Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability

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Authors' objectives
To evaluate the efficacy and tolerability of selective serotonin reuptake inhibitors (SSRIs) against tricyclic antidepressants (TCAs) in depressed patients.

Searching
MEDLINE was searched up to May 1997 using the search terms: drug name, 'randomised controlled trial', 'controlled trial', 'depression' and variants. Previous meta-analyses and reviews were also searched and manual cross-referencing was performed. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

Specific interventions included in the review
Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, fluvoxamine, paroxetine, sertraline or citalopram) compared with tricyclic antidepressants (TCAs) (clomipramine, amitriptyline, imipramine, dothiepin, desipramine, doxepin, nortriptyline, nomifensine and lofepramine). Maprotiline was also included in the analysis as it has the same mechanism as TCAs. Studies comparing SSRIs with older atypical antidepressants (i.e. those that do not inhibit monoamine reuptake) were excluded, as were studies of newer antidepressants (nefazodone, venlafaxine and mirtazapine). The median duration of active treatment was six weeks with 55 studies lasting this time. Twenty-eight studies lasted four or five weeks and 20 studies more than six weeks, but only one lasted more than 12 weeks.

Participants included in the review
People with unipolar major depressive illnesses. Eighty-two of the 102 included studies used American Psychiatric Association criteria (DSM-III, DSM-III-R), Feighner or Research Diagnostic Criteria for major depression. Patients were either from general practice, inpatients, or out-patients.

Outcomes assessed in the review
The relative reduction in rating scale scores. The 17- or 21-item Hamilton Rating Scale for Depression (HAMD) was the most commonly used measure of efficacy in the included trials, while the Montgomery and Asberg Depression Rating Scale (MADRS) was used in nine studies.

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

Assessment of study quality
The author does not state that they assessed validity.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on study year, diagnostic criteria, whether data was complete or not, and location of study (general practice, out-patient or in-patient).
Methods of synthesis
How were the studies combined?
Efficacy data from the studies were pooled to provide a summary variance-weighted effect size. Where possible the author used values that included the maximum number of patients (i.e. intention-to-treat or last observation carried forward rather than completer analysis). Tolerability data were combined to give variance-weighted relative risk of drop out for all reasons and for adverse effects from each study. The extent of publication bias was examined by means of a funnel plot.

How were differences between studies investigated?
Sensitivity analysis was performed by analysing separately the larger studies (>100 patients), those which were placebo-controlled and, for efficacy, those with complete data. The effect of age, treatment setting, severity and TCA dose were examined as well as the performance of individual SSRIs and TCAs where there were sufficient studies.

Results of the review
A total of 102 randomised controlled trials (10,706 patients) were included. The median number of patients assessed in the trials was 60 (range 14 to 953). Tolerability data were available from 95 studies (10839 patients).

There was no overall difference in efficacy between SSRIs and TCAs (effect size -0.03, 95% confidence interval -0.09 to 0.03). TCAs appeared more effective in in-patients (-0.23, -0.40 to -0.05) and amitriptyline was more effective than SSRI comparators (-0.14, -0.25 to -0.03) but publication bias cannot be excluded. The SSRIs were better tolerated, with significantly lower rates of treatment discontinuations overall (relative risk 0.88, 0.83 to 0.93; number needed to treat 26) and due to side effects (0.73, 0.67 to 0.80; number needed to treat 33). Individual SSRIs showed a similar advantage except for fluvoxamine which did not differ from the TCAs. Individual TCAs showed a similar disadvantage in tolerability compared to SSRIs except for dothiepin against which SSRI treatment results in more side-effect related drop outs (2.64, 1.50 to 4.63; number needed to harm 12).

Authors' conclusions
Overall efficacy between the two classes is comparable but SSRIs are not proven to be as effective as TCAs in in-patients and against amitriptyline. SSRIs have a modest advantage in terms of tolerability against most TCAs.

CRD commentary
This is an important review which includes a large number of studies. The search was adequate, but no attempt was made to locate unpublished trials which could have resulted in publication bias. However, the extent of publication bias was examined by means of a funnel plot, which did not suggest that publication bias accounted for the advantage of the SSRIs. Few details were provided about the methodology of the review, and only one author is named on the review. Furthermore, no assessment of study validity was performed. Study details are adequate, and the author’s conclusions appear to follow on from the results of the review.

Implications of the review for practice and research
Practice: The author states that the conclusion reached in a previous meta-analysis by the authors, that amitriptyline is the antidepressant of choice whilst maximising efficacy, still holds.

Research: The author did not state any implications for further research.

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