The efficacy of drug treatments for dysthymia: a systematic review and meta-analysis

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Authors' objectives
To assess the role of pharmacological treatment for dysthymia.

Searching
The following sources were searched: electronic databases including Biological Abstracts (1984 to 1997), MEDLINE (1966 to Jan 1997); PsycLIT (1974 to Jan 1997), EMBASE (1980 to Jan 1997), LILACS (1982 to Jan 1997), and the Cochrane Library (1998); handsearching of relevant specialist journals; Cochrane Schizophrenia Group and the Cochrane Depression, Anxiety, and Neurosis Group register of trials; conference abstracts for references; personal communication with authors of included studies seeking published or unpublished material; pharmaceutical companies for unpublished material; and citations in book chapters on treatment of chronic depression. Details were given of the search terms employed for searching electronic databases.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled trials (RCTs) were eligible. Actual studies of parallel group design were included if graded either A or B on validity criteria (see below). Actual study duration ranged from 4 to 12 weeks. Studies were excluded if results were not reported separately for patients with dysthymia and major depression.

Specific interventions included in the review
Comparisons of the following active drugs with placebo (either active or inert) were eligible: antidepressant drugs (tricyclic and related antidepressant drugs: TCA); monoamine-oxidase inhibitors (MAOIs); selective serotonin re-uptake inhibitors (SSRIs); benzodiazepines; stimulants; and miscellaneous drugs. Actual active drugs included were: TCA (desipramine and imipramine); SSRIs (fluoxetine and sertraline); MAOIs (phenelzine and moclobemide); amisulpride; and ritanserin. Study settings included hospital, psychiatric clinics and primary care.

Participants included in the review
Patients with a primary diagnosis of dysthymia (non-major depression with at least 2 years duration irrespective of gender, age or nationality) were eligible. Actual participants all met American Psychiatric Association (APA) DSM-III or DSM-III-R criteria for the diagnosis of dysthymic disorder and were predominately adult out-patients and some patients with very chronic illness were included. The sensitivity analyses included patients with other non-major depressive states. Patients with depression secondary to other disorders were excluded.

Outcomes assessed in the review
The primary outcome was a dichotomous treatment response defined as improvement in the symptoms of dysthymia on any depression scale of at least 50% or absence of sufficient symptoms to meet diagnostic criteria for dysthyemic disorder or score of "very much improved" or "much improved" on Clinical Global Impression (CGI) scale score. Other outcomes assessed included the following: full remission (a more stringent criterion); total number of participants dropping out during the trial and post-randomisation exclusions; and number of patients reporting adverse events (side-effects). The Hamilton Depression Scale (HAM-D) was the most frequently used outcome measure followed by the Montgomery-Asberg Depression Rating Scale (MADRS). The most frequently used dichotomous outcome was "responder" followed by "full remission" defined either as patients no longer meeting APA DSM-III-R criteria for dysthymia and with a score of 0 on HAM-D item 1 (depressed mood) or symptom score no longer met plus absence of depressed mood and HAM-D end point 17-item score ≤5 in Versiani et al or ≤7 in Vanelle (see Versiani and Vanelle under Other Publications of Related Interest no.1 and no.2).

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
Validity was assessed using the criteria advised by Mulrow and Oxman (see Other Publications of Related Interest no.3): graded A if low risk of bias (adequate allocation concealment); grade B if moderate risk of bias (some doubt about allocation concealment); and grade C if non risk of allocation bias. Two independent reviewers assessed validity.

Data extraction
The following data were independently extracted by two reviewers: author; year of publication; study characteristics; participants; interventions; outcome used; and outcome unable to use. Disagreements were discussed and if necessary the authors of the original articles contacted to resolve the issue. Relative risks (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. All post-randomisation exclusion or drop-outs were identified. If no information was available it was assumed that drop-out was because of side-effects or treatment failure.

Methods of synthesis
How were the studies combined?
A random-effects model was used to calculate overall RR and 95% CI and treatment response was also assessed by each class of compound. When overall results were significant the number-needed-to-treat (NNT) and 95% CI was calculated to produce one outcome. The number needed to harm (NNH) was calculated for adverse reactions. Publication bias was assessed using a funnel plot and investigated using subgroup analysis according to number of patients randomised (> 200 patients vs < 200 patients).

How were differences between studies investigated?
Statistical heterogeneity was assessed by examining graphical presentations and the RR obtained in subgroups. Three reasons for heterogeneity were identified a priori and investigated using the outcome of treatment response: length of follow-up (< 6 weeks duration vs 6 weeks or more); different drugs; and patient diagnosis ("pure" dysthymia vs inclusion of patients with "double depression" defined as dysthymic patients with concurrent major depression). Pre-specified analysis was also conducted comparing included trials with those using diagnosis other than dysthymia (minor depression/ neurotic depression and other non-major depressive states).

