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Benefits and Risks of Pharmacotherapy for Dysthymia

A Systematic Appraisal of the Evidence

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Abstract

Background: Dysthymia is a prevalent form of subthreshold depressive disorder, associated with considerable disability and high co-morbidity. This paper systematically appraises the evidence for the efficacy and acceptability of the pharmacological treatment for this condition.

Methods: Randomised, controlled trials evaluating the efficacy of drug therapies for dysthymia were included. A comprehensive search of the literature was performed, aiming to avoid publication bias. Pooled relative risks (RR) and 95% CIs were calculated with the Random Effect Model method. The number needed to treat (NNT) and number needed to harm (NNH) were estimated for statistically significant results.

Results: Twenty-five trials were included for the main comparisons. Regarding placebo-controlled trials (n = 16), similar results were obtained in terms of efficacy for different groups of drugs, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and other drugs (sulpiride, amineptine, and ritanserin). The pooled RR for treatment response was 0.68 (95% CI 0.57–0.81) for TCA and the NNT was 4.3 (95% CI 3.2–6.5); 0.68 (95% CI 0.56–0.82) for SSRIs (NNT 5.1; 95% CI 3.9–7.7); 0.59 (95% CI 0.48–0.71) for MAOIs (NNT 2.9; 95% CI 2.2–4.3). Other drugs (amisulpride, amineptine and ritanserin) showed similar results. The equivalent efficacy between antidepressants as found in trials where active medications were compared confirmed the efficacy findings from placebo trials. In general, patients treated with a TCA were more likely to report adverse events, compared with placebo and SSRIs.

Conclusions: Pharmacotherapy for dysthymia appears to be an effective short-term treatment for dysthymic disorder. Newer antidepressants are equally effective and have better acceptability than TCAs, although their higher cost must be balanced against this assumed advantage.

Dysthymia is a prevalent depressive disorder, associated with increased healthcare utilisation and healthcare costs. Twenty years ago the nosological status of dysthymia was defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III.[1,2] Compared with major depressive states, symptoms of dysthymia are less severe, but more chronic. Marked disturbance of appetite and libido are uncommon[3] and patients may experience considerable disability.[4] The natural history of dysthymia is poor, with more than two-thirds of patients remaining symptomatic for one decade or more. Even with treatment, many patients experience incomplete recovery.[5]

It is established that antidepressants are an effective treatment for major depressive disorder. However, the pharmacological treatment of less severe subtypes of depression such as dysthymia is uncertain. In fact, systematic research on the psychopathology and treatment of this disorder has been accomplished only during the past two decades.[6]

The efficacy and acceptability of antidepressants in depression have been addressed in a recent systematic review.[7,8] This review included all placebo-controlled randomised trials, and the main findings support the use of antidepressants in dysthymia.

In this paper, we report an updated survey and critical appraisal of the literature, including trials where two or more compounds were compared in the treatment of dysthymia. The aim was to assess systematically the benefits and risks of pharmacotherapy for this disorder.

Methods

Search Strategy

A broad search strategy, which was used for the Cochrane review[7] was developed aiming to identify all relevant trials addressing the pharmacological treatment of dysthymia. For the purpose of this paper the search strategy has been extended to comparative trials and updated as follows. The following electronic databases were searched: Biological Abstracts (1984–2001); Medline (1966–Dec 2001); PSYCLIT (1974–Dec 2001); Embase (1980–Dec 2001); LILACS (1982–Dec 2001) and Cochrane Library (Cochrane Library, 2002). A search strategy was used searching these databases, containing the following specific terms: dysthymi* 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)))]. This search was then completed with scan of reference list of relevant articles.

Inclusion/Exclusion Criteria

Trials were eligible for inclusion if participants had a primary diagnosis of dysthymia, as defined by any structured diagnosis system, irrespective of gender, age or nationality. All pharmacological studies were eligible, including placebo-controlled trials and studies with direct comparisons between drugs. Any drugs used for the treatment of dysthymia were considered, including antidepressants (tricyclic and related antidepressant drugs [TCAs]; monoamine-oxidase inhibitors [MAOIs]; selective serotonin re-uptake inhibitor [SSRIs]); benzodiazepines, stimulants and miscellaneous drugs.

