Authors' objectives
To evaluate the benefits and adverse effects of newer pharmacotherapies and herbal treatments for depressive disorders in adults and adolescents.

Searching
The Cochrane Collaboration Depression, Anxiety and Neurosis Group's Controlled Trials Register was searched from 1980 to January 1998. The search terms used were 'depression', depressive disorder', and 'dysthymic disorder' together with terms specific to newer antidepressants and herbal remedies. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Only studies of a minimum duration of 6 weeks were eligible for inclusion in the review.

Specific interventions included in the review
Selected newer antidepressants (selective serotonin re-uptake inhibitors, serotonin and norepinephrine re-uptake inhibitors, norepinephrine re-uptake inhibitors, reversible inhibitors of monoamine oxidase A, 5-HT2 receptor antagonists, 5-HT1a receptor agonists, gamma-aminobutyric acid mimetics, dopamine re-uptake inhibitors), antagonists, herbal remedies (St. John's Wort) and older antidepressants (mixed serotonin and norepinephrine re-uptake inhibitors, first-generation tricyclic antidepressants, second-generation tricyclic antidepressants, tetracyclic antidepressants, triazolopyridines, monoamine oxidase inhibitors) were investigated. All individual drugs are listed in the review article. Comparisons were made between any newer antidepressant and any other (newer or older) antidepressant, placebo, or psychosocial intervention. Studies of herbal remedies were also included.

Participants included in the review
The review included participants with depressive disorders; predominantly major depression, but also dysthymia, subsyndromal depression, mixed-anxiety depression and heterogeneous groups. There was a majority of female participants within every category of depression and the mean age of participants ranged from 40 to 53 years. Populations with appetite disorders or schizophrenia were excluded.

Outcomes assessed in the review
The primary outcomes were symptomatic response rate (defined as 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), total discontinuation rates, and rates of discontinuation due to adverse events. Secondary outcomes were health-related quality-of-life, functional status and suicide. Uncommon, serious adverse effects were investigated.

How were decisions on the relevance of primary studies made?
Two or more independent reviewers identified the trials for inclusion in the review.

Assessment of study quality
The validity of studies included in the review was assessed in terms of blinding, the quality of the blinding, the quality of randomisation, allocation and concealment, cointerventions and the number of withdrawals. Two authors independently assessed the validity of each trial.

Data extraction
Two authors independently extracted data from each trial. The categories of data included participant and diagnostic
descriptors, study design, details of the intervention, and clinical outcomes. Response rates were computed by using a modified intention to treat approach that assumed that all drop-outs gained no treatment benefit. A sensitivity analysis was based on an end point method, whereby the denominator for the risk ratio was the number of participants who completed follow-up or whose last observation was carried forward.

**Methods of synthesis**

**How were the studies combined?**

Within the review, studies were grouped by type of comparison and type of depression. Where studies were conceptually homogeneous, quantitative analyses were performed using an empirical Bayes random-effects estimator method to calculate a point estimate with 95% confidence intervals (CIs), and the results were displayed as forest plots. Otherwise, the studies were combined narratively.

Funnel plots along with Begg's rank-order correlation test and Egger's regression approach were used to estimate the possibility of publication bias.

**How were differences between studies investigated?**

Conceptual homogeneity required similar drug classes, diagnostic homogeneity, and adequate numbers of trials to justify pooling. Statistical homogeneity was evaluated using the chi-squared test for homogeneity and Galbraith Plots to identify outliers.

**Results of the review**

A total of 315 trials were included in the review. Within these trials there were 355 paired comparisons (n=36,509). Most comparisons (206) were of newer with older antidepressants. There were 114 comparisons of newer antidepressants with placebo and 37 comparisons between newer antidepressants. There were 14 trials that compared St. John’s Wort (hypericum) with either placebo (8 studies) or older antidepressants (6 studies), but none that compared hypericum with newer antidepressants.

The following 24 questions were asked in this review.

Are newer antidepressants more effective than placebo or older antidepressants for treating adult patients with major depression?

Are newer antidepressants more effective than placebo or older antidepressants for treating adult patients with dysthymia?

Are newer antidepressants more effective than placebo or older antidepressants for treating adult patients with mixed-anxiety depression?

Are newer antidepressants more effective than placebo or older antidepressants for treating adult patients with subsyndromal depressive disorders?

Are newer antidepressants more effective than placebo or older antidepressants for treating adult patients with recurrent depression?

Are newer antidepressants more effective than older antidepressants for treating adult patients with refractory depression?

Is hypericum more effective than placebo or standard antidepressants for treating depressive disorders in adults?

Are valeriana and kava more effective than placebo or standard antidepressants for treating depressive disorders in adults?

Are newer antidepressants more effective than placebo or older antidepressants for treating depressive disorders in children and adolescents?
Are newer antidepressants more effective than placebo or older antidepressants for treating older persons with depressive disorders? Are newer antidepressants more effective than placebo or older antidepressants for treating patients with co-morbidity?

