Cochrane
Library

Cochrane Database of Systematic Reviews

Pharmacotherapy for dysthymia (Review)

Silva de Lima M, Hotopf M

Silva de Lima M, Hotopf M.
Pharmacotherapy for dysthymia.
Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004047.
DOI: [10.1002/14651858.CD004047](https://doi.org/10.1002/14651858.CD004047).

www.cochranelibrary.com

Pharmacotherapy for dysthymia (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	1
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	5
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	14
DATA AND ANALYSES	26
Analysis 1.1. Comparison 1 SSRIs vs TCA, Outcome 1 Non treatment response.	26
Analysis 1.2. Comparison 1 SSRIs vs TCA, Outcome 2 Absence of full remission.	27
Analysis 1.3. Comparison 1 SSRIs vs TCA, Outcome 3 Number of dropouts.	27
Analysis 2.1. Comparison 2 MAOIs vs TCA, Outcome 1 Non treatment response.	28
Analysis 2.2. Comparison 2 MAOIs vs TCA, Outcome 2 Absence of full remission.	28
Analysis 2.3. Comparison 2 MAOIs vs TCA, Outcome 3 Number of dropouts.	28
Analysis 2.4. Comparison 2 MAOIs vs TCA, Outcome 4 Number of people reporting adverse events.	29
Analysis 3.1. Comparison 3 OTHER DRUGS vs TCA, Outcome 1 Non treatment response.	30
Analysis 3.3. Comparison 3 OTHER DRUGS vs TCA, Outcome 3 Number of dropouts.	30
Analysis 3.4. Comparison 3 OTHER DRUGS vs TCA, Outcome 4 Number of people reporting adverse events.	31
Analysis 4.1. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 1 Non treatment response.	32
Analysis 4.2. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 2 Changes from baseline on 21-item HAM-D.	32
Analysis 4.3. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 3 Number of dropouts.	32
Analysis 4.4. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 4 Number of people reporting adverse events.	33
Analysis 5.1. Comparison 5 ADDITIONAL COMPARISONS BETWEEN ADs, Outcome 1 Non treatment response.	34
Analysis 5.2. Comparison 5 ADDITIONAL COMPARISONS BETWEEN ADs, Outcome 2 Number of dropouts.	34
Analysis 5.3. Comparison 5 ADDITIONAL COMPARISONS BETWEEN ADs, Outcome 3 Number of people reporting adverse events.	35
Analysis 6.1. Comparison 6 ANY ANTIDEPRESSANT vs IMIPRAMINE, Outcome 1 Non treatment response.	36
Analysis 6.2. Comparison 6 ANY ANTIDEPRESSANT vs IMIPRAMINE, Outcome 2 Dropouts.	37
WHAT'S NEW	38
HISTORY	38
DECLARATIONS OF INTEREST	38
SOURCES OF SUPPORT	38
NOTES	38
INDEX TERMS	39

[Intervention Review]

Pharmacotherapy for dysthymia

Mauricio Silva de Lima¹, Matthew Hotopf²

¹Medical, Eli Lilly & Co, Basingstoke, UK. ²Department of Psychological Medicine, The Institute of Psychiatry, London, UK

Contact address: Mauricio Silva de Lima, Medical, Eli Lilly & Co, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL, UK.
msilvadelima@yahoo.com.br, limama@lilly.com.

Editorial group: Cochrane Common Mental Disorders Group

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Silva de Lima M, Hotopf M. Pharmacotherapy for dysthymia. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD004047. DOI: [10.1002/14651858.CD004047](https://doi.org/10.1002/14651858.CD004047).

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Many drug treatments have been proposed for the treatment of dysthymia, but with so many potential comparisons it is not possible at the present time to determine which is the treatment of choice. There is a need to know whether the different classes of antidepressants have similar efficacy. In addition, the tolerability of treatments may be even more important, since dysthymia is a chronic condition characterised by less severe symptoms than major depression.

Objectives

To conduct a systematic review of all randomised controlled trials comparing two or more active drug treatments for dysthymia.

Search methods

Electronic searches of Cochrane Library, EMBASE, MEDLINE, PsycLIT and LILACS, Biological Abstracts; reference searching; personal communication; unpublished trials from pharmaceutical industry.

Selection criteria

Only randomised and quasi-randomised controlled trials were included. Trials had to compare at least two active drug treatments in the treatment of dysthymia. Exclusion criteria were: non-randomised studies, studies which included patients with mixed major depression/dysthymia and studies on depression/dysthymia secondary to other disorders (e.g. substance abuse).

Data collection and analysis

The reviewers extracted the data independently and odds ratios, weighted mean difference and number needed to treat were estimated. The reviewers assumed that people who died or dropped out had no improvement and tested the sensitivity of the final results to this assumption.

Main results

A total of 14 trials were eligible for inclusion in the review. All studied drugs promoted similar clinical responses, although with different side effect profiles. The evidence for TCAs and SSRIs was the most robust, considering the number of trials and participants.

Authors' conclusions

The conclusion is that the choice of drug must be made based on consideration of drug-specific side effect properties.

PLAIN LANGUAGE SUMMARY

Drug treatments for dysthymia

Pharmacotherapy for dysthymia (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Many drug treatments have been proposed for the treatment of dysthymia. There is a need to know whether the different classes of antidepressants have similar efficacy. The tolerability of treatments may be even more important, since dysthymia is a chronic condition characterised by less severe symptoms than major depression. A total of 14 trials were included in this review. All drugs promoted similar clinical responses, although with different side effect profiles. There are no significant differences in efficacy between different classes of antidepressants in the treatment of dysthymia, although side effect profiles may be different. The evidence for TCAs and SSRIs was the most robust. The conclusion is that the choice of drug must be made based on consideration of drug-specific side effect properties.

BACKGROUND

Many drug treatments have been proposed for the treatment of minor chronic depression - otherwise known as dysthymia (International Classification of Diseases, 10th edition and the Diagnostic Statistical Manual 4th edition (APA 1994). The first review in this series addressed the question of whether drugs are an effective treatment for dysthymia using placebo-controlled randomised controlled trials (RCTs). This review aimed to assess the relative efficacy and acceptability of active pharmacological treatments for dysthymia.

A wide range of treatments have been proposed for dysthymia, including different classes of antidepressants, neuroleptics, benzodiazepines and stimulants. Some of these treatments have been compared in randomised controlled trials, but with so many potential comparisons it is not possible at the present time to determine which is the treatment of choice.

In the treatment of depression there is some evidence that different classes of antidepressants have similar efficacy (Magni 1988; Song 1993; Howland 1991). There is a need to determine whether this holds for dysthymia.

One important difference between treatments for depression which previous systematic reviews have identified is that some antidepressants are better tolerated than others (Anderson 1994; Hotopf 1997). This may have direct impact on cost-effectiveness. As dysthymia is a chronic condition characterised by less severe symptoms than major depression, the tolerability of treatments may be even more important than for major depression.

OBJECTIVES

The objectives of this study were:

- i) To investigate the relative efficacy and dropout rates of different antidepressants and other pharmacological treatments in dysthymia
- ii) Where possible, to perform a meta-analytic synthesis of the studies.

More specifically we aimed to test the following hypotheses:

- i) Because dysthymia is an affective disorder we predicted that antidepressants would be more efficacious than other treatments (benzodiazepines, neuroleptics and stimulants).
- ii) Newer antidepressants (specifically the selective serotonin reuptake inhibitors) would be better tolerated than older tricyclic antidepressants in terms of dropout from trials.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials which compared two or more active pharmacological treatments for dysthymia. Quasi-randomised trials were also included and a sensitivity analysis would compare the main results from these trials with those from randomised controlled trials.

Types of participants

People with any primary diagnosis of dysthymia: non-major depression of at least two years in duration. Participants with

disorders such as depressive neurosis, depressive personality disorder, neurotic depression, persistent anxiety-depression, mild chronic depression and minor depression were also included as long as the duration of illness was longer than 2 years, irrespective of gender, age or nationality.

Exclusion criteria: where those with dysthymia and major depression were included together in the same study (not providing separate data for dysthymic patients), where depression was secondary to other disorders, for example substance abuse, and where the degree of affective illness fulfilled criteria for major depression.

Types of interventions

1) Any antidepressant drugs:

- a) Tricyclic and related antidepressant drugs: desipramine, imipramine, amitriptyline, tianeptine, clomipramine, nortriptyline, dothiepin, doxepin, maprotiline, trazodone, trimipramine, amoxapine, lofepramine, viloxazine
- b) Monoamine-oxidase inhibitors (MAOIs) and related drugs: phenelzine, isocarboxazide, tranylcypromine, moclobemide
- c) SSRIs and related antidepressants: paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram.

2) Other drugs used in the treatment of depression

- a) neuroleptics
- b) tryptophan
- c) benzodiazepines or other anxiolytic drugs (e.g. alprazolam)
- d) lithium
- e) stimulants: dexamphetamine sulphate, methylphenidate hydrochloride, pemoline

This list would be changed if our search found additional active treatments. Trials with combined drug therapies or augmentation were also included.

Types of outcome measures

Primary outcomes of interest were:

1. Dysthymia changes at the end of trial
 - (a) improvement rates in the symptoms of dysthymia on any depression scale
 - (b) absence of sufficient symptoms to meet diagnostic criteria for dysthymic disorder
 - (c) score of 'very much improved' or 'much improved' on CGI scale
 - (d) group mean scores on HRSD scale
 - (e) group mean scores on any depression scale.
2. Acceptability of the treatment: measured by numbers of people dropping out during the trial and post-randomisation exclusions.
3. Side effects.
4. Relapse.
5. Quality of life measures: average change on any scale at the end of treatment.

