BMJ open

Citalopram for major depressive disorder in adults: a systematic review and meta-analysis of published placebo-controlled trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000106
Article Type:	Research
Date Submitted by the Author:	25-Feb-2011
Complete List of Authors:	Apler, Alex; Park House, Department of Psychiatry
Subject Heading:	Psychiatry
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Clinical trials < THERAPEUTICS

Citalopram for major depressive disorder in adults: a systematic review and meta-analysis of published placebo-controlled trials

Dr Alex Apler

Park House, Liverpool Hospital, Liverpool, NSW, 2170, Australia
Dr Alex Apler, MBBS, FRANZCP, MSc (LSHTM)
Psychiatrist

Correspondence to: alexapler@gmail.com

I have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from me) and declare: I had financial support from the New South Wales Institute of Psychiatry, in the form of a Research Fellowship, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

ABSTRACT

Objective To assess effectiveness of citalopram for Major Depressive Disorder (MDD) in adults, in a systematic review of all published, randomized, double-blind studies comparing it to a placebo.

Data sources Cochrane Central Register of Controlled Trials, Medline, PsychINFO and Embase.

Study selection Randomised, double-blind, placebo-controlled studies of citalopram in adults with MDD were included. Studies with medically-ill or treatment resistant subjects were excluded, as were studies of relapse prevention. Remission of MDD was defined as a primary outcome, and response or change from baseline scores were defined as secondary.

Data extraction Remission, response and symptom improvement scores on the HAM-D, MADRS and CGI-S scales were extracted. Random-effects meta-analysis was carried out on symptom improvement scores. Included studies were examined for the presence of bias.

Results Eight studies (n=2025) met the inclusion criteria. Only two studies provided data on remission, showing no statistically significant difference between citalopram and placebo. The response rates were inconsistent, with five out of eight studies reporting citalopram to be significantly superior to placebo. Meta-analysis of change from baseline scores in five studies (n=1541) gave a standardised mean difference (Hedges'*g*) of -0.27 (95%CI -0.38 to -0.16), showing reduction in MDD symptoms to be statistically, but not clinically, significant for citalopram relative to placebo. Overall quality of reporting was poor, with insufficient information about the methodology or outcomes. Seven studies received industry sponsorship.

Conclusions There is no evidence that remission of MDD is significantly better with citalopram treatment than with placebo. Response of MDD to citalopram might be better than to placebo, but the data are inconclusive. Symptom reduction in citalopram-treated patients with MDD is significantly better statistically, but not clinically, relative to placebo. Greater transparency, improvement in reporting standards and independent studies of citalopram are necessary to more definitively assess the effectiveness of citalopram for MDD.

ARTICLE SUMMARY

Article focus

• Systematic review and meta-analysis of published randomised double blind studies comparing citalopram to placebo in adults with MDD
• Evaluation of the quality of published studies and the risk of bias

Key messages

• Citalopram has a statistical but not clinically-significant advantage in improving symptoms of MDD
• Data on the response rates for MDD are inconsistent, and there is no evidence that remission rates are significantly better for citalopram than placebo
• Published studies comparing citalopram to placebo may be affected by bias, and the quality of reporting in published studies is poor

Strengths and Limitations of this study

• This review is based on a thorough search for published placebo-controlled studies of citalopram for adults with MDD, using a broad search strategy. In a departure from previously

published reviews, this study assesses bias and includes a meta-analysis of randomised, placebo-controlled trials. This study would have been further enhanced if original data were obtained from the authors for a more complete analysis, and unpublished studies satisfying inclusion criteria were incorporated into this review.

INTRODUCTION

Citalopram is a selective serotonin reuptake inhibitor antidepressant, commonly used in the treatment of Major Depressive Disorder (MDD). It is often recommended as a first line treatment for this condition in guidelines for managing depression, such as those published by NICE [1].

Whether citalopram is sufficiently effective to recommend it as treatment of MDD depends on the quality of studies evaluating this drug, and measures of effectiveness utilised. These issues have not been adequately addressed in previous reviews. While earlier reviews have concluded that citalopram is effective for MDD[2 3], these conclusions can be questioned in the light of more recent research highlighting the potential presence of bias in industry-sponsored systematic reviews[4] and randomised trials[5].

A re-examination of the role of citalopram in the treatment of MDD is therefore necessary, taking into account the quality of studies, risk of bias, and different measures of effectiveness. *Remission* of MDD is, arguably, the most rigorous and clinically-relevant measure of effectiveness that should be sought when evaluating citalopram for MDD[6-8]. The emphasis on remission when evaluating effectiveness can be contrasted with earlier reviews of citalopram, focussing on *symptom improvement* or *response* as the main measures of outcome. Filling this gap in the literature, I systematically reviewed all published randomised, placebo-controlled studies of citalopram in adults with MDD. I examined the quality of published studies and the risk of bias, setting remission of MDD as the primary measure of effectiveness in this review.

METHODS

Selection Criteria

I selected published, randomized, double-blind studies comparing citalopram to placebo among adult participants over the age of 18, who were diagnosed with MDD using DSM-III [9], DSM-IIIR [10], DSM-IV [11], ICD-9 [12] or ICD-10 [13]. No upper age limit for study participants was set. Studies with a third comparator (eg another antidepressant) were included, if a direct comparison between citalopram and placebo treatments was possible. Studies involving patients with severe medical illness, other psychiatric disorder or substance abuse were excluded from this review. Studies of MDD that focused on relapse prevention, treatment augmentation or

treatment-resistant cases were also excluded, as these studies would have introduced additional heterogeneity into this evaluation.

Outcomes

Primary outcome. Remission of MDD. Remission was defined as: a score of 7 or less on the 17-item Hamilton Depression Scale (HAM-D) [14]; 8 or less on longer versions of HAM-D; 11 or less on the Montgomery Asberg Depression Rating Scale (MADRS) [15] or "not ill or borderline mentally ill" on Clinical Global Impression – Severity (CGI-S) scale [16]. These cut-off points provide a consistent definition of "remission"[17 18].

Secondary outcomes. (a) Response of MDD. Response was defined as a reduction of at least 50% on the HAM-D or MADRS scales; or "much or very much improved" on the CGI-I (CGI-Improvement) scale. HAM-D, MADRS and CGI-I have a similar sensitivity to change in depression symptom ratings [19]. (b) Any change from baseline scores on the HAM-D, MADRS or CGI scales.

Search methods

I carried out an electronic search of the Cochrane Central Register of Controlled Trials, Medline (from 1950), PsychINFO (from 1967) and EMBASE (from 1980) up to February 2011. Articles with "citalopram", "placebo" and "major or severe depression", as keywords or exploded MeSH terms, were searched by combining (exp citalopram/ OR citalopram.mp) AND (exp placebo/ OR placebo*.mp) AND (exp depressive disorder/ OR (depress* adj2 (major* or severe*)).mp). The term "placebos" was used as a MeSH heading in the Medline, Cochrane and EMBASE database searches and "major depression" was used as a MeSH heading in the PsychINFO search. No limits were set for these searches, apart from the EMBASE search, which was limited to the adult population because of the large number of ineligible studies produced by the unrestricted search.

I examined the abstracts of all identified studies, selecting randomised double blind studies of citalopram in patients with major depressive disorder. Reference lists of review articles and other studies of citalopram were also searched for publications satisfying the inclusion criteria. I then obtained full text copies of these articles and excluded those that: lacked a placebo control group; involved children, adolescents, medically ill or treatment resistant population; or were studies of relapse prevention or of patients with another psychiatric illness.

Data collection

I extracted data into an electronic form with sections for each study describing the methods used, study participants, interventions and measured outcomes, as well as sections for bias evaluation.

Data on the characteristics of study participants were entered into a table, recording age and sex of participants, sample sizes in the citalopram and placebo treatment groups, medication doses, drop-out rates and treatment duration. The number of subjects randomised, and the number included in outcome evaluation, were extracted from each study where possible. I recorded baseline measures of symptom severity and the treatment setting for each study.

I tabulated the proportions of patients that achieved response or remission in the citalopram and placebo arms of selected studies. I included the definitions of "response" and "remission" terms used and extracted the change from baseline measures on the HAM-D, MADRS or CGI depression scales.

Data analysis

Risk of bias was evaluated in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [20], and the Revised CONSORT Statement [21], using the following parameters: adequacy of sequence generation; allocation concealment; blinding; whether incomplete data in the studies had been addressed; selective outcome reporting; and industry sponsorship. I entered (+) into the table when the criterion was satisfied, (-) when it was not satisfied, and (?) when I had insufficient information to reach a conclusion.

