Authors' objectives
To provide evidence-based recommendations to guide primary health care professionals in their use of antidepressants in the treatment of adults with depression, and for whom the agreed course of action is to prescribe an antidepressant.

Searching
The authors searched MEDLINE and EMBASE from 1966 and 1974 onwards, respectively, using drug names as search textwords or MeSH terms (where available). There were no language restrictions. Additional studies were retrieved from reference lists and through communication with study authors. Duplicate publications were excluded.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind comparative trials were included.

Specific interventions included in the review
Selective serotonin re-uptake inhibitors (SSRIs) and related drugs (venlafaxine and nefazodone), tricyclics and tricyclic-related drugs. The authors also reviewed moclobemide. Further details are given in the report.

Participants included in the review
Adults with depression, for whom the agreed course of action is to prescribe an antidepressant.

Outcomes assessed in the review
Efficacy based on a standardised effect size (SES) to compare relative efficacy of SSRI with other antidepressants. SES allows pooling of results from various rating scales for depression.

Total drop-outs was chosen as the most valid estimate of overall compliance. The authors state that this measure was chosen rather than a disease-specific outcome because it is the most valid estimate of overall compliance with treatment. It therefore reflects overall tolerability.

How were decisions on the relevance of primary studies made?
One reviewer selected the studies.

Assessment of study quality
The authors evaluated the quality of included studies by assessment of concealment of allocation during the randomisation process (see Other Publications of Related Interest no.1).

Papers were grouped according to a study design (6 categories) adapted from the US Agency for Health Care Policy and Research Classification (see Other Publications of Related Interest no.2). Four grades, A (strongest) to D (weakest), were developed from these 6 classifications for the strength assigned to recommendations. The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted for the categories of: study identification and year of publication, methods of analysis and active treatment duration, participants' inclusion criteria and participant characteristics, interventions and outcomes.
Data were extracted on an intention to treat basis; where this was not possible, end point data for trial completers was used.

Additional information and unpublished study data were requested from study authors, and from companies distributing relevant products.

**Methods of synthesis**

**How were the studies combined?**

Pooled SES with 95% confidence intervals (CIs) were calculated for continuous data, for an estimate of relative efficacy between SSRIs and other antidepressants, using a fixed-effect model.

Pooled relative risks (RRs) with 95% CIs were calculated for the binary data on total drop-outs using the DerSimonian and Laird random-effects model (see Other Publications of Related Interest no.3).

**How were differences between studies investigated?**

The authors tested for homogeneity of treatment effect using the Q statistic for both pooling measures used.

Sensitivity analyses were conducted to determine the robustness of findings to the assumptions made.

**Results of the review**

One hundred and twenty-five RCTs were included in the review. Data were missing on drop-out rates in 5 studies, and on efficacy in 33 studies.

Ninety-eight studies were included in the analysis of efficacy (SSRIs and related drugs versus others; n=5,044 for treatment with an SSRI or related drug and n=4,510 for treatment with an alternative antidepressant).

One hundred and twenty-three studies were included in the analysis of drop-out rate (n=7,032 for treatment with an SSRI or related drug and n=6,334 for treatment with an alternative antidepressant).

Tricyclic antidepressants appear slightly more efficacious than SSRIs or related drugs, although this effect is of uncertain practical importance. SES for SSRIs and related drugs versus alternative antidepressants was 0.034 (95% CI: -0.007, 0.075; Q=149.34, d.f.=98, p<0.001), which was not statistically significant.

The result was fairly robust to assumptions on inclusion: SES for SSRIs alone, compared with tricyclics, was 0.030 (95% CI: -0.018, 0.092; Q=88.64, d.f.=66, p=0.03), which was not statistically significant.

Results were also robust to the type of analysis used: the SES for SSRIs and related antidepressants, using a random-effects model, was 0.045 (95% CI: -0.010, 0.101) whilst the SES for SSRIs alone versus tri-cyclic antidepressants was 0.042 (95% CI: -0.020, 0.104).

In the group of studies comparing SSRIs with tricyclic antidepressants in in-patients, the SES using a random-effects model was 0.10 (95% CI: -0.072, 0.272; Q=49.1, d.f.=22, p=0.008).

SSRIs and related drugs are slightly better tolerated than tricyclic antidepressants, reducing the risk of drop-out by about 4% during 6 weeks of treatment in double-blind randomised trials.

