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

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ABSTRACT

Background. Dysthymia is a common mental disorder, associated with considerable disability and high co-morbidity. This review assessed the role of pharmacological treatment.

Methods. All randomized-controlled trials that compared active drug *versus* placebo for dysthymic patients were included. Pooled relative risks (RR) and 95% confidence intervals (CI) were calculated with the Random Effect Model method. Where possible, number needed to treat and number needed to harm were estimated.

Results. Fifteen trials were included for the main comparisons. Similar results were obtained in terms of efficacy for different groups of drugs, such as tricyclic (TCA), selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI) and other drugs (sulpiride, amineptine, and ritanserin). The pooled RR treatment response was 0·68 (95% CI 0·59–0·78) for TCA, 0·64 (95% CI 0·55–0·74) for SSRIs, 0·59 (95% CI 0·48–0·71) for MAOIs. Other drugs (amisulpride, amineptine and ritanserin) showed similar results. Patients treated on TCA were more likely to report adverse events, compared with placebo. There were no differences in response to active treatment when dysthymia was compared to either dysthymia plus major depression or briefer non-major depressive states.

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

INTRODUCTION

Dysthymia is an elusive category spanning from normal mood states to better characterized disorders such as major depression. Until recently, the work on the nosological status of dysthymia was limited by variability in the definitions of chronic depressive states and by lack of population-based data (Weissman *et al.* 1988). While the symptoms of dysthymia are less severe than those of major depression and marked disturbance of appetite and libido are uncommon (Akiskal, 1983), patients may experience considerable disability, and have increased use of both medical services and non-specific psychotropic drugs (Thase *et al.* 1996). When left untreated, the natural history of dysthymia is poor with more than two-thirds of patients remaining symptomatic for one decade or more. Even with treatment, many patients experience incomplete recovery (WPA, Dysthymia Working Group, 1995).

There has been much debate over the relative merits of pharmacotherapy as a primary treatment option for dysthymic disorder (Howland, 1991). The efficacy and acceptability of antidepressants in depression have been addressed in some systematic reviews and meta-analysis, but none present data separately for dysthymic patients (Magni *et al.* 1989; Song *et al.* 1993; Anderson & Tomenson, 1994; Hotopf *et al.* 1997*a*). Traditional narrative reviews on dysthymia have not have used meta-analytical synthesis or explicit methods in order to limit bias and improving reliability and accuracy of conclusions for clinical outcomes (Howland, 1991; Harrison & Stewart, 1995; WPA

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Dysthymia Working Group, 1995). As a result, there is a lack of a systematic overview using meta-analytical synthesis to summarize the pharmacological treatment of dysthymia.

The aims of this review were (*i*) to investigate the efficacy and acceptability of antidepressants in dysthymia compared to placebo using, where possible, meta-analytical synthesis of individual studies: (*ii*) to compare the results from studies using DSM-III definitions (APA, 1980, 1987) of dysthymia with those that assess patients with non-major depressive states (minor depression, neurotic depression, depressive neurosis, reactive depression, non-endogenous depression), conducted before the introduction of the dysthymia concept.

METHOD

Search strategy

The search strategy aimed to identify widely defined non-major depressive states. This was because the diagnosis of dysthymia is a relatively recent one and we wanted the search to be as sensitive as possible. We also intended to perform a pre-specified subgroup analysis comparing the treatment of dysthymia with that of other non-major depressive states. The following sources of studies were searched looking at Randomized Controlled Trials (RCT).

(*i*) Electronic databases: BIOLOGICAL ABSTRACTS (1984–1997); MEDLINE (1966–Jan 1997); PSYCLIT (1974–Jan 1997); EMBASE (1980–Jan 1997); LILACS (1982–Jan 1997) and COCHRANE LIBRARY (Cochrane Library, 1998). A search strategy was used searching these databases, containing the following specific terms: DYSTHYMI* or DISTIMI* or DYSTIMI* or (NEURASTHENI* or DYSPHORI*) or [(MINOR or MILD* or MODERAT*) or (DEPRESS* or UNHAPP*) or (ATYPICAL or NON-TYPICAL or NEUROTIC* or NUEROS?S) and (CHRONIC* or PERSISTENT* or LONG-STANDING or LONG-TERM or (LONG near (STANDING or TERM)))].

(*ii*) Handsearching of specialist journals: journals most likely to contain trials in this area have been searched by the Cochrane Depression, Anxiety and Neurosis Group (Oakley-Browne *et al.* 1998) and the Schizophrenia Group (Adams *et al.* 1998).

(*iii*) The Cochrane Schizophrenia Group and the Depression, Anxiety and Neurosis Group register of trials.

(*iv*) Conference abstracts were searched for references.

(*v*) Personal communication: the authors of included studies were consulted to find out if they knew of any published or unpublished RCTs of pharmacological treatment of dysthymia, which were as yet unidentified. A list of all RCTs/CCTs identified through consulting other sources was sent to the authors.

(*vi*) Attempts were made to obtain unpublished trials from the pharmaceutical industry.

(*vii*) Citations in book chapters on treatment of chronic depression were scrutinized (Harrison & Stewart, 1995; Kocsis, 1997).

Inclusion/exclusion criteria

All relevant RCTs were considered for this review. Trials were eligible if subjects had a primary diagnosis of dysthymia: i.e. non-major depression with at least 2 years duration, irrespective of gender, age or nationality. Those suffering from other non-major depressive states (depressive neurosis, depressive personality disorder, neurotic depression, persistent anxiety–depression, mild chronic depression and minor depression) were also included in order to conduct sensitivity analyses. Studies were excluded if depression was secondary to other disorders, or where they included patients with dysthymia and major depression, but did not report the results for the two conditions separately.

Types of interventions

Trials were eligible if they compared any drug with a placebo (either active or inert). Any drugs used for the treatment of dysthymia were considered, including antidepressants (tricyclic and related antidepressant drugs (TCA): monoamine-oxidase inhibitRRs (MAOIs); Selective Serotonin Re-uptake Inhibitors (SSRIs), benzodiazepines, stimulants and miscellaneous drugs.