Search methods for identification of studies

1. Electronic databases:

The following electronic databases were searched;

BIOLOGICAL ABSTRACTS (DATA)

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 NEUROS?S) and
(CHRONIC* or PERSISTENT* or LONG-STANDING or LONG-TERM or
(LONG near (STANDING or TERM)))]]

MEDLINE (1966-4/2003)

DYSTHYMI* or
DISTIMI* or
DYSTIMI* or
"DYSTHYMIC DISORDER"/ all subheadings or
(NEURASTHENI* or "NEURASTHENIA"/ all subheadings) or
DYSPHORI* or
[(MINOR or MILD* or MODERAT*) and
("DEPRESSION"/ all subheadings or explode "DEPRESSIVE-
DISORDER"/ all subheadings] or
[(DEPRESS* or UNHAPP*) or
(ATYPICAL or NON-TYPICAL or NEUROTIC* or NEUROS?S)
and ("CHRONIC-DISEASE"/ all subheadings) or (CHRONIC* or
PERSISTENT* or LONG-STANDING or LONG-TERM or (LONG near
(STANDING or TERM)))]]

PSYCLIT (1/1974 - 12/2003)

"DYSTHYMIC DISORDER"/ all subheadings or
DYSTHYMI* or
DISTIMI* or
DYSTIMI* or
(NEURASTHENI* or "NEURASTHENIA"/ all subheadings) or
DYSPHORI* or
[(MINOR or MILD* or MODERAT*) and
("DEPRESSION"/ all subheadings or explode "DEPRESSIVE-
DISORDER"/ all subheadings] or
[(DEPRESS* or UNHAPP*) or
(ATYPICAL or NON-TYPICAL or NEUROTIC* or NEUROS?S)
and ("CHRONIC-DISEASE"/ all subheadings) or (CHRONIC* or
PERSISTENT* or LONG-STANDING or LONG-TERM or (LONG near
(STANDING or TERM)))]]

EMBASE (1980-2003)

"AFFECTIVE NEUROSIS"/ all subheadings or
(NEURASTHENI* or "NEURASTHENIA"/ all subheadings) or
(DYSTHYMI* or DISTIMI* or DYSTIMI* in ti, abs, keywords) or
MINOR DEPRESSION in ti, abs, keywords or
MILD* DEPRESSION in ti, abs, keywords or
MODERAT* DEPRESSION in ti, abs, keywords or
[(ATYPICAL or NON-TYPICAL) and DEPRESSION] in ti, abs, keywords
or [(NEUROTIC* or NEUROS?S) and DEPRESSION] in ti, abs,
keywords or
CHRONIC DEPRESSION in ti, abs, keywords or
[(LONG-STANDING or LONG-TERM or (LONG near (STANDING or
TERM)))] and depression] in ti, abs, keywords

LILACS (the search was carried out in English, Spanish and Portuguese)

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 NEUROS?S) and
(CHRONIC* or PERSISTENT* or LONG-STANDING or LONG-TERM or
(LONG near (STANDING or TERM)))]]

COCHRANE LIBRARY

DYSTHYMI* or
DISTIMI* or
DYSTIMI* or
"DYSTHYMIC DISORDER"/ all subheadings or
NEURASTHENI* or
"NEURASTHENIA"/ all subheadings or
[(ATYPICAL or NON-TYPICAL or NEUROTIC* or NEUROS?S) or
(MINOR or MILD* or MODERAT*) and
("DEPRESSION"/ all subheadings or explode "DEPRESSIVE-
DISORDER"/ all subheadings] or
[(DEPRESS* or UNHAPP* or DYSPHORI*) and
("CHRONIC-DISEASE"/ all subheadings or (CHRONIC* or
PERSISTENT* or LONG-STANDING or LONG-TERM or (LONG near
(STANDING or TERM)))]]

2. The register of trials kept by the Cochrane Schizophrenia Group and the Depression, Anxiety and Neurosis Group were also searched.

3. Personal Communication: in order to ensure that as many as possible RCTs and CCTs were identified, the authors of the included studies were consulted to find out if they knew of any published or unpublished RCTs/ CCTs of pharmacological treatment of dysthymia which were not yet identified. A list of all identified RCTs/ CCTs identified through consulting others' sources was sent to the authors.

4. Attempts were made to obtain unpublished trials from pharmaceutical industry.

Data collection and analysis

Selection of trials

One reviewer (MSL) screened the abstracts of all publications which were obtained by the search strategy. A distinction was made between:

- 1) eligible studies, with any pharmacological treatments' comparison
 - 2) pharmacological treatments without any control element, or general treatment studies rather than pharmacological.
- For articles that were thought to be possible RCTs the full article was obtained and inspected to assess their relevance to this review based on the criteria for inclusion.

Quality assessment

In order to ensure that variation was not caused by systematic errors in the design of a study, the methodological quality of the selected trials was assessed by two independent reviewers (MSL and MH). The criteria based on the guidelines included in the Cochrane Collaboration Handbook were used to assess the quality of the trials. It is based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment and is defined as below:

- A. Low risk of bias (adequate allocation concealment);
- B. Moderate risk of bias (some doubt about the results);
- C. High risk of bias (inadequate allocation concealment).

In this first analysis, trials were included if they met the criteria A or B at the Handbook.

In a second quality assessment, a modified version of those from (Hazell 1995) and (Churchill 1996) was used. In this scheme, studies were rated considering the following features:

- a. degree to which randomisation was truly blind (allocation concealment)
- b. degree to which assessor of outcome were blind to the treatment allocation
- c. blinding of subjects or attempts to equalise expectations
- d. length of acute phase of treatment
- e. length of follow-up
- f. assessment of compliance
- g. clear definition of inclusion criteria (use of diagnostic criteria)
- h. statement of criteria for improvement
- i. treatment standardized or monitored
- j. inclusion of data from subjects who withdrew after randomisation
- k. control for baseline differences

Scores for the individual quality item were summed for the analysis. Discrepancies in the scores were resolved by consensus. The primary results of the review when employing these different rating scales were compared.

Data Management

Data were independently extracted by both reviewers. Any disagreement was discussed, the decisions documented and, where necessary, the authors of the studies contacted to help resolve the issue. All exclusion/ dropouts were identified whenever available in the report. If no information was available (either from the report or the authors) it was assumed that dropout was because of side effects/ treatment failure. The sensitivity of the results was tested to see if the inclusion of this assumption caused any substantial changes.

We expected that some trials would use a crossover design. In this case, in order to exclude the potential additive effect in the second or more stages on these trials only data from the first stage would be analysed.

Data Analysis

Relative risk analyses (with 95% CI) were calculated for dichotomous outcome data (relative risk was preferred to odds ratio as it is a more conservative statistic and appropriate where the outcome is not a rare event). When overall results were significant, the number needed to treat 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 estimates of relative risk were based on the random effects model.

Continuous outcomes were analysed according to their difference in mean treatment effects and its' standard error. If multiple outcome measures were described in a single study, for the purposes of pooling results, a single 'best available' outcome measure was chosen for each study, according to the authors' specification as the principle outcome or what was reported first. The effect sizes could be calculated using this best available outcome.

Meta-analytical methods for continuous data assume that the underlying distribution of the measurements is normal. The ratio of the mean to its' standard deviation gives a crude way of assessing skew: if this ratio was less than 1.65 for any group in a trial the results were log-transformed before being included in the analysis.

Heterogeneity in the results of the trials was assessed both by inspection of graphical presentations and by calculating a test of heterogeneity. Two possible reasons for heterogeneity were pre-specified: (i) that response differed according to different lengths of follow-up; (ii) that response differed according to the different drugs. These would be assessed by looking at separate subgroups of trials [(i) and (ii)]. A further subgroup analysis would be conducted comparing 'dysthymic disorder' trials with 'minor depression/neurotic depression' trials if there were available data.

Tables were used to display characteristics of eligible trials including those that were excluded with the reasons for exclusion. Outcomes were also presented graphically. Review Manager software developed by the Cochrane Collaboration was used to organise and process the results.

Statistical advice was provided by the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group.

RESULTS

Description of studies

Search

The general search for this series of systematic reviews on the treatment of dysthymia generated 167 references which were related to trials with at least two active drug treatments being compared. 90 references were checked reading the full paper.

- Fourteen trials used diagnostic criteria for dysthymia and had evaluable data, which could be included in this review (1659 patients in total). Data from five (Bakish 1993, Boyer 1996, Stewart 1989, Thase 1996, and Versiani 1997) have already been used for placebo comparisons in the first review (Lima 2001).

- 36 studies were excluded because the patients could not be considered as suffering from dysthymia or they did not describe appropriate methods of randomisation.

Design

All the included studies were described as randomised and used a parallel group design. Most of them (11) were double blind. The duration of the trials ranged from 4 weeks to 12 weeks.

Settings

Four trials were conducted in the United States of America (Stewart 1989; Thase 1996; Hellerstein 1994; Rosenthal 1992), one in Italy (Smeraldi 1996), two in France (Boyer 1996; Guelfi 1989), one in Denmark (Geisler 1992), one in Colombia (Leon 1994), two in Spain (Vallejo 1987; Otero 1994) and one in Canada (Bakish 1993). One trial was an International Multicenter Study (Versiani 1997), involving three countries. One trial did not report the country where the trial was conducted (Salzmänn 1995).

All trials studied outpatients from general practice, psychiatric clinics or from the community.

Participants

All trials included for the main comparisons used DSM-III or DSM-III-R criteria for the diagnosis of dysthymic disorder.

The number of participants randomised in the trials ranged from 18 to 410. In two studies, patients had 'double depression' (Boyer 1996, Hellerstein 1994). In Smeraldi (Smeraldi 1996), 15 patients from a total of 281 had major depression in partial remission. Some studies selected subjects with very chronic illness (such as Thase 1996). Stewart (Stewart 1989) reported that 80% of patients also had atypical depression.

Comparisons

Seventeen different compounds were compared in the trials. Imipramine was the main comparison drug (six trials). Amisulpiride and fluoxetine were compared to other drugs in three studies; trazadone and phenelzine in two. In one trial (Otero 1994) an augmentation scheme was adopted (fluoxetine + bentazepam) and compared to fluoxetine alone.

Outcomes

All trialists used symptom scales in assessing treatment effects. The Hamilton Depression Scale (HAM-D) was the most widely used, followed by Montgomery-Asberg Depression Rating Scale (MADRS). However, most of trials lacked data on standard deviations, and in other cases showed skewed data distribution. Continuous data from one study were provided by the author (Hellerstein 1994).

Four dichotomous outcomes were used in this review. The most used dichotomous outcome was 'responder': for the majority of the included trials, Clinical Global Impression (CGI) scoring 1 or 2 on the item 2 and a decrease of at least 50% on final HAM-D scores.

The second outcome was 'full remission', which is a more stringent criteria of improvement. It was defined as 'patients no longer meet DSM-III-R criteria for dysthymia and achieve a score of 0 on HAM-D item 1 - depressed mood' (such as Thase 1996), and as 'symptom criteria no longer met plus absence of depressed mood and HAM-D endpoint 17-item score below 5) in Versiani 1997.

Dropouts were the third outcome used, and were extracted in 13 trials. Thase 1996 gave the total number of dropouts for each group, but as for the other outcomes, there were 6 post-randomisation exclusions with no information about group distribution.

The number of patients reporting any adverse event was the fourth outcome. It was not possible to use other outcomes concerning side effects on account of different profiles for each drug group.

Reason for excluding studies: most of the excluded studies, particularly from the 1970s and 1980s, have failed on lack of definition of the illness, not specifying the duration of the depressive state or including patients suffering from brief depressive states or other conditions.

Risk of bias in included studies

Only two trials (Hellerstein 1994 and Versiani 1997) were classified as 'A' criteria according to the first quality assessment (Mulrow 1999) because the authors provided further information in answer to our enquiry. The remaining trials did not provide information on allocation concealment and were classified as 'B'.

Data reporting and analysis: in general, the quality of reporting was poor. All trials reported the randomisation procedure without any information on allocation concealment. Some trials did not report the number of dropouts and post-randomisation exclusions. Most of the trials did not use an intention-to-treat approach, including

data for 'completers' only. The omission of standard deviations was also common, as well as basic information about the studied population (setting, demographic data).

See results section for further information on quality.

Effects of interventions

COMPARISON 1 - TCAs VERSUS SSRIs

Only one study (Thase 1996) compared SSRIs (134) against TCAs (136). This study used sertraline (50-200 mg daily), imipramine (50-200 mg daily) and placebo. Its purpose was to evaluate the safety and efficacy of these drugs for the treatment of dysthymia.