The drop-out rate for participants treated with an SSRI or related drug, compared to that of participants treated with an alternative antidepressant, was 27.7% (1,948 out of 7,032 participants) versus 32.7% (2,072 out of 6,334 participants); RR was 0.87 (95% CI: 0.80, 0.95).

These results were robust to assumptions on inclusion (RR 0.88, 95% CI: 0.83, 0.95; Q=104.8, d.f.=86, p=0.08). The results for both analyses were also robust to the type of model used: similar findings were obtained for both analyses when a fixed-effect model was used.
Lofepramine appears similar in efficacy and tolerability to alternative antidepressants.

Monoamine oxidase inhibitors other than moclobemide, have considerable side-effects and are unlikely to be appropriate for initiation in general practice. Moclobemide, however, is less prone to dangerous side-effects and appears to have similar tolerability and efficacy to other antidepressants.

There is a substantial range of toxicity associated with different antidepressants as currently used in primary care. The SSRIs and lofepramine are associated with the smallest risk of fatal poisoning.

**Cost information**
The authors performed an economic assessment for the British health care setting. The authors state that a general policy of switching from tricyclics to SSRIs does not appear cost-effective. Where the toxic effects of tricyclic antidepressants give cause for concern, substitution with lofepramine appears relatively cost-effective.

**Authors' conclusions**
The authors state that there is good trial evidence on the short-term relative efficacy and tolerability of the various groups of antidepressants in first-line treatment of depression. Tricyclic antidepressants appear slightly more efficacious than SSRIs or related drugs, although this effect is of uncertain practical importance. SSRIs and related drugs are slightly better tolerated than tricyclic antidepressants, as measured by reducing the risk of drop-out in trials.

**CRD commentary**
The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be thorough. The authors have also contacted other researchers and include searches for unpublished and grey literature. The quality of the included studies was formally assessed. The authors have reported how the articles were selected, but they do not report who performed the quality assessment and data extraction.

The method section wrongly implies that the drop-out rate, as an outcome, is used as the primary surrogate for both efficacy and tolerability. It is clear from the 'Guidelines' section in the report that this is not the case.

The data extraction is reported in tables and discussed in the text of the review. The studies were combined in meta-analyses using both fixed-effect and random-effects models. There were tests for heterogeneity, and further subgroup analyses were performed to investigate the influence of inclusion criteria and method of analysis on the results.

**Implications of the review for practice and research**
**Practice:** The authors make several recommendations for practice.

1. Tricyclic antidepressants should be used as the routine first-line drug treatment for depression in primary care, though the choice of antidepressant should be based on individual patient factors such as: the desirability or otherwise of sedation or other effects associated with a particular drug; previous response to a particular drug; co-morbid psychiatric or medical conditions; and concurrent drug therapy.

2. If the toxic effects of the older tricyclic antidepressants are perceived to be a problem, then lofepramine is a more cost-effective initial choice than an SSRI. The dose of tricyclic antidepressants should be titrated up to the doses used in the clinical trials. Lower doses should be used initially in older patients. If patient compliance is a concern, tricyclic antidepressants can be given in a once-daily dosage.

3. Evidence on second-line therapy is lacking and an evidence-based recommendation cannot be made, but when faced with a patient not responding to first-line drug therapy, reasonable options would be: review the diagnosis; check compliance with drug therapy; consider a change in drug treatment; consider the potential contribution of maintaining factors (e.g. co-morbidity, poor housing etc.); and consider referral to a psychiatrist.

**Research:** The authors state that the guidelines development group identified the need for high quality 'real world'
trials in primary care, to examine the relative efficacy of antidepressants in adults and the elderly. Current phase III trials, although large in number, do not examine a directly relevant population of depressed patients. Trials need to address both clinical and economic end points, and use both a disease-specific and generic patient outcome measure.

**Bibliographic details**
University of Newcastle upon Tyne. Centre for Health Services Research; University of York. Centre for Health Economics. The choice of antidepressants for depression in primary care. Newcastle upon Tyne: University of Newcastle upon Tyne, Centre for Health Services Research. Evidence Based Clinical Practice Guideline; 91. 1998

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antidepressive Agents /therapeutic use; Depression /drug therapy; Family Practice; Primary Health Care

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**Record Status**
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.