Studies were excluded if depression was secondary to other disorders, or where they included patients with dysthymia and major depression, but did not report the results for the two conditions separately.

Quality Assessment

Quality of trials was assessed using a criterion based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment.[9] Trials were considered with low risk of bias if they had adequate allocation concealment ('A' criteria) and with high risk of bias if an inadequate allocation of concealment was performed ('B' criteria). When there was no

doubt about the allocation concealment trials were classified as 'C'.

Analysis

Dichotomous outcomes were analysed by calculating relative risks (RR) and 95% CIs. The RRs from the individual trials were combined in a meta-analysis. Whenever possible, analyses were performed according to the 'intention to treat' principles, assuming that patients who did not complete the trial had no clinical response.

For significant results, the number needed to treat (NNT) to produce one outcome was calculated by combining the overall RR with an estimate of the prevalence of the event in the control group of the trials. The NNT is an estimate of the number of patients a clinician would have to treat in order to observe one outcome due to that treatment, and it is calculated by taking the reciprocal of the absolute risk reduction. For a highly effective treatment associated with a common outcome, the NNT will be low. Where the outcome is less common, or the treatment is less effective, the NNT will be higher. When the treatment causes harm, the NNT will be negative (number needed to harm – NNH).[10]

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

Heterogeneity was assessed by inspection of graphical presentations and the RRs obtained in subgroups. Review Manager 4.1 software developed by the Cochrane Collaboration was used to organise and process the results.

Results

Search

The search strategy generated 5513 references, 5232 of which were excluded because they did not meet the criteria for dysthymia or were not randomised, controlled trials. We found 114 papers describing placebo-controlled trials. A further 167 references were related to trials which compared at least two active drug treatments. The remaining studies were excluded because the participants were not definitely experiencing dysthymia or they did not describe appropriate methods of randomisation. Crossover trials, which do not provide data for the first phase, were not included in the analysis.

Overall, 25 trials with 4207 participants had available data that could be included. Table I shows the main characteristics of the placebo-controlled studies (n = 16).

Data from further three maintenance studies were not used because they used different randomisation schemes making it impossible to pool the results.[28-30]

Design and Settings

All studies included in this review used a parallel-group design, and most were double-blind. In nine studies at least two antidepressants were compared, with no placebo group. The duration of the trials ranged from 4–12 weeks. Studies were mainly conducted in North America or Europe, and only three trials included hospitalised patients.[16,17,25] The remainder studied outpatients from psychiatric clinics or primary care.

Participants

All trials used DSM-III[1] or DSM-III-R[11] criteria for the diagnosis of dysthymia. Selected populations were comparable across trials, which involved mainly adult outpatients. The number of

Table I. Methodological characteristics of randomised placebo-controlled trials in the pharmacological treatment of dysthymia