Types of outcomes

The main areas of interest were as follows.

1 Treatment response: improvement in the symptoms of dysthymia on any depression scale of at least 50%, or absence of sufficient

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symptoms to meet diagnostic criteria for dysthymic disorder or score of 'very much improved' or 'much improved' on Clinical Global Impression (CGI) scale score.

2 Full remission: more stringent criteria of improvement (for instance, score zero on item 1 of Hamilton Depression Scale (HAM-D) at the end of trial and not fulfilling DSM criteria for dysthymia).

3 Total number of people dropping out during the trial and post-randomization exclusion.

4 Number of patients reporting adverse events (side-effects).

Quality assessment

The methodological quality of the selected trials was assessed by two independent reviewers. Criteria (A, B, C) were based on guidelines (Mulrow & Oxman, 1998) to assess the quality of clinical trials: these guidelines are based on the strong relationship between quality of allocation concealment and potential bias.

A Low risk of bias (adequate allocation concealment): i.e. patients were randomized by researchers who were not responsible for recruiting participants, and precautions were taken to prevent manipulation of randomization codes (for example using numbered or coded bottles and serially numbered, sealed, opaque envelopes).

B Moderate risk of bias (some doubt about the results): i.e. when trials do not report any concealment approach, but state that patients were randomly allocated.

C High risk of bias (inadequate allocation concealment): i.e. inadequate approaches to concealment allocation, such as alternation, reference to case record numbers, dates of birth, day of the week or any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers.

Trials were included if they met the criteria A or B.

Data management

Data were independently extracted by two reviewers. Any disagreement was discussed, the decisions documented and, where necessary, the authors of the original studies contacted to resolve the issue. All post-randomization exclusion or dropouts were identified. If no information was available (either from the report or the authors) it was assumed that dropout was because of side effects/treatment failure.

Analysis

Dichotomous outcomes were analysed by calculating relative risks (RR) and 95% confidence intervals. The RR from the individual trials were combined in a meta-analysis. When overall results were significant, the number needed to treat (NNT) to produce one outcome was calculated by combining the overall relative risk with an estimate of the prevalence of the event in the control group of the trials. The NNT is an estimate of the number of patients a clinician would have to treat in order to observe one outcome due to that treatment. This is calculated by taking the reciprocal of the absolute risk reduction. For a highly effective treatment associated with a common outcome, the NNT will be low. Where the outcome is less common, or the treatment is less effective, the NNT will be higher. A negative NNT indicates that the treatment causes harm, and is sometimes referred to as the number needed to harm (NNH). For a discussion of the calculation of confidence intervals for NNT see Altman (1998).

The estimates of RR were based on the random effects model that takes into account any between study differences (even if there is no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no between study variance. For the main efficacy outcome (treatment response) we first assessed outcome by each class of compound. If no heterogeneity between classes was present, results were pooled. Continuous outcomes were not analysed in this review because many different scales (or versions of the same scale) were used, skewed data were common, and standard deviations were often not reported.

Sensitivity analyses were conducted to investigate possible sources of heterogeneity in the results of the trials. Heterogeneity was assessed by inspection of graphical presentations and the RRs obtained in subgroups. Three *a priori* reasons for heterogeneity were identified: (*i*) response differs according to different length of follow-up; (*ii*) response differs according to the different drugs; (*iii*) response differs between trials including only patients with 'pure' dysthymia and those including patients with

Table 1. *Characteristics of included randomized controlled trials*

Author/year	Methods	Participants	Interventions	Outcomes used	Outcomes unable to use
Stewart *et al.* (1983)	2 parallel groups, double blind, no information on allocation concealment. Duration 6 weeks, non-ITT* analysis	21 out-patients with pure dysthymic disorder (DSM-III), using an algorithm for diagnosis. Mean age 40 years, sex distribution unknown for dysthymic patients	(1) Desipramine ($N = 9$); mean dose 279 mg/day (2) Placebo ($N = 9$)	Responders (CGI 1 or 2)	Dropouts (three patients dropped out post-randomization, but there is no information on drug groups); SCL-90; 21-item HAM-D
Reyntjens *et al.* (1986)	2 parallel groups, double-blind, an open list of random numbers was used for randomization. Duration 5–6 weeks, non-ITT analysis	93 adult dysthymic patients (DSM-III) without concurrent major depression. No information provided on age, sex and setting	(1) Ritanserin ($N = 47$; dropouts 36%); dose 10 mg day (2) Placebo ($N = 46$; dropouts 41%)	Responders (CGI 1 or 2); dropouts	Side effects; HAM-D
Kocsis (1992), Kocsis *et al.* (1988*a*, *b*)	2 parallel groups, double blind. Subjects were randomly assigned according to an open list of random numbers by a person who was not involved in the recruiting of participants. Duration 6 weeks, non-ITT analysis	54 out-patients with dysthymic disorder (DSM-III). Mean age 40 years, 70% females; 96% had MD at time of admission; 16% had atypical depression. Mean duration of illness: 19 years. HAM-24 baseline scores: 22·8	(1) Imipramine ($N = 29$; dropouts 24%); mean dose 198 mg/day (2) Placebo ($N = 25$; dropouts 4%)	Responders (6 or less on HAM-D, at least 10 of improvement on GAS and absence of symptoms to meet DSM-III criteria); dropouts	HAM-D; GAS; side-effects, atypical depression diagnosis scales, SAS
Botte *et al.* (1992)	2 parallel groups, double blind, no information available on allocation concealment. Duration 4 weeks, no information on analysis	47 in and out-patients 'mainly' with diagnosis of dysthymic disorder (DSM-III). Age range 20–76, sex distribution unknown	(1) Moclobemide ($N = 23$; dropouts 9%) dose 300–500 mg/day (2) Placebo ($N = 24$; dropouts 46%)	Responders (final reduction of at least 50% on HAM-D score); dropouts	HAM-D means
Bella *et al.* (1990)	2 parallel groups, double blind, no information on allocation concealment. Duration 8–9 weeks, non-ITT analysis	60 in-patients (at the beginning of the trial) with dysthymic disorder (DSM-III). Age range 60–80, sex distribution unknown. Baseline scores on HAM-D; ~ 22	(1) Acetyl-L-Carnitine ($N = 30$; dropouts 13%); dose 3 g/day (2) Placebo ($N = 30$; dropouts 33%)	Dropouts	HAM-D scores; BDI, SCA

