SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability

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Authors' objectives
To evaluate the efficacy and tolerability of selective serotonin re-uptake inhibitors (SSRIs) against nonselective and noradrenergic re-uptake inhibitors in the treatment of depressed in-patients. The latter inhibitors were mainly tricyclic antidepressants (TCAs).

Searching
MEDLINE was searched up to May 1997. The search terms were not provided. In addition, previous meta-analyses and reviews were searched and manual cross-referencing was performed.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) comparing SSRIs with TCAs. The length of the treatment was not stated.

Specific interventions included in the review
Antidepressants: SSRIs versus noradrenergic re-uptake inhibitors. The SSRIs studied were citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The TCAs studied were amitriptyline, imipramine, maprotiline, clomipramine and desipramine.

Participants included in the review
In-patients with the equivalence of major depressive illness were included. The age and gender of the patients was not stated.

Outcomes assessed in the review
The efficacy and tolerability of the antidepressants was assessed. All studies used the Hamilton Depression Rating Scale to measure the efficacy of the antidepressants.

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 authors do 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. Intention-to-treat or last-observation-carried forward analyses were used in preference to complete analysis.

The efficacy of the comparator drugs for each individual study was calculated as an effect size (Hedges d) from the difference in reduction in the rating scale scores (initial minus final mean score), divided by the pooled final deviation. For studies where the standard deviations of the rating scale scores were not supplied, the pooled variance from the studies with complete data were used.

Tolerability was assessed by calculating the relative risk for total drop-outs and for those due to side-effects (see Other Publications of Related Interest no.1). The results for drop-outs due to treatment failure were also calculated. The
absolute risk difference was calculated for significant results.

**Methods of synthesis**

How were the studies combined?

A summary variance-weighted effect size was calculated using a fixed-effect model for homogeneous data and a random-effects model for heterogeneous data (see Other Publications of Related Interest no.2). A negative effect size indicated TCA were advantageous, whilst a positive one indicated SSRIs were advantageous.

A fixed-effect model was used for the variance-weighted pooling of individual results for tolerability, as there was no significant heterogeneity for any analysis. A relative risk of less than one indicated an advantage to SSRIs, and greater than one, an advantage to TCAs.

How were differences between studies investigated?

Heterogeneity was examined using Cochran's Q. Sensitivity analyses were carried out separately for larger studies with more than 100 patients and those with complete data (for the efficacy analysis). Separate efficacy analyses of studies using dual action drugs (clomipramine and amitriptyline) and more selective noradrenaline re-uptake inhibitors (imipramine, desipramine, and maprotiline) were also performed. Individual antidepressants were examined where there were at least 4 studies.

**Results of the review**

Twenty-five studies with a total of 1,377 patients were included in the analyses.

No eligible studies on sertraline in in-patients were identified.

Overall, TCAs were significantly more effective than the SSRIs (effect size, ES -0.23, 95% confidence interval, CI: -0.40, -0.05, p=0.011). The studies showed significant heterogeneity (Q=57.3529, d.f.=24, p=0.0001). Sensitivity analyses using 5 of the larger studies (with greater than 100 patients) and those providing complete data (15 studies) reduced the advantage of TCAs to a non significant trend (p<0.10). When TCAs were grouped into those with dual action on 5-hydroxytryptamine and noradrenaline re-uptake (clomipramine and amitriptyline), and those with predominantly noradrenaline re-uptake, only the dual action TCAs had greater efficacy than the SSRIs (ES -0.30, 95% CI: -0.54, -0.05, p=0.017). When TCAs were considered individually, only amitriptyline was significantly more effective than the SSRIs (ES -0.37, 95% CI: -0.67, -0.07, p=0.015). When considering the SSRIs separately, there was a significant advantage to the TCAs over paroxetine (ES -0.44, 95% CI: -0.78, -0.11, p=0.009), but not to fluvoxamine or fluoxetine.

Tolerability results (22 studies) indicated that more patients discontinued treatment on TCAs than on SSRIs (29 versus 25.5%; not significant). However, significantly more patients stopped treatment due to adverse effects with TCAs than with SSRIs (14.2 versus 9.1%; relative risk 0.66, 95% CI: 0.50, 0.87, p=0.003). However, there was no significant difference in discontinuations due to treatment failure: 10% with TCAs versus 11.6% with SSRIs. Analysis according to the size of the study, type of TCA, and type of SSRI showed the same pattern of results.

**Authors' conclusions**

This meta-analysis suggested that TCAs have superior efficacy to SSRIs in depressed in-patients, but are more poorly tolerated. The subgroup analyses should be interpreted with caution; the superior efficacy seems to be accounted for by studies using amitriptyline, and possibly clomipramine. One possible explanation for this is that the increased efficacy is due to a dual action in inhibiting noradrenaline and 5-hydroxytryptamine re-uptake.

**CRD commentary**

This review is an update of a previous meta-analysis by the same author (see Other Publications of Related Interest no.3), which focused on hospitalised depressed patients.

The author presented a well-defined review question. The inclusion criteria were clearly stated. The primary studies
were combined appropriately. The search was not very thorough and could have been extended to include other databases, such as EMBASE, and an attempt to identify unpublished literature. No validity assessment of the included studies was undertaken. Some details of the primary studies were presented. However, it would have been useful to have included information on the age and gender of the included patients, and the length of treatment and follow-up in the individual studies. The results of this meta-analysis should be interpreted with caution due to the heterogeneity of combined studies, and the small sample sizes of some of the included studies. The author met his objectives and the conclusions follow from the results.

**Implications of the review for practice and research**
The author states that in situations where it is important to maximise efficacy, amitriptyline remains a drug of first choice. The author concluded that one possible reason why TCAs such as amitriptyline, and possibly clomipramine, may have increased efficacy is due to a dual action in inhibiting noradrenaline and 5-hydroxytryptamine re-uptake. He suggests that it is important that future research explores whether this is also true of newer drugs with a dual action, e.g. venlafaxine and mirtazapine.

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