Reference	Methods	Participants	Interventions (daily dose, no. of patients randomised)	Main efficacy outcome
Stewart et al.[12]	Double-blind, duration 6wk, non-ITT analysis	21 outpatients with pure dysthymia (DSM-III), mean age 40y	Desipramine (279mg, n = 9) Placebo (n = 9)	Responders (CGI 1 or 2)
Reyntjens et al.[13]	Double-blind, duration 5–6wk, non-ITT analysis	93 adult dysthymic patients (DSM-III). No information on age, sex and setting	Ritanserin (10mg, n = 47) Placebo (n = 46)	Responders (CGI 1 or 2)
Kocsis et al.[14]	Double-blind, duration 6wk, non-ITT analysis	54 outpatients with dysthymia and MD, mean age 40y, 70% females	Imipramine (198mg, n = 29) Placebo (n = 25)	Responders (≤6 on HAM-D, ≥10 of improvement on GAS, no longer meeting DSM-III criteria)
Stewart et al.[15]	Double-blind, duration 6wk, non-ITT analysis	57 dysthymic patients (DSM-III), sex and age distributions not given	Imipramine (265mg, n = 12) Phenelzine (73mg, n = 18) Placebo	Responder (CGI 1 or 2)
Botte et al.[16]	Double-blind, 4wk, non-information on analysis	47 in- and outpatients with dysthymia (DSM-III). Age range 20-76y	Moclobemide (300-500mg, n = 23) Placebo (n = 24)	Responders (final reduction of at least 50% on HAM-D score)
Bella et al.[17]	Double-blind, duration 8–9wk, non-ITT analysis	60 inpatients with dysthymia (DSM-III). Age range 60-80y	Acetyl-L-Carnitine (3g, n = 30) Placebo (n = 30)	HAM-D (SD not provided)
Costa e Silva[18]	Double-blind, 4wk, non-information on analysis	40 dysthymic patients (DSM-III-R). Mean age 43y, 56% females	Amisulpride (50mg, n = 20) Placebo (n = 19)	Responders (major or satisfactory improvement)
Bersani et al.[19]	Double-blind, duration 5wk, non-ITT analysis	30 dysthymic subjects (DSM-III-R); mean age 42y, 59% females	Ritanserin (dose unknown, n = 15) Placebo (n = 16)	Responder (CGI 1 or 2)
Bakish et al.[20]	Double-blind, duration 7wk, non-ITT analysis	50 outpatients with dysthymia (DSM-III), age 38y, 48% females	Ritanserin (50mg, n = 17) Imipramine (200mg, n = 16) Placebo (n = 17)	HAM-D (SD not provided)
Hellerstein et al.[21]	Double-blind, duration 8wk, non-ITT analysis	35 dysthymic patients (DSM-III), age 36y, 50% females	Fluoxetine (32.7mg, n = 19) Placebo (n = 16)	Responders (50% or greater decrease on HAM-D)
Boyer & Lecrubier[22]	Double-blind, duration 12wk, ITT analysis for most outcomes	323 outpatients with dysthymia or dysthymia with MD (DSM-III), mean age 48y, 70% females	Amisulpride (50mg, n = 104) Amineptine (200mg, n = 111) Placebo (n = 108)	Responders (CGI 1 or 2)
Thase et al.[4]	Double-blind, duration 12wk, non-ITT analysis	416 dysthymic subjects (DSM-III-R), mean age 42y, 65% females	Sertraline (140mg, n = 134) Imipramine (199mg, n = 136) Placebo (n = 140)	Responder (CGI 1 or 2); Full remission (no longer fulfilling DSM-III-R criteria)
Ravindran et al.[23]	Double-blind, duration 12wk, ITT analysis	310 outpatients, dysthymia (DSM-III-R), age 45y, 66% females	Sertraline (50-200mg, n = 158) Placebo (n = 152)	Responders (CGI 1 or 2)
Reyntjens et al.[24]	Double-blind, duration 5–6wk, non-ITT analysis	93 dysthymic patients (DSM-III); no information provided on age, sex and setting	Ritanserin (10mg, n = 47) Placebo (n = 46)	Responders (CGI 1 or 2)
Vanelle[25]	Multicentre, double-blind, duration 12wk, ITT analysis (mainly)	140 in- and outpatients with dysthymia (DSM-III-R). Mean age 43y, 75% females	Fluoxetine (20mg, n = 91) Placebo (n = 49)	Responder (>50% decrease in HAM-D + score 1 or 2 on CGI)

