Amitriptyline for inpatients and SSRIs for outpatients with depression: systematic review and meta-regression analysis

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CRD summary

This review examined the influence of study setting on the effect of amitriptyline compared with other antidepressants. The authors concluded that it may be reasonable to use newer antidepressants as first-line treatment in out-patients with depression, and to use amitriptyline for in-patients with severe depression. Differences among the studies were not examined adequately, thus the conclusions may not be reliable.

Authors' objectives

To examine the effect of study setting (in-patient versus out-patient) on outcomes in clinical trials comparing amitriptyline with other antidepressants (ADs).

Searching

The Cochrane Depression, Anxiety and Neurosis Group's Controlled Trials Register was searched, as were MEDLINE and EMBASE (from 1966 to 1998); the search terms were stated. The reference lists of relevant papers and previous systematic reviews were also checked for published reports and references to unpublished studies. Pharmaceutical companies were contacted.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion. Crossover studies were excluded.

Specific interventions included in the review

Studies that compared amitriptyline with any other tricyclic antidepressant (TCA), heterocyclic or related AD, or selective serotonin re-uptake inhibitor (SSRI), were eligible for inclusion. Studies were conducted in in- and out-patient settings. Studies of in-patient settings included those recruiting in-patients from psychiatric wards of general hospitals or psychiatric hospitals and following the patients up as out-patients. Out-patient settings included public or private out-patient psychiatric settings, general practice, or any other out-patient services.

Participants included in the review

Studies that used any criteria to define patients with depression were eligible for inclusion. Patients with a concurrent diagnosis of another psychiatric disorder were included, whereas patients with concurrent medical illness were not. Most of the participants were aged 18 to 65 years, although some studies were conducted in patients aged over 65 years.

Outcomes assessed in the review

The review assessed depression using the Hamilton Depression Rating Scale (HDRS), Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), or any other rating scale used in the individual studies. The review also assessed adverse effects. The mean length of follow-up was 53 weeks (median 5; range: 3 to 24).

How were decisions on the relevance of primary studies made?

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality

The studies were assessed and scored using a quality rating checklist (see Other Publications of Related Interest). The maximum possible score was 46 points. The authors did not state who performed the quality assessment.
Data extraction
Two reviewers independently extracted data, including the number of patients randomised and the number who dropped out. The number of patients with a 50% reduction in the HDRS or the MADRS or, if these were not available, the number 'much improved' or 'improved' on the CGI or any other rating scale reported in the primary studies, were extracted.

Peto odds ratios (ORs) and 95% confidence interval (CIs) were calculated for dichotomous outcomes for each study. For continuous outcomes, mean scores and standard deviations (SDs) at the end point of reported rating scales were extracted and used to calculate standardised mean differences (SMDs). Where required, standard errors were converted into SDs.

Methods of synthesis
Studies of in-patients and out-patients were combined separately using random-effects meta-analyses. Pooled weighted ORs and 95% CIs were calculated for dichotomous outcomes, while pooled SMDs and 95% CIs were calculated for continuous outcomes.

How were differences between studies investigated?
Characteristics (sample size, duration of follow-up, diagnostic criteria and quality score) were compared between studies of in-patients and out-patients. Meta-regression was used to examine the effect of study setting on the treatment effect. Separate meta-analyses were used to compare amitriptyline with TCAs and amitriptyline with SSRIs.

Results of the review
A total of 181 RCTs with 14,790 participants met the inclusion criteria: 136 RCTs (n=9,150) compared amitriptyline with another TCA or related AD, while 45 RCTs (n=5,640) compared amitriptyline with an SSRI. Nine RCTs in which the setting was unclear were excluded from the meta-analyses. The meta-analyses included 81 RCTs of out-patients and 91 RCTs of in-patients.

Most of the studies were double-blind. Four studies used inadequate allocation concealment. Sixty studies used implicit diagnostic criteria for depression, 54 used explicit criteria, and 67 used explicit criteria and a specification of severity of illness at baseline. The studies averaged medium to low quality; the quality scores ranged from 8 to 32 out of 46 points (mean 18).