Costa e Silva (1990)	2 parallel groups, double blind, no information on allocation concealment. Duration 4 weeks, no information on analysis	40 patients with dysthymic disorder (DSM-III-R); mean age 43 years, 56% females; baseline scores on 26-item HAM-D ~ 19	(1) Amisulpride ($N = 20$; no dropouts); dose 50 mg/day (2) Placebo ($N = 19$; no dropouts)	Responders (patients with major or satisfactory improvement); adverse events	Dropouts (missing information about one patient); HAM-D; SANS; Widlocher Scale
Bersani *et al.* (1991)	2 parallel groups, double blind, no information on allocation concealment. Duration 5 weeks, non-ITT analysis	30 subjects from the community with dysthymia (DSM-III-R) and score > 20 on 19-item HAM-D; mean age 42 years, 59% females	(1) Ritanserin ($N = 15$; dropouts 20%); no information on doses (2) Placebo ($N = 16$; dropouts 27%)	Responder (CGI 1 or 2); dropouts; side-effects	HAM-D and HAM-A scores; State-Trait Anxiety Inventory (STAI X-1); Global Severity Score
Bakish *et al.* (1994)	3 parallel groups, double blind, no information available on allocation concealment. Duration 7 weeks, non-ITT analysis	50 out-patients with dysthymic disorder (DSM-III), Mean age 38 years, 48% females; mean age of onset of symptoms 26 years, mean duration of present episode 5·7 years. Baseline scores on 17-item HAM-D > 15	(1) Ritanserin ($N = 17$; dropouts 18%); dose 50 mg/day (2) Imipramine ($N = 16$; dropouts 31%); dose 200 mg/day (3) Placebo ($N = 17$; dropouts 41%)	Dropouts	HAM-D scores, CGI results (no figures)
Hellerstein *et al.* (1993)	2 parallel groups, double blind. Randomization: a list of bottle numbers and bottle contents was generated and kept confidential and sealed in an opaque envelope in the senior trialist's possession until the end of the study. Duration 8 weeks, non-ITT analysis	35 subjects from the community with diagnosis of dysthymic disorder (DSM-III). Mean age 36 years, 50% females; 87·5% began illness in adolescence. Baseline scores on 24-item HAM-D ~ 19	(1) Fluoxetine ($N = 19$; dropouts 16%), mean dose 32·7 mg/day (2) Placebo ($N = 16$; no dropouts)	Responders (50% or greater decrease on HAM-D); dropouts	CGI scores, Cornell Dysthymia Scale; SCL-58

Table 1. (*cont.*)

Author/year	Methods	Participants	Interventions	Outcomes used	Outcomes unable to use
Stewart *et al.* (1985, 1988, 1989, 1992, 1993)	3 parallel groups, double blind, no information on allocation concealment. Duration 6 weeks, non-ITT analysis	57 out-patients with dysthymic disorder (DSM-III) without MD. Sex and age distributions not given for dysthymic patients; 80% had atypical depression and reported having been depressed virtually their entire adult lives	(1) Imipramine ($N = 12$); mean dose 265 mg/day (2) Phenelzine ($N = 18$), mean dose 73 mg/day (3) Placebo	Responder (CGI 1 or 2)	Dropouts; HAM-D, SCL-90 and SADS-C scores; symptom scale, atypical items score; personality scales; chronicity scale
Boyer & Lecrubier (1996)	3 parallel groups, double blind, no information on allocation concealment. Duration 12 weeks, ITT analysis for most outcomes	323 out-patients with dysthymia or dysthymia with MD according to DSM-III. Mean age 48 years, 70% females. Baseline scores on MADRS ~ 18	(1) Amisulpride ($N = 104$; dropouts 36%); dose 50 mg/day (2) Amineptine ($N = 111$; dropouts 36%), dose 200 mg/day (3) Placebo ($N = 108$; dropouts 39%)	Responders (CGI 1 or 2); dropouts; side effects	MADRS, SANS and SET scores
Thase *et al.* (1996)	3 parallel groups, double blind, randomization by a computer-generated schedule, but gives no information on allocation concealment. Duration 12 weeks, non-ITT analysis (patients with at least 1 post-randomization efficacy evaluation)	416 subjects from community with diagnosis of dysthymic disorder (DSM-III-R) with no concurrent MD. Mean age 42 years, 65% females. Average age of onset 12 years, with an average duration of illness of 31 years. Baseline scores on 17-item HAM-D ~ 13	(1) Sertraline ($N = 134$; dropouts 16%); mean dose 140 mg/day (2) Imipramine ($N = 136$; dropouts 33%); mean dose 199 mg/day (3) Placebo ($N = 140$; dropouts 24%)	Responder (CGI 1 or 2); full remission (no longer fulfilling DSM-III-R criteria); dropouts; Quality of Life Enjoyment and Satisfaction Questionnaire (results described)	HAM-D, MADRS, IDS-SR, SAS-SR and Hopkins Symptom Checklist scores; Longitudinal Interval Scale Follow-up Evaluation; side effects.
Ravindran & Wiseman (1997)	Multicentre, 2 parallel groups, double blind, no information on allocation concealment. Duration 12 weeks, ITT analysis	310 out-patients with diagnosis of dysthymic disorder (DSM-III-R) without MD. Mean age 45 years, 66% females, at least 5 years of duration of illness. Baseline scores on 21-item HAM-D 21	(1) Sertraline ($N = 158$; dropouts, 23%); dose range 50–200 mg (2) Placebo ($N = 152$; dropouts 25%)	Responders (CGI 1 or 2); dropouts; adverse events	HAM-D, HAM-D atypical, MADRS, CGI-S and HAM-A scores

