Review: selective serotonin reuptake inhibitors are as effective as tricyclic antidepressants overall but may be less effective in some patient subgroups


QUESTION: In patients with major depression, how effective and tolerable are selective serotonin reuptake inhibitors (SSRIs) compared with tricyclic antidepressants (TCAs)?

Data sources
Studies were identified by searching Medline up to May 1997 and by reviewing previous meta-analyses and reviews.

Study selection
Studies were selected if they were randomised controlled trials investigating the effectiveness of SSRIs versus TCAs in patients with unipolar major depression.

Data extraction
Data were extracted on patient age, disease severity, treatment setting, type and dose of treatment, and outcome measures.

Main results
95 trials involving 10,553 patients were pooled to evaluate effectiveness. No statistically significant differences existed between SSRIs and TCAs in the total patient population (effect size −0.03, 95% CI −0.09 to 0.03) or in subgroup analyses that compared older and younger patients, patients with less and more severe depression based on their score on the Hamilton Rating Scale for Depression (HRSD), and high and low dose groups. In 1 subgroup of inpatients, TCAs showed an advantage over SSRIs (effect size −0.23, CI −0.40 to −0.05). In another subgroup analysis, amitriptyline was more effective than SSRIs (effect size −0.14, CI −0.25 to −0.03).

95 trials involving 10,706 patients were pooled to evaluate tolerability. The SSRIs were better tolerated, with lower rates of treatment discontinuations overall and due to side effects (table). When evaluating individual SSRIs all showed a similar advantage except for fluvoxamine which did not differ from TCAs. When evaluating individual TCAs, all showed a similar disadvantage in tolerability compared with SSRIs except for dothiepin against which SSRIs resulted in more dropouts due to side effects (relative risk increase with SSRIs 164%, 95% CI 50% to 363%; number needed to harm 12, CI 6 to 53).

Conclusions
Overall, in patients with depression, selective serotonin reuptake inhibitors (SSRIs) are as effective as tricyclic antidepressants but are better tolerated. SSRIs may be less effective in some patient subgroups.

*Numbers calculated from data in article.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ARR (95% CI) favouring SSRIs</th>
<th>RRR (CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment discontinuation</td>
<td>4% (2 to 6)</td>
<td>12% (7 to 17)</td>
<td>26 (18 to 46)</td>
</tr>
<tr>
<td>Treatment discontinuation due to side effects</td>
<td>3% (2 to 5)</td>
<td>27% (20 to 33)</td>
<td>33 (22 to 67)</td>
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</tbody>
</table>

†Abbreviations defined in glossary; RRR and CI calculated from data in article.

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COMMENTARY
With over 100 studies evaluating the efficacy and tolerability of SSRIs compared with TCAs, it is difficult for the clinician to look at the results of all these studies. Therefore, meta-analyses such as this by Anderson are urgently needed and clinically relevant. From this meta-analysis we can conclude that SSRIs are to be preferred to TCAs in outpatients; SSRIs and TCAs are equally effective but SSRIs lead to fewer discontinuations. In contrast, TCAs are to be preferred in inpatients; in this subgroup TCAs are more effective and do not lead to substantially more discontinuations.

The difference in efficacy between SSRIs and TCAs in inpatients cannot be explained simply by a difference in severity of depression. No differences were shown between SSRIs and TCAs for patients with high baseline depression scores and those with low scores on the HRSD. Other factors that led to hospital admission are possibly involved as well, such as suicidality and melancholic or psychotic features.

What has not been taken into account in this meta-analysis is whether the dosages of the TCAs were adjusted on the basis of plasma levels. It is known for at least some of the TCAs (amitriptyline, nortriptyline, imipramine, desipramine, and clomipramine) that the outcome can be further improved when optimal plasma levels are strived for. This aspect can also explain the results of 2 studies by the Danish University Antidepressant Group in which clomipramine was more effective than citalopram and sertraline in inpatients.1,2

An interesting finding in this meta-analysis is the statistically significant but nevertheless rather small difference in discontinuation rates between SSRIs and TCAs: 26 patients would need to be treated to prevent 1 additional dropout among patients treated with a SSRI compared with a TCA. It should be realised, however, that this finding cannot be generalised to all patients with major depression because patients with somatic comorbidity were excluded in most of the clinical trials. This aspect may also explain why no statistically significant difference in discontinuation rates was found in elderly patients.

Finally, it should be noted that other groups of antidepressants, such as mirtazapine, moclobemide, nefazodone, and venlafaxine, exist. Meta-analyses comparing these antidepressants with SSRIs, TCAs, and each other are much needed.

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