Table I. Contd

Reference	Methods	Participants	Interventions (daily dose, no. of patients randomised)	Main efficacy outcome
Versiani et al.[26]	Double-blind, duration 8wk, ITT analysis for some outcomes	315 outpatients with dysthymia (DSM-III) Mean age 42y, 70% females	Moclobemide (675mg, n = 108) Imipramine (220mg, n = 103) Placebo (n = 104)	Responder (no longer met DSM-III-R criteria)
Williams et al.[27]	Blindness for patients on paroxetine and placebo, and outcome raters. Duration: 11wk, ITT for some outcomes	182 patients with dysthymia (DSM-III-R); Mean age 71y, 40% females	Paroxetine (20-40mg, n = 57) Problem-solving treatment-primary care (n = 63) Placebo (n = 62)	Remission (score <7 on HAM-D)

CGI = clinical global impression; **DSM-III** = Diagnostic and Statistical Manual of Mental Disorders III;[1] **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders III revised;[11] **GAS** = global assessment scale; **HAM-D** = Hamilton Depression Scale; **ITT** = intention-to-treat; **MD** = major depression; **SD** = standard deviation.

participants randomised in the trials ranged from 21–416.

Comparisons

A range of different compounds was compared in the trials. Regarding comparative trials, imipramine was the main active comparator (six trials). In one trial[31] an augmentation scheme was adopted (fluoxetine plus bentazepam) and compared with fluoxetine alone.

Quality Findings

Five trials[14,21,26,27,32] were classified as 'A' criteria regarding allocation concealment.[9] The other trials were classified as 'B', since information on allocation concealment was not provided in the papers. None were classified as 'C'.

Data Reporting and Analysis

All trials included in this review reported the randomisation procedure but did not provide information on allocation concealment. Some trials did not report the number of patients who withdrew from therapy and post-randomisation exclusions.[12,15,27] Most of trials did not use an intention-to-treat approach in the original report, 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).

Placebo-Controlled Trials: Synthesis of the Main Findings

Efficacy

A preliminary analysis showed no difference in response rates between different drugs and groups of drugs. In order to perform a sensitivity analysis and because of this lack of heterogeneity, trials that compared more than one active treatment with placebo were dealt with by combining all active treatment subjects together in order to calculate a pooled RR for treatment versus placebo. The meta-analysis confirmed the efficacy of drugs for patients with dysthymia. All but three trials showed significant differences between active drugs and placebo (figure 1). For all drugs, the pooled RR for treatment response was 0.68 (95% CI 0.60–0.73), favouring drugs (figure 1). The mean response rate for patients receiving placebo was 31% compared with 55% for those receiving active drug giving a difference in response rate of 25% and an NNT of 4.1 (95% CI 3.5–4.9).

Full Remission

This outcome, a more restricted definition of clinical improvement, was reported in three trials.[4,25,26] Results from individual studies were