Vanelle (1997)	Multicentre, two-phases, 2 parallel groups, double blind, randomization unbalanced, 2/3 of patients in the active drug group. No information on allocation concealment. Duration 12 weeks, ITT analysis (mainly). One centre was excluded because of outlier data	140 in- and out-patients with diagnosis of dysthymic disorder (DSM-III-R). Mean age 43 years, 75% females, average duration of illness 6 years. Baseline scores on 21-item HAM-D ~ 21	(1) Fluxoetine ($N = 91$; dropouts 13%); dose 20 mg/day (2) Placebo ($N = 49$; dropouts 27%)	Responder (> 50% decrease in HAM-D + score 1 or 2 on CGI); dropouts; side-effects	Remission (HAM-D score ⩽ 7 non-ITT data); HAM-D, GAF-S, SCL-58 and AMDP-5 scores; Paykel Life Events Scale
Versiani *et al.* (1997)	Parallel groups, double blind, central randomization, with coded blisters for each number. The trialists were not aware on the allocation group until the trial was finished. Duration 8 weeks, ITT analysis for some outcomes.	315 out-patients with diagnosis of dysthymic disorder (DSM-III). Mean age 42 years, 70% females, average duration of illness 11 years. Baseline scores on 17-item HAM-D ~ 21	(1) Moclobemide ($N = 108$; dropouts 12%); mean dose 675 mg/day (2) Imipramine ($N = 103$; dropouts 15%); mean dose 220 mg/day (3) Placebo ($N = 104$; dropouts 14%)	Responder (no longer met DSM-III-R criteria); full remission (symptom criteria no longer met + absence of depressed mood) and HAM-D endpoint < 5; dropouts; adverse events	HAM-D SLC-90 and CGI scores

AMDP-5, Echelle de signes somatiques (Association de Méthodologie et de Documentation en Psychiatrie); BDI, Beck Depression Inventory; CGI, Clinical Global Impression; CGI-S, Clinical Global Impressions of Severity; GAF-S, Global Assessment of Functioning Scale; GAS, Global Assessment Scale; HAM-D, Hamilton Scale for Depression; HAM-A, Hamilton Scale for Anxiety; IDS-SR, Inventory for Depressive Symptomatology, self-reported version; ITT, intention to treat analysis; MADRS, Montgomery and Åsberg Depressive Rating Scale; SCA Sandoz Clinical Assessment-Geriatric Scale; SADS-C, Schedule for Affective Disorders and Schizophrenia-Change; SANS, Scale for the Assessment of Negative Symptoms; SAS-SR, Social Adjustment Scale, self-rated version; SCL-58, Hopkins Symptom Checklist; SCL-90, 90-item symptom checklist; SET, Lecrubier Scale for the Evaluation of Thymasthenia.

* No intention to treat.

Table 2. *Randomized controlled trials not using DSM-III diagnostic criteria dysthymia* (*neurotic depression and other non-major depressive states*)

Author/year	Methods	Participants	Interventions	Definition of responder
Bohm *et al.* (1990)	2 parallel groups study, no information on allocation concealment, double-blind, duration: 4 weeks	20 out-patients with neurotic depression (ICD-9), age at least 65 years, no information on sex distribution. Baseline scores on 21-item HAM-D ~ 20	(1) Buspirone 15 mg/day ($N = 12$) (2) Placebo ($N = 8$)	Marked improvement on CGI
De Paula *et al.* (1980)	2 parallel groups, double-blind, no information available on allocation concealment. Duration 4 weeks, ITT analysis	40 out-patients with neurotic, reactive or exhaustion depression ('psychiatric diagnosis'), mean age 24 years, 65% females. Most of patients had brief depressive states (1–3 months). Baseline scores on 23-item HAM-D ~ 22	(1) Diclofensine 100 mg/day ($N = 20$) (2) Placebo ($N = 20$)	Very good to good improvement on CGI
Goldberg & Finnerty (1980)	3 parallel groups study; double-blind, randomization: computer-generated pattern in blocks of six. Duration 6 weeks, non-ITT analysis	184 out-patients with neurotic depression (New York University criteria), mean age 36·5 years, 73% females. The severity of depression was 'marked' for 58 patients and chronic for 30 patients. Four patients had additional diagnosis	(1) Trazodone 150–400 mg daily ($N = 62$) (2) Amitriptyline 75–200 mg daily ($N = 60$) (3) Placebo ($N = 62$)	50% reduction in total score on the HAM-D at the final evaluation
Harrer & Sommer (1993)	2 parallel groups, double blind, no information available on allocation concealment. Duration 4 weeks, no information on analysis	105 patients from 3 practices, with neurotic depression or short-term depressive irritation. Sex and age distributions unknown. Baseline scores on 21-item HAM-D ~ 16	(1) St. John's Wort extract 300 mg/day ($N = 50$) (2) Placebo ($N = 55$)	50% reduction on HAM-D at the final evaluation
Petrie *et al.* (1980)	3 parallel groups, double blind, no information on allocation concealment. Duration 4 weeks, ITT analysis	33 in- and out-patients with depressive neurosis, mean age 32 years, 82% females, mean duration of illness 18 months. Patients had a minimum total score of 20 on HAM-D at admission	(1) Viloxazine; dose range 150–450 mg/day ($N = 12$) (2) Imipramine; dose range 75–225 mg/day ($N = 9$) (3) Placebo ($N = 11$)	Improvement on CGI