1. Non treatment response

This outcome was assessed by the Clinical Global Impressions improvement score of 1 or 2 (very much or much improved). No significant difference was found (RR 1.14 95% CI 0.84 - 1.54).

2. Absence of full remission

The authors established a criterion for full remission which was: patients no longer meet DSM-III-R criteria for dysthymia and achieve a score of 0 on HAM-D item 1. A second remission criterion was a HAM-D cutoff score of 4 or less. This study also did not reach statistical significance (RR 1.01 95% CI 0.80 - 1.29).

3. Number of dropouts

More patients in the imipramine group discontinued treatment, mainly because of more adverse events than in the sertraline group (RR 0.47 95% CI 0.20-0.75).

COMPARISON 2 - TCAs VERSUS MAOIs

Three studies compared TCAs (N= 141) against MAOIs (N= 139), in which the drugs used were: imipramine, in the TCAs 'group, phenelzine and moclobemide in the MAOIs 'group. The drug protocol was flexible, accepting high doses. The outcomes "absence of full remission" and "number of people reporting adverse events" were described in one study only (Versiani 1997).

1. Non treatment response

Two studies assessed this outcome measured by the CGI rating scale. However, they used different drugs: Stewart 1989 compared imipramine versus phenelzine and Versiani 1997 analysed imipramine against moclobemide. There was a discrepancy between them: whilst Stewart 1989 presented a difference favouring imipramine, Versiani 1997 showed an advantage in the usage of moclobemide, but neither of the two results was statistically significant (RR 1.02 95% CI 0.45-2.31).

2. Absence of full remission

One single trial approached this outcome (Versiani 1997), comparing moclobemide with imipramine, favouring the former (RR 0.79 95% CI 0.62-1.01).

3. Number of dropouts

Two studies analysed this outcome: Versiani 1997 (imipramine versus moclobemide) and Vallejo 1987 (imipramine versus phenelzine). No statistical differences were recorded in these trials.

4. Number of people reporting adverse events

Only Versiani 1997 (N= 211) reported this outcome, showing better results for MAOIs with a statistically significant difference (RR 0.84 95% CI 0.71-0.99). The main adverse events were: dry

mouth, tremor, constipation, sweating, blurred vision, sleepiness, dizziness, headache, insomnia and nausea.

COMPARISON 3 - TCA VERSUS OTHER DRUGS

The TCAs used were: amitriptyline and imipramine, in medium doses. [Guelfi 1989](#) compared tianeptine (N=135) against amitriptyline (N=130). [Salzmänn 1995](#) compared minaprine (N=33) with imipramine (N=34). [Bakish 1993](#) compared ritanserin (N=17) with imipramine (N=16), and the last one only contributed to the outcome 'number of dropouts'.

1. Non treatment response

[Guelfi 1989](#) and [Salzmänn 1995](#) reported this outcome and neither of them showed a difference between the analysed drugs, although in the first one the results slightly favoured amitriptyline (RR 1.33 95% CI 0.95-1.86).

2. Number of dropouts

Three studies assessed this outcome and there was no significant difference in drop-out rates between the groups, despite a trend favouring ritanserin, amitriptyline and minaprine.

3. Number of people reporting adverse events

Only [Salzmänn 1995](#) reported this outcome. There was no significant difference in terms of numbers of adverse events in both treatment groups (RR 0.72 95% CI 0.44-1.17).

COMPARISON 4 - SSRIs VERSUS OTHER DRUGS

Two studies compared fluoxetine (N=20) versus trazodone (N=18), but only [Hellerstein 1994](#) analysed the outcome changes from baseline on 21-item HAM-D, given the fact that patients met criteria for both dysthymia and major depression. [Otero 1994](#) compared fluoxetine versus fluoxetine +bentazepan to analyse if fluoxetine could accelerate the onset of antidepressant effects. [Smeraldi 1996](#) compared amisulpride at low doses (50 mg/day) versus fluoxetine (20mg/day).

1. Non treatment response

Three studies assessed this outcome, two of them comparing trazodone versus fluoxetine and one comparing amisulpride versus fluoxetine. In the first group, results favoured trazodone (RR 1.43 95% CI 0.81-2.51) whilst in the second one fluoxetine had an advantage over amisulpride at low doses (RR 0.82 95% CI 0.57-1.20)

2. Changes from baseline on 21-item HAM-D

Only [Hellerstein 1994](#) reported this outcome showing a slightly advantage in the use of trazodone (WMD 2.75 95% CI -1.37-6.47).

3. Number of dropouts

[Otero 1994](#) and [Smeraldi 1996](#) found a lower number of dropouts in the groups using fluoxetine compared to those receiving other drugs such as amisulpride and bentazepan, but the differences did not reach statistical significance. [Hellerstein 1994](#) and [Rosenthal 1992](#) compared trazodone versus fluoxetine and found no significant difference favouring trazodone (RR 2.59 95% CI 0.44 - 15.32).

4. Number of people reporting adverse events

No statistical differences were recorded in the [Otero 1994](#) trial regarding data on the number of people reporting adverse events when fluoxetine alone was compared to fluoxetine with bentazepan (RR 0.94 95% CI 0.46 - 1.91). In [Smeraldi 1996](#), no difference was observed between amisulpride and fluoxetine.

COMPARISON 5 - ADDITIONAL COMPARISONS BETWEEN ANTIDEPRESSANTS

[Geisler 1992](#) compared 5-10 mg ritanserin (N=33) and 1-2 mg flupenthixol (N=37) for a period of 6 months, only contributing with the outcome 'number of dropouts'. Two studies compared amisulpride at low doses (50 mg/daily) to viloxazine 150mg/daily ([Leon 1994](#)) and amineptine in doses of 200mg/day ([Boyer 1996](#)).

1. Non treatment response

[Leon 1994](#) found a significant difference favouring amisulpride over viloxazine (RR 0.45 CI 95% 0.25 - 0.83). No differences were found between amisulpride and amineptine in [Boyer 1996](#)'s trial (RR 0.95 CI 95% 0.73 - 1.25).

2. Number of dropouts

None of the three trials that assessed this outcome demonstrated significant differences between any drugs.

3. Number of people reporting adverse events

A similar rate of subjects reporting adverse events was seen in both groups (amisulpride and amineptine) in the only study ([Boyer 1996](#)) that evaluated this outcome (RR 0.88 CI 95% 0.70 - 1.11).

COMPARISON 6 - ANY ANTIDEPRESSANTS VERSUS IMIPRAMINE

Five studies assessed imipramine against any other antidepressants ([Salzmänn 1995](#); [Stewart 1989](#); [Thase 1996](#); [Vallejo 1987](#); [Versiani 1997](#)). The drugs used in these trials were: minaprine, phenelzine, sertraline, phenelzine and moclobemide. Only [Vallejo 1987](#) contributed to the outcome of 'dropouts'.

1. Non treatment response

Although a trend favouring moclobemide over imipramine was found in [Versiani 1997](#)'s study, there were no statistical differences when all results concerning response to treatment were pooled (RR 0.95 95% CI 0.73-1.24).

2. Number of dropouts

A pooled estimate suggested that dropouts were more likely to occur amongst those taking imipramine (RR 0.60 95% CI 0.43-0.82). The best results were obtained when sertraline was compared to imipramine in the trial conducted by [Thase 1996](#).

DISCUSSION

Results from our previous work on placebo controlled trials assessing the efficacy of antidepressants for dysthymia have shown that all studied drugs promote similar clinical responses, although with different side effect profiles. The evidence for TCAs and SSRIs is the most robust, considering the number of trials and participants. The conclusion is that the choice of drug must be made in consultation with patients, taking drug-specific side effect properties into consideration ([Lima 2001](#)).

The one trial comparing SSRIs and TCAs found an effect very similar to trials in depression, that is, there is a similar treatment efficacy and SSRIs cause less dropouts. The difference here is much greater (RR 0.479, 95%CI 0.30-0.95; NNH 5.74, 95%CI 3.64-13.52) but is based on one study only.

The trial of phenelzine and moclobemide versus imipramine gives somewhat different results, but the difference is not statistically significant. It could be said that there is no advantage of phenelzine and little, therefore, to warrant its obvious disadvantages in terms of interactions. Moclobemide is an easier drug to prescribe and

take, but again these results are based in one trial (Versiani 1997). Furthermore, such non-significant advantage for moclobemide against TCAs is not seen in major depression trials (Mulrow 1999).

No relevant conclusions can be drawn from other comparisons, including trials where other drugs were compared to TCA or SSRIs. On the other hand, the high number of distinct comparisons and the fact that sometimes the reference drug could not be considered as a standard treatment (amisulpiride versus viloxazine, in Leon 1994) makes it difficult to draw conclusions. It was not possible to use the funnel plot, therefore publication bias can not be discarded.

Current results must be analysed carefully given that replication in other trials would be necessary for a more robust conclusion. In addition, it is likely that some of the comparisons will not ever be compared in future investigations because of higher priority questions regarding the efficacy of treatments in dysthymia (see below).

AUTHORS' CONCLUSIONS

Implications for practice

TCAs, SSRIs and MAOIs seem to be reasonable choices for those suffering from dysthymia, although SSRIs are probably the better

choice because of their acceptability. This review provides no specific information on relevant matters such as how long the pharmacological treatment should be continued, at what dose, or at what threshold of severity of dysthymia.

Implications for research

There is a clear need for larger and long-term studies of the comparative efficacy of drugs in dysthymia. As far the decision-making process for treating patients with dysthymia is concerned, It would be of particular interest in these future trials to use a standard set of comparative compounds (such as TCAs or SSRIs) and relevant outcomes like full remission both at short and long term, quality of life, and patient satisfaction.

ACKNOWLEDGEMENTS

The authors would like to thank the Cochrane Depression, Anxiety and Neurosis Review Group (CCDAN) and Clive Adams for their help and advice.

REFERENCES

References to studies included in this review

Bakish 1993 {published data only}

* Bakish D, Lapierre YD, Weinstein, Klein J, Wiens A, Jones B, et al. Ritanerlin, Imipramine and placebo in the treatment of dysthymic disorder. *Journal of Clinical Psychopharmacology* 1993;**13**(6):409-14.

Bakish D, Ravindran A, Hooper C, Lapierre Y. Psychopharmacological treatment response of patients with a DSM-III diagnosis of dysthymic disorder. *Psychopharmacology Bulletin* 1994;**30**(1):53-9.

Boyer 1996 {published data only}

* Boyer P, Lecrubier Y. Atypical antipsychotic drugs in dysthymia: placebo controlled studies of amisulpride versus imipramine, versus amineptine.. *European Psychiatry* 1996;**11**(Suppl 3):135-40.

Geisler 1992 {published data only}

* Geisler A, Mygind S, Knudsen R, Sloth-Nielsen M. Ritanerlin and flupenthixol in dysthymic disorder. *Nordic Journal of Psychiatry* 1992;**46**(4):237-43.