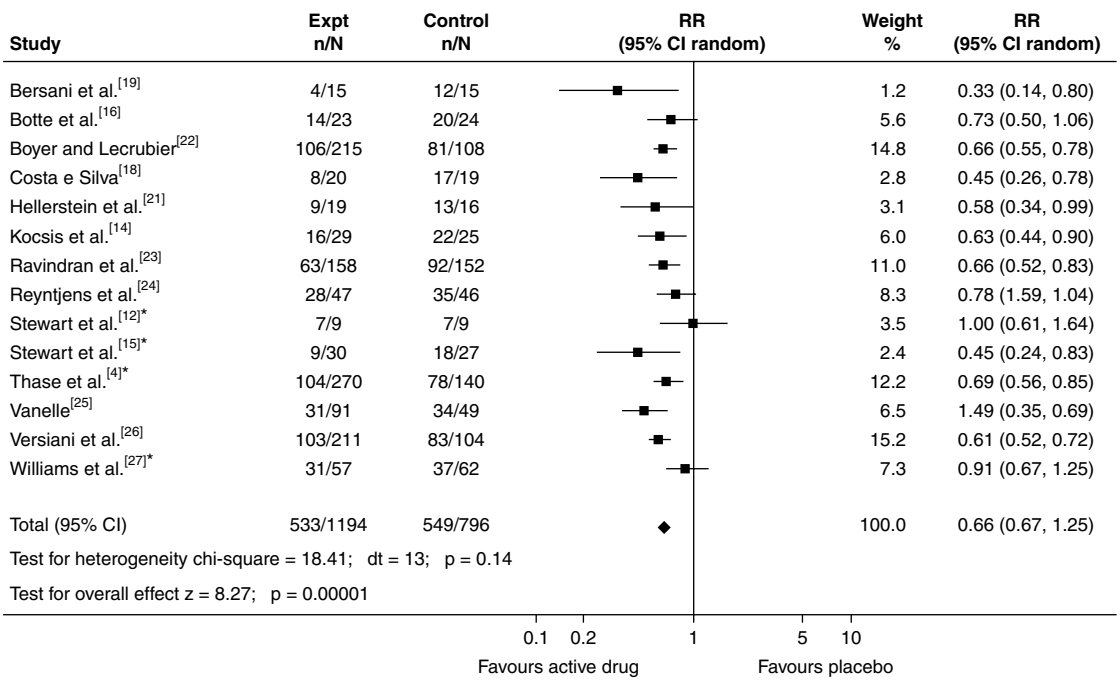

Fig. 1. Placebo-controlled randomised trials of the pharmacological treatment of dysthymia. **Expt** = experimental group; **n** = number of participants who presented with the event; **N** = total number of randomised participants; **RR** = relative risk. * Data available in the reports did not allow an intention-to-treat estimate.

very similar to the pooled estimation for treatment response (pooled RR = 0.68; 95% CI 0.61–0.75; chi-square for heterogeneity = 0.82).

Treatment Discontinuation Rate

In placebo-controlled trials, no significant differences were found on treatment discontinuation rates between antidepressants and placebo, not allowing calculation of NNH. The RR for TCA provided by four imipramine trials was 1.21 (95% CI 0.79–1.24). The pooled RR for SSRIs (fluoxetine and sertraline) was 0.74 (95% CI 0.49–1.11). The pooled RR for MAOI, obtained from two moclobemide trials was 0.45 (95% CI 0.11–1.92). Other drugs including amisulpride (overall RR = 0.91; 95% CI 0.64–1.30), amineptine (one trial, RR = 0.93 (95% CI 0.66–1.31), ritanserin (three trials, RR = 0.78 (95% CI 0.50–1.21) and acetyl-L-carnitine (one trial, RR = 0.40 (95% CI 0.14–1.14) reported similar results for treatment discontinuation.

Adverse Events

Patients receiving a TCA were more likely to report at least one adverse effect than those receiving placebo (RR = 1.37; 95% CI 1.14–1.66). The NNH was 4.6 (95% CI 2.9–10.2), given a prevalence of adverse events of 59% in the placebo group, but these results are reported in one trial only[26] No significant increase in adverse effects was found for SSRIs (RR = 1.13, 95% CI 0.83–1.55); or moclobemide (RR = 1.15, 95% CI 0.94–1.42). The highest RR for adverse events was found for ritanserin: RR = 2.5 (95% CI 1.00–6.23), reported in one trial.[19] The NNH was 2.5 (95% CI 1.38–13.72). In the study by Boyer and Lecrubier,[22] amineptine was associated with a higher number of subjects reporting adverse

events, compared with placebo; the RR was 1.4 (95% CI 1.08–1.81), the NNH being 5.64 (3.25–21.24).

Comparisons Between Active Drugs: Synthesis of the Main Findings

Table II shows the comparisons that have been made between active pharmacological treatments in the management of dysthymia. Most of these studies were small and, perhaps not surprisingly given that they all compared two active treatments, very few statistically significant differences were found in terms of efficacy or adverse effects. Many of the compounds used are only rarely used in routine clinical practice, and the utility of these small studies is doubtful. Given the wide range of compounds compared it is not possible to provide a sensible meta-analysis to deal with the lack of statistical power.