I carried out a meta-analysis of the change-from-baseline HAM-D scores for participants included in outcome evaluation, using Stata 9.2. I applied a random effects model to calculate Hedges' *g* for standardised mean differences between citalopram and placebo groups. Standard deviations (SD) were computed from the p-values, taken at the upper limit and converted into a t-statistic. I used the formula $SD = SE/\sqrt{(1/N_e+1/N_c)}$, where SE (standard error) = difference in means of the two change from baseline scores divided by the t-statistic, and N_e and N_c are the sample sizes in the experimental and control groups respectively. I multiplied the result by -1 to convert a measure of symptom reduction into an improvement score.

RESULTS

A search of the Cochrane Central Register of Controlled Trials using the above search terms produced 31 articles, Medline 244, PsychINFO 60 and EMBASE 202, giving a total of 537 articles, after removing duplicates. The selection process is described in Figure 1.

I inspected the abstracts from the above searches and selected 29 studies for possible inclusion. After examining full text copies of these studies, I compiled a final list of eight studies[22-29] that satisfied the inclusion and exclusion criteria. Excluded studies lacked a placebo control [30-34], focused on relapse prevention [35 36], or were studies of children [37 38], medically ill [39-47] or treatment-resistant subjects [48 49]. The study by Montgomery [50] was excluded as the data in this study were reported in a larger trial by Lepola [26].

Characteristics of included studies

Characteristics of included studies are described in Table 1. The studies were brief, only two to eight weeks in duration, apart from one study [29] which was 24 weeks in length. The combined sample from the eight studies consisted of 1237 subjects in the citalopram group and 788 in the placebo group (total = 2025). The mean age of participants was 42 years, with the age ranging between 18 and 74 years. Females constituted two-thirds of the sample in most studies, and the dose of citalopram ranged from 10 to 80mg a day. One study [24] had only 16 participants. All patients recruited in these studies were diagnosed with MDD using the criteria in the Diagnostic and Statistical Manual of Mental Disorders III, III-R or IV. Most participants were recruited in outpatient settings.

Risk of bias

The risk of bias in included studies is summarised in Table 2. Most studies provided insufficient information to determine whether the random sequence generation was adequate. The study by Gastpar *et al.* [25] was an exception, providing detailed information on the randomization method employed. None of the studies provided sufficient information for assessing the adequacy of allocation concealment. Four reports [22 23 25 28] described the blinding methods used but none of the studies had commented on whether the adequacy of blinding had been assessed.

Data in the study by Montgomery *et al.* [28] were incomplete, with no data provided on patients leaving the study in the first three weeks. In contrast, Feighner *et al.* [23] undertook efficacy analyses on all "patients randomly assigned to study medication" and Frank *et al.* [24] provided outcome data for all 16 participants. The intention-to-treat samples in the remaining studies were defined as randomized patients who took at least one dose of study medication and had at least one post-baseline outcome assessment.

Selective reporting of outcome data was evident in all studies, as easily extractable summary statistics like remission and response rates were often omitted from publication. Only one study [29] provided remission rates for both placebo and citalopram groups. Three of the studies [23 28 29] did not provide response rates and two of the studies [24 28] did not provide data on changes in outcome measures compared to baseline. All studies except one [25] received industry sponsorship.

Baseline characteristics of subjects

Hamilton Depression Scale (HAM-D). Baseline characteristics of patients in included studies are described in Table 3. Five studies provided mean baseline HAM-D scores[22 23 25 27 29]. The patients

in these studies had mean baseline HAM-D scores above 17, showing that they were moderately to severely depressed.

Montgomery-Asberg Depression Rating Scale (MADRS). Baseline mean MADRS scores were provided in four studies[22 23 26 29]. The mean MADRS scores in these studies were above 22, indicating that patients were moderately (scores between 22 and 29) to severely (scores of 30 or above) depressed.

Clinical Global Impressions-Severity (CGI-S). All studies, except for Frank *et al.* [24] and Montgomery *et al.* [28] provided mean baseline CGI-S scores. Average baseline scores in these study populations were above four, indicating a moderate level of illness severity. In the study by Gastpar *et al.*[25], more than 92% of patients were assessed as moderately, markedly or severely depressed.

Outcomes

Remission. Remission and response rates are presented in Table 4. Stahl [29] reported a 45% remission rate in the citalopram group, and 28% remission rate in the placebo group at the end of a 24 week trial, with remission defined as a score of less than 8 on HAMD-17. The difference between the two groups was not statistically significant. Lepola *et al.* [26] reported a remission rate of 42.8% in the citalopram group, with remission defined as a score of less than 12 on MADRS, but this rate was not significantly different from placebo. This evaluation was based on observed cases only and no comparable data for the placebo group was provided. Gastpar *et al.* [25] provided combined data on the proportion of patients that achieved a reduction to a score of less than 10 or an improvement of 50% on HAMD, but no separate data on remission rates in his study. Remission rates in other studies were not published.

Response rates. Burke *et al.* [22] and Mendels *et al.* [27] found significantly superior response rates in the citalopram group, compared to placebo. Stahl [29] and Feighner *et al.* [23] also reported significantly superior response rates in the citalopram groups, but did not publish the actual data for these results. Gastpar *et al.* [25] found a significant difference in response rates but used a mixed definition of "response" – 50% improvement or a final score of less than 10 on HAMD – making it difficult to compare his results to other studies.

Response rates for citalopram were not significantly superior to placebo in other studies. Montgomery *et al.* [28] reported no significant difference in response rates, without publishing the data to support this finding. There was also no significant difference in response rates in the study by: Frank *et al.* [24], which used a small sample and may not have had sufficient power to detect a difference; and Lepola *et al.* [26], which relied on observed cases to assess response.

Change from baseline. Change from baseline scores are set out in Table 5. Five studies [22 23 25 27 29] reported significant improvement in depression scores with citalopram, relative to placebo.

Montgomery *et al.* also reported depression scores in the citalopram group to be significantly superior to placebo, but did not provide the actual data for this comparison. Lepola *et al.* [26 51] found no statistically significant difference in score improvements between the two groups, and Frank *et al.* [24] provided no information on this outcome measure.

Meta-analysis of change from baseline scores

Five studies, with a total of 1541 subjects, were included in the meta-analysis. The study by Lepola *et al.* was excluded as it provided no information for calculating standard deviations, and the studies by Frank *et al.* and Montgomery *et al.* did not report the change from baseline measures for their subjects.

Hedges' *g* for the standardised mean difference in the change from baseline scores, comparing citalopram to the placebo group, was -0.27 (95% confidence interval -0.38 to -0.16), which converted to an improvement score of 0.27. This result indicates that the subjects treated with citalopram had a small but significant improvement in their baseline HAM-D scores, relative to those treated with placebo. There was no significant heterogeneity in the change from baseline HAM-D measures in the studies included in meta-analysis.

DISCUSSION

Summary of main results

Citalopram is not significantly better than placebo in producing remission of MDD in adults, according to two studies reporting this outcome measure. Citalopram may be significantly better than placebo in producing a response in MDD, but this is inconclusive, as five studies reported statistically significant differences in response between the two groups, and three did not. The use of inconsistent definitions of "response" in these studies complicates evaluation of this outcome. Most of the studies were probably too brief to adequately assess remission and response rates in patients with MDD, as longer trials are necessary to adequately assess the effect of citalopram on these outcome variables[52 53].

Meta-analysis of standardised mean differences in the change from baseline HAM-D scores indicates that there is a small but statistically significant improvement in symptom scores with citalopram treatment, relative to placebo. However, statistically significant improvement does not necessarily point to a clinically significant benefit for patients with MDD. Using a medium effect size of 0.5 as a cut-off for clinical significance adopted by NICE[1], treatment with citalopram may produce a small but not clinically-significant improvement in symptoms of MDD[54]. Clinical advantage of citalopram is more likely to be evident in patients with severe MDD similar to those recruited in these studies; those with mild to moderate MDD often have a smaller response to antidepressant treatment[55 56].

Improvement, response or remission?

The studies reviewed in this paper focus on the change from baseline scores as the main outcome variable. Focus on this outcome measure has been criticised by Keller [7] as satisfying industry and research imperatives rather than clinical needs. Demonstration of statistically significant improvement in scores of citalopram-treated patients may be sufficient to fulfil regulatory requirements for drug registration, and may provide interim data in longer trials. Statistical measure of improvement, however, may not help clinicians assess whether citalopram would be of benefit for MDD, a disorder with a "dynamic and changeable" symptomatic course.[57]

Response is more clinically-meaningful than improvement, as a measure of symptom amelioration, but may still be of limited value in clinical settings, for instance, when deciding whether to alter treatment. Furthermore, response is a relative measure, with the degree of improvement necessary for a "response" being influenced by baseline symptom severity. As Nierenberg [58] points out, patients with severe depression scoring 32 on HAM-D would achieve response with the score falling to 16, but this lower rating may still be sufficiently high for them to be considered depressed.

