Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis
Steffens D C, Krishnan K R, Helms M J

Authors’ objectives
To assess the efficacy and drop-out rates for tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Frequency of reported side effects was also studied.

Searching
The authors searched MEDLINE for English language publications dating back to 1980. The authors searched for trials of ‘imipramine’, ‘amitriptyline’, ‘nortriptyline’, ‘desipramine’, ‘doxepin’, ‘clomipramine’, ‘fluoxetine’, ‘sertraline’ and ‘paroxetine’. Other sources of data were identified through manual cross-referencing and expert consultation. Letters to authors were also sent out requesting information on missing data. The search was restricted to publications in English. Care was taken to exclude multiple publications by centres involved in multicentre trials.

Study selection
Study designs of evaluations included in the review
Random, double-blind clinical trials (RCTs).

Specific interventions included in the review
Tricyclic antidepressants (TCAs) (imipramine, amitriptyline, nortriptyline, desipramine, doxepin, clomipramine) and selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, and paroxetine) and placebo. Dosages and treatment regimens are not reported. Studies of SSRIs which included non-TCA comparators (e.g. trazodone, mianserin, monoamine oxidase inhibitors) were excluded.

Participants included in the review
Patients suffering from major depression as defined by the American Psychiatric Association (DSM-III or DSM-III-R criteria).

Outcomes assessed in the review
Efficacy response rates to treatment (defined as at least a 50% reduction in score on the Hamilton Depression Scale (HDRS) or a final HDRS score ranging from less than or equal to 6 to less than or equal to 12), drop-out rates due to adverse events, lack of efficacy or both adverse events and lack of efficacy, and reported side effects. Side effects were measured in the following categories: abdominal pain/nausea; anxiety/agitation/nervousness/ overexcitement; somnolence/sedation/drowsiness; lightheadedness/dizziness; dry mouth; dyspepsia; diarrhea; constipation; sexual dysfunction; and asthenia/fatigue.

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

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state who, or how many of the reviewers, performed the data extraction.

For all measurements (efficacy, side-effects and drop-out rates) percentages were converted to counts and absolute numbers were used. When side effects were presented in graphic form, the authors estimated absolute numbers from visual inspection of the bar graph. For each side effect, the authors calculated a ratio of reported side effects to number.
of SSI- or TCA-treated individuals across all studies. A sub-group of 21 studies was used to analyse response rates where HDRS scores had been used.

Methods of synthesis

How were the studies combined?
The random-effects model of DerSimonian and Laird (see Other Publications of Related Interest) to calculate the common risk difference statistics with 95% confidence intervals (CIs) for each outcome measure.

To investigate the side-effects data the authors also performed an additional descriptive analysis based on the categories of side-effects listed above.

How were differences between studies investigated?
The authors used the Cochran Q statistic to test for homogeneity between studies.

Results of the review

Thirty-six (36) RCTs were included in the review (total number of participants not stated). Thirty (30) trials were included in the analysis of efficacy with 4,076 participants in the intention-to-treat group (2,074 SSRI participants and 2,002 TCA participants) and 2,254 participants in the completer group (1,167 SSRI participants and 1,087 TCA participants).

Thirty-four trials were included in the analysis of drop-outs due to adverse events, lack of efficacy or for either reason. For lack of efficacy and both adverse event and lack of efficacy there were 2,262 SSRI participants and 2,161 TCA participants. For adverse events, there were 2,294 SSRI participants and 2,193 participants. Twenty-one trials were included in the analysis where HDRS scores were used to determine response rates with 1,628 SSRI participants and 1,557 TCA participants.

The numbers of trials and participants included in the side-effects analysis are reported for each category in a table of results.

The percentage of patients responding in the intention-to-treat group was 48% for SSRI versus 48.6% for TCA for which there was no statistical difference. The common risk difference was 0.007, 95% CI: -0.042, 0.055).

The response rate for all studies in the completer group was 63.2% for SSRI versus 68.2% for TCA which was statistically significant in favour of the TCA group. The common risk difference (TCA-SSRI) was 0.060, 95% CI: 0.003, 0.118.

The response rate for HDRS studies (n = 21) in the intention-to-treat group was 45.3% for SSRI versus 47.3% for TCA for which there was a statistical difference. The common risk difference was 0.031, 95% CI: -0.026, 0.088).

The efficacy for HDRS studies in the completer group was 62.1% for SSRI versus 68.3% for TCA which was statistically significant in favour of the TCA group. The common risk difference was 0.086, 95% CI: 0.021, 0.152).

Drop-out rate due to adverse events for all studies was 15.9% for SSRI versus 22.4% for TCA which was statistically significant in favour of the SSRI group. The common risk difference was 0.053, 95% CI: 0.021, 0.085).

Drop-out rate due to lack of efficacy for all studies was 9.3% for SSRI versus 7.8% for TCA. There was no statistically significant difference between the two groups. The common risk difference was -0.007, 95% CI: -0.020, 0.006).

Drop-out rate due to adverse event or lack of efficacy for all studies was 24.7% for SSRI versus 30% for TCA which was statistically significant in favour of the SSRI group. The common risk difference was 0.048, 95% CI: 0.012, 0.085).

Using the random-effects model all tests for homogeneity were statistically non-significant.
Patients taking SSRIs experienced significantly more abdominal pain/nausea.

Treatment with TCAs produced significantly more complaints of somnolence/sedation/drowsiness, lightheadedness/dizziness, dry mouth and constipation.

There were no differences between the drugs in the remaining categories.

An adjusted Q test for homogeneity implied homogeneity across all studies for all side effects examined except for abdominal pain/nausea, where p = 0.014.

**Authors' conclusions**

For the intention-to-treat groups there were no differences in efficacy between the two drugs; however, among treatment completers, TCAs were statistically more efficacious than SSRIs. Analysis of drop-outs revealed that patients taking TCAs discontinued treatment due to adverse reactions more frequently than did patients on SSRIs. There was no difference in drop-outs due to lack of efficacy. Patients exposed to either SSRIs or TCAs report a great degree of side effects. With efficacy similar to TCAs, a favourable drop-out rate, less laboratory monitoring, and fewer office visits for dosage adjustments, SSRIs may prove to be the better initial choice for treatment of outpatients with depression despite higher drug cost.

**CRD commentary**

The authors have stated their research question but have omitted inclusion and exclusion criteria for the review. The literature search is poor because the authors have searched only one database which may have missed studies that were published outside of the United States. The authors do not report the dates of the search and have restricted the search to English language publications. For these reasons, it is possible that relevant studies may have been missed.

The authors have not reported on how the articles were selected or how the quality of the included studies was assessed, and there is no report as to who, or how many of the reviewers, selected the articles or extracted the data.

The studies analysing efficacy and drop-out rates are combined in a statistical analysis which was appropriate and the authors have tested for homogeneity. The data for side effects was statistically combined and then reported in a narrative summary. The individual studies and results are reported in several tables. The conclusions of the review follow from the results, however because of the lack of detail about the selection, inclusion, and quality assessment in the review, the results should be viewed with caution.

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

Practice: The authors state that the judicious use of certain TCAs can also be recommended for specific populations.

Research: There are no stated implications for research.

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**Other publications of related interest**

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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.