McEvoy *et al.* (1980)	3 parallel groups, double blind, no information on allocation concealment. Duration 4 weeks, ITT analysis	31 in- and out-patients with depressive neurosis (DSM-II), mean age 37·5 years, 55% females. Minimum baseline scores of 19 on HAM-D	(1) Viloxazine; dose range 150–450 mg/day ($N = 10$) (2) Doxepin; dose range 75–225 mg/day ($N = 10$) (3) Placebo ($N = 11$)	Improvement on CGI
Rickels *et al.* (1968)	2 parallel groups, double blind, no information on allocation concealment. Duration 4 weeks, non-ITT analysis	94 out-patients from private offices with neurotic and character neurotic depression, mean age 45 years, 77% females. Patients were mildly to moderately depressed, 60% had duration of illness higher than 1 year, and 20% were using diet pills	(1) Iprindole ($N = 47$); mean dose 90 mg/day (2) Placebo ($N = 47$)	Global endpoint improvement criteria
Shipley *et al.* (1967)	2 parallel groups, double blind, no information available on allocation concealment. Duration 6 weeks, non-ITT analysis	31 in- and out-patients (2/3) with neurotic depression, mean age 38 years in the active drug group, 32 in placebo group, 77% females. Mean baseline score on HAM-D ~ 22	(1) U-23, 807A (benzhydrol hydrochloride) 10 mg/day; ($N = 14$) (2) Placebo ($N = 17$)	Moderate or marked improvement on Global Ratings of Improvement
Standal (1977)	2 parallel groups, double blind, no information on allocation concealment. Duration 4 weeks, ITT analysis	20 out-patients from a social psychiatric practice with minor to moderate depression, no information available on age, 30% females	(1) Pizotifen: range dose 8–10 mg/day ($N = 9$) (2) Placebo ($N = 11$)	Antidepressant effect very good or good
Tetreault *et al.* (1966)	Patients were divided in 11 blocks of 3. In a block, one of the drugs or placebo was attributed at random. Evaluation and treatment of each randomized block was the responsibility of one psychiatrist, 3 parallel groups study, double-blind, duration: 6 weeks, non-ITT analysis	33 hospitalized female patients with neurotic depression (Kiloh & Garside criteria), no information on age. Patients with endogenous depression were excluded	(1) Opipramol 200 mg/day (2) Imipramine 100 mg/day (3) Placebo	Global improvement at the end of the trial according to psychiatrists assessment
Van Der Velde (1981)	3 parallel groups, double blind, no information on allocation concealment. Duration 4 weeks, non-ITT	79 out-patients with neurotic depression (DSM-II), with at least 18 points on HAM-D. Age range 18–65, 65% females	(1) Maprotiline; dose range 50–300 mg/day ($N = 25$) (2) Imipramine; dose range 50–300 mg/day ($N = 27$) (3) Placebo ($N = 27$)	Marked or moderate improvement on global psychiatric evaluation

'double depression' (dysthymic patients with concurrent major depression). These were assessed by looking at separate subgroups of trials. A further pre-specified subgroup analysis was conducted comparing included trials with those using other diagnosis rather than dysthymia – minor depression/neurotic depression and other non-major depressive states.

Review Manager software (Mulrow & Oxman, 1998) developed by the Cochran Collaboration was used to organize and process the results.

RESULTS

Search

The search strategy generated 5513 references, 5227 of which were excluded because they did not meet the criteria for dysthymia or were not randomized clinical trials and 172 did not present comparisons with placebo. The remaining 114 (79 studies) were checked reading the full paper. When multiple publications of the same trials were found, all reports were checked and in case of any discrepancy authors were contacted.

Thirty-one reports describing 15 trials (1964 patients in total) had available data that could be included. The first authors of these papers were contacted for further information. Five authors answered the letter providing further information. Table 1 shows the main characteristics of the included studies.

Fifty-six trials were excluded because the patients could not be considered as suffering from dysthymia or those with dysthymia and major depression were added together in the same study (not providing separate data for dysthymic patients). However, 22 of these trials defined subjects as suffering from non-major depressive states. Because these studies were in all other respects eligible for inclusion, we used 11 of them for an additional separate analysis to determine whether active treatments were effective in these mild depressive disorders. The characteristics of these studies are shown in Table 2.

The remaining trials ($N = 11$) included 699 patients suffering from non-major depressive states but had no results on treatment response as a categorical variable (Rickels *et al*. 1971*a*, *b*; Gilbert & Koepke, 1975; Raskin & Crook, 1976; Shammas, 1977; Murphy, 1981; Rowan *et al*. 1982; Georgia, 1984; Imlah, 1985; Heller *et al*. 1990). Using depression scales and other efficacy assessments all but one (Imlah, 1985) showed better response rates for active drugs comparing with placebo.

Five further studies on dysthymia/minor depression were excluded for other reasons, such as inclusion of patients with residual major depression or lack of information on outcomes required for this review (Davidson & Turnbull, 1983; Cassacchia *et al*. 1984; Kivela & Lehtomaki, 1987; Tyrer *et al*. 1990; Lecrubier *et al*. 1997). Data from a further three maintenance studies were not used because they used different randomization schemes making it impossible to pool the results (Kocsis *et al*. 1991, 1996; Harrison *et al*. 1986).

Design and settings

All the studies used a parallel group design. The duration of the trials ranged from 4 weeks to 12 weeks. Most trials were from North America or Europe. Only three trials included hospitalized patients (Bella *et al*. 1990; Botte *et al*. 1992; Vanelle, 1997). The remainder studied out-patients from psychiatric clinics or primary care.

Participants

All included trials used DSM-III or DSM-III-R criteria for the diagnosis of dysthymic disorder. The study populations were comparable, mostly involving adult out-patients. The number of participants randomized in the trials ranged from 21 to 416. Some studies selected subjects with very chronic illness: in oral trial (Thase *et al*. 1996) the average duration of illness was 31 years.