Guelfi 1989 {published data only}

* Guelfi JD, Pichot P, Dreyfus JF. Efficacy of tianeptine in anxious-depressed patients: results of a controlled multicenter trial versus amitriptyline. *Neuropsychobiology* 1989;**22**(1):41-8.

Hellerstein 1994 {published data only}

* Hellerstein DJ, Yanowitch P, Rosenthal J, Hemlock C, Kasch K, Samstag LW, et al. Long-term treatment of double depression: a preliminary study with serotonergic antidepressants. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 1994;**18**(1):139-47.

Leon 1994 {published data only}

* Leon CA, Vigoya J, Conde S, Campo G, Castrillon E, Leon A. Therapeutic efficacy of amisulpride and viloxazine in the treatment of dysthymia: a comparison [Comparacion del efecto de la amisulprida y la viloxacina en el tratamiento de la distimia]. *Acta Psiquiatrica y Psicologica de America Latina* 1994;**40**(1):41-9.

Otero 1994 {published data only}

* Otero FJ, Hernandez-Herrero C, Martinez-Arevalo MJ, Garrido J, Armenteros S, Velasco J. Fluoxetine/benzazepam combination in the treatment of dysthymic disorders. *Current Therapeutic Research* 1994;**55**(5):519-31.

Rosenthal 1992 {published data only}

* Rosenthal J, Hemlock C, Hellerstein DJ, Yanowitch P, Kasch K, Schupak C, et al. A preliminary study of serotonergic antidepressants in treatment of dysthymia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 1992;**16**(6):933-41.

Salzmann 1995 {published data only}

* Salzmann E, Robin JL. Multicentric double-blind study comparing efficacy and safety of minaprine and imipramine in dysthymic disorders. *Neuropsychobiology* 1995;**31**(2):68-75.

Smeraldi 1996 {published data only}

Smeraldi E. Amisulpride versus fluoxetine in patients with dysthymia or major depression in partial remission - a double blind, comparative study. *Journal of Affective Disorders* 1998;**48**(1):47-56.

* Smeraldi E, Haefele E, Crespi G, Casadei GL, Biondi F, Vigorelli E. Amisulpride versus fluoxetine in dysthymia: Preliminary results of a double-blind comparative study. *European Psychiatry* 1996;**11**(Suppl 3):141-3.

Stewart 1989 {published data only}

* Stewart JW, McGrath PJ, Quitkin FM, Harrison W, Markowitz J, Wager S, et al. Relevance of DSM-III depressive subtype and chronicity of antidepressant efficacy in atypical depression. *Archives of General Psychiatry* 1989;**46**(12):1080-7.

Thase 1996 {published data only}

* Thase M, Fava M, Halbreich U, Kocsis JH, Koran L, Davidson J, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Archives of General Psychiatry* 1996;**53**(9):777-84.

Vallejo 1987 {published data only}

* Vallejo J, Gastro C, Catalan R, Salamero M. Double-blind study of imipramine versus phenelzine in melancholias and dysthymic disorders. *British Journal of Psychiatry* 1987;**151**:639-642.

Versiani 1997 {published data only}

* Versiani M, Amrein R, Stabl M and the International Collaborative Study Group. Moclobemide and imipramine in chronic depression (dysthymia): an international double-blind, placebo-controlled trial.. *International Clinical Psychopharmacology* 1997;**12**(4):183-93.

References to studies excluded from this review

Akiskal 1993 {published data only}

* Akiskal H. Dysthymic disorder and its treatment [La dysthymie et son traitement]. *L'Encéphale* 1993;**9**(375-B):375-8.

Alby 1993 {published data only}

* Alby JM, Cabane J, Ferreri M, Bougerol T. Efficacy and acceptability of tianeptine in major depressive disorder and in dysthymia (DSM-IIIIR) with somatic complaints: double blind study versus fluoxetine. *European Neuropsychopharmacology* 1993;**3**(3):333.

Banerji 1989 {published data only}

* Banerji JR, Brantingham P, McEwan GD, Mason J, Munt DF, Renton RL, et al. A comparison of alprazolam with amitriptyline

in the treatment of patients with neurotic or reactive depression. *Irish Journal of Medical Science* 1989;**158**(5):110-3.

Barnes 1977 {published data only}

* Barnes RJ. Clinical depression: a study of desipramine and amitriptyline in depressive neurosis. *Current Therapeutic Research* 1977;**22**(4):435-45.

Battegay 1985 {published data only}

* Battagay R, Hager M, Rauchfleisch U. Double-blind comparative study of paroxetine and amitriptyline in depressed patients of a university psychiatric outpatient clinic (pilot study).. *Neuropsychobiology* 1985;**13**(1-2):31-7.

Bennie 1984 {published data only}

* Bennie EH, Khan MC, Tyler SP, Siddiqui U, Ankier SI. Comparison of trazodone and mianserine in depressive illness. *Current Medical Research and Opinion* 1984;**9**(4):253-8.

Bertolino 1988 {published data only}

* Bertolino A, Crippa D, Di Dio S, Fichte K, Musmeci G, Porro V, et al. Rolipram versus imipramine in inpatients with major, "minor" or atypical depressive disorder: a double-blind double-dummy study aimed at testing a novel therapeutic approach. *International Clinical Psychopharmacology*, 1988;**3**(3):245-53.

Bilikiewicz 1971 {published data only}

* Bilikiewicz T, Bilikiewicz A. Results of treatment of dysthymic attacks with carbamazepine [Wyniki leczenia karbamazepina napadów dystymicznych]. *Neurologia i neurochirurgia polska* 1971;**5**(3):345-50.

Bornstein 1979 {published data only}

* Bornstein S. Cross-over trial comparing the antideressant effects of amineptine and maprotiline. *Curr. Med. Res. Opin.* *Current Medical Research and Opinion* 1979;**6**(2):107-10.

Buck 1980 {published data only}

* Buck RP. Analysis of controlled studies comparing mianserin and clomipramine [Analyse des études contrôlées comparant la miansérine et la clomipramine]. *L'Encéphale* 1981;**7**(4 suppl):455-72.

Casacchia 1994 {published data only}

* Casacchia M, Bolino F, Marola W, Pirro R, Nivoli G, Rapisarda V, et al. Controlled multicentre study of teniloxazine in mild depression of the elderly. *New Trends in Experimental and Clinical Psychiatry* 1994;**10**(4):187-92.

Cecchini 1978 {published data only}

* Cecchini S, Petri P, Ardito R, Bareggi SR, Torriti A. A comparative double-blind trial of the new antidepressant caroxazone and amitriptyline. *Journal of International Medical Research* 1978;**6**(5):388-94.

De M. Lima 1997 {published data only}

* De Mendonça Lima CA, Vandel S, Bonin B, Bechtel P, Carron R. Maprotiline versus fluvoxamine: comparison of their effects on the hypothalamo-hypophyseal-thyroid axis [Maprotiline versus fluvoxamine: comparaison entre leurs actions sur

l'axe hypothalamohypophysothyroïdien]. *L'Encéphale*, 1997;**23**(1):48-55.

De Maio 1975 {published data only}

* De Maio D, Caponeri MA, Mellado C, Nielsen NP, Sciegghi G. [Scelta e modalità di uso dei farmaci antidepressivi in rapporto alla valutazione clinico-psicometrica dei diversi quadri clinici. Relazione presentata alla Tavola rotonda: " Aggiornamento sulla terapia delle depressione "]. XXXII Congresso nazionale della Società italiana di psichiatria (Bologna. 19-23 marzo 1975). 1975.

Desilverio 1970 {published data only}

* Desilverio RV, Rickels MD, Weise CC, Clark EL, Hutchinson J. Perphenazine-amitriptyline in neurotic depressed outpatients: a controlled collaborative study. *American Journal of Psychiatry* 1970;**127**(3):322-8.

Donbak 1995 {published data only}

* Donbak SO, Turkçapar MH, Kiliç EZ, Demirergi N, Akdemir A, Sirin A, et al. Moclobemide and sertraline in the treatment of depressive disorders: a comparative study. *Acta Psychiatrica Belgica* 1995;**95**(3):139-51.

DUAG1986 {published data only}

* Danish University Antidepressant Group. Citalopram: Clinical effect profile in comparison with clomipramine. A controlled multicenter study. *Psychopharmacology* 1986;**90**(1):131-8.

Dunbar 1985 {published data only}

* Dunbar GC, Naarala M, Hiltunen H. A double-blind group comparison of mianserin and treatment of mildly depressed psychiatric out-patients. *Acta Physiologica Scandinavica. Supplementum* 1985;**320**:60-6.

Dunner 1996 {published data only}

* Dunner DL, Schmaling KB, Hendrickson H, Becker J, Lehmen A, Bea C. Cognitive therapy versus fluoxetine in the treatment of dysthymic disorder. *Depression* 1996;**4**(1):34-41.

Dwivedi 1990 {published data only}

* Dwivedi VS, Berger AB, Khong TK, Hamilton BA, Jones PG, Brantingham P, et al. Depression in general practice: a comparison of flupenthixol dihydrochloride and dothiepin hydrochloride. *Current Medical Research and Opinion* 1990;**12**(3):191-7.

Faltus 1978 {published data only}

* Faltus F, Lanecková E, Malá H. A comparison of the antidepressive effects of danitracene and imipramine [Srovnání antidepressivního účinku danitracenu a imipraminu]. *Ceskoslovenska Psychiatrie* 1978;**74**(2):61-6.

Fann 1984 {published data only}

* Fann WE, Lyle FA, Higginbotham W. Nomifensine vs. imipramine in depressed patients. *Journal of Clinical Psychiatry* 1984;**45**(4 Sec 2):60-2.

Fontan 1991 {published data only}

* Fontan JM. Beneficial effects of a fixed combination of amino acids and B12 vitamin as an antidepressant therapy [Beneficios

del uso de una asociacion de aminoacidos y vitamina B12 como tratamiento coadyuvante del sindrome depresivo]. *Prensa Medica Argentina* 1991;**78**(8):415-9.

Forrest 1977 {published data only}

* Forrest A, Hewett A, Nicholson P. Controlled randomized group comparison of nomifensine and imipramine in depressive illness. *British Journal of Clinical Pharmacology* 1977;**4**(Suppl 2):215-20.

Goldberg 1977 {published data only}

* Goldberg HL, Finnerty RJ. Which tricyclic for depressed outpatients, imipramine pamoate or amitriptyline?. *Diseases of the Nervous System* 1977;**38**(10):785-9.

Goldstein 1982 {published data only}

* Goldstein SE, Birnbom F, Laliberte R. Nomifensine in the treatment of depressed geriatric patients. *Journal of Clinical Psychiatry* 1982;**43**(7):287-9.

Gonella 1990 {published data only}

* Gonella G, Ecari U. Fluvoxamine and imipramine in the treatment of depressive patients: a double-blind controlled study. *Current Medical Research and Opinion* 1990;**12**(3):177-84.

GPCT 1969 {published data only}

* General Practitioner Research Group. Chlordiazepoxide with amitriptyline in neurotic depression. *Practitioner* 1969;**202**(209):437-40.

