The efficacy, safety and tolerability of antidepressants in late life depression: a meta-analysis


Authors' objectives
To determine the efficacy, safety and tolerability of antidepressants in depressed elderly patients.

Searching
MEDLINE was searched from 1966 to 1996, and EMBASE from 1974 to 1996. The MEDLINE subject headings were: 'antidepressant agent', 'tricyclic antidepressant (TCA)', 'selective serotonin reuptake inhibitor (SSRI)', 'monoamine oxidase inhibitor (MAOI)', 'antidepressant agent', 'second generation (ATYP)', and individual antidepressant drugs by their non-proprietary name. The searches were limited by the age of the patients (greater than 65 years; 80 years and over). The following EMBASE headings were used: 'antidepressant agent', 'tricyclic antidepressant', 'selective serotonin reuptake inhibitor' and 'monoamine oxidase inhibitor'. A search for the individual agents by name was also conducted. The searches were limited to 'aged'. Manual cross-referencing of trials and review articles, and expert opinion, were used to identify all randomised controlled trials examining TCAs, SSRIs, MAOIs, and ATYPS in the depressed elderly. The search was not limited to studies published in the English language. Unpublished studies were not sought.

Study selection
Study designs of evaluations included in the review
Randomised controlled double-blind studies with a minimum duration of 4 weeks were included. The duration of the studies ranged from 4 to 8 weeks (mean: 5 weeks).

Specific interventions included in the review
Antidepressants. Comparative studies of the following were considered: tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), and second-generation atypical (ATYP) antidepressant agents.

Participants included in the review
The participants had a diagnosis of major depressive disorder or unipolar depression, according to criteria defined by the American Psychiatric Association (e.g. DSM IIIR, DSM-IV). They also had baseline moderate to severe depression, as determined by the interviewer-rated Hamilton Depression Rating Scale (HAMD greater than or equal to 15) and the Montgomery Asberg Depression Rating Scale (MADRS greater than or equal to 18). The study participants were at least 60 years old.

Outcomes assessed in the review
Efficacy (i.e. response to treatment) and tolerability were assessed. Efficacy was defined as the proportion of individuals with at least a 50% decrease in depressive symptoms over the course of the study, as assessed by the HAMD or MADRS. Efficacy was also defined as the percentage change from baseline. Tolerability was assessed by examining the overall proportion of study patients experiencing adverse effects and the proportion of those who dropped out of the studies.

How were decisions on the relevance of primary studies made?
Two reviewers examined the papers for the inclusion criteria. Any disagreements between the reviewers were examined by a third reviewer and a consensus was reached.

Assessment of study quality
The overall quality of each article was assessed using a comprehensive structured quality checklist, which was used to identify crucial aspects of a randomised clinical trial. These included blinding, randomisation, the presence of basic descriptive material, trial design, analytical procedures, and sample size calculation. Studies were scored on a 4-point
ordinal scale (0=unavailable, 1=fair, 2=good, 3=excellent). The quality of those articles meeting the inclusion criteria was evaluated by blinded reviewers.

Data extraction
Two reviewers examined the papers for the outcome measures. Any disagreements between the reviewers were examined by a third reviewer and a consensus was reached.

Methods of synthesis
How were the studies combined?
The methods of Cochran (see Other Publications of Related Interest no.1) and DerSimonian and Laird (see Other Publications of Related Interest no.2), i.e. a random-effects model (single-arm; comparative), were used to combine study effect sizes. This was considered an appropriate pooling technique because of the relative heterogeneity of the elderly depressed population.

How were differences between studies investigated?
Homogeneity of the effect size was assessed by calculating the Q statistic, which follows a chi-squared distribution.

A sensitivity analysis was also conducted on the data, by pooling all those studies conducted in out-patients only and those studies that were considered to be of a good quality.

Results of the review
Sixteen studies (1,104 participants in total) were included in the pooled analysis of antidepressant efficacy: there were 4 studies of TCAs, 8 of SSRIs, 2 of ATYP antidepressants, and 2 of placebo.

Thirty-nine studies (1,274 participants in total) were included in the pooled analysis of tolerability (adverse effects): there were 8 studies of TCAs, 11 of SSRIs, 4 of RIMAs, 12 of ATYP antidepressants, and 4 of placebo.

Sixty-three studies (3,180 participants in total) were included in the pooled analysis of drop-out rates: there were 19 studies of TCAs, 19 of SSRIs, 3 of RIMAs, 16 of ATYP antidepressants, and 6 of placebo.