Outcomes

The Hamilton Depression Scale (HAM-D) was the most widely used outcome for efficacy, followed by Montgomery-Åsberg Depression Rating Scale (MADRS). However, some trials lack data on standard deviations, or showed skewed data distribution. The most frequently used dichotomous outcome was 'responder' The second outcome was 'full remission', which is a more stringent criteria of improvement. This was defined as patients no longer meeting DSM-III-R criteria for dysthymia and with a score of 0 on HAM-D item 1 (depressed mood) in Thase *et al*. (1996); as symptom criteria no longer met,

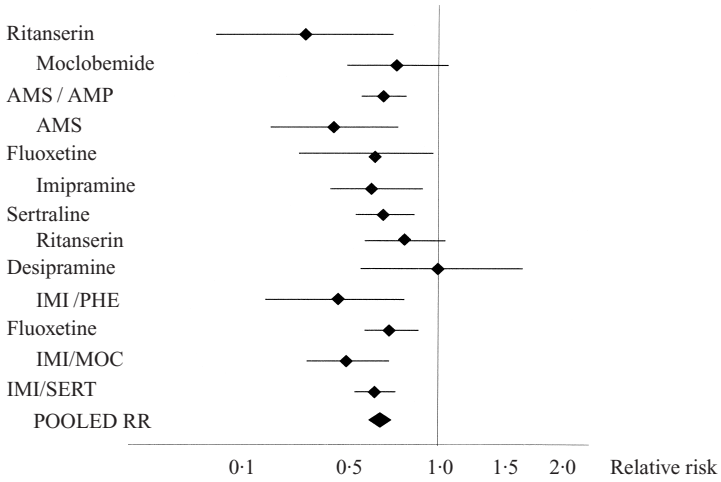

FIG. 1. Drug treatment response in dysthymia: meta-analysis of randomized control trials. Pooled relative risk = 0·64 (95% CI = 0·59 to 0·70). (AMS, Amisulpride; AMP, Amineptine; IMI, Imipramine; PHE, Phenelzine; MOC, Moclobemide; SER, Sertraline.)

plus absence of depressed mood and HAM-D endpoint 17-item score < 5 in Versiani *et al.* (1997); and as 'HAM-D score $\leqslant 7$' in Vanelle (1997).

Total dropouts and number of patients reporting any adverse event were further outcomes. Data on dropouts were available in 12 trials. Side effects provided difficult to assess because of different side-effect profiles for each drug group. Only trials that reported the number of subjects reporting at least one adverse event could be used for the comparisons.

Quality findings

Only three trials (Kocsis *et al.* 1988; Hellerstein *et al.* 1993; Versiani *et al.* 1997) were classified as 'A' criteria regarding allocation concealment (Mulrow & Oxman, 1998) because the authors provided further information in answer to our enquiry. The other trials were classified as 'B', not giving information on allocation concealment. None were classified as 'C'.

Data reporting and analysis

In general, the quality of reporting was patchy. Some trials did not report the number of dropouts and post-randomization exclusions. Although many trials reported an intention-to-treat analysis, some of them excluded patients after randomization because of protocol violations. Standard deviations for outcome measures were frequently not reported.

Synthesis of the main findings

Efficacy

The meta-analysis confirmed the efficacy of drugs for patients with dysthymia. All but three trials showed significant differences between active drugs and placebo (see Fig. 1). Table 3 reports the main findings for each group of drugs: TCA, SSRIs, MAOIs and others (ritanserin, amisulpride and amineptine). A preliminary analysis showed no difference in response rates between different drugs and groups of drugs. In order to perform a sensitivity analysis and because of this lack of heterogeneity, trials which compared more than one active treatment with placebo were dealt with by combining all active treatment subjects together in order to calculate a pooled RR for treatment *versus* placebo. For all drugs, the pooled RR for treatment response was 0·64 (95% CI 0·60–0·70), favouring drugs (Fig. 1). The mean response rate on placebo was 30% compared to 55% on active drugs giving a difference in response rate of 25% and an NNT of 3·9 (95% CI 3·3–4·7).

The funnel plot is shown in Fig. 2. Funnel plots assume that as the sample size of studies increase the variability around a hypothetical underlying treatment effect is reduced (Egger *et al.* 1997). Thus, when the weight of each study is plotted against treatment effect one expects to see a symmetrical pattern with the larger trials closer to the pooled effect. If publication bias is

Table 3. *Treatment response for active drugs and placebo: individual and pooled relative risk (95% CI) and number needed to treat*

Study/Class	Drug	Sample size	Drug (%)	Placebo (%)	RR (95% CI)	NNT (95% CI)
Stewart *et al.* (1985)	DES	21	22	22	1·00 (0·61–1·64)	—
Kocsis *et al.* (1988*a*, *b*)	IMI	54	45	12	0·63 (0·44–0·90)	—
Stewart *et al.* (1989)	IMI	57	78	33	0·33 (0·13–0·82)	—
Thase *et al.* (1966)	IMI	416	64	44	0·65 (0·49–0·85)	—
Versiani *et al.* (1997)	IMI	315	45	20	0·69 (0·57–0·85)	—
Total TCAs		863	55	32	0·68 (0·57–0·76)	4·33 (3·24–6·50)
Hellerstein *et al.* (1993)	FLO	35	53	19	058 (0·34–0·99)	—
Vanelle (1997)	FLO	140	66	31	0·49 (0·35–0·69)	—
Ravindran & Wiseman (1997)	SER	310	60	39	0·66 (0·52–0·83)	—
Thase *et al.* (1996)	SER	416	59	44	0·74 (0·57–0·95)	—
Total SSRIs		901	61	39	0·64 (0·55–0·74)	4·66 (3·52–6·89)
Stewart *et al.* (1989)	PHE	57	58	33	0·62 (0·30–1·28)	—
Botte *et al.* (1992)	MOC	47	39	17	0·73 (0·50–1·06)	—
Versiani *et al.* (1997)	MOC	315	57	20	0·53 (0·42–0·68)	—
Total MAOIs		419	55	22	0·59 (0·48–0·71)	2·89 (2·17–4·31)
Boyer & Lecrubier (1996)	AMS	212	52	25	0·64 (0·51–0·80)	—
Costa e Silva (1990)	MAS	39	60	11	0·45 (0·26–0·78)	—
Total Amisulpride		251	53	23	0·61 (0·49–0·75)	3·29 (2·39–5·27)
Boyer & Lecrubier (1996)	AMN	323	49	25	0·67 (0·54–0·83)	4·07 (2·71–8·22)
Bersani *et al.* (1991)	RIT	30	73	20	0·33 (0·14–0·80)	—
Reyntjens *et al.* (1986)	RIT	93	40	24	0·78 (0·59–1·04)	—
Total Ritanserin		123	48	23	0·63 (0·38–1·05)	3·93 (2·40–10·96)

* Some studies compared two active drugs with placebo. In that case, placebo subjects were considered just once. Convention: DES, desipramine; IMI, imipramine; FLO, Fluoxetine; SER, sertraline; PHE, phenelzine; MOC, moclobemide; AMS, amisulpride; AMN, amineptine; RIT, ritanserin.