Granier 1985 {published data only}

* Granier F, Girard M, Schmitt L, Boscredon J, Oules J, Escande M. Depression and anxiety: mianserin and nomifensine compared in a double-blind multicentre trial. *Acta Physiologica Scandinavica. Supplementum* 1985;**320**:67-74.

Hamilton 1989 {published data only}

* Hamilton BA, Jones PG, Hoda AN, Keane PM, Majid I, Zaidi SI. Flupenthixol and fluvoxamine in mild to moderate depression: a comparison in general practice. *Pharmatherapeutica* 1989;**5**(5):292-7.

Hyde 1983 {published data only}

* Hyde C, Goldberg D. Labelling and drug effects in the treatment of neurotic affective disorders: an experimental investigation. *Psychological Medicine* 1983;**13**(2):399-405.

James 1985 {published data only}

* James RT, Dean BC. Comparison of Limbitrol (Chlordiazepoxide/amitriptyline) and amitriptyline alone as a single night-time dose for the treatment of depression with anxiety. *Journal of International Medical Research* 1985;**13**(2):84-7.

Johnson 1979 {published data only}

* Johnson DA. A double-blind comparison of flupenthixol, nortriptyline and diazepam in neurotic depression. *Acta Psychiatrica Scandinavica* 1979;**59**(1):1-8.

Jonghe 1991 {published data only}

* de Jonghe F, Swinkels J, Tuijnman-Qua H. Randomized double-blind study of fluvoxamine and maprotiline in treatment of depression. *Pharmacopsychiatry* 1991;**24**(1):21-7.

Kleber 1979 {published data only}

* Kleber RJ. A double-blind comparative study of desipramine hydrochloride and diazepam in the control of mixed anxiety/depression symptomatology. *Journal of Clinical Psychiatry* 1979;**40**(4):165-70.

Kocur 1991 {published data only}

* Kocur J, Rydzynski Z, Duszyk S, Gruszczynski W, Trendak W. Fluoxetine (Prozac) in depression of adults.. 33rd Psychopharmacol. meeting, Jeseník Spa. 1991.

Kok 1995 {published data only}

* Kok LP, Tsoi WF. A controlled double-blind trial of moclobemide and imipramine in the treatment of depression. *Singapore Medical Journal* 1995;**36**(1):38-40.

Larsen 1991 {published data only}

* Larsen JK, Gjerris A, Holm P, Andersen J, Bille A, Christensen EM, et al. Moclobemide in depression: a randomized, multicentre trial against isocarboxazide and clomipramine emphasizing atypical depression. *Acta Psychiatrica Scandinavica* 1991;**84**(6):564-70.

Laws 1990 {published data only}

* Laws D, Ashford JJ, Anstee JA. A multicentre double-blind comparative trial of fluvoxamine versus lorazepam in mixed anxiety and depression treated in general practice. *Acta Psychiatrica Scandinavica* 1990;**81**(2):185-9.

Levin 1985 {published data only}

* Levin A, Schlebusch L. Mianserin is better tolerated and more effective in depression than a nomifensine-clobazam combination: a double-blind study. *Acta Psychiatrica Scandinavica. Supplementum* 1985;**320**:75-80.

Lindberg 1979 {published data only}

* Lindberg D, Ahlfors UG, Dencker SJ, Fruensgaard K, Hanstén S, Jensen K, et al. Symptom reduction in depression after treatment with L-tryptophan or imipramine. *Acta Psychiatrica Scandinavica* 1979;**60**(3):287-94.

Linnoila 1980 {published data only}

* Linnoila M, Seppala T, Mattila MJ, Vinko R, Pakarinen A, Skinner T. Clomipramine and doxepin in depressive neurosis. Plasma levels and therapeutic response. *Archives of General Psychiatry* 1980;**37**(11):1295-9.

Lomas 1977 {published data only}

* Lomas DM. A comparative study of maprotiline (Ludiomil) and viloxazine in the management of depressed patients in general-practice. *Journal of International Medical Research* 1977;**5**(Suppl 4):39-50.

Lonnqvist 1994 {published data only}

* Lonnqvist J, Sintonen H, Syvälahti E, Appelberg B, Koskinen T, Mannikko T, et al. Antidepressant efficacy and quality of life

in depression: a double-blind study with meclonemide and fluoxetine. *Acta Psychiatrica Scandinavica* 1994;**89**(6):363-9.

Mariategui 1978 {published data only}

* Mariategui J, Chavez H, Olivares A. Lofepamine: a comparative clinical study with amitriptyline [Loferamina: estudio clínico comparativo con amitriptilina]. *Acta Physiologica Latinoamericana* 1978;**24**(3):201-9.

Mountjoy 1977 {published data only}

* Mountjoy CQ, Roth M, Garside RF, Leitch IM. A clinical trial of phenelzine in anxiety depressive and phobic neuroses. *British Journal of Psychiatry* 1977;**131**:486-92.

Oules 1983 {published data only}

* Oules J, Boscredon J. Amineptine versus imipramine: a double-blind controlled study [Amineptine versus imipramine. Etude controlee a double insu]. *Presse Medicale* 1983;**12**(36):2243-6.

Pande 1996 {published data only}

* Pande AC, Birkett M, Fechner-Bates S, Haskett RF, Greden JF. Fluoxetine versus phenelzine in atypical depression. *Biological Psychiatry* 1996;**40**(10):1017-20.

Polaino 1991 {published data only}

* Polaino A, Barcelo M, Maldonado CL. Attributional versatility and pharmacological treatment of depression [Versatilidad atribucional y tratamiento farmacológico de la depresión]. *Revista de Psiquiatria de la Facultad de Medicina de Barcelona* 1991;**18**(4):173-84.

Ravenna 1980 {published data only}

* Ravenna C. Comparative trial of bromazepam and lorazepam in the management of neurotic depression [Confronto tra bromazepam e lorazepam nel trattamento della depressione nevrotica]. *Clinica Terapeutica* 1980;**95**(2):147-56.

Richards 1982 {published data only}

* Richards HH, Midha RN, Miller S. A double-blind study of trazodone and mianserin in the treatment of depression in general practice. *Journal of International Medical Research* 1982;**10**(3):147-56.

Rickels 1968 {published data only}

* Rickels K, Jenkins BW, Zamostien B, Raab E, Kanther M. Pharmacotherapy in neurotic depression.. *The Journal of Nervous and Mental Disease* 1968;**145**(6):475-85.

Rickels 1970 {published data only}

* Rickels K, Gordon PE, Weise CC, Bazilian SE, Feldman HS, Wilson DA. Amitriptyline and trimipramine in neurotic depressed outpatients: A collaborative study. *American Journal of Psychiatry* 1970;**127**(2):126-36.

Rickels 1971a {published data only}

* Rickels K, Laquer KG, Rial WY, Rosenfeld H, Schneider B, Wagner G. The combination of protriptyline and oxazepam in depressed neurotic general practice patients. *Psychosomatics* 1971;**12**(5):341-8.

Rickels 1971b {published data only}

* Rickels K, Gordon PE, Jenkins EW, Sablosky L, Vlachos VA, Weise CC, et al. Combination of meprobamate and benactyzine and constituents in neurotic depressed outpatients. *Diseases of the Nervous System* 1971;**32**(7):457-7.

Rickels 1972 {published data only}

* Rickels K, Hutchison JC, Weise CC, Csanalosi I, Chung HR, Case WG. Doxepin and amitriptyline-perphenazine in mixed anxious-depressed outpatients: a collaborative controlled study. *Psychopharmacologia* 1972;**23**(4):305-18.

Russel 1978 {published data only}

* Russel GF, Niaz U, Wakeling A, Slade PD. Comparative double-blind trial of mianserin hydrochloride (organon GB94) and diazepam in patients with depressive illness. *British Journal of Clinical Pharmacology* 1978;**5**(Suppl 1):57-65.

Schweitzer 1989 {published data only}

* Schweitzer I, Tiller J, Maguire K, Davies B. Treatment of atypical depression with moclobemide: A sequential double-blind controlled study. *International Journal of Clinical Pharmacology Research* 1989;**9**(2):111-7.

Sederberg-Olsen 1981 {published data only}

* Sederberg-Olsen P, Lauritsen B, Husfeldt P, Ronne H, Ekstrom K, Bjorndal F, et al. Treatment of depressive states in general practice. Controlled trials of the efficacy of maprotiline (Ludiomil) and flupentixol (Fluanxol) [Depressive tilstande, forekomst og behandling i almen praksis. Randomiseret undersogelse over effekten af maprotilin (Ludiomil) og flupentiksol (Fluanxol)]. *Ugeskr laeger*, 1981;**143**(22):1383-7.

Shaw 1981 {published data only}

* Shaw SH. Management of depressive neurosis. *Practitioner* 1981;**225**(1352):228-30.

Singh 1988 {published data only}

* Singh AN, Nair NP, Suranyi-Cadotte B, Schartz G, Lizondo E. A double-blind comparison of alprazolam and amitriptyline hydrochloride in the treatment of nonpsychotic depression. *Canadian Journal of Psychiatry* 1988;**33**(3):218-22.

Sletvold 1989 {published data only}

* Sletvold H, Gøtestam KG. Placebo and antidepressive effects: Zimelidine and doxepin in a double-blind extended placebo study on outpatients with minor depression. *European Journal of Psychiatry* 1989;**3**(3):151-6.

Stratta 1991 {published data only}

* Stratta P, Bolino F, Cuppillari M, Casacchia M. A double-blind parallel study comparing fluoxetine with imipramine in the treatment of atypical depression. *International Clinical Psychopharmacology*, 1991;**6**(3):193-6.

Szegedi 1997 {published data only}

* Szegedi A, Wetzel H, Angersbach D, Dunbar GC, Schwarze H, Philipp M, et al. A double blind study comparing paroxetine and maprotiline in depressed outpatients. *Pharmacopsychiatry* 1997;**30**(3):97-105.

Szegedi A, Wetzel H, Angersbach D, Philipp M, Benkert O. Response to treatment in minor and major depression: results of a double blind comparative study with paroxetine and maprotiline. *Journal of Affective Disorders* 1997;**45**(3):167-71.

Tiller 1989 {published data only}

* Tiller J, Schweitzer I, Maguire K, Davies B. Is Diazepam an antidepressant?. *British Journal of Psychiatry* 1989;**155**:483-9.

Toru 1976 {published data only}

* Toru M, Moriya H, Yamamoto K, Shimazono Y. A double-blind comparison of sulpiride with chlordiazepoxide in neurosis. *Folia Psychiatrica Neurologica Japonica* 1976;**30**(2):153-64.

Tudor 1994 {published data only}

* Tudor S, Zaharia M. Comparative study of the treatment with tetracyclic and tricyclic antidepressants with minor depressive disorders. *Romanian Journal of Neurology and Psychiatry* 1994;**32**(3):185-98.

Valle-Jones 1983 {published data only}

* Valle-Jones JC, Craven JR, Wallis TD, Schiff AA. Mixed anxiety/depressive illness in general practice. A therapeutic comparison of nomifensine with fluphenazine/nortriptyline. *Acta Psychiatrica Scandinavica* 1983;**68**(6):494-500.

