Authors' objectives
To evaluate antidepressant treatments for patients with severe depression.

Searching
MEDLINE was searched from 1985 to the present for studies published in the English language. Search terms included the following: 'depressive disorders', 'depression' and 'severe, hospitalized', 'melancholic' or 'melancholia', 'psychotic' and 'endogenous'.

Study selection
Study designs of evaluations included in the review
The author defined inclusion criteria as randomised, double blind trials (RCTs) of the treatment of severe depression with objective and independent measures of outcome variables (which were defined prior to study inception). Reviews, meta-analyses, and retrospective studies were also included in the review. Studies included comparisons between tricyclic antidepressants and placebo controlled trials. Study duration ranged from 4 weeks or less to 12 weeks or more.

Specific interventions included in the review
The following antidepressant treatments were included: SSRIs (fluvoxamine, paroxetine, fluoxetine, citalopram, sertraline); newer agents (mirtazapine, bupropion, nefazodone, venlafaxine); and tricyclic antidepressants (clomipramine, imipramine, amitriptyline, desipramine) and unspecified tricyclic antidepressants (TCA). Placebo arms were also included.

Participants included in the review
Patients with severe depression as defined by the following were included: hospitalisation; severe depression as defined by DSM-IV; score of 25 or higher on the 17-item Hamilton Rating Scale for Depression (HAM-D); a score of 50 or less (range 0 to 90) on the Global Assessment Scale (GAS) or by depressive subtype features (psychotic or melancholic depression).

Outcomes assessed in the review
Changes in HAM-D scores were evaluated. One study that did not use HAM-D as an outcome measure was stated as being excluded. However some studies with alternative outcomes were included such as the Clinical Global Impressions Scale (CGI 1-2) and Montgomery-Asberg Depression Rating scale.

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

Assessment of study quality
Some aspects of validity were mentioned briefly but no formal assessment was undertaken.

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

Methods of synthesis
How were the studies combined?
Studies of treatment for severe depression were classified as inpatients, outpatients or mixed populations and combined in a narrative review.

How were differences between studies investigated?
Some differences were discussed in the text.

Results of the review
Sixteen trials and 2 meta-analysis were used to evaluate treatment for severe depression.

Four trials and one meta-analysis were used to evaluate treatment for melancholic depression.

Statistical results were not generally given thus making interpretation difficult. Some results were only given in the text and were not included in the tabular presentation of study characteristics.

Severe depression in inpatients: comparison of selective serotonin re-uptake inhibitors (SSRI) vs TCA (6 trials and one meta-analysis): in 4 trials and the meta-analysis, the reduction in HAM-D score was comparable for SSRI and TCA and in 2 trials the TCA was more effective.

Mixed inpatients and outpatients (2 trials with 132 patients treated for 6 weeks and one meta-analysis): no statistically significant difference in changes in HAM-D scores in one trial and the meta-analysis. The other trial favoured SSRI to TCA.

Outpatients: 2 trials with 794 patients treated for between 6 and 8 weeks: compared SSRI, TCA and placebo: inconsistent results with one trial reporting greater improvement with SSRI compared to TCA and placebo and the other reporting SSRI to be equal to TCA with both being better than placebo (P < 0.05).

Melancholic patients (3 trials and one meta-analysis evaluated SSRI): some patients appear to have had HAM-D scores of less than the 25 required to diagnose severe depression.

Tolerability of SSRI s vs TCAs in severe depression: a number of adverse anticholinergic and cardiovascular effects were significantly more common with TCA than SSRIs in other trials no significant difference in adverse effects was reported. No supporting data was presented.

Venlafaxine: one study with 67 patients compared venlafaxine with fluoxetine in hospitalised patients with severe depression over 6 weeks and reported results as changes in Montgomery-Asberg Depression Rating scale. One study with 93 patients compared venlafaxine with placebo in melancholic depression over 4 weeks and reported results as changes in Montgomery-Asberg Depression Rating scale. Both studies favoured venlafaxine. No data was given for changes in HAM-D.

Mirtazepine: one study with 133 patients compared mirtazepine with fluoxetine and reported no significant difference at 6 weeks. One study with 150 patients compared mirtazepine, TCA and placebo and reported both active treatments to be significantly better than placebo at 6 weeks.

Nefazodone: one study with 120 patients compared nefazodone with placebo over 6 weeks and reported nefazodone to be superior to placebo.

Bupropion 2 studies with 141 patients compared bupropion with placebo over 4 weeks and reported bupropion to be significantly superior to placebo.

Combination therapy for severe depression: one retrospective uncontrolled trial included 3 patients considered to be treatment resistant.

Electroconvulsive therapy: one study was mentioned. No details were given.
**Authors' conclusions**

Selective serotonin uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are comparably effective for the treatment of severe or melancholic depression. SSRIs and other newer agents appear to be better tolerated than TCAs, specifically lacking adverse anticholinergic and cardiovascular side-effects that may limit the use of TCAs. Emerging data with venlafaxine and mirtazapine in severely depressed patients with or without melancholia support the efficacy of these treatments. Nefazodone and bupropion were found to be effective in hospitalized depressed patients. Electroconvulsive therapy (ECT) or combined antidepressant therapy may be useful in some patients with severe depression. Patients with severe psychotic depression may respond better to an antipsychotic- antidepressant combination.

**CRD commentary**

Some relevant details of the primary studies was tabulated. The text mentions the following limitations in the primary studies: high drop-out rates; lack of reporting of baseline HAM-D scores; and low dose of TCA.

The literature search was confined to articles published in the English language and identified in one database. Inclusion criteria were not applied consistently. The inclusion criteria indicated that only RCTs would be included but other types of study such as meta-analysis were also included. It was not stated whether the meta-analyses referred to in this review included the primary studies. The included meta-analyses were not subjected to any critical appraisal. The inclusion criteria for participants included several options some of which were not well defined. Outcomes other than HAM-D were reported. No details were given of methods used to select primary studies or extract data. Validity was not assessed. High drop-out rates were reported in some studies but it was not stated whether analysis was on an intention to treat basis. Adverse effects were not systematically evaluated. Results were not generally presented as data. Heterogeneity was neither assessed nor discussed. Studies were generally of less than 8 weeks duration. In view of the above limitations, it cannot be considered that the evidence presented supports the conclusion of the author.

**Implications of the review for practice and research**

Practice: The author suggests that combined antidepressant-antipsychotic therapy should be considered for patients with psychotic depression.

Research: The author considers that further research is required to determine the optimal dose of SSRIs.

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