Results of the review
Fifteen trials were included for the main comparisons (1964 patients).

Validity: 3 RCTs were classified as “A”.

Data reporting and analysis: some trials did not report the number of drop-outs, post-randomisation exclusions, or standard deviations of outcome measures.

There were differences in terms of definition of illness, duration of treatment and drugs used.

Overall treatment response:
Pooled RR favoured drug treatment with RR = 0.64 (95% CI: 0.60, 0.70). NNT = 3.9.
(95% CI: 3.3, 4.7). No evidence of heterogeneity was found.

Treatment response by drug group: a statistically significant improvement was found for all active drug treatment groups except ritanserin.

TCA (5 RCTs, 863 patients): RR = 0.68 (95% CI: 0.57, 0.76). NNT = 4.33 (95% CI: 3.24, 6.50).

SSRIs (4 RCTs, 901 patients): RR = 0.64 (95% CI: 0.55, 0.74). NNT = 4.66 (95% CI: 3.52, 6.89).
MAOIs (3 RCTs, 419 patients): RR = 0.59 (95% CI: 0.48, 0.71). NNT = 2.89 (95% CI: 2.17, 4.31).

Amisulpride (2 RCTs, 251 patients): RR = 0.61 (95% CI: 0.49, 0.75). NNT = 3.29 (95% CI: 2.39, 5.27).

Ritanserin (3 RCTs, 123 patients): RR = 0.63 (95% CI: 0.38, 1.05). NNT = 3.93 (95% CI: 2.40, 10.96).

Full remission (3 RCTs): pooling was not possible but results were similar to the pooled estimate for treatment response.

Total drop-outs:
Active drug treatment was not associated with a significant increase in drop-out rates. No statistically significant results were found on drop-out rates between and within classes of drugs.

TCA (4 RCTs): RR = 1.24 (95% CI: 0.91, 1.68).

SSRIs (4 RCTs): RR = 0.76 (95% CI: 0.58, 1.01).

MAOIs (2 RCTs): RR = 0.53 (95% CI: 0.22, 1.30).

Adverse events:
TCA (one RCT of imipramine): significantly more adverse reactions were reported for those on TCA compared to placebo. RR = 1.37 (95% CI: 1.14, 1.66). NNH = 4.6 (95% CI: 2.9, 10.2).

SSRIs: no significant increase in adverse events. RR = 1.45 (95% CI: 0.71, 2.99).

Moclobemide: no significant increase in adverse events. RR = 1.15 (95% CI: 0.94, 1.42).

Amisulphide, aminedipine, and ritanserin: significant increase in adverse reactions. Pooled RR = 1.37 (95% CI: 1.14, 1.65). NNH = 5.2 (95% CI: 3.4, 11.0). No heterogeneity was found. The highest RR was found for ritanserin (one RCT) with RR = 2.5 (95% CI: 1.00, 6.23). NNH = 2.5 (95% CI: 1.38, 13.72).

Publication bias:
The funnel plot suggested a degree of publication bias with few studies reporting moderate effects. Subgroup analysis according to number of patients randomised implied that even if publication bias were present this would not attenuate the overall treatment effect. RR for 4 trials with > 200 patients = 0.65 (95% CI: 0.59, 0.71) vs 9 trials with < 200 patients had RR = 0.62 (95% CI: 0.52, 0.74).

Authors' conclusions
Drug treatment appears to be effective in the short-term management of dysthyemic disorder. The choice of drug should take into account specific side-effects profile of each drug.

CRD commentary
The aim and inclusion criteria in terms of study design, participants, intervention and outcome were clearly defined. Several relevant databases were searched, details of the search strategy were given and attempts made to locate unpublished material. Publication bias was assessed and its influence on the results explored. Methods used to assess validity according to defined criteria and extract data were described. Only studies classified as being of higher quality were eligible for inclusion. Statistical heterogeneity was assessed and subgroup analyses determined a priori. Meta-analysis was appropriate given the lack of statistical heterogeneity. Relevant details of the primary studies were presented in tabular format. The discussion includes consideration of the following limitations of the review: likely presence of publication bias; only short-term results were available; a number of papers reported results only on "completers" rather than performing a true intention-to-treat analysis; and the comparisons reported were not direct
comparisons between different classes of antidepressants.

It was not clear whether language restrictions were applied to the literature search or to what extent data were extracted on an intention to treat basis and methods used to select primary studies were not described.

The evidence presented supports the authors' conclusions.

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

Practice: The authors state that decisions on treatment should be based on the balance between equal efficacy, better tolerability but higher cost of newer anti-depressants versus tricyclics, and that such judgments can only be informed by long duration pragmatic trials with economic and quality-of-life outcomes, none of which exist for dysthymia.

Research: The authors state that longer-term pragmatic, randomised controlled trials are required to evaluate alternative approaches for dysthymia.

**Bibliographic details**


**PubMedID**

10616934

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

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