Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials
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CRD summary
The authors concluded that remission rates are highest and drop-out rates are lowest with serotonin-norepinephrine re-uptake inhibitors compared with selective serotonin re-uptake inhibitors and tricyclic antidepressants, suggesting that they are clinically superior for treating major depression. These conclusions should be treated with caution as they are not based on comparisons of treatments within trials.

Authors' objectives
To compare rates of remission, drop-outs and adverse drug reactions (ADRs) between three classes of drugs used for treating major depressive disorder (MDD): serotonin-norepinephrine re-uptake inhibitors (SNRIs), selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).

Searching
MEDLINE, EMBASE, International Pharmaceutical Abstracts and the Cochrane Library were searched from 1980 to December 2005; some search terms were reported. No language restrictions were applied.

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

Specific interventions included in the review
Studies that directly compared at least two active drugs from the following three specified classes of antidepressants were eligible for inclusion: SNRIs (duloxetine, milnacipran and venlafaxine), SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and TCAs (doxepin, amitriptyline, nortriptyline, maprotiline, desipramine, trimipramine, protriptyline, clomipramine and imipramine). Treatment regimens had to have included a 1- to 2-week wash-out period, followed by a minimum of 6 weeks’ oral administration of a therapeutic dose of the active drug. No additional antidepressant drugs other than those being evaluated, or any other drugs which could interfere with the interpretation of study results, could be taken concomitantly. However, hypnotic agents and tranquillisers were allowed. The included studies evaluated SNRIs (duloxetine, milnacipran and venlafaxine), SSRIs (citalopram, escitalopram, fluoxetine, paroxetine and sertraline) and TCAs (amitriptyline, clomipramine and imipramine). The duration of the included studies ranged from 6 to 24 weeks; most studies were of 8 weeks' duration.

Participants included in the review
Studies of adults aged 18 years or over with moderate to severe MDD (diagnosed using any standard scale) were eligible for inclusion. Participants had to have scored 18 or more on the Montgomery Asberg Depression Rating Scale (MADRS) or 15 or more on any version of the Hamilton Depression Rating Scale (HAMD), have no concurrent psychiatric, endocrine or metabolic disease and not be taking any drugs that might hinder the interpretation of the study data. Where reported in the included studies, the mean age ranged from 37.3 to 74.2 years and the percentage of women ranged from 47 to 84%.

Outcomes assessed in the review
The primary review outcome was remission, defined as 7 or less on the HAMD scale or 12 or less on the MADRS scale. The secondary outcomes were drop-outs due to loss of efficacy and ADRs, with important ADRs assessed separately.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements on inclusion through consensus.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements on inclusion through consensus. For each study, the number of patients successfully and unsuccessfully treated, the numbers of drop-outs and completers, remission rates and drop-out rates (both with 95% confidence intervals, CIs) were presented for each drug treatment arm.

Methods of synthesis
How were the studies combined?
Pooled event rates with 95% CIs were calculated separately for each drug class of interest using a random-effects model weighted by inverse variance. Data were analysed on an intention-to-treat (ITT) basis and a per protocol basis. Differences between drug classes were tested using Z-scores, as described by Rosenthal, where the variances between comparators were homogeneous. Where the variances were heterogeneous, a Mann-Whitney U test was used to test treatment differences. Publication bias was assessed using a funnel plot and tested using the Begg-Mazumdar statistic.

How were differences between studies investigated?
Data from in-patients and out-patients were combined separately. Where there were sufficient data, subgroup analyses were performed for individual drugs. Statistical heterogeneity was assessed using the Q-statistic. Attempts were made to identify studies and the variables within these studies that were responsible for the heterogeneity. The characteristics of the participants were compared between the studies evaluating the three drug classes.

Results of the review
Fifteen RCTs (n=2,458) were included. These studies provided 30 treatment arms. Ten studies (n=836) evaluated SNRIs, 11 studies (n=916) evaluated SSRIs and 9 studies (n=706) evaluated TCAs.

Significant statistical heterogeneity was found for all three drug classes for remission and drop-out rates. The authors could find no apparent explanations for this heterogeneity.

Patients in the TCA and SNRI treatment arms were significantly older than patients in the SSRI treatment arms (53.7 and 52.5 years, respectively, versus 40.9 years, p<0.05). Patients in the SSRI treatment arms were significantly heavier than patients in the TCA treatment arms (75.4 kg versus 62.6 kg, p<0.05).

Remission rates: ITT analysis.
Patients in the SNRI and TCA treatment arms had significantly higher rates of remission than patients in the SSRI treatment arms (49% and 44.1%, respectively, versus 37.7%, p<0.001 for both comparisons). There was no significant difference between the SNRI and TCA treatment arms. Remission rates varied within each drug class: from 31 to 70% within the SNRI treatment arms, from 19 to 70% within SSRIs, and from 23 to 54% within TCAs.

Remission rates: per protocol analysis.
TCAs were associated with significantly higher rates of remission than SNRIs and SSRIs (69% versus 64% and 54%, respectively, p<0.001 for both comparisons). There was no significant difference between the SNRI and SSRI treatment arms.

Drop-out rates.
ITT analysis: patients in the TCA treatment arms had significantly higher drop-out rates than patients in the SSRI and SNRI treatment arms (35.7% versus 28.4% and 26.1%, respectively, p<0.05 for both comparisons). There was no significant difference between the SNRI and SSRI treatment arms.
Drop-outs due to ADRs were significantly higher in the TCA treatment arms than in the SNRI and SSRI treatment arms (19.8% versus 10.3% and 8.3%, respectively, p<0.05).

There was no significant difference between the three drug classes for drop-outs due to loss of efficacy.

ADRs.

Patients in the TCA treatment arms had the highest rates of occurrence for most selected ADRs, including dry mouth (58%), sweating (28%) and constipation (26%).

The authors stated that the funnel plot suggested the presence of publication bias but the Begg-Mazumdar test found no strong evidence for it.

**Authors' conclusions**

Remission rates are highest and drop-out rates are lowest with SNRIs compared with SSRIs and TCAs, suggesting that they are clinically superior for the treatment of major depression.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. However, it is not clear why only RCTs were eligible given that the analyses were not based on within-study treatment comparisons. Several relevant sources were searched and no language restrictions were imposed. No attempts to minimise publication bias were reported, although the authors did assess the potential for it and found no convincing evidence of major bias. Methods were used to minimise reviewer error and bias in the study selection and data extraction processes. Adequate details of the included studies were presented. The majority of the studies were of relatively short duration, with most lasting 8 weeks. The studies were pooled using meta-analysis and statistical heterogeneity was found for all three drug classes. Meta-analysis graphs were not presented but inspection of the tables showed variation within drug classes and the overall results for the drug class may not reflect treatment effects of individual drugs; the authors did mention this. Conclusions regarding the relative effects of different antidepressant drug classes were not based on direct comparisons of treatments within trials. Any conclusions drawn about the relative effects of SSNRIs, SSRIs and TCAs are not, therefore, definitive.

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

Practice: The authors stated that clinical information about the specific drug and results from well-designed comprehensive pharmacoeconomic analysis should be taken into account when deciding on the most appropriate drug.

Research: The authors stated that there is a need for an economic analysis based on data presented in this review.

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