None of these studies found any statistically significant difference in treatment efficacy between active compounds. The only statistically significant differences reported were: (i) discontinuation rates on sertraline were lower than on imipramine[4] (RR 0.47; 95% CI 0.30–0.95); and (ii) imipramine was associated with more adverse effects than moclobemide[26] (RR 0.84; 95% CI 0.81–0.99).

Discussion

We used a sensitive search strategy to identify as many published or unpublished trials on pharmacotherapy for dysthymia as possible. Our results suggest that drug (mainly but not exclusively antidepressants) treatment for dysthymia is more effective than placebo. In placebo-controlled trials, the NNT was about four for treatment response. This indicates that four patients have to be treated to cause one clinical improvement, suggesting a good cost : benefit ratio. In a recent Cochrane systematic review, Furukawa et al.[40] compared the NNTs for some psychiatric conditions. Considering clinical improvement in major depression for patients taking an antidepressant plus a benzodiazepine, NNT = 7; global improvement for people with schizophrenia who are treated with chlorpromazine, NNT = 7; and for lithium in acute mania, NNT = 4. Two other systematic reviews found similar NNTs for clinical improvement promoted by antidepressants in binge episodes[41] (NNT = 4); and clinical improvement in generalised anxiety disorder in patients using imipra-

Table II. Studies comparing active pharmacological treatments for dysthymia

Study	Drug 1 (daily dose; no. of patients randomised)	Drug 2 (daily dose; no. of patients randomised)
Bakish et al.[20]	Ritanserin (50mg; n = 17)	Imipramine (200mg; n = 16)
Boyer & Lecrubier[22]	Amisulpride (50mg; n = 104)	Amineptine (200mg; n = 111)
Geisler et al.[33]	Ritanserin (7.4mg; n = 33)	Flupenthixol (1.3mg; n = 37)
Guelfi et al.[34]	Tianeptine (37.5mg; n = 135)	Amitriptyline (75mg; n = 130)
Hellerstein et al.[32]	Fluoxetine (40.8mg; n = 8)	Trazodone (300mg; n = 10)
Leon et al.[35]	Amisulpride (50mg; n = 40)	Viloxacine (150mg; n = 40)
Otero et al.[31]	Fluoxetine (20mg; n = 29)	Fluoxetine (20mg) + bentazepam (50mg; n = 31)
Rosenthal et al.[36]	Fluoxetine (30.9mg; n = 12)	Trazodone (241.7mg; n = 8)
Salzmann & Robin[37]	Minaprine (200mg; n = 33)	Imipramine (100mg; n = 34)
Smeraldi et al.[38]	Amisulpride (50mg; n = 142)	Fluoxetine (20mg; n = 139)
Stewart et al.[15]	Imipramine (265mg; n = 12)	Phenelzine (73mg; n = 18)
Thase et al.[4]	Sertraline (139.6mg; n = 134)	Imipramine (199mg; n = 136)
Vallejo et al.[39]	Imipramine (250mg; n = 20)	Phenelzine (75mg; n = 19)
Versiani et al.[26]	Moclobemide (675mg; n = 108)	Imipramine (220mg; n = 103)

