inclusion criteria; details of the number and reasons for withdrawal by group; and outcome measures described clearly or use of validated instruments. Two reviewers appear to have undertaken the quality assessment.
Data extraction
Two reviewers independently extracted the data and resolved any disagreements by discussion. For continuous outcomes, the standardised mean differences or weighted mean differences were calculated. For binary outcomes, the relative risk and the number-needed-to-treat were calculated. Where the authors did not provide standard deviations (or they were unavailable), the highest known standard deviations from the included studies were used.

Methods of synthesis
How were the studies combined?
The studies were combined by meta-analysis, applying a fixed-effect model. Results obtained using a random-effects model were compared.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. Effectiveness was examined both with and without low-quality studies and studies with extrapolated data.

Results of the review
Eleven RCTs with 2,954 participants were included in the review.

Most of the included studies were small and were supported by commercial funding. Many of the assessed studies were of a low methodological quality and/or did not present adequate data for analysis. Funnel plots indicated no obvious publication or related bias.

The efficacy between SSRIs and TCAs did not differ significantly, based on 6 trials with final mean depression scores; the standardised weighted mean difference using a fixed-effect model was 0.07 (95% confidence interval, CI: -0.02, 0.15, P=0.11). Efficacy also did not differ significantly in 3 trials using clinical global impression.

Significantly more patients receiving a TCA withdrew from treatment (based on 6 trials); the relative risk was 0.78 (95% CI: 0.68, 0.90, P=0.0007). Significantly more withdrew specifically due to side-effects (based on 7 trials); the relative risk was 0.73 (95% CI: 0.60, 0.88, P=0.001).

Authors’ conclusions
The authors concluded that the evidence on the relative efficacy of SSRIs and TCAs is sparse and of variable quality. The results implied that, in the short term, no significant differences exist in efficacy between SSRIs and TCAs in patients in primary care. However, significantly lower rates of drop-out were found for SSRIs than for TCAs. The study setting is likely to be an important factor in assessing the efficacy and tolerability of treatment with antidepressants.

CRD commentary
The inclusion criteria were stated for the study design, participants, intervention and outcomes. Searching was based on the Cochrane Collaboration Depression, Anxiety and Neurosis Group's Specialised Register, but no details of how the register was searched were given. Foreign language papers were eligible for inclusion, and attempts were made to find unpublished material and to assess publication bias. A quality assessment was performed and the effects of study quality on the results were investigated. Adequate study details were provided. Classes of drugs were pooled, but differences between drugs in the same class were not explored. The results were presented with and without lower quality studies and studies with extrapolated data. The review process involved more than one reviewer, which serves to minimise bias. The reviewers’ conclusions follow from their results and highlight the differences in treatment response between primary and secondary care patients.

Implications of the review for practice and research
Practice: The authors stated that it may be appropriate for bodies that grant drug licences to ensure that studies have been carried out in appropriate settings before granting specific antidepressants their licence.
Research: The authors stated that there is a need to conduct studies that include only minor or milder presentations of depression.

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