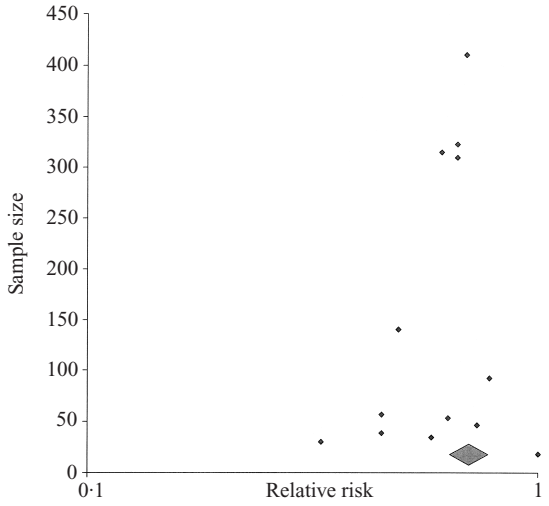

FIG. 2. Funnel plot: the effect of drug treatment in dysthymia. (◆, represents the pooled estimate.)

present, it is more likely to affect small 'negative' trials than large ones. The funnel plot suggests that some degree of publication bias is present in this review, with few studies reporting moderate treatment effects.

To investigate this further we performed a subgroup analysis according to the number of subjects randomized. The RR for treatment effect in trials with over 200 subjects ($N = 4$) was 0·65 (95% CI 0·59–0·71) and for those with < 200 subjects ($N = 9$) the RR was 0·62 (95% CI 0·52–0·74). This implies even if publication bias is present this will not attenuate the overall treatment effect.

Full remission

This outcome was reported in three trials (Thase *et al.* 1996; Vanelle, 1997; Versiani *et al.* 1997). Results from individual studies could not be pooled but were very similar to the pooled estimation for treatment response.

Total dropouts

No statistically significant results were found on dropout rates between and within classes of drugs, thus NNH was not calculated. The RR for TCA provided by four imipramine trials was 1·24 (95% CI 0·91–1·68). The pooled RR for SSRIs (fluoxetine and sertraline) was 0·76 (95% CI 0·58–1·01). The pooled RR for MAOI, obtained from two moclobemide trials was 0·53

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(95% CI 0·22–1·30). Other drugs including amisulpride (overall RR = 0·92 (95% CI 0·65–1·30), amineptine (one trial, RR = 0·93 (95% CI 0·66–1·31), ritanserin (three trials, RR = 0·78 (95% CI 0·50–1·21) and acetil-L-carnitine (one trial, RR = 0·40 (95% CI 0·70–1·06)) reported similar results for dropouts.

Adverse events

TCA showed a statistically significant result for adverse events: RR = 1·37 (95% CI 1·14–1·66), but this result is from one imipramine trial only. The NNH was 4·6 (95% CI 2·9–10·2), given a prevalence of adverse events of 59% in the placebo group. No significant increase in side effects were found for SSRIs (RR = 1·45, 95% CI 0·71–2·99); $\chi^2 = 5{\cdot}09$; $P = 0{\cdot}15$) or moclobemide (RR = 1·15, 95% CI 0·94–1·42). No heterogeneity was found between 'other drugs' (amisulpride, amineptine and ritanserin): RR = 1·37 (95% CI 1·14–1·65; $\chi^2 = 3{\cdot}78$; $P = 0{\cdot}36$), NNH = 5·2 (95% CI 3·4–11·0), for a prevalence of 41% in the placebo group. The highest RR for adverse events was found for ritanserin: RR = 2·5 (95% CI 1·00–6·23), reported by one trial (Bersani *et al*. 1991). The NNH was 2·5 (95% CI 1·38–13·72). Results from one trial (Boyer & Lecrubier, 1996) showed that amineptine was also associated with a higher number of subjects reporting adverse events, comparing to placebo: the RR was 1·4 (95% CI 1·08–1·81), the NNH being 5·64 (3·25–21·24).

Sensitivity analyses

These analyses were subsidiary to the main review question and based on non-randomized comparisons. We used the comparison 'any drug *v*. placebo' in order to study the main outcome (treatment response) according to the following criteria.

(*i*) *Length of studies*

Two groups of studies were compared: those which duration was less than 6 weeks (Reyntjens *et al*. 1986; Botte *et al*. 1989; Costa e Silva, 1990; Bersani *et al*. 1991) and those of 6 weeks or more (Stewart *et al*. 1983, 1993; Kocsis *et al*. 1988*a*, *b*; Hellerstein *et al*. 1993; Boyer & Lecrubier, 1996; Thase *et al*. 1996; Ravindran & Wiseman, 1997; Vanelle, 1997; Versiani *et al*. 1997). No differences were found between these two groups.

(*ii*) *Drugs used*

Comparisons were made between and within classes of drugs concerning treatment response and no significant differences were found.

(*iii*) *Dysthymia and 'neurotic/mild/moderate depression'*

Twenty-three trials did not use the concept of dysthymia but included patients suffering from briefer non-major depressive states. Eleven provided data on treatment response and were compared with included trials. The RRs were nearly the same: 0·64 (95% CI 0·60–0·70) for dysthymia trials and 0·58 (95% CI 0·45–0·74) for neurotic depression trials.