Does the efficacy of newer agents vary between men and women and between different ethnic groups?

Are newer antidepressants more effective than placebo or older antidepressants for treating adult primary care patients with depressive disorders?

Are newer antidepressants more effective than placebo or older antidepressants in the postpartum setting?

Are combinations of newer antidepressants with other antidepressants more efficacious than a single antidepressant for treating major depressive disorder in adults?

Are combinations of newer antidepressants with other antidepressants or anxiolytics more efficacious than a single antidepressant for specific disorders and symptoms?

Is the combination of newer antidepressants with psychosocial therapies better than newer antidepressants alone for treating or maintaining remission for depressive disorders in adults?

Are newer pharmacotherapies plus augmenting agents (e.g. lithium, pindolol) more effective than pharmacotherapy alone for treating adults with depressive disorders?

Are newer antidepressants more effective than placebo, older agents, or psychosocial therapies for maintaining remission in adults with depressive disorders?

What common adverse effects of newer antidepressants have been identified in RCTs, and does their frequency vary significantly from one agent to another?

Do trials show varying adherence rates among newer antidepressants and between newer agents and older ones?

Do trials show varying rates between total drop-out, drop-out for adverse events and drop-outs for lack of efficacy?

What uncommon but serious adverse effects of newer antidepressants have been reported, and what is their frequency?

The main findings of this report, which are summarised in the published journal article (see Other Publications of Related Interest), are as follows:

Newer antidepressants compared with placebo in major depression (81 trials): overall, 51% of patients assigned to active treatment, compared with 32% of those assigned to placebo, experienced at least a 50% improvement in depressive symptoms. Relative benefit (calculated from 47 trials) was 1.6 (95% CI: 1.5, 1.7).

Statistically-significant publication bias was discovered for these trials (p=0.002).

Newer antidepressants compared with placebo in dysthymia (5 trials): overall, 59% of patients assigned to active treatment, compared with 37% of those assigned to placebo, experienced at least a 50% improvement in depressive symptoms. Relative benefit (calculated from 4 trials) was 1.7 (95% CI: 1.3, 2.3).

Newer antidepressants appear to be effective in elderly patients and in primary care patients. Data are insufficient to determine the relative efficacy of newer antidepressants and placebo in subsyndromal depression, depression with coexisting medical or psychiatric illness, or depression in adolescents.

Newer antidepressants were found to be as effective as older ones in major depression (150 trials) and in dysthymia (5 studies).

No difference between the efficacy of newer antidepressants was found, although there was a trend for fluoxetine to be less efficacious than other individual selective serotonin re-uptake inhibitors.
Overall drop-out rates did not differ between any of the newer antidepressants. Adverse events are discussed.

Hypericum versus placebo in mixed depressive disorders (6 studies): overall, 62% of patients assigned to hypericum, compared with 38% of those assigned to placebo, experienced at least a 50% improvement in depressive symptoms. Relative benefit (calculated from 6 trials) was 1.9 (95% CI: 1.2, 2.8).

Hypericum versus tricyclic antidepressants in mixed depressive disorders (5 studies): overall, 62% of patients assigned to hypericum, compared with 61% of those assigned to tricyclic antidepressants, experienced at least a 50% improvement in depressive symptoms. Relative benefit (calculated from 6 trials) was 1.2 (95% CI: 1.0, 1.4).

Publication bias was identified (p=0.009)

Authors’ conclusions
Newer antidepressants are clearly effective in treating depressive disorders in diverse settings. However, both newer and older antidepressants should be considered when making treatment decisions because of their similar efficacy. Better information is urgently needed on the efficacy of newer antidepressants in patients with non-major depression and in special populations, including adolescents.

CRD commentary
This was a very long and detailed review. It addressed an appropriate, but wide ranging question using well-defined inclusion criteria. The authors based their search strategy on the Cochrane Collaboration specialised registry, with no language restrictions, and therefore, was adequately comprehensive. Even so, some evidence of publication bias was detected, indicating that the pooled findings in support of the efficacy of newer antidepressants in major depression and the efficacy of hypericum might be overstated. Formal validity assessment of the studies included in the review was performed, and the effect that trial quality might have had on the findings is discussed. Details of the trials included in the review are given. The statistical meta-analyses appear appropriate and the results of heterogeneity tests are reported. The authors’ findings and conclusions appear to be justified.

This review was funded by the Agency for Healthcare Research and Quality, which specified certain aspects of the study, such as a technical advisory panel and the report format.

Implications of the review for practice and research
Practice: The authors state 'Because of similar efficacy, both newer and older antidepressants should be considered when making treatment decisions'.

Research: The authors state 'Better information is urgently needed on the efficacy of newer antidepressants in patients with non-major depression and in special populations, including adolescents'.

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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.