No differences were found between studies of in-patients and out-patients with respect to sample size, duration of follow-up, diagnostic criteria and quality score.

Dichotomous outcomes.
Amitriptyline was significantly more effective than other ADs in in-patients (OR 1.22, 95% CI: 1.04, 1.42), but not out-patients (OR 1.01, 95% CI: 0.88, 1.17). Among in-patients, amitriptyline was significantly more effective than TCAs (OR 1.20, 95% CI: 1.02, 1.42; 46 RCTs), but not more effective than SSRIs (OR 1.30, 95% CI: 0.87, 1.96; 5 RCTs). For out-patients, there was no statistically significant difference between amitriptyline and TCAs (OR 0.98, 95% CI: 0.81, 1.17; 31 RCTs), or between amitriptyline and SSRIs (OR 1.08, 95% CI: 0.86, 1.35; 10 RCTs).

Continuous outcomes.
Amitriptyline was significantly more effective than other ADs in in-patients (SMD 0.28, 95% CI: 0.08, 0.46; 18 RCTs), but not in out-patients (SMD 0.10, 95% CI: -0.02, 0.23; 31 RCTs). Among in-patients, amitriptyline was significantly more effective than TCAs (SMD 0.23, 95% CI: 0.03, 0.44; 11 RCTs), but not more effective than SSRIs (SMD 0.34, 95% CI: -0.03, 0.72; 7 RCTs). For out-patients, there was no statistically significant difference between amitriptyline and TCAs (SMD 0.13, 95% CI: -0.14, 0.40; 16 RCTs), or between amitriptyline and SSRIs (SMD 0.08, 95% CI: -0.05, 0.20; 15 RCTs).

Adverse effects.
Amitriptyline was significantly less well tolerated than other ADs in out-patients (OR 0.90, 95% CI: 0.81, 0.99; 80 studies with 8,360 patients), but there was no statistically significant difference between treatments among in-patients (OR 1.09, 95% CI: 0.95, 1.25; 66 studies with 4,627 patients). Among in-patients, there was no statistically significant difference between amitriptyline and TCAs, or between amitriptyline and SSRIs. Among out-patients, amitriptyline was significantly less well tolerated than SSRIs (OR 0.77, 95% CI: 0.67, 0.89), but there was no statistically significant difference between amitriptyline and TCAs.

The meta-regression showed that in studies in out-patients, amitriptyline was associated with significantly lower response rates than control ADs.

Authors’ conclusions
It may be reasonable to use newer ADs as first-line treatment in out-patients with depression, and to use amitriptyline for in-patients with severe depression.

CRD commentary
The review addressed a clear question in terms of the participants, intervention, outcomes and study design, although the inclusion criteria were explicit for interventions and study design only. The search included attempts to locate unpublished studies, but it was not stated whether any language restrictions were applied. Methods were used to minimise bias in the data extraction process, but since the methods used to select the studies and to assess quality were not described, it is not known whether any efforts were made to reduce errors and bias. Quality was assessed using specified established criteria.

The studies were combined in meta-analysis but statistical heterogeneity was not assessed. In addition, it was difficult to judge whether pooling was appropriate because no meta-analysis graphs showing the results from individual studies were drawn. Information on this might have been given in the appendix, but this was located on the journal website and needed a subscription for access. Without some information on the homogeneity of the results among individual studies, it cannot be assumed that the results from the meta-analysis apply to all patients in the specified settings. This may have undermined the validity of the subsequent analyses examining the effect of different control ADs. In addition, studies using different outcome measures were combined and the effect of this on the pooled results was unknown. The lack of an adequate examination of differences among the studies means that the conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors suggested that newer agents be used as first-line treatment in out-patients with depression, and that amitriptyline be used for in-patients with severe depression.

Research: The authors did not state any implications for further research.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

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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.