Van Moffaert 1983 {published data only}

* Van Moffaert M, Diereck M, De Meulemeester F, Vereecken A. Treatment of depressive anxiety states associated with psychosomatic symptoms A double-blind multicentre clinical study: mianserin versus melitracen-flupentixol. *Acta Psychiatrica Belgica* 1983;**83**(5):525-39.

Van Moffaert 1989 {published data only}

* Van Moffaert M, Vogels C, Beckers G, Vereecken A, Dermaux P, Wolfrum C. Moclobemide versus amitriptyline in the treatment of depression: two double blind multicenter studies in Belgium. *New Trends in Experimental and Clinical Psychiatry* 1989;**5**(3):167-77.

Young 1976 {published data only}

* Young PR, Hughes WC, Lader MH. A controlled comparison of flupentixol and amitriptyline in depressed outpatients. *BMJ* 1976;**1**(6018):1116-8.

Young 1979 {published data only}

* Young JP, Lader MH, Hughes WC. Controlled trial of trimipramine, monoamine oxidase inhibitors, and combined treatment in depressed outpatients. *BMJ* 1979;**2**(6201):1315-7.

Additional references

Akiskal 1983

Akiskal HS. Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. *American Journal of Psychiatry* 1983;**140**(1):11-20.

Anderson 1994

Anderson IM, Tomenson BM. The efficacy of selective serotonin re-uptake inhibitors in depression: a meta-analysis

of studies against tricyclic antidepressants. *Journal of Psychopharmacology* 1994;**8**(4):238-49.

APA 1968

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-II). 2nd Edition. Washington, DC: American Psychiatric Association, 1968.

APA 1980

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III). 3rd Edition. Washington, DC: American Psychiatric Association, 1980.

APA 1987

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

APA 1994

American Psychiatric Association. Diagnostic & Statistical Manual of Mental Disorders. 4th Edition. Washington, DC: American Psychiatric Association, 1994.

Churchill 1996

Churchill R. A systematic review and meta-analysis of the effects of pharmacotherapy and psychotherapy for the treatment of depression in primary care: A preliminary report. MSc dissertation. LSHTM. A preliminary report. MSc dissertation, LSHTM 1996.

Hazell 1995

Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *BMJ* 1995;**310**(6984):897-901.

Hotopf 1997

Hotopf M, Hardy R, Lewis G. Discontinuation rates of SSRIs and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. *British Journal of Psychiatry* 1997;**170**:120-7.

Howland 1991

Howland RH. Pharmacotherapy of dysthymia: a review. *Journal of Clinical Psychopharmacology* 1991;**11**(2):83-92.

Kessler 1994

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* 1994;**51**(1):8-19.

Lima 2001

Lima MS, Moncrieff J. A comparison of drugs versus placebo for the treatment of dysthymia. *Cochrane Library* 2001, Issue 3.

Magni 1988

Magni G, Garreau M, Orofiamma B, Palminteri R. Fengabine, a new GABA-mimetic agent in the treatment of depressive disorders: an overview of six double-blind studies versus tricyclics. *Neuropsychobiology* 1988;**20**(3):126-31.

Mulrow 1999

Mulrow CD, Williams JW Jr, Trivedi M, et al. Treatment of depression: Newer pharmacotherapies. Evidence Report/Technology Assessment No. 7. Rockville, MD: Agency for Health Care Policy and Research, 1999.

Song 1993

Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, et al. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *VMJH* 1993;**306**(6879):683-7.

Weissman 1988

Weissman MM, Leaf PJ, Bruce ML, Florio L. The epidemiology of dysthymia in five communities: rates, risks, comorbidity and treatment. *American Journal of Psychiatry* 1988;**145**(7):815-9.

WHO 1978

World Health Organization. The ninth revision of the international classification of diseases and related health problems (ICD-9). 9th Edition. Geneva: World Health Organization, 1978.

WHO 1992

World Health Organization. The tenth revision of the international classification of diseases and related health problems (ICD-10). 10th Edition. Geneva: World Health Organization, 1992.

WPA 1995

WPA Dysthymia Working Group. Dysthymia in clinical practice. *British Journal of Psychiatry* 1995;**166**:174-83.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bakish 1993

Methods	Randomised: yes, but gives no information on allocation concealment. Blindness: double-blind Duration: 7 weeks Design: parallel groups study Analysis: non intention-to-treat	
Participants	Diagnosis: primary dysthymia (DSM-III) Age: mean = 37.6 years Sex: 48% females Number: 50 Setting: outpatients History: mean age of onset of symptoms=26.4 yrs, durations of present episode=5.7 years	
Interventions	1. Ritanserin (n=17); 50 mg/day 2. Imipramine (n=16); 200 mg/day	
Outcomes	USED: drop-outs OUTCOMES UNABLE TO USE: HAM-D (SD not provided); CGI results (no figures).	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Boyer 1996

Methods	Randomised: yes, but gives no information on allocation concealment. Blindness: double-blind	
---------	---	--

Pharmacotherapy for dysthymia (Review)

Boyer 1996 (Continued)

Duration: 3 months
Design: parallel groups multicenter study
Analysis: ITT for most of the outcomes

Participants	Diagnosis: dysthymia or dysthymia with major depression (DSM-III-R) Age: mean 48 years Sex: more than 70% of females in all groups Number: 323 Setting: outpatients
Interventions	1. Amisulpride (n=104); dose 50 mg/day 2. Amineptine (n=111); dose 200 mg/day
Outcomes	USED: responders (CGI); Drop-outs; Side effects OUTCOMES UNABLE TO USE: Improvement on MADRS; SANS and SET at end-point
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Geisler 1992

Methods	Randomised: yes, but details not provided Blindness: double blind Duration: 6 weeks Design: 2 parallel groups Analysis: non intention-to-treat
Participants	Diagnosis: dysthymia (DSM-III) Age: mean 48 Sex: 73% females Number: 70 Setting: outpatients from general practice
Interventions	1. Ritanserin (n=33); mean dose 7.4 mg 2. Flupenthixol (n=37); mean dose 1.3 mg
Outcomes	USED: dropouts OUTCOMES UNABLE TO USE: HAM-D and CGI scores (number of CGI responders not provided); side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Guelfi 1989

Methods	Randomised: yes, but details not provided Blindness: double-blind Duration: 6 weeks Design: 2 parallel groups, multicenter Analysis: completer analysis and ITT
Participants	Diagnosis: dysthymia (DSM-III) Age: mean 43.5 years Sex: 68% females Number: 265 Setting: outpatients History: average duration of current episode 11 weeks
Interventions	1. Tianeptine (n=135); mean dose 37.5 mg/day 2. Amitriptyline (n=130); mean dose 75 mg/day
Outcomes	USED: responders (improvement of at least 50% on MADRS); dropouts OUTCOMES UNABLE TO USE: MADRS, HAM-D, Hopkins Symptoms check-list and Check-list for Evaluation of Somatic Symptoms (CHESS) scores.
Notes	Control for baseline differences. Withdraws symptoms were assessed 8 days after discontinuation of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hellerstein 1994

Methods	Randomised: medication bottles randomly assigned using a random numbers chart. The person who conducted this scheme was not involved in patient recruitment or treatment. Blindness: open label trial Duration: 3 months, with follow up at 5 months Design: 2 parallel groups, patients unable to tolerate a 12 week trial of one medication because of side effects were crossed over to the other medication Analysis: non intention-to-treat
Participants	Diagnosis: double depression (DSM-III-R) Age: mean 38 years Sex: 78% females Number: 18 Setting: outpatients History: 50% reported onset of illness in childhood (age lower than 13) and 6 as teenagers
Interventions	1. Fluoxetine (n=8); mean dose 40.8 mg/day 2. Trazodone (n=10); mean dose 300 mg/day
Outcomes	USED: responders (50% or greater decrease from initial HAM-D score and score 1 or 2 on item 2 of CGI); HAM-D scores; dropouts

Hellerstein 1994 (Continued)

OUTCOMES UNABLE TO USE: SCL-58 scores

Notes	Patients were extracted from a larger pool of 38 subjects (see Rosenthal 1992).	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Leon 1994

Methods	Randomised: yes. The allocation was performed by a person who was not involved with recruitment of patients. Blindness: double-blind Duration: 4 weeks Design: 2 parallel groups Analysis: non intention-to-treat	
Participants	Diagnosis: 'pure' dysthymia (DSM-III-R) Age: range 18-60 years Sex: 94% females Number: 80 Setting: outpatients from a psychiatric hospital and primary care practice History: average duration of illness 16 years	
Interventions	1. Amisulprida (n=40); 50 mg/day 2.Viloxacina (n=40); 150 mg/day	
Outcomes	USED: clinical response (full remission or good improvement on psychiatrist assessment at end point); dropouts OUTCOMES UNABLE TO USE: HAM-D, Widlocher and SANS scores	
Notes	Withdraws were replaced.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Otero 1994

Methods	Randomised: yes, but details not provided Blindness: open label trial Duration: 4 weeks Design: 2 parallel groups, with 3 months follow up Analysis: non information available	
Participants	Diagnosis: dysthymia (DSM-III-R) Age: mean 42 years Sex: 77% females Number: 60	

Pharmacotherapy for dysthymia (Review)

Otero 1994 (Continued)

Setting: patients from a mental health center in Madrid

Interventions	1. Fluoxetine (n=29); dose 20 mg/day 2. Fluoxetine + bentazepam (n=31); dose 20 mg/day + 50 mg/day, respectively
Outcomes	USED: side effects; dropouts OUTCOMES UNABLE TO USE: HAM-D, HAM-A and STAI scores
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rosenthal 1992

Methods	Randomised: yes, but details not provided Blindness: open label trial Duration: 3 months, with follow up at 5 months Design: 2 parallel groups, patients unable to tolerate a 12 week trial of one medication because of side effects were crossed over to the other medication Analysis: non intention-to-treat
Participants	Diagnosis: 'pure' dysthymia (DSM-III-R) Age: mean 42.3 years Sex: 70% females Number: 20 Setting: outpatients History: 30% reported onset of illness in childhood (age lower than 13)
Interventions	1. Fluoxetine (n=12); mean dose 30.9 mg/day 2. Trazodone (n=8); mean dose 241.7 mg/day
Outcomes	USED: responders (50% or greater decrease from initial HAM-D score and score 1 or 2 on item 2 of CGI); dropouts OUTCOMES UNABLE TO USE: HAM-D and SCL-58 scores
Notes	Patients were extracted from a larger pool of 38 subjects (see Hellerstein 1994).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Salzmann 1995

Methods	Randomised: according to randomisation lists (blocks of 6) Blindness: double-blind
---------	---

Pharmacotherapy for dysthymia (Review)

Salzmann 1995 (Continued)

Duration: 6 weeks
Design: 2 parallel groups, multicenter
Analysis: non ITT

Participants	Diagnosis: dysthymia (DSM-III) Age: mean 55 years Sex: 81% females Number: 67 Setting: outpatients
Interventions	1. Minaprine (n=33); mean dose 200 mg/day 2. Imipramine (n=34); mean dose 100 mg/day
Outcomes	USED: responder (at least 50% of improvement in HAM-D); dropouts; adverse events OUTCOMES UNABLE TO USE: HAM-D, CGI, Figure Symbol Test and Subjective Well-being Scale scores
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Smeraldi 1996

Methods	Randomised: yes, but details not provided Blindness: double-blind Duration: 12 weeks (1 week of single-blind placebo run-in) Design: 2 parallel groups, multicentre study; 1-week single-blind placebo run-in to exclude placebo responders Analysis: non intention-to-treat
Participants	Diagnosis: dysthymia (DSM-III-R; 266 patients) or major depression in partial remission (15 patients) Mean age: 49 years Number: 281 (13 post-randomization exclusion). Sex: 67% females Setting: outpatients History:
Interventions	1. Amisulpride (n=142); 50 mg/day 2. Fluoxetine (n=139); 20 mg/day
Outcomes	USED Responders (reduction equal or greater than 50% in MADRS scores from baseline to endpoint) Dropouts
Notes	In order to use data for dysthymic patients only it was not possible to use ITT analysis. Results were similars if patients with major depression were included in the analysis. However, data on dropouts include 15 major depressive patients in partial remission.