(*iv*) *'Pure' dysthymia and 'double expression'*

Trials including patients with 'double depression' (Reyntjens *et al*. 1986; Kocsis *et al*. 1988*a*, *b*; Botte *et al*. 1989; Bersani *et al*. 1991; Boyer & Lecrubier, 1996; Versiani *et al*. 1997) reported RR = 0·65 (95% CI 0·59–0·72). The RR for those including only patients with 'pure dysthymia' was nearly the same: RR = 0·63, 95% CI 0·54–0·72.

DISCUSSION

The main findings of this review are: (1) active drug treatment of dysthymia appears to be effective, at least for the relatively short time course of most of these studies; (2) tricyclic antidepressants, but not MAOIs or SSRIs are associated with higher drop outs and more adverse events rates than placebo; and (3) similar treatment responses are noted in less rigorously defined minor depressive categories.

Efficacy

This review suggests that active pharmacological treatments are more effective than placebo in the short-term treatment of patients with dysthymia. Although there were differences in terms of definition of illness, duration of treatment, and drugs used, a consistent and homogeneous therapeutic effect was found. The NNT was about 4 for treatment response. This indicates that four patients have to be treated to cause one clinical improvement. These NNTs are small compared to those found for many other widely

used medical interventions (Sackett *et al.* 1997), suggesting a good cost benefit ratio.

Dropouts and adverse events

Total dropouts were the main outcome used to assess whether treatments were tolerated as this information was given in most studies. Total dropouts may be due to adverse events or lack of efficacy of the treatment. It is likely that patients on placebo who dropped out, were more likely to do so because of lack of efficacy than those on active treatment. Tricyclics were associated with higher risk of dropout than other drugs, which implies they are less well tolerated. However, the comparisons reported in this review are between active treatments and placebo and are not direct comparisons between different classes of antidepressants. A further review of trials making such direct comparisons is underway. As expected, active treatments caused more adverse events than placebo, but these differences were not significant except for tricyclics.

Methodological considerations

The review used a highly sensitive search strategy that should have identified all published trials, including those published in the 'grey literature'. Funnel plots are useful to assess the validity of meta-analysis (Egger *et al.* 1997), despite criticisms that they are a non-specific and partially validated screening test for bias (Naylor, 1997). Our funnel plot suggested that some degree of publication bias was present in this review, with few studies reporting moderate treatment effects. As our search was highly sensitive and inclusive, this finding could suggest that some 'negative trials' have not been published. This bias probably would produce lower pooled treatment response rates and as a result higher NNT. We believe that the main findings nevertheless still hold, because the distribution on the funnel plot suggests that missing trials would fall between our estimate of pooled treatment effect and a relative risk of one. Furthermore, our subgroup analysis showed that the relative risk for treatment response for the larger trials was nearly the same than for the small ones, indicating that publication bias is unlikely to alter greatly the estimated treatment effect.

It is important to note that only short-term results are available in what is by definition a long-term problem. Clinically, it is common to see short-term improvement in such situations with subsequent relapse. Longer term pragmatic randomized controlled trials are required to evaluate alternative treatment approaches for dysthymia. As we anticipated from prior experience of RCTs in depression (Hotopf *et al.* 1997*b*), there were a number of concerns regarding the quality of reporting of these RCTs. Many papers lacked important information, such as details about the population, randomization, number of dropouts and standard deviations for continuous data, meaning that we have relied on dichotomous outcomes. Some trials were reported more than once, including preliminary results and subsamples with *post hoc* analysis. We also found that a number of papers reported results only for 'completers' rather than performing a true intention to treat analysis.

A recent American report from a National Institute of Mental Health (NIMH) conference provided consensus concerning some of the issues addressed in this review, particularly definition of response and procedures to guide future research on dysthymia (Gwirtsman *et al.* 1997). The main efficacy outcomes used in this review – treatment response and full remission – are among those proposed by the report. The third essential measure according to the report was 'recovery', an outcome which may be evaluated as long as carefully designed follow-up studies are available. In addition, the conferees considered that it is essential that therapeutic trials of dysthymia use measures extending beyond syndromal changes (such as psychosocial functioning, quality of life, work productivity, and health care utilization).

This review used stringent inclusion criteria to evaluate the efficacy of pharmacotherapy in dysthymia. This led to many studies being excluded. We deliberately took this approach in order to ensure that the pooled data reflected a relatively homogeneous clinical population.

Clinical features

No significant differences were found between trials including patients with 'pure dysthymia' and those including 'double depressive' patients. We suggest that the distinction between 'double depression' and 'pure dysthymia' does not have treatment implications, which is not surprising

given that most dysthymic patients have major depression some time in their lives (WPA Dysthymic Working Group, 1995). However, there were insufficient data from the studies identified in this review to allow this issue to be fully explored. It is difficult to define a single 'pure' dysthymia subtype and it may be that patients who are entered into 'pure dysthymia' treatment trials have either a subthreshold or early depressive illness and it is this, rather than the core syndrome of dysthymia that is responding to treatment. Some research on minor depression (Paykel *et al.* 1988) suggests that there may be a threshold level of a HRSD score of 13, albeit based on small numbers and multiple testing of interaction terms.

We also found similar treatment responses in less rigorously defined minor depressive categories. It may be that patients with 'minor depression', according to ICD-9 or DSM-II classifications, could have in fact what is now called major depression. In this case, the results may simply reflect the known efficacy of antidepressants in major depression. We based our assumption of comparability between these two groups of trials because patients were defined as having 'mildly to moderate depressive states' in some trials (Rickels *et al.* 1968; Standal, 1977), and/or had low baseline scores on the HAM-D indicating relatively mild depression.

Conclusion

Our findings suggest that active drugs are more effective than placebo in the short-term treatment of dysthymia. Although there are some differences between drugs in dropouts and side effects, particularly the high occurrence of these outcomes for patients taking tricyclics, there are no differences in terms of efficacy. Decisions on treatment must, therefore, be based on the balance between equal efficacy, better tolerability but higher cost of newer antidepressants *versus* tricyclics. Such a judgement can only be informed by long duration pragmatic trials with economic and quality of life outcomes, none of which exist for dysthymia.

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