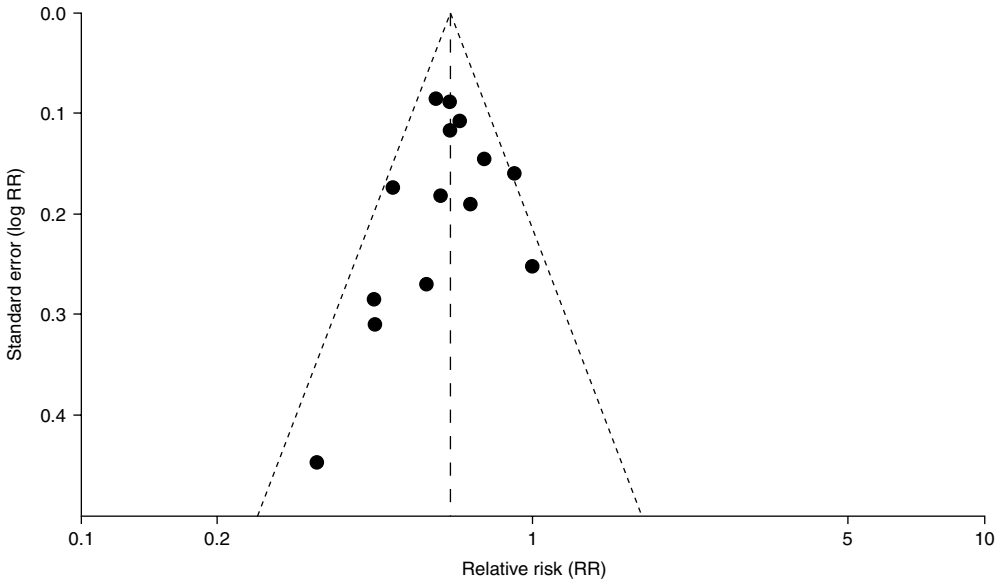

Fig. 2. The pharmacological treatment of dysthymia: a funnel plot for clinical response (all placebo-controlled trials).

mine[42] (NNT = 4). Thus, the NNTs for clinical improvement in dysthymia does confirm the efficacy of the pharmacological treatment of this condition, being comparable with those NNTs estimated for other psychiatric disorders.

These studies also indicate that other less-well characterised types of minor depression may be amenable to drug treatment; however, it was not our primary objective to study these, and the search strategy may not have uncovered all papers relating to such treatments.

However, it is possible that some degree of publication bias may have affected our results, as demonstrated in the funnel plot (figure 2). We believe that the main findings still hold, because the distribution on the funnel plot suggests that not many trials were missed, and their results would fall between our estimate of pooled treatment effect and a relative risk of one, indicating that publication bias is unlikely to greatly alter the estimated treatment effect.

The literature does not provide sufficient data to enable us to recommend one treatment over any other. The tricyclics, when compared with placebo, were more likely to be associated with adverse effects, a pattern which was not found for other classes of drug. When direct comparisons were made, there was some evidence that tricyclics were less well tolerated than the SSRI sertraline or the reversible inhibitor of monoamine oxidase, moclobemide. Taking the results of a trial comparing moclobemide to imipramine,[26] it could be said that the MAOI is an easier drug to prescribe and take. However, such advantage is statistically non-significant and it is not seen in major depression trials.[43]

Regarding SSRIs, this pattern is similar to that shown in the treatment of depressive disorder with SSRIs.[44] Thus, many would argue that newer drugs such as SSRIs should be first-line treatment for dysthymia, as they have made the same case in depressive disorder. For dysthymia we believe there are insufficient data to make such a case, and

the choice of the treatment will probably be based more the patient's profile of symptoms, their experience of adverse effects with previous treatments, and medical comorbidity.

It is important to note that only short-term results are available in what is by definition a long-term problem. Clinically it is common to see short-term improvement in such situations with subsequent relapse. Long-term pragmatic randomised controlled trials are required to evaluate alternative treatment approaches for dysthymia.

There are a number of concerns regarding the quality of reporting of the randomised, controlled trials included in this review. Many papers lacked important information, such as details about demographic characteristics of the population, randomisation, number of patients withdrawing from treatment and standard deviations for continuous data. Other clinically relevant outcomes are missing in the vast majority of studies (social functioning, quality of life, work productivity, and healthcare utilisation).

The high number of comparisons found in this review and the fact that sometimes the reference drug could not be considered as a standard treatment (e.g. amisulpride vs viloxazine[35]) also deserves attention. It is likely that some of the comparisons will never be compared in future investigations because there are more important questions regarding the efficacy of treatments in dysthymia.

There is still a clear need for larger and long-term studies of the comparative efficacy of drugs in dysthymia, and the efficacy of drugs versus psychotherapies. As far as the decision-making process for treating patients with dysthymia is concerned, it would be of particular interest in 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. The availability of these outcomes in naturalistic settings would make extrapolations from research to real-life situations easier.

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