The majority of analyses had significant homogeneity (P<0.05), meaning that the studies aggregated were considered heterogeneous. Only 3 of the analyses were homogeneous: ATYP-efficacy assessment, TCA-efficacy assessment and placebo-efficacy assessment.

Efficacy and tolerability.

ATYP antidepressants: 33.4% (95% confidence interval, CI: 5.2, 61.7) of the participants responded to treatment. Adverse effects were reported in 37.5% (95% CI: 29.1, 45.9) of users, and 11.2% (95% CI: 6.9, 45.6) of the patients dropped out of the trials.

RIMAs: efficacy results for patients prescribed RIMAs, based upon the percentage of responders, were unavailable because they were not reported according to the categorical definition. Adverse effects were reported in 57.7% (95% CI: 35.7, 79.7) of RIMA users and the drop-out rate was 27.1% (95% CI: -1.2, 55.5).

SSRIs: 57.7% (95% CI: 45.5, 69.8) of the participants responded to treatment. Adverse effects were reported in 59.1% (95% CI: 44.2, 74.0) of users and the drop-out rate was 18.5% (95% CI: 14.3, 22.8).

TCAs: 63.1% (95% CI: 57.4, 76.7) of the participants responded to treatment. Adverse effects were reported in 60.3% (95% CI: 31.3, 89.2) of TCA users and the drop-out rate was 23.2% (95% CI: 17.0, 29.4).

Placebo: 27.2% (95% CI: 22.1, 32.2) of the participants responded to placebo. Adverse effects were reported in 39.6% (95% CI: 6.9, 72.4) of placebo takers and the drop-out rate was 25.6% (95% CI: 11.5, 39.7).
Comparative analyses: SSRIs were shown to have superior efficacy to ATYP antidepressants. The pooled difference (ATYP minus SSRI) in efficacy was -36.9% (95% CI: -65.4, -8.4, p=0.01). No other antidepressant class was shown to be superior with respect to efficacy, safety, or drop-outs. ATYP antidepressants were not shown to be superior to placebo.

Sensitivity analysis: when only high-quality studies were included in the analyses, no significant differences were observed. When only out-patients were included in the analyses, the results appeared similar to those incorporating both in- and out-patients. The authors did not report whether any of the differences were significant.

**Authors’ conclusions**
There were no significant differences with respect to efficacy and tolerability (adverse effects and drop-out rates) for four antidepressant classes, i.e. TCAs, SSRIs, MAOIs and ATYP antidepressants.

**CRD commentary**
Clear objectives were provided. The inclusion and exclusion criteria were clear and appropriate. The validity of the included studies was adequately assessed.

The search strategy was thorough, with the exception that the authors did not search for unpublished material; this could lead to a possible publication bias.

Details of the individual studies were provided, although more of the patients’ characteristics (e.g. gender and socioeconomic status) could have been included.

The results should be treated with caution because the majority of the studies that were combined were heterogeneous. In addition, the authors pointed out a number of other limitations of this meta-analysis. These included the following: the small sample size and lack of power; the lack of interchangeable instruments; the lack of extractable data; the lack of overdose or suicide information; definition of the outcomes; duplication of the study results; confounding by individual antidepressant agents; the quality of the studies; the short duration of the studies; and the reliance on the reported statistical significance. The short duration of the trials may have limited the rates of response, due to the slow rate of antidepressant onset. The mean study duration was 5 weeks, which may not have been long enough to ensure complete response.

This was a thorough meta-analysis in which the conclusions follow clearly from the results.

**Implications of the review for practice and research**
The authors suggest that there would be little advantage to prescribing one agent over another in the depressed elderly. They suggest that more studies examining the efficacy and tolerability of antidepressants for elderly patients are required to help clinicians decide on the appropriate agents to use. Trials of newer agents should ideally include the following features: comparison with placebo and a ‘gold’ standard (e.g. secondary amine), large numbers, samples with both young-old and old-old, use of well-recognised outcome measures (e.g. HAMD, MADRS), and reports of adverse events and their severity. The authors also suggest that administrative databases may be useful for overdose statistics, while effectiveness studies may provide information on the actual clinical response of antidepressants in the elderly.

**Bibliographic details**

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Other publications of related interest

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Subject indexing assigned by NLM

MeSH
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