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Pharmacotherapy for dysthymia (Review)

Smeraldi 1996 (Continued)

Allocation concealment?	Unclear risk	B - Unclear
-------------------------	--------------	-------------

Stewart 1989

Methods	Randomisation: yes, but gives no information on allocation concealment. Blindness: double-blind Duration: 6 weeks Design: parallel groups Analysis: non intention-to-treat
Participants	Diagnostic: dysthymic disorder without MD (DSM-III), 80% of them with reactivity of mood (atypical depression) Age and sex: not provided for dysthymic patients; 61% females and 36 yrs mean age for the whole sample Number: 57 Setting: outpatients History: patients reported having been depressed virtually their entire adult lives
Interventions	1. Imipramine (n=12); 265 mg/day 2. Phenelzine (n=18); 73 mg/day
Outcomes	USED: responder (CGI 1 or 2) OUTCOMES UNABLE TO USE: dropouts; HAM-D; SCL-90; SADS-C; symptom scale; atypical items score; personality scales; chronicity scale.
Notes	47 dropouts, without information regarding diagnostic and drug groups, making impossible to perform intention-to-treat analysis of outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Thase 1996

Methods	Randomised: by a computer-generated schedule, but gives no information on allocation concealment. Blindness: double-blind Duration: 12 weeks (preceded by 1 week placebo washout). Design: parallel groups, multicenter Analysis: patients who had at least 1 postrandomization efficacy evaluation
Participants	Diagnosis: primary dysthymia (DSM-III-R) Age: 25-65, mean: 42. Number: 416 (6 post-randomization exclusion). 412 received at least one dose of double-blind medication. Sex: 65% females Setting: community History: average age of onset: 12 years, average duration of illness: 30.6(10.4) years.
Interventions	1. Sertraline (n=134); 139.6 mg/day

Thase 1996 (Continued)

2. Imipramine (n=136); 199 mg/day

Outcomes	<p>USED</p> <p>Dropouts; Full remission (DSM-III-R criteria for dysthymia); Responder (CGI improvement 1 or 2); Quality of Life Enjoyment and Satisfaction Questionnaire (results described).</p> <p>OUTCOMES UNABLE TO USE</p> <p>Level of depression (HAM-D 17 and 29 item; Hopkins symptom Checklist; MADRS; ETC) - skewed data.; IDS-SR; SAS-SR; Longitudinal Interval Scale Follow-up Evaluation; side effects.</p>
Notes	<p>The mean baseline scores were higher for imipramine patients than for those treated with sertraline or placebo. Six patients were excluded after randomization, with no information about their group, making impossible to perform a real intention-to-treat analysis of the main outcomes.</p> <p>Authors contacted for further information</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Vallejo 1987

Methods	<p>Randomised: yes, but details not provided</p> <p>Blindness: double-blind</p> <p>Duration: 6 weeks</p> <p>Design: 2 parallel groups</p> <p>Analysis: non intention-to-treat</p>
Participants	<p>Diagnosis: dysthymia (DSM-III)</p> <p>Age: 40.2 years</p> <p>Sex: 87.5% females</p> <p>Number: 39</p> <p>Setting: outpatients</p>
Interventions	<p>1. Imipramine (n=20); 250 mg/day</p> <p>2. Phenelzine (n=19); 75 mg/day</p>
Outcomes	<p>USED: dropouts</p> <p>OUTCOMES UNABLE TO USE: HAM-D, Zung and Eysenck Personality Inventory scores.</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Versiani 1997

Methods	<p>Randomised: central randomization, with coded blisters for each number. The trialists were not aware about the allocation group until the trial was finished.</p>
---------	--

Pharmacotherapy for dysthymia (Review)

Versiani 1997 (Continued)

Blindness: double-blind
Duration: 8 weeks
Design: multicenter, international, RCT
Analysis: intention-to-treat for some outcomes. For the most: standard analysis (excluding those with major protocol violations and patients who were treated less than 3 weeks)

Participants	Diagnosis: dysthymia (DSM-III-R), primary type, with severity at baseline at least moderate on CGI Age: 18-65 (mean= ~ 42 years) Sex: 70% females Number: 315 Setting: outpatients History: mean duration of illness = 11 years
Interventions	1. Moclobemide (n=108); 675 mg/day 2. Imipramine (n=103); 220 mg/day
Outcomes	USED: responder (no longer met DSM-III-R criteria for dysthymia); Full remission (symptom criteria no longer met plus absence of depressed mood and HAMD endpoint 17-item score below 5); Dropouts; Adverse events. OUTCOMES UNABLE TO USE: HAM-D change from baseline (skewed data), SLC-90, CGI.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

* Non Intention-to-treat analysis

HDS = Hamilton Depression Rating Scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Akiskal 1993	Study evaluating the use of fluoxetine and TCA in dysthymic patients but does not provide information about randomisation.
Alby 1993	Clinical study comparing tianeptine and fluoxetine in major depressive disorder and dysthymia; no information about randomisation procedures and no separate data for dysthymic patients.
Banerji 1989	RCT, double-blind study evaluating alprazolam and amitriptyline in depressed patients, but provides data only for neurotic-reactive depression.
Barnes 1977	RCT comparing desipramine versus amitriptyline in depressive neurosis: does not specify duration of illness.
Battegay 1985	RCT, double-blind study of paroxetine and amitriptyline in depressed patients, but provides data only for neurotic-reactive depression.
Bennie 1984	RCT comparing mianserine and trazodone in depressive illness, but does not specify duration of illness.

Study	Reason for exclusion
Bertolino 1988	A randomised double-blind double-dummy study comparing rolipram versus imipramine in patients with major, minor and atypical disorder. Does not give separate data for dysthymic patients.
Bilikiewicz 1971	Non-randomised study evaluating the use of carbamazepine.
Bornstein 1979	RCT, double-blind, cross-over study comparing amineptine and maprotiline in depressive illness, but provides only data for neurotic-reactive depression.
Buck 1980	Clinical study comparing mianserine and clomipramine in endogenous and exogenous depression; no information about randomisation.
Casacchia 1994	RCT comparing teniloxazine with minaprine for mild depression in the elderly but does not provide separate data for dysthymic patients.
Cecchini 1978	RCT, double-blind study evaluating amitriptyline and caroxazone in neurotic and endogenous depression; does not specify duration of illness.
De M. Lima 1997	RCT evaluating the use of maprotiline and fluvoxamine in depressive illness; no separate data for dysthymic patients.
De Maio 1975	Clinical study comparing amitriptyline with dibenzapine in neurotic depression; does not specify duration of illness or randomisation procedures.
Desilverio 1970	RCT, double-blind study assessing perphenazine and amitriptyline in depressive illness but provide data only for neurotic depression.
Donbak 1995	RCT, compared the efficacy and tolerability of moclobemide and sertraline, but does not provide separate data for minor depressive patients.
DUAG1986	RCT, double-blind multicenter study comparing citalopram versus clomipramine for treating endogenous and non-endogenous inpatients.
Dunbar 1985	RCT, double-blind, evaluating the use of mianserin and clomipramine in the treatment of mildly depressed psychiatric out-patients, but duration of illness was less than 1 year for most of patients.
Dunner 1996	RCT comparing cognitive therapy versus fluoxetine in the treatment of dysthymic disorder.
Dwivedi 1990	Rct, double-blind study comparing flupenthixol and dothiepin in mild or moderate depression; no specification of duration of illness.
Faltus 1978	Study comparing imipramine versus danitracen, but there is no mention of a randomised selection of patients.
Fann 1984	A double-blind random assignment study comparing nomifensine vs. imipramine in depressed inpatients, but the average duration of illness was 31 weeks for nomifensine and 24 weeks for imipramine.
Fontan 1991	RCT evaluating the combination of aminoacids and B12 vitamin added to Amitriptyline but not specifying the duration or severity of depressive illness.
Forrest 1977	Rct, double-blind study comparing nomifensine and imipramine in depressive illness; no give separate data for dysthymic patients.
Goldberg 1977	RCT evaluating imipramine and amitriptyline in depressed outpatients but few patients had 3 years or more of duration of illness.

Study	Reason for exclusion
Goldstein 1982	RCT, double-blind study assessing nomifensine and amitriptyline in patients with endogenous and reactive depression; no separate data for dysthymic patients..
Gonella 1990	RCT, double-blind study comparing fluvoxamine versus imipramine in the treatment of depressive patients; no separate data for dysthymic patients.
GPCT 1969	RCT assessing combination of chlordiazepoxide and amitriptyline for neurotic depression.
Granier 1985	RCT, double-blind study comparing mianserin with nomifensine in depression and anxiety.
Hamilton 1989	RCT assessing flupenthixol and fluvoxamine in mild and moderate depression; 33 from 72 patients had duration of illness less than 4 weeks.
Hyde 1983	RCT, factorial design, double blind study comparing diazepam and nortriptyline for the treatment of anxiety-depressive neuroses. Only 24 patients from 118 had a duration of illness higher than 1 year.
James 1985	RCT, double-blind study comparing Limbitrol (chlordiazepoxide/amitriptyline) and amitriptyline for the treatment of depression with anxiety but does not specify duration of illness.
Johnson 1979	RCT, double-blind study assessing flupenthixol, nortriptyline and diazepam in neurotic depression.
Jonghe 1991	RCT, double-blind study evaluating maprotiline and fluvoxamine in treatment of depression; no separate information for dysthymic patients.
Kleber 1979	RCT double-blind study assessing desipramine and diazepam in mixed anxiety/depressive illness.
Kocur 1991	Clinical study comparing fluoxetine with imipramine on the treatment of depression; no specification of duration of illness or randomization procedures.
Kok 1995	A controlled double-blind trial comparing moclobemide and imipramine; no separate data for minor depression and duration of illness was less than 2 years.
Larsen 1991	RCT, double-blind study evaluating the use of moclobemide, isocarboxazide and clomipramine in patients with atypical depression but does not providing separate data for dysthymic patients.
Laws 1990	RCT, double-blind study evaluating fluvoxamine with lorazepam in mixed anxiety and depression.
Levin 1985	RCT, double-blind study comparing nomifensine and clobazam versus mianserin in depressive illness but provides data only for neurotic depression.
Lindberg 1979	RCT, double-blind study comparing L-tryptophan and imipramine in non-endogenous depressed patients.
Linnoila 1980	RCT, double-blind study evaluating tryptophan, clomipramine and doxepin in neurotic depression but the duration of illness was less than 4 months.
Lomas 1977	RCT comparing maprotiline and viloxazine; patients were not defined as dysthymics.
Lonqvist 1994	RCT, double-blind study assessing fluoxetine and moclobemide in depression but does not provide separate data for dysthymic patients.
Mariategui 1978	Clinical study evaluating loferamine and amitriptyline in neurotic and endogenous depression; no specification of duration of illness or randomisation procedures.
Mountjoy 1977	RCT double-blind study evaluating phenelzine, diazepam and placebo in neurotic patients; no information about duration of illness.

