A review of the efficacy of serotonergic and noradrenergic reuptake inhibitors for treatment of major depression

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Authors' objectives
To compare serotonergic and noradrenergic re-uptake inhibitors for the treatment of major depression.

Searching
MEDLINE was searched and the bibliographies of identified studies were examined. Reports in press, abstracts of poster presentations, and data on file were included if the patient sample, drug administration, methods of assessment, and outcome were well described. Further study details were supplied by Forest Laboratories, Pfizer Pharmaceuticals, and Pharmacia and Upjohn.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible. The trials ranged in duration from 4 to 12 weeks.

Specific interventions included in the review
Studies comparing serotonergic and noradrenergic re-uptake inhibitors were eligible. The drug treatments were: the selective serotonergic drugs fluoxetine (20 to 80 mg), paroxetine (20 to 30 mg), sertraline (50 to 150 mg), fluvoxamine (100 to 300 mg), citalopram (40 to 60 mg) and zimelidine (200 mg); and the selective noradrenergic drugs lofepramine (70 to 210 mg), maprotiline (50 to 150 mg), desipramine (100 to 300 mg), nortryptiline (25 to 125 mg) and reboxetine (8 to 10 mg). Two studies also included a placebo arm. Studies of doxepin and bupropion were excluded.

Participants included in the review
Patients with nonpsychotic major depression or a similarly defined syndrome were eligible. Depression was defined according to American Psychiatric Association DSM-III or III-R criteria for major depression (in all but four studies), Feighner criteria, Kielholz/Poelinger criteria, and Newcastle criteria. The participants were mainly out-patients, although some studies included in-patients. All studies selected unipolar patients, bar one, which also included bipolar patients.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. All but one study assessed change in the Hamilton Depression Rating Scale (HAMD) or the Montgomery-Asberg scale (MADRS). The most common method of defining response rates was a 50% improvement in the HAMD or the MADRS. Clinical Global Improvement or similar ratings were also used to define response.

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
Only double-blind RCTs were eligible for inclusion. No formal validity assessment was undertaken.

Data extraction
The author does not state how data were extracted for the review, or how many of the reviewers performed the data extraction. The tables presented reported the following information: author and year of publication; sample size; drug and dose; study duration; outcome measures; and response. The group included in the analysis of the primary studies
was generally the ‘evaluable’ sample, i.e. patients who had completed at least one rating for response, with this rating being carried forward. If the evaluable response rates were not reported, intention to treat rates were used, and failing this, completion rates were used.

**Methods of synthesis**

**How were the studies combined?**

An overall response rate was calculated. The Mantel-Haenszel method (see Other Publications of Related Interest) was used to estimate a pooled odds ratio (OR) for response rate, along with its 95% confidence intervals (CIs). Study characteristics were also combined in a narrative review.

**How were differences between studies investigated?**

Potential causes of differences between the studies were discussed.

**Results of the review**

Fifteen double-blind RCTs were included. There was a discrepancy in the number of patients involved: the authors reported 1,563 patients whereas calculations suggested there were 1,935 patients.

There was no significant difference in response rates between noradrenergic and serotonergic antidepressants for patients with major depression. Overall, response rates were 59.5 and 31.4% for noradrenergic and serotonergic antidepressants, respectively. The pooled OR for response rate was 1.08 (95% CI: 0.88, 1.33, p=0.65). None of the individual studies found any statistically-significant difference in response rates.

Factors considered to have the potential to influence results included the adequacy of drug dosage, study duration and the method of analysis.

**Authors’ conclusions**

Noradrenergic and serotonergic antidepressants appear to be equally effective. It remains to be determined whether they are best suited to treating the same, or different, groups of patients.

**CRD commentary**

The aims were stated and the inclusion criteria were defined in terms of the participants, study design and intervention. There were no details provided of the keywords used for the search, the search dates, any language restrictions, or the methods used to select studies. By limiting the search to one database, albeit supplemented by material from less formal sources, other relevant studies may have been omitted. The included studies were restricted to double-blind RCTs although no further formal validity assessment was undertaken. Some relevant data were presented in tabular format, but the methods used to extract data were not described. Study characteristics were discussed in a narrative review and results were combined through a meta-analysis, though without an assessment of statistical heterogeneity. Some potential causes of heterogeneity were discussed.

The evidence presented supports the author's conclusions, although caution is advised when considering long-term treatment since only one study lasted longer than 8 weeks; most studies lasted 6 weeks or less.

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

The author did not state any implications for further research and practice.

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Other publications of related interest

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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.