The most clinically-helpful measure is remission, but most studies reviewed here do not provide remission rates for MDD. The study authors may be reluctant to provide these data because only 20% to 30% of patients treated with selective serotonin reuptake inhibitors achieve remission during short-term therapy [6 59]. As Keller [7] points out, higher remission rates may be achieved by administering drugs in greater doses, using a flexible dosing regime, with augmentation strategies and for longer periods[60]. However, such a treatment approach may not fit the objectives of industry-sponsored trials designed to demonstrate the efficacy and safety of a specific drug. In the absence of data on remission rates favouring citalopram, preference may be given to other drugs with superior remission rates, relative to placebo, when treating MDD[61 62].

Bias

Inadequate description of research methodology in the included studies raises apprehension of bias. There was little information in the reviewed papers about the methods used to generate random sequences[63], conceal treatment allocation[64] and blind participants, clinicians and evaluators[65]. Such information is essential for evaluating trial integrity, and while the absence of this information does not in itself establish bias, it can cause doubt in the audience about the validity of published results. For instance, Moncrieff [66], after highlighting the methodological shortcomings in antidepressant trials, questioned the effectiveness of antidepressants.

Industry sponsorship of the reviewed studies adds to the apprehension of bias. Industry-sponsored research may be influenced by "potentially massive financial gains" associated with

research demonstrating drug effectiveness [67]. The desire to show a drug to be more effective than its comparator, or the belief that it is so, may be described as a "wish bias" in antidepressant research [68]. This "wish" for a particular outcome in drug research can be contrasted with the objective, dispassionate stance that scientific research demands.

Agreements and disagreements with other studies or reviews

I estimated the effectiveness of citalopram, relative to placebo, as Hedges' *g* of 0.27 in this meta-analysis of five published studies. This result is similar to Hedges' *g* of 0.31 calculated by Turner on the basis of published studies[69]. Importantly, his estimation of citalopram's effectiveness was revised down to 0.01 after including unpublished results.

My assessment of citalopram's effectiveness in the treatment of MDD differs from the conclusions of previous reviews [2 3 70 71], which focus on the change from baseline scores and conclude that citalopram has a significant advantage over placebo. Three of these reviews received industry support. In contrast, I find that: citalopram has a statistical but not clinically significant advantage over placebo, as shown by the change from baseline scores; data concerning response rates are inconsistent; and remission rates for citalopram have not been demonstrated to be significantly better than for placebo.

CONCLUSION

The role of citalopram in the treatment of MDD can be questioned in view of the evidence of its limited effectiveness presented in this paper. Other antidepressants, with better remission rates relative to placebo, may be preferable for this condition. Revision of the depression treatment guidelines may be necessary in the light of this finding.

The articles reviewed in this paper are of insufficient quality to definitively evaluate the effectiveness of citalopram for MDD. More research into the effectiveness of citalopram for MDD in longer trials may be necessary, but more importantly, greater transparency is required for research into this drug. That transparency is difficult to achieve when the research data are proprietary, which increases the importance of providing detailed information about the research in published reports.

Ethics approval: Not required

Competing interests: None

Funding / acknowledgements: This publication is based on a project report submitted to the London School of Hygiene and Tropical Medicine in part satisfaction of course requirements for MSc Epidemiology. Publication of this article was supported by a research fellowship from the New South Wales Institute of Psychiatry. I am the sole author of this article.

Data sharing: The technical appendix is available from the corresponding author at alexapler@gmail.com

References

1. National Institute for Clinical Excellence. *Depression : management of depression in primary and secondary care. Clinical Practice Guideline 23*. London: National Institute for Clinical Excellence, 2004.
2. Keller MB. Citalopram therapy for depression: a review of 10 years of European experience and data from U.S. clinical trials. *J Clin Psychiatry* 2000;61(12):896-908.
3. Montgomery SA, Djarv L. The antidepressant efficacy of citalopram. *Int Clin Psychopharmacol* 1996;11 Suppl 1:29-33.
4. Yank V, Rennie D, Bero LA. Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study. *BMJ* 2007;335(7631):1202-5.
5. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326(7400):1167-70.
6. Ferrier IN. Treatment of major depression: is improvement enough? *J Clin Psychiatry* 1999;60 Suppl 6:10-4.
7. Keller MB. Remission versus response: the new gold standard of antidepressant care. *J Clin Psychiatry* 2004;65 Suppl 4:53-9.
8. Thase ME. Evaluating antidepressant therapies: remission as the optimal outcome. *J Clin Psychiatry* 2003;64 Suppl 13:18-25.
9. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III)*. 3rd ed. ed. Washington, DC: American Psychiatric Association, 1980.
10. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III-R)*. 3rd ed rev. ed. Washington, DC: American Psychiatric Association, 1987.
11. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV)*. 4th ed. ed. Washington, D.C.: American Psychiatric Association, 1994.
12. World Health Organization. *The ninth revision of the international classification of diseases and related health problems (ICD-9)*. Geneva: World Health Organization, 1978.
13. World Health Organization. *The tenth revision of the international classification of diseases and related health problems (ICD-10)*. 10th revision. ed. Geneva: World Health Organization, 1992.
14. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
16. Guy W, Bonato RR, editors. *Manual for the ECDEU Assessment Battery 2*: National Institute of Mental Health, Chevy Chase, Md, 1970.
17. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res* 2004;38(6):577-82.
18. Hawley CJ, Gale TM, Sivakumaran T. Defining remission by cut off score on the MADRS: selecting the optimal value. *J Affect Disord* 2002;72(2):177-84.

19. Khan A, Brodhead AE, Kolts RL. Relative sensitivity of the Montgomery-Asberg depression rating scale, the Hamilton depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials: a replication analysis. *Int Clin Psychopharmacol* 2004;19(3):157-60.
20. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 4.2.6 [updated September 2006]*: The Cochrane Collaboration, 2006.
21. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134(8):663-94.
22. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002;63(4):331-6.
23. Feighner JP, Overo K. Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. *J Clin Psychiatry* 1999;60(12):824-30.
24. Frank MG, Hendricks SE, Burke WJ, Johnson DR. Clinical response augments NK cell activity independent of treatment modality: a randomized double-blind placebo controlled antidepressant trial. *Psychol Med* 2004;34(3):491-8.
25. Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. *Pharmacopsychiatry* 2006;39(2):66-75.
26. Lepola UM, Loft H, Reines EH. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003;18(4):211-7.
27. Mendels J, Kiev A, Fabre LF. Double-blind comparison of citalopram and placebo in depressed outpatients with melancholia. *Depress Anxiety* 1999;9(2):54-60.
28. Montgomery SA, Rasmussen JG, Lyby K, Connor P, Tanghoj P. Dose response relationship of citalopram 20 mg, citalopram 40 mg and placebo in the treatment of moderate and severe depression. *Int Clin Psychopharmacol* 1992;6 Suppl 5:65-70.
29. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 2000;48(9):894-901.
30. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. *Psychopharmacology* 1986;90(1):131-8.
31. Karlsson I, Godderis J, Augusto De Mendonca Lima C, Nygaard H, Simanyi M, Taal M, et al. A randomised, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. *Int J Geriatr Psychiatry* 2000;15(4):295-305.
32. Kyle CJ, Petersen HE, Overo KF. Comparison of the tolerability and efficacy of citalopram and amitriptyline in elderly depressed patients treated in general practice. *Depress Anxiety* 1998;8(4):147-53.
33. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol* 2005;20(3):131-7.
34. Shaw DM, Thomas DR, Briscoe MH, Watkins SE, Crimmins R, Harris B, et al. A comparison of the antidepressant action of citalopram and amitriptyline. *Br J Psychiatry* 1986;149:515-7.

35. Montgomery SA, Rasmussen JG, Tanghoj P. A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. *Int Clin Psychopharmacol* 1993;8(3):181-8.
36. Robert P, Montgomery SA. Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. *Int Clin Psychopharmacol* 1995;10 Suppl 1:29-35.
37. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hulten A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol* 2006;26(3):311-5.
38. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry* 2004;161(6):1079-83.
39. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. *Stroke* 1994;25(6):1099-104.
40. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biol Psychiatry* 2005;58(11):865-70.
41. Devos D, Dujardin K, Poirot I, Moreau C, Cottencin O, Thomas P, et al. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. *Mov Disord* 2008;23(6):850-7.
42. Fraguas R, da Silva Telles RM, Alves TC, Andrei AM, Rays J, Iosifescu DV, et al. A double-blind, placebo-controlled treatment trial of citalopram for major depressive disorder in older patients with heart failure: the relevance of the placebo effect and psychological symptoms. *Contemp Clin Trials* 2009;30(3):205-11.
43. Kraus MR, Schafer A, Schottker K, Keicher C, Weissbrich B, Hofbauer I, et al. Therapy of interferon-induced depression in chronic hepatitis C with citalopram: a randomised, double-blind, placebo-controlled study. *Gut* 2008;57(4):531-6.
44. Lesperance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007;297(4):367-79.
45. Nyth AL, Gottfries CG, Lyby K, Smedegaard-Andersen L, Gylding-Sabroe J, Kristensen M, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. *Acta Psychiatr Scand* 1992;86(2):138-45.
46. Roose SP, Sackeim HA, Krishnan KR, Pollock BG, Alexopoulos G, Lavretsky H, et al. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004;161(11):2050-9.
47. Wermuth L, Sørensen PS, Timm S, Christensen B, Utzon NP, Boas J, et al. Depression in idiopathic Parkinson's disease treated with citalopram: A placebo-controlled trial. *Nordic Journal of Psychiatry* 1998;52(2):163-69.
48. Altamura AC, Dell'Osso B, Buoli M, Bosi M, Mundo E. Short-term intravenous citalopram augmentation in partial/nonresponders with major depression: a randomized placebo-controlled study. *Int Clin Psychopharmacol* 2008;23(4):198-202.
49. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant

depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol* 1996;16(4):307-14.
50. Montgomery SA, Loft H, Sanchez C, Reines EH, Papp M. Escitalopram (S-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. *Pharmacol Toxicol* 2001;88(5):282-6.
51. Lepola U, Wade A, Andersen HF. Do equivalent doses of escitalopram and citalopram have similar efficacy? A pooled analysis of two positive placebo-controlled studies in major depressive disorder. *Int Clin Psychopharmacol* 2004;19(3):149-55.
52. Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome?. The effects of placebo control and treatment duration in antidepressant trials. *Psychother Psychosom* 2009;78(3):172-81.
53. Deshauer D, Moher D, Fergusson D, Moher E, Sampson M, Grimshaw J. Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. *CMAJ* 2008;178(10):1293-301.
54. Turner EH, Rosenthal R. Efficacy of antidepressants. *BMJ* 2008;336(7643):516-7.
55. Barbui C, Garattini S. Mild depression in general practice: is the automatism of antidepressant prescribing an evidence-based approach? *Acta Psychiatr Scand* 2006;113(6):449-51.
56. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008;5(2):e45.
57. Judd LL, Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry* 1998;55(8):694-700.
58. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry* 2001;62 Suppl 16:5-9.
59. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163(1):28-40.
60. Quitkin FM, McGrath PJ, Stewart JW, Deliyannides D, Taylor BP, Davies CA, et al. Remission rates with 3 consecutive antidepressant trials: effectiveness for depressed outpatients. *J Clin Psychiatry* 2005;66(6):670-6.
61. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;178:234-41.
62. Sobocki P, Ekman M, Agren H, Runeson B, Jonsson B. The mission is remission: health economic consequences of achieving full remission with antidepressant treatment for depression. *Int J Clin Pract* 2006;60(7):791-8.
63. Roberts C, Torgerson D. Randomisation methods in controlled trials. *BMJ* 1998;317(7168):1301.
64. Torgerson DJ, Roberts C. Understanding controlled trials. Randomisation methods: concealment. *BMJ* 1999;319(7206):375-6.
65. Even C, Siobud-Dorocant E, Dardennes RM. Critical approach to antidepressant trials. Blindness protection is necessary, feasible and measurable. *Br J Psychiatry* 2000;177:47-51.
66. Moncrieff J. Are antidepressants overrated? A review of methodological problems in antidepressant trials. *J Nerv Ment Dis* 2001;189(5):288-95.
67. Lancet. Depressing research. *Lancet* 2004;363(9418):1335.

68. Barbui C, Cipriani A, Brambilla P, Hotopf M. "Wish bias" in antidepressant drug trials? *J Clin Psychopharmacol* 2004;24(2):126-30.
69. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358(3):252-60.
70. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. *CNS Spectr* 2002;7(4 Suppl 1):40-4.
71. Parker NG, Brown CS. Citalopram in the treatment of depression. *Ann Pharmacother* 2000;34(6):761-71.

APPENDIX

Figure 1. Summary of the article selection process

<table>
<tr><td colspan="2">Searches: Medline (n=250)
Embase (n=348)
Cochrane (n=166)
PsychINFO (n=163)
TOTAL = 927
↓</td></tr>
<tr><td colspan="2">Abstracts screened, excluding duplicates (n=537)</td></tr>
<tr><td>↓
→→→
↓</td><td>Did not meet inclusion criteria (n=508)</td></tr>
<tr><td colspan="2">Full text articles assessed for eligibility (n=29)</td></tr>
<tr><td>↓
→→→
↓</td><td>Met exclusion criteria (n=21)
No placebo control (n=5)
Children and adolescents (n=2)
Treatment resistant (n=2)
Medically ill (n=9)
Relapse prevention (n=2)
Data reported in larger trial (n=1)</td></tr>
<tr><td colspan="2">Articles included in this review (n=8)</td></tr>
</table>

Table 1. Characteristics of included studies

Study	Female (%)	Mean age (range) in years	Sample[a] (total[b]) placebo	Sample[a] (total[b]) citalopram	Completers [c] (%)	Citalopram dose (mg)	Treatment (weeks)	Treatment setting (O)utpatient (I)npatient
Burke 2002	61	40 (18-65)	119 (122)	125 (125)	76	40	8	O
Feighner 1999	60	39 (18-65)	129 (n/p)	521 (n/p)	67	10-60	6	O
Frank 2004	50	40 (29-50)	8 (8)	8 (8)	100	20	4	O
Gastpar 2006	69	49 (18-74)	130 (n/p)	127 (n/p)	95	20	6	O
Lepola 2003	69-72	44 (18-65)	154 (n/p)	159 (n/p)	93	20-40	8	O
Mendels 1999	32-35	43 (18-65)	91 (91)	89 (89)	54	20-80	4	O
Montgomery 1992	69	44 (18-70)	50 (65)	105 (134)	86	20,40	6	O and I
Stahl 2000	58	38 (18-60)	107 (108)	103 (107)	40	20-60	24	O?

Note: [a] participants included in outcome evaluation; [b] total randomized population; [c] proportion of participants completing the study; (n/p) data not published

Table 2. Risk of bias in included studies

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Sponsor?
Burke 2002	?	?	+	+	-	Forest
Feighner 1999	?	?	+	+	-	Lundbeck
Frank 2004	?	?	+	+	-	Forest
Gastpar 2006	+	?	+	+	-	None
Lepola 2003	?	?	+	+	-	Lundbeck
Mendels 1999	?	?	?	+	-	Pfizer
Montgomery 1992	?	?	+	-	-	Lundbeck
Stahl 2000	?	?	+	+	-	Forest

Note: (+) criterion addressed; (-) criterion not addressed; (?) unclear whether the criterion has been addressed

Table 3. Baseline mean scores in included studies

Study	HAM-D placebo	HAM-D citalopram	MADRS placebo	MADRS citalopram	CGI-S placebo	CGI-S citalopram
Burke 2002	25.8	25.9[(c)]	29.5	29.2	4.2	4.3
Feighner 1999	24.6	24.6[(b)]	27.1	27.5	4.3	4.3
Frank 2004	n/p	n/p[(b)]	-	-	-	-
Gastpar 2006	22	21.8[(a)]	-	-	92.3% [(d)]	92.9% [(d)]
Lepola 2003	-	-	28.7	29.2	4.22	4.3
Mendels 1999	24.1	23.9[(a)]	-	-	4.7	4.6
Montgomery 1992	n/p	n/p[(a)]	n/p	n/p	n/p	n/p
Stahl 2000	26.4	26.5[(b)]	31.1	32.4	4.32	4.38

Note: [(a)] HAMD-17 scale; [(b)] HAMD-21 scale; [(c)] HAMD-24 scale; [(d)] percentage of patients rated as moderately, markedly or severely ill; (n/p) data not published; (-) measurement scale not utilised

Table 4. Outcome measures: response or remission

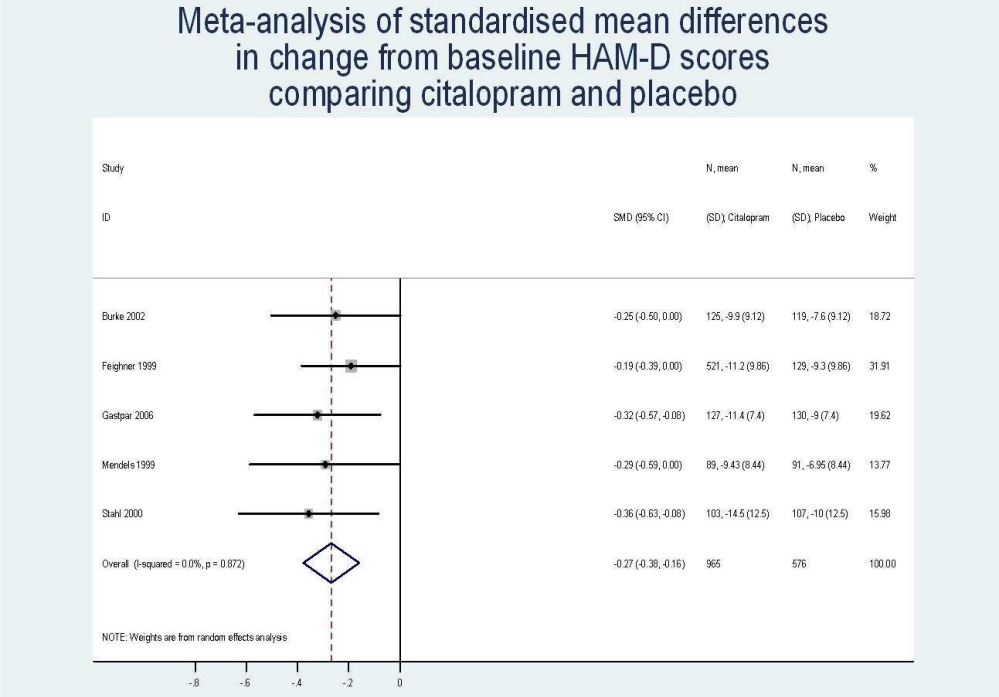
Study	Response placebo (%)	Response citalopram (%)	Response criteria	Remission placebo (%)	Remission citalopram (%)	Remission criteria
Burke 2002	27.7	45.6[(b)]	50% improvement on MADRS	n/p	n/p	n/p
Feighner 1999	n/p	n/p[(a)]	50% improvement on MADRS	n/p	n/p	n/p
Frank 2004	50	63	50% reduction in HAMD score	n/p	n/p	n/p
Gastpar 2006	39.2	55.9[(b)]	HAMD <10 or 50% improvement	n/p	n/p	n/p
Lepola 2003	48.2	52.6 [(c)]	50% improvement on MADRS	n/p	42.8 [(c)]	MADRS < 12
Mendels 1999	47	81[(a)]	Very much or much improved on CGI-I	n/p	n/p	n/p
Montgomery 1992	n/p	n/p	50% improvement on MADRS or HAMD	n/p	n/p	n/p
Stahl 2000	n/p	n/p[(b)]	50% improvement on HAMD	28	45	HAMD-17 <8

Note: [(a)] significantly different from placebo, p<0.05; [(b)] significantly different from placebo, p<0.01; [(c)] observed cases only; (n/p) data not published

Table 5. Outcome measures: change from baseline on HAM-D, MADRS and CGI-S scales

Study	HAM-D placebo	HAM-D citalopram	MADRS placebo	MADRS citalopram	CGI-S placebo	CGI-S citalopram
Burke 2002	-7.6	-9.9[(a)]	-9.4	-12.0[(a)]	-0.8	-1.2[(a)]
Feighner 1999	-9.3	-11.2[(a)]	-9.4	-12.7[(b)]	-1.1	-1.4[(a)]
Frank 2004	n/p	n/p	-	-	-	-
Gastpar 2006	-9.0	-11.4[(b)]	-	-	-34.4% [(c)]	-51.7%[(b)(c)]
Lepola 2003	-	-	-12.1	-13.6	-1.42 [(e)]	-1.58 [(e)]
Mendels 1999	-6.95	-9.43[(a)]	-	-	n/p	n/p[(a)]
Montgomery 1992	n/p	n/p[(a)(d)]	n/p	n/p[(a)(d)]	n/p	n/p [(a)(d)]
Stahl 2000	-10.0	-14.5[(b)]	-11.1	-18.0[(b)]	-1.2	-1.8[(b)]

Note: [(a)] significantly different from placebo, p<0.05; [(b)] significantly different from placebo, p<0.01; [(c)] Decrease in the percentage of patients rated as moderately, markedly or severely ill; [(d)] significant only for citalopram 40mg; [(e)] data from Lepola (2004); (n/p) data not published; (-) scale not utilized



META-ANALYSIS
342x238mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2-3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ open

Citalopram for major depressive disorder in adults: a systematic review and meta-analysis of published placebo-controlled trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000106.R1
Article Type:	Research
Date Submitted by the Author:	16-Jun-2011
Complete List of Authors:	Apler, Alex; Park House, Department of Psychiatry
Primary Subject Heading:	Psychiatry
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Clinical trials < THERAPEUTICS

Citalopram for major depressive disorder in adults: a systematic review and meta-analysis of published placebo-controlled trials

Dr Alex Apler

Park House, Liverpool Hospital, Liverpool, NSW, 2170, Australia
Dr Alex Apler, MBBS, FRANZCP, MSc (LSHTM)
Psychiatrist

Correspondence to: alexapler@gmail.com

I have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from me) and declare: I had financial support from the New South Wales Institute of Psychiatry, in the form of a Research Fellowship, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

ABSTRACT

Objective To assess effectiveness of citalopram for Major Depressive Disorder (MDD) in adults, in a systematic review of all published, randomized, double-blind studies comparing it to a placebo.

Data sources Cochrane Central Register of Controlled Trials, Medline, PsychINFO and Embase.

Study selection Randomised, double-blind, placebo-controlled studies of citalopram in adults with MDD were included. Studies with medically-ill or treatment resistant subjects were excluded, as were studies of relapse prevention. Remission of MDD was defined as a primary outcome, and response or change from baseline scores were defined as secondary.

Data extraction Remission, response and symptom improvement scores on the HAM-D, MADRS and CGI-S scales were extracted. Random-effects meta-analysis was carried out on the

response rates and symptom improvement scores. Included studies were examined for the presence of bias and small study effects.

Results Eight studies (n=2025) met the inclusion criteria. Two studies provided data on remission, but only one of these showed a significant difference between citalopram and placebo (risk ratio=1.59, 95% confidence interval 1.10 to 2.31). Meta-analysis of response rates in five studies (n=1010) revealed significant superiority of citalopram (relative risk=1.42, 95%CI 1.17 to 1.73). Meta-analysis of change from baseline scores in five studies (n=1541) gave a standardised mean difference (Hedges'*g*) of -0.27 (95%CI -0.38 to -0.16), showing reduction in MDD symptoms to be significant for citalopram relative to placebo. There was no evidence of significant small study effects. Overall quality of reporting was poor, with insufficient information about the methodology or outcomes. Seven studies received industry sponsorship.

Conclusions Data concerning remission rates for citalopram, relative to placebo, is inconclusive. Response rates and symptom reduction scores in citalopram-treated patients with MDD are significantly better relative to placebo treatment, according to a meta-analysis of published reports. Evaluation of unpublished data is necessary to more definitively assess the effectiveness of citalopram for MDD.

ARTICLE SUMMARY

Article focus

- Systematic review and meta-analysis of published randomised double blind studies comparing citalopram to placebo in adults with MDD
- Evaluation of the quality of published studies and the risk of bias

Key messages

- Data on remission rates for citalopram in MDD, relative to placebo, is inconclusive
- Response rates and symptom improvement scores are significantly better in citalopram-treated patients than in those taking placebo
- The quality of reporting in published studies is poor
- Further evaluation of citalopram is necessary, incorporating unpublished research

Strengths and Limitations of this study

- This review is based on a thorough search for published placebo-controlled studies of citalopram for adults with MDD, using a broad search strategy. In a departure from previously

Deleted: showing no statistically significant difference between citalopram and placebo.

Deleted: The response rates were inconsistent, with five out of eight studies reporting citalopram to be significantly superior to placebo.

Deleted: statistically, but not clinically,

Deleted: There is no evidence that remission of MDD is significantly better with citalopram treatment than with placebo. Response of MDD to citalopram might be better than to placebo, but the data are inconclusive.

Deleted: S

Deleted: is

Deleted: statistically, but not clinically,

Deleted: Greater transparency, improvement in reporting standards and

Deleted: independent studies of citalopram

Deleted: are

Deleted: Citalopram has a statistical but not clinically-significant advantage in improving symptoms of MDD .

Deleted: Data on the

Deleted: r

Deleted: for MDD are inconsistent, and there is no evidence that remission rates are significantly better for citalopram than placebo .

Deleted: P

Formatted: Indent: Left: 0 pt, Hanging: 7.1 pt, Bulleted + Level: 1 + Aligned at: 0 pt + Tab after: 0 pt + Indent at: 18 pt

Deleted: comparing citalopram to placebo may be affected by bias, and the quality of reporting in published studies is poor

published reviews, this study assesses the risk of bias and includes remission as a primary outcome.

- This study would have been enhanced if the missing data were available for a more complete analysis, and unpublished studies satisfying inclusion criteria were incorporated into this review.

INTRODUCTION

Citalopram is a selective serotonin reuptake inhibitor antidepressant, commonly used in the treatment of Major Depressive Disorder (MDD). It is often recommended as a first line treatment for this condition. This recommendation, however, depends on the quality of studies evaluating this drug, and measures of effectiveness utilised. These issues have not been adequately addressed in previous reviews[1 2]

A re-examination of the role of citalopram in the treatment of MDD is therefore necessary, taking into account the quality of studies, risk of bias, and different measures of effectiveness. *Remission* of MDD is the most clinically-relevant measure of effectiveness that should be sought when evaluating citalopram for MDD[3-5]. The emphasis on remission when evaluating effectiveness can be contrasted with earlier reviews of citalopram, focussing on *symptom improvement* or *response* as the main measures of outcome. Filling this gap in the literature, I systematically reviewed all published randomised, placebo-controlled studies of citalopram in adults with MDD. I examined the quality of published studies and the risk of bias, setting remission of MDD as the primary measure of effectiveness in this review.

METHODS

Selection Criteria

I selected published, randomized, double-blind studies comparing citalopram to placebo among adult participants over the age of 18, who were diagnosed with MDD using DSM-III [6], DSM-IIIR [7], DSM-IV [8], ICD-9 [9] or ICD-10 [10]. No upper age limit for study participants was set. Studies with a third comparator (eg another antidepressant) were included, if a direct comparison between citalopram and placebo treatments was possible. Studies involving patients with severe medical illness, other psychiatric disorder or substance abuse were excluded from this review. Studies of MDD that focused on relapse prevention, treatment augmentation or treatment-resistant cases were also excluded, as these studies would have introduced additional heterogeneity into this evaluation.

Outcomes

Deleted: a meta-analysis of randomised, placebo-controlled trials.

Deleted: further

Deleted: original

Deleted: obtained from the authors

Deleted: in guidelines for managing depression, such as those published by NICE

Deleted: [1]

Deleted: .¶
¶
Whether citalopram is sufficiently effective to recommend it as treatment of MDD

Formatted: Font: Not Bold

Deleted: . While earlier reviews have concluded that citalopram is effective for MDD

Deleted: , these conclusions can be questioned in the light of more recent research highlighting the potential presence of bias in industry-sponsored systematic reviews

Deleted: [4]

Deleted: and randomised trials

Deleted: [5]

Deleted: , arguably,

Deleted: rigorous and

Primary outcome. Remission of MDD. Remission was defined as: a score of less than 8 on the 17-item Hamilton Depression Scale (HAM-D) [11]; less than 9 on longer versions of HAM-D; less than 12 on the Montgomery Asberg Depression Rating Scale (MADRS) [12] or "not ill or borderline mentally ill" on Clinical Global Impression – Severity (CGI-S) scale [13]. These cut-off points provide a consistent definition of "remission"[14 15].

Secondary outcomes. (a) Response of MDD. Response was defined as a reduction of at least 50% on the HAM-D or MADRS scales; or "much or very much improved" on the CGI-I (CGI-Improvement) scale. HAM-D, MADRS and CGI-I have a similar sensitivity to change in depression symptom ratings [16]. (b) Any reduction in the severity of depression, measured as a reduction in scores relative to baseline values (change from baseline), on the HAM-D, MADRS or CGI scales.

Deleted: 7 or

Deleted: 8 or

Deleted: 11 or

Formatted: Font: Calibri, 12 pt

Deleted: Any change from baseline scores on the HAM-D, MADRS or CGI scales.

Search methods

I carried out an electronic search of the Cochrane Central Register of Controlled Trials, Medline (from 1950), PsychINFO (from 1967) and EMBASE (from 1980) up to February 2011. Articles with "citalopram", "placebo" and "major or severe depression", as keywords or exploded MeSH terms, were searched by combining (exp citalopram/ OR citalopram.mp) AND (exp placebo/ OR placebo*.mp) AND (exp depressive disorder/ OR (depress* adj2 (major* or severe*)).mp). The term "placebos" was used as a MeSH heading in the Medline, Cochrane and EMBASE database searches and "major depression" was used as a MeSH heading in the PsychINFO search. No limits were set for these searches, apart from the EMBASE search, which was limited to the adult population because of the large number of ineligible studies produced by the unrestricted search.

I examined the abstracts of all identified studies, selecting randomised double blind studies of citalopram in patients with major depressive disorder. Reference lists of review articles and other studies of citalopram were also searched for publications satisfying the inclusion criteria. I then obtained full text copies of these articles and excluded those that: lacked a placebo control group; involved children, adolescents, medically ill or treatment resistant population; or were studies of relapse prevention or of patients with another psychiatric illness.

Data collection

I extracted data into an electronic form with sections for each study describing the methods used, study participants, interventions and measured outcomes, as well as sections for bias evaluation. I reviewed each paper on at least two occasions, to check for accuracy of selection and data extraction, over a three month period.

Formatted: Font: Calibri, 12 pt

Data on the characteristics of study participants were entered into a table, recording age and sex of participants, sample sizes in the citalopram and placebo treatment groups, medication

doses, drop-out rates and treatment duration. The number of subjects randomised, and the number included in outcome evaluation, were extracted from each study where possible. I recorded baseline measures of symptom severity and the treatment setting for each study.

I tabulated the proportions of patients that achieved response or remission in the citalopram and placebo arms of selected studies. I included the definitions of "response" and "remission" terms used and extracted the change from baseline measures on the HAM-D, MADRS or CGI depression scales.

Data analysis

Risk of bias was evaluated in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*[17], using the following parameters: adequacy of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; and selective outcome reporting. Small study effects were investigated using a funnel plot. Meta-analysis of response rates was performed to calculate an overall relative risk of a response to citalopram, compared to placebo, in a random effects model, using Stata 9.2.

I carried out a meta-analysis of the change-from-baseline scores on the 17, 21 and 24-item HAM-D scales for participants included in outcome evaluation. I applied a random effects model to calculate Hedges' *g* for standardised mean differences between citalopram and placebo groups. Standard deviations (SD) were computed from the p-values, taken at the upper limit and converted into a t-statistic. I used the formula $SD = SE/\sqrt{(1/N_e+1/N_c)}$, where SE (standard error) = difference in means of the two change from baseline scores divided by the t-statistic, and N_e and N_c are the sample sizes in the experimental and control groups respectively. I multiplied the result by -1 to convert a measure of symptom reduction into an improvement score.

RESULTS

A search of the Cochrane Central Register of Controlled Trials using the above search terms produced 31 unique articles, Medline 244, PsychINFO 60 and EMBASE 202, giving a total of 537 articles, after removing duplicates. The selection process is described in Figure 1.

I inspected the abstracts from the above searches and selected 29 studies for possible inclusion. After examining full text copies of these studies, I compiled a final list of eight studies[18-25] that satisfied the inclusion and exclusion criteria. Excluded studies lacked a placebo control [26-30], focused on relapse prevention [31 32], or were studies of children [33 34], medically ill [35-43] or treatment-resistant subjects [44 45]. The study by Montgomery [46] was excluded as the data in this study were reported in a larger trial by Lepola [22].

Characteristics of included studies

Deleted:
Deleted: [21]
Deleted: and the Revised CONSORT Statement
Deleted: [22]
Deleted: ,
Deleted: whether
Deleted: in the studies had been addressed
Deleted: ; and industry sponsorship
Deleted: I entered (+) into the table when the criterion was satisfied, (-) when it was not satisfied, and (?) when I had insufficient information to reach a conclusion.¶
Formatted: Indent: Left: 0 pt
Deleted: HAM-D
Formatted: Font: Calibri, 12 pt
Formatted: Font: Calibri, 12 pt
Deleted: , using Stata 9.2

The combined sample from eight studies consisted of 1237 subjects in the citalopram group and 788 in the placebo group (total = 2025). The studies were brief, two to eight weeks in duration, apart from one study [25] which was 24 weeks in length. The mean age of participants was 42 years, with the age ranging between 18 and 74 years. Females constituted two-thirds of the sample in most studies, and the dose of citalopram ranged from 10 to 80mg a day. One study [20] had only 16 participants. All patients recruited in these studies were diagnosed with MDD using the criteria in the Diagnostic and Statistical Manual of Mental Disorders III, III-R or IV. Most participants were recruited in outpatient settings. All studies, except for Gastpar 2006, received industry sponsorship.

Risk of bias

The risk of bias in included studies is summarised in Table 1. Most studies provided insufficient information to determine whether the random sequence generation, allocation concealment and blinding of outcome assessors were adequate. Selective reporting of outcome data was evident in all studies, as easily extractable summary statistics like remission and response rates were often omitted from publication, or data were presented in a form that could not be incorporated into a meta-analysis. Most studies reported blinding of participants and intention to treat analyses, using the last observation carried forward approach.

Baseline characteristics of subjects

Hamilton Depression Scale (HAM-D). Five studies provided mean baseline HAM-D scores[18 19 21 23 25]. The patients in these studies had mean baseline HAM-D scores above 17, showing that they were moderately to severely depressed.

Montgomery-Asberg Depression Rating Scale (MADRS). Baseline mean MADRS scores were provided in four studies[18 19 22 25]. The mean MADRS scores in these studies were above 22, indicating that patients were moderately (scores between 22 and 29) to severely (scores of 30 or above) depressed.

Clinical Global Impressions-Severity (CGI-S). All studies, except for Frank *et al.* [20] and Montgomery *et al.* [24] provided mean baseline CGI-S scores. Average baseline scores in these study populations were above four, indicating a moderate level of illness severity. In the study by Gastpar *et al.*[21], more than 92% of patients were assessed as moderately, markedly or severely depressed.

Outcomes

Remission. Two of the eight studies reported remission rates. Stahl [25] reported a 45% remission rate in the citalopram group, and 28% remission rate in the placebo group at the end of a 24

Deleted: Characteristics of included studies are described in Table 1.

Deleted: only

Deleted: The combined sample from the eight studies consisted of 1237 subjects in the citalopram group and 788 in the placebo group (total = 2025).

Deleted: 2

Deleted: was

Deleted: The study by Gastpar *et al.*

Deleted: [26]

Deleted: was an exception, providing detailed information on the randomization method employed. None of the studies provided sufficient information for assessing the adequacy of allocation concealment. Four reports [23 24 26 29] described the blinding methods used but none of the studies had commented on whether the adequacy of blinding had been assessed.¶
¶
Data in the study by Montgomery *et al.*

Deleted: [29]

Deleted: were incomplete, with no data provided on patients leaving the study in the first three weeks. In contrast, Feighner *et al.*

Deleted: [24]

Deleted: undertook efficacy analyses on all "patients randomly assigned to study medication" and Frank *et al.*

Deleted: [25]

Deleted: provided outcome data for all 16 participants. The intention-to-treat samples in the remaining studies were defined as randomized patients who took at least one dose of study medication and had at least one post-baseline outcome assessment.¶ ... [1]

Deleted: Only one study

Deleted: [30]

Deleted: provided remission rates for both placebo and citalopram grou ... [2]

Deleted: [26]

Deleted: received industry sponsorship.

Deleted: Baseline characteristics of patients in included studies are de ... [3]

Deleted: Remission and response rates are presented in Table 4.

week trial (risk ratio=1.59, 95% confidence interval 1.10 to 2.31), with remission defined as a score of less than 8 on HAMD-17. Lepola *et al.* [22] reported a remission rate of 42.8% in the citalopram group, with remission defined as a score of less than 12 on MADRS, but this rate was not significantly different from placebo. This evaluation was based on observed cases only and no comparable data for the placebo group was provided. Meta-analysis of this small and incomplete dataset of only two studies was not carried out, given the risk of producing an unreliable result.

Response rates. Five studies (n=1010) reported response rates, and these were included in the meta-analysis (Figure 2). Overall risk ratio for symptom response with citalopram, relative to placebo, was 1.42 (95% confidence interval 1.17 to 1.73), indicating that response of MDD in citalopram-treated subjects was 42% more likely than in those taking placebo. There was no significant heterogeneity between studies (I^2=50.9%, p=0.087). The study by Gastpar *et al.* [21] was considered suitable for inclusion in this meta-analysis, despite it using a mixed definition of "response" – 50% improvement or a final score of less than 10 on the HAM-D.

A funnel plot based on the odds ratios of response rates in these five studies did not reveal any significant small study effects (Figure 3).

Change from Baseline. Five studies, with a total of 1541 subjects, were included in the meta-analysis of change from baseline scores (Figure4). The study by Lepola *et al.* was excluded as it provided no information for calculating standard deviations, and the studies by Frank *et al.* and Montgomery *et al.* did not report the change from baseline measures for their subjects.

Hedges' *g* for the standardised mean difference in the change from baseline scores, comparing citalopram to the placebo group, was -0.27 (95% confidence interval -0.38 to -0.16), which converted to a small but significant improvement score of 0.27. This result indicates that the improvement in the HAM-D scores of subjects treated with citalopram was 0.27 standard deviations better than the improvement in those treated with placebo. There was no significant heterogeneity in the change from baseline HAM-D measures (I^2=0%; p=0.872) in the studies included in meta-analysis.

DISCUSSION

Summary of main results

Two studies provided data on remission rates for citalopram relative to placebo: the difference in remission rates was statistically significant in one study, but not the other. It is therefore not possible to draw definite conclusions regarding this outcome on the basis of the published data, and further evaluation is required, incorporating unpublished results.

Deleted: The difference between the two groups was not statistically significant.

Deleted: Gastpar *et al.*

Deleted: [26]

Deleted: provided combined data on the proportion of patients that achieved a reduction to a score of less than 10 or an improvement of 50% on HAMD, but no separate data on remission rates in his study. Remission rates in other studies were not published.

Deleted: ¶

Formatted: Space Before: 12 pt

Deleted: Burke *et al.*

Deleted: [23]

Deleted: and Mendels *et al.*

Deleted: [28]

Deleted: found significantly superior response rates in the citalopram group, compared to placebo. Stahl

Deleted: [30]

Deleted: and Feighner *et al.*

Formatted: Superscript

Deleted: [24]

Deleted: also reported significantly superior response rates in the citalopram groups, but did not publish the actual data for these results.

Deleted: found a significant difference in response rates but used

Deleted: –

Deleted: making it difficult to co ... [4]

Deleted: [29]

Deleted: reported no significan ... [5]

Deleted: [25]

Deleted: , which used a small sa ... [6]

Deleted: [27]

Deleted: , which relied on obser ... [7]

Deleted: *Change from baseline.* ... [8]

Deleted: [25]

Deleted: provided no informati ... [9]

Deleted: n

Deleted: had a small but signif ... [10]

Formatted: Superscript

Response rates and change from baseline scores for citalopram, relative to placebo, were statistically significant in these meta-analyses, each one based on a subset of five studies. No significant heterogeneity between these studies was detected. These data provide support for the use of citalopram in MDD, at least in the first eight weeks of treatment.

Small study effects were not evident in this review, as there was no marked asymmetry on the visual inspection of the funnel plot. However, a formal test of asymmetry was not performed, given the small sample of five studies in this analysis. Publication bias is one potential source of plot asymmetry, not evident here, although this should be more fully assessed after obtaining unpublished research.

The quality of reporting in the reviewed studies was generally poor, with insufficient data to reach conclusions regarding the adequacy of randomisation, allocation concealment and blinding of assessors. Most studies omitted data on the remission rates, and none of the studies reported a full set of outcome variables in a way that can be incorporated in a meta-analysis. Inadequate reporting and industry sponsorship of these studies raises the possibility of bias and carries a risk to the validity of this review.

Agreements and disagreements with other studies or reviews

My estimation of the standardised mean difference for the change from baseline scores is similar to Hedges' *g* of 0.31 calculated by Turner on the basis of published studies[47]. Importantly, Turner revised the estimation of citalopram's effectiveness to 0.01 after including unpublished results. My conclusions regarding the effect of citalopram on the response and symptom improvement in MDD is consistent with the earlier reviews of this drug[1 48-50]. Those reviews, however, have not examined the risk of bias in published studies, or the effect of citalopram on remission of MDD. Remission is an important outcome in clinical practice[4 5], and my study highlights the limited data on this outcome in published research.

Limitations

This systematic review is limited to published studies. Its results are subject to a review of unpublished research and outcome data that is missing from published reports. Nevertheless, this review may serve as a useful summary of published data, highlighting the risk of bias and the paucity of published research into the effect of citalopram on remission of MDD.

This review has been undertaken by a single reviewer. While a single reviewer may be able to select and extract unambiguous data, additional reviewers can help reach consensus regarding areas of ambiguity in published reports. That consensus, however, should not replace missing or ambiguous data, or substitute the importance of adequate reporting that is necessary for a systematic review.

Deleted: ¶
Citalopram is not significantly better than placebo in producing remission of MDD in adults, according to two studies reporting this outcome measure. Citalopram may be significantly better than placebo in producing a response in MDD, but this is inconclusive, as five studies reported statistically significant differences in response between the two groups, and three did not. The use of inconsistent definitions of "response" in these studies complicates evaluation of this outcome. Most of the studies were probably too brief to adequately ... [11]

Deleted: [1]

Deleted: , treatment with citalo ... [12]

Deleted: [55]

Deleted: . Clinical advantage of ... [13]

Deleted: [7]

Deleted: as satisfying industry ... [14]

Deleted: [58]

Deleted: ¶ ... [15]

Deleted: [59]

Deleted: points out, patients w ... [16]

Deleted: [7]

Deleted: points out, higher re ... [17]

Deleted: [61]

Deleted: . However, such a tre ... [18]

Deleted: [64]

Deleted: , conceal treatment allocation

Deleted: [65]

Deleted: and blind participant ... [19]

Deleted: [66]

Deleted: . Such information is ... [20]

Deleted: [67]

Deleted: , after highlighting th ... [21]

Deleted: [68]

Deleted: . The desire to show a ... [22]

Deleted: [69]

Deleted: . This "wish" for a par ... [23]

Deleted: I estimated the effect ... [24]

Deleted: I

Deleted: his

Deleted: was revised down

CONCLUSION

The reviewed published studies show that citalopram has a statistically significant advantage over placebo with respect to symptom improvement and response rates in adults with MDD. Its role in symptom remission is less clear, given the contradictory findings of the two studies with remission data in this review. The quality of reporting in the reviewed studies is poor, and further evaluation of citalopram, incorporating unpublished research, is necessary to more definitively evaluate its effectiveness in MDD.

Ethics approval: Not required

Competing interests: None

Funding / acknowledgements: This publication is based on a project report submitted to the London School of Hygiene and Tropical Medicine in part satisfaction of course requirements for MSc Epidemiology. Publication of this article was supported by a research fellowship from the New South Wales Institute of Psychiatry. I am the sole author of this article.

Data sharing: The technical appendix is available from the corresponding author at alexapler@gmail.com

Deleted: My assessment of citalopram's effectiveness in the treatment of MDD differs from the conclusions of previous reviews [1 2 48 49], which focus on the change from baseline scores and conclude that citalopram has a significant advantage over placebo. Three of these reviews received industry support. In contrast, I find that: citalopram has a statistical but not clinically significant advantage over placebo, as shown by the change from baseline scores; data concerning response rates are inconsistent; and remission rates for citalopram have not been demonstrated to be significantly better than for placebo. ¶
¶

Deleted: The role of citalopram in the treatment of MDD can be questioned in view of the evidence of its limited effectiveness presented in this paper. Other antidepressants, with better remission rates relative to placebo, may be preferable for this condition. Revision of the depression treatment guidelines may be necessary in the light of this finding.¶
¶
The articles reviewed in this paper are of insufficient quality to definitively evaluate the effectiveness of citalopram for MDD. More research into the effectiveness of citalopram for MDD in longer trials may be necessary, but more importantly, greater transparency is required for research into this drug. That transparency is difficult to achieve when the research data are proprietary, which increases the importance of providing detailed information about the research in published reports.¶
¶

References

1. Keller MB. Citalopram therapy for depression: a review of 10 years of European experience and data from U.S. clinical trials. *J Clin Psychiatry* 2000;61(12):896-908.
2. Montgomery SA, Djarv L. The antidepressant efficacy of citalopram. *Int Clin Psychopharmacol* 1996;11 Suppl 1:29-33.
3. Ferrier IN. Treatment of major depression: is improvement enough? *J Clin Psychiatry* 1999;60 Suppl 6:10-4.
4. Keller MB. Remission versus response: the new gold standard of antidepressant care. *J Clin Psychiatry* 2004;65 Suppl 4:53-9.
5. Thase ME. Evaluating antidepressant therapies: remission as the optimal outcome. *J Clin Psychiatry* 2003;64 Suppl 13:18-25.
6. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III)*. 3rd ed. ed. Washington, DC: American Psychiatric Association, 1980.
7. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III-R)*. 3rd ed rev. ed. Washington, DC: American Psychiatric Association, 1987.
8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV)*. 4th ed. ed. Washington, D.C.: American Psychiatric Association, 1994.
9. World Health Organization. *The ninth revision of the international classification of diseases and related health problems (ICD-9)*. Geneva: World Health Organization, 1978.

10. World Health Organization. *The tenth revision of the international classification of diseases and related health problems (ICD-10)*. 10th revision. ed. Geneva: World Health Organization, 1992.
11. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
13. Guy W, Bonato RR, editors. *Manual for the ECDEU Assessment Battery 2*: National Institute of Mental Health, Chevy Chase, Md, 1970.
14. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *J Psychiatr Res* 2004;38(6):577-82.
15. Hawley CJ, Gale TM, Sivakumaran T. Defining remission by cut off score on the MADRS: selecting the optimal value. *J Affect Disord* 2002;72(2):177-84.
16. Khan A, Brodhead AE, Kolts RL. Relative sensitivity of the Montgomery-Asberg depression rating scale, the Hamilton depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials: a replication analysis. *Int Clin Psychopharmacol* 2004;19(3):157-60.
17. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*: The Cochrane Collaboration, 2011.
18. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002;63(4):331-6.
19. Feighner JP, Overo K. Multicenter, placebo-controlled, fixed-dose study of citalopram in moderate-to-severe depression. *J Clin Psychiatry* 1999;60(12):824-30.
20. Frank MG, Hendricks SE, Burke WJ, Johnson DR. Clinical response augments NK cell activity independent of treatment modality: a randomized double-blind placebo controlled antidepressant trial. *Psychol Med* 2004;34(3):491-8.
21. Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. *Pharmacopsychiatry* 2006;39(2):66-75.
22. Lepola UM, Loft H, Reines EH. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003;18(4):211-7.
23. Mendels J, Kiev A, Fabre LF. Double-blind comparison of citalopram and placebo in depressed outpatients with melancholia. *Depress Anxiety* 1999;9(2):54-60.
24. Montgomery SA, Rasmussen JG, Lyby K, Connor P, Tanghoj P. Dose response relationship of citalopram 20 mg, citalopram 40 mg and placebo in the treatment of moderate and severe depression. *Int Clin Psychopharmacol* 1992;6 Suppl 5:65-70.
25. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 2000;48(9):894-901.
26. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. *Psychopharmacology* 1986;90(1):131-8.
27. Karlsson I, Godderis J, Augusto De Mendonca Lima C, Nygaard H, Simanyi M, Taal M, et al. A randomised, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. *Int J Geriatr Psychiatry* 2000;15(4):295-305.

28. Kyle CJ, Petersen HE, Overo KF. Comparison of the tolerability and efficacy of citalopram and amitriptyline in elderly depressed patients treated in general practice. *Depress Anxiety* 1998;8(4):147-53.
29. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol* 2005;20(3):131-7.
30. Shaw DM, Thomas DR, Briscoe MH, Watkins SE, Crimmins R, Harris B, et al. A comparison of the antidepressant action of citalopram and amitriptyline. *Br J Psychiatry* 1986;149:515-7.
31. Montgomery SA, Rasmussen JG, Tanghoj P. A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. *Int Clin Psychopharmacol* 1993;8(3):181-8.
32. Robert P, Montgomery SA. Citalopram in doses of 20-60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. *Int Clin Psychopharmacol* 1995;10 Suppl 1:29-35.
33. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hulten A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol* 2006;26(3):311-5.
34. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry* 2004;161(6):1079-83.
35. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. *Stroke* 1994;25(6):1099-104.
36. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biol Psychiatry* 2005;58(11):865-70.
37. Devos D, Dujardin K, Poirot I, Moreau C, Cottencin O, Thomas P, et al. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. *Mov Disord* 2008;23(6):850-7.
38. Fraguas R, da Silva Telles RM, Alves TC, Andrei AM, Rays J, Iosifescu DV, et al. A double-blind, placebo-controlled treatment trial of citalopram for major depressive disorder in older patients with heart failure: the relevance of the placebo effect and psychological symptoms. *Contemp Clin Trials* 2009;30(3):205-11.
39. Kraus MR, Schafer A, Schottker K, Keicher C, Weissbrich B, Hofbauer I, et al. Therapy of interferon-induced depression in chronic hepatitis C with citalopram: a randomised, double-blind, placebo-controlled study. *Gut* 2008;57(4):531-6.
40. Lesperance F, Frasure-Smith N, Koszycki D, Laliberte MA, van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007;297(4):367-79.
41. Nyth AL, Gottfries CG, Lyby K, Smedegaard-Andersen L, Gylding-Sabroe J, Kristensen M, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. *Acta Psychiatr Scand* 1992;86(2):138-45.
42. Roose SP, Sackeim HA, Krishnan KR, Pollock BG, Alexopoulos G, Lavretsky H, et al. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo-controlled trial. *Am J Psychiatry* 2004;161(11):2050-9.

43. Wermuth L, Sørensen PS, Timm S, Christensen B, Utzon NP, Boas J, et al. Depression in idiopathic Parkinson's disease treated with citalopram: A placebo-controlled trial. *Nordic Journal of Psychiatry* 1998;52(2):163-69.

44. Altamura AC, Dell'Osso B, Buoli