Authors' objectives
To review the literature to summarise the efficacy of recently introduced medications in the treatment of depression in adult patients in the primary care setting.

Searching
English and non-English literature sources were identified using the Cochrane Collaboration Depression Anxiety and Neurosis group's specialised registry of 8451 clinical trial articles (1980 to January 1998). The search terms used were 'depression', 'depressive disorder', or 'dysthymic disorder' and these were combined with the names of the 32 medications to be covered by the review. References from clinical trial and meta-analyses articles were checked and experts were consulted.

Study selection
Study designs of evaluations included in the review
Studies were included if they were randomised controlled trials (RCTs), comparing a newer antidepressant with either, another newer antidepressant, an older antidepressant, a placebo, or a psychosocial intervention. Studies had to have had an active intervention period of at least 6 weeks.

Specific interventions included in the review
Thirty-two specific agents from nine classes of antidepressants, i.e selective serotonin re-uptake inhibitors (SSRIs), selective norepinephrine re-uptake inhibitors, norepinephrine re-uptake inhibitors, reversible inhibitors of monoamine oxidase A, 5-HT2-receptor antagonists, 5-HT1A-receptor agonists, Gabaminetics, dopamine antagonists, and dopamine re-uptake inhibitors. Herbal remedies and other miscellaneous agents were also included. Various dose regimens were used.

Participants included in the review
Adult patients in the primary care setting requiring treatment for depression. Patients included those with mild, moderate or major depression, endogenous depression, depression requiring treatment, dysthymia, or mixed anxiety depression.

Outcomes assessed in the review
All studies had to have measured a clinical outcome such as depression, functional status or quality of life. The primary outcome measure was response rate (defined as the proportion of patients having a 50% or greater improvement in symptoms as assessed by a depression symptoms rating scale) or a rating of much or very much improved, as assessed by a global assessment method.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The studies were checked for adequacy of randomisation, level of blinding, cointerventions and number of drop-outs. Two independent investigators (a physician and a pharmacologist) performed the validity assessment.

Data extraction
Two independent investigators (a physician and a pharmacologist) abstracted data from each trial and a third independent investigator verified information about type of depression diagnosis, number of drop-outs, reasons for
dropouts and outcomes. Specific data extracted included: intervention and dose, diagnosis, sample size, duration of intervention, specific inclusion criteria relating to rating scales for depression, and reported outcomes.

Methods of synthesis
How were the studies combined?
The studies were combined using a quantitative synthesis. Studies were grouped by a diagnosis of 'major depression' (12 studies) or other ('depression requiring treatment', 'depressive illness', 'dysthymia', or 'mixed anxiety depression'). The DerSimonian and Laird empirical Bayes random-effects estimator was used to estimate the pooled measures of treatment efficacy estimated as the log of the ratios of the response rates. A sensitivity analysis was performed in which the denominator was the number of patients who completed follow-up or whose last response as carried forward (end point analysis). Publication bias was assessed with funnel plots.

How were differences between studies investigated?
Tests for heterogeneity were performed with Galbraith plots (see Publications of Related Interest no.1).

Results of the review
A total of 28 RCTs were included in the review (n=5940). The sample size of individual studies ranged from 23 to 1019 patients.

Average response rates were 63% for newer agents, 35% for placebo and 60% for tricyclic agents. Modified intention-to-treat analyses showed that newer antidepressant agents were significantly more effective than placebo (risk ratio = 1.6 (95% CI: 1.2, 2.1), but similar to tricyclic agents (risk ratio 1.0 (95% CI: 0.9, 1.1) in efficacy. Response rates appeared similar among the different depressive disorders although there were too many types of disorders and too few studies to evaluate this quantitatively.

Sensitivity analysis:
End point analyses gave similar risk ratios (newer versus placebo risk ratio = 1.5 (95% CI: 1.1, 20); newer versus tricyclic agent risk ratio = 1.0 (95% CI: 0.9, 1.1).

Heterogeneity:
Tests for heterogeneity were significant (newer agents vs. placebo p = 0.03, newer vs. tricyclic agents p = 0.003). Two placebo-controlled trials in frail elderly patients and a trial in patients with dysthymia were identified with Galbraith plots as being at least partially responsible for this heterogeneity. When these were excluded from the analyses the degree of heterogeneity was no longer significant, but the risk ratios were not changed (newer agent versus placebo risk ratio 1.8 (95% CI:1.5, 2.2) and newer agents versus tricyclics risk ratio 1.5 (95% CI: 1.2, 1.9). Adverse events were statistically significantly less common with the newer agents than with tricyclics (8% compared with 13% (p< 0.05).

Publication bias:
There was no statistically significant evidence of publication bias.

Authors' conclusions
In primary care settings newer antidepressants are more effective than placebo and have similar efficacy compared with tricyclic agents in the acute treatment of depression. Drop-out rates as a result of adverse effects are lower with newer than with tricyclic agents. Future studies should compare the effectiveness of different therapies among primary care patients with less severe depression and greater medical and psychiatric comorbidity.

CRD commentary
This review addressed an appropriate question regarding the efficacy of newly introduced antidepressant drugs in the treatment of patients in the primary care setting and the inclusion/exclusion criteria are clearly defined. The literature
search conducted was comprehensive, utilising an appropriate inclusive electronic database, supplemented by manual
searches and consultation of experts. The papers included in the review were checked for validity by two or three
independent reviewers and details of the individual studies are clearly presented. The studies were checked for
heterogeneity and pooled quantitatively. The authors tested for publication bias and found no statistically significant
evidence of any. The results of the review support the authors conclusions regarding the relative efficacy and
tolerability of the newer agents and tricyclic agents.

Implications of the review for practice and research
Practice: The author states that 'In primary care settings newer antidepressants are more effective than placebo and have
similar efficacy compared with tricyclic agents in the acute treatment of depression. Dropout rates as a result of adverse
effects are lower with newer than with tricyclic agents'.

Research: The author states that 'Future studies should compare the effectiveness of different therapies among primary
care patients with less severe depression and greater medical and psychiatric comorbidity'.

Bibliographic details

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11059441

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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Inhibitors /therapeutic use; Phytotherapy; Plants, Medicinal; Primary Health Care; Publication Bias; Randomized
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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.