Study	Reason for exclusion
Oules 1983	RCT double-blind comparing amineptine and imipramine in neurotic disorder.
Pande 1996	RCT comparing fluoxetine versus phenelzine in atypical depression but does not provide separate data for dysthymic patients.
Polaino 1991	Non-randomised study comparing lofepramine and maprotiline in depressed patients.
Ravenna 1980	Clinical study comparing bromazepan and larazepan in neurotic depression; no information about randomization.
Richards 1982	RCT, double blind, three parallel groups study (trazodone, mianserin, diazepam) on depression, does not specify duration of illness.
Rickels 1968	RCT, double-blind study evaluating fluphenazine and amitriptyline in neurotic depressed outpatients.
Rickels 1970	RCT, double-blind study comparing amitriptyline, trimipramine and placebo in neurotic depressed outpatients.
Rickels 1971a	RCT, double-blind study assessing the combination of protriptyline and oxazepam in neurotic depression.
Rickels 1971b	Rct, double-blind study evaluating meprobamate and benactyzine in neurotic depressed patients.
Rickels 1972	RCT evaluating doxepin versus amitriptyline-perphenazine in mixed anxiety depression.
Russel 1978	RCT, double-blind study evaluating mianserin and diazepam in moderate to severe depression.
Schweitzer 1989	Non-randomised study of moclobemide and diazepam in patients with atypical depression.
Sederberg-Olsen 1981	RCT, double-blind study assessing maprotiline with flupenthixol in non endogenous depression.
Shaw 1981	Rct evaluating amitriptyline and butriptyline in depressive neurosis; no information about duration of illness.
Singh 1988	RCT, double-blind study evaluating amitriptyline and alprazolam in nonpsychotic depression but provides data only for neurotic depression.
Sletvold 1989	RCT, double-blind study evaluating zimelidine and doxepin in outpatients with minor depression, but does not specify duration of illness.
Stratta 1991	RCT, double-blind study evaluating fluoxetine and imipramine in atypical depression.
Szegedi 1997	RCT comparing paroxetine and maprotiline for major and minor depression (RDC criteria). Duration of illness for minor depressive patients not specified.
Tiller 1989	Double-blind sequential trial comparing diazepam with moclobemide in patients with atypical depression.
Toru 1976	RCT, double-blind study assessing sulpiride and chlordiazepoxide in neurosis; patients were not defined as dysthymics.
Tudor 1994	RCT comparing imipramine and mianserine in patients with minor depressive disorders; no separate data for dysthymic patients. Only 35 from 100 had dysthymia.
Valle-Jones 1983	RCT evaluating nomifensine versus fluphenazine/nortriptyline in mixed anxiety/depressive states.

Study	Reason for exclusion
Van Moffaert 1983	RCT, double-blind study evaluating mianserin and melitracen-flupentixol in depression/anxiety states.
Van Moffaert 1989	Non-randomised study comparing moclobemide and amitriptyline in the treatment of depression but does not specify the duration of illness.
Young 1976	RCT comparing flupentixol and amitriptyline for mild or moderately severe depression. Mean duration of illness was 18 months in the flupentixol group.
Young 1979	RCT, double-blind study evaluating the use of trimipramine, monoamine oxidase, and combined treatment in depressed outpatients; the average duration of illness was 12-17 months.

DATA AND ANALYSES

Comparison 1. SSRIs vs TCA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non treatment response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Sertraline vs Imipramine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Absence of full remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Sertraline vs Imipramine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Number of dropouts	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Sertraline vs Imipramine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 SSRIs vs TCA, Outcome 1 Non treatment response.

Study or subgroup	SSRI n/N	TCA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 Sertraline vs Imipramine				
Thase 1996	55/134	49/136		1.14[0.84,1.54]

Analysis 1.2. Comparison 1 SSRIs vs TCA, Outcome 2 Absence of full remission.

Analysis 1.3. Comparison 1 SSRIs vs TCA, Outcome 3 Number of dropouts.

Comparison 2. MAOIs vs TCA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non treatment response	2	241	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.45, 2.31]
1.1 Phenelzine vs Imipramine	1	30	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.63, 5.59]
1.2 Moclobemide vs Imipramine	1	211	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.02]
2 Absence of full remission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Moclobemide vs Imipramine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Number of dropouts	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Moclobemide vs Imipramine	1	211	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.65]
3.2 Phenelzine vs Imipramine	1	39	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.20, 3.07]
4 Number of people reporting adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Moclobemide vs Imipramine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 MAOIs vs TCA, Outcome 1 Non treatment response.

Analysis 2.2. Comparison 2 MAOIs vs TCA, Outcome 2 Absence of full remission.

Analysis 2.3. Comparison 2 MAOIs vs TCA, Outcome 3 Number of dropouts.

Analysis 2.4. Comparison 2 MAOIs vs TCA, Outcome 4 Number of people reporting adverse events.

Comparison 3. OTHER DRUGS vs TCA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non treatment response	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Tianeptine vs Amitriptyline	1	265	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.95, 1.86]
1.2 Minaprine vs Imipramine	1	67	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.33]
3 Number of dropouts	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Ritanserin vs Imipramine	1	33	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.16, 1.99]
3.2 Tianeptine vs Amitriptyline	1	265	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.86, 2.34]
3.3 Minaprine vs Imipramine	1	67	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.67]
4 Number of people reporting adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Minaprine vs Imipramine	1	67	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.44, 1.17]

Analysis 3.1. Comparison 3 OTHER DRUGS vs TCA, Outcome 1 Non treatment response.

Analysis 3.3. Comparison 3 OTHER DRUGS vs TCA, Outcome 3 Number of dropouts.

Analysis 3.4. Comparison 3 OTHER DRUGS vs TCA, Outcome 4 Number of people reporting adverse events.

Comparison 4. OTHER DRUGS vs SSRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non treatment response	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Trazodone vs Fluoxetine	2	38	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.81, 2.51]
1.2 Amisulpride vs Fluoxetine	1	253	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.20]
2 Changes from baseline on 21-item HAM-D	1	13	Mean Difference (IV, Fixed, 95% CI)	2.55 [-1.37, 6.47]
2.1 Trazodone vs Fluoxetine	1	13	Mean Difference (IV, Fixed, 95% CI)	2.55 [-1.37, 6.47]
3 Number of dropouts	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Trazodone vs Fluoxetine	2	38	Risk Ratio (M-H, Random, 95% CI)	2.59 [0.44, 15.32]
3.2 Fluoxetine + Bentazepan vs Fluoxetine	1	60	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 4.89]
3.3 Amisulpride vs Fluoxetine	1	281	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.52, 1.17]
4 Number of people reporting adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Fluoxetine + Bentazepan vs fluoxetine	1	60	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.46, 1.91]
4.2 Amisulpride vs Fluoxetine	1	278	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.89, 1.52]

Analysis 4.1. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 1 Non treatment response.

Analysis 4.2. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 2 Changes from baseline on 21-item HAM-D.

Analysis 4.3. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 3 Number of dropouts.

Analysis 4.4. Comparison 4 OTHER DRUGS vs SSRIs, Outcome 4 Number of people reporting adverse events.

Comparison 5. ADDITIONAL COMPARISONS BETWEEN ADS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non treatment response	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Amisulpride vs Amineptine	1	215	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.25]
1.2 Amisulpride vs Viloxacina	1	80	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.25, 0.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of dropouts	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Amisulpride vs Amineptine	1	215	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.41]
2.2 Ritanserin vs Flupenthixol	1	70	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.17, 7.52]
2.3 Amisulprida vs Viloxacina	1	80	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.46, 4.91]
3 Number of people reporting adverse events	1	215	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.70, 1.11]
3.1 Amisulpride vs Amineptine	1	215	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.70, 1.11]

Analysis 5.1. Comparison 5 ADDITIONAL COMPARISONS BETWEEN ADs, Outcome 1 Non treatment response.

Analysis 5.2. Comparison 5 ADDITIONAL COMPARISONS BETWEEN ADs, Outcome 2 Number of dropouts.

Analysis 5.3. Comparison 5 ADDITIONAL COMPARISONS BETWEEN ADs, Outcome 3 Number of people reporting adverse events.

Comparison 6. ANY ANTIDEPRESSANT vs IMIPRAMINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non treatment response	4	578	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.24]
1.2 Minaprine vs Imipramine	1	67	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Phenelzine vs Imipramine	1	30	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.63, 5.59]
1.4 Sertraline vs Imipramine	1	270	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.84, 1.54]
1.5 Moclobemide vs Imipramine	1	211	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.02]
2 Dropouts	5	620	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.43, 0.82]
2.1 Ritanserin vs Imipramine	1	33	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.16, 1.99]
2.3 Minaprimine vs Imipramine	1	67	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.67]
2.4 Sertraline vs Imipramine	1	270	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.30, 0.75]
2.5 Phenelzine vs Imipramine	1	39	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.20, 3.07]
2.6 Moclobemide vs Imipramine	1	211	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.65]

Analysis 6.1. Comparison 6 ANY ANTIDEPRESSANT vs IMIPRAMINE, Outcome 1 Non treatment response.

Analysis 6.2. Comparison 6 ANY ANTIDEPRESSANT vs IMIPRAMINE, Outcome 2 Dropouts.

WHAT'S NEW

Date	Event	Description
4 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 2003

Date	Event	Description
27 April 2003	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

MSL took up a position with Eli Lilly in 2003.

SOURCES OF SUPPORT

Internal sources

- Institute of Psychiatry - London, UK.

External sources

- CAPES (Ministry of Education - Brazil), Brazil.
- Medical Research Council, UK.
- Universidade Federal de Pelotas, Brazil.

NOTES

There has been a change to the title of this review. First publication of the review (in Issue 3, 2003) was entitled 'A comparison of active drugs for the treatment of dysthymia'.

INDEX TERMS**Medical Subject Headings (MeSH)**

Antidepressive Agents [*therapeutic use]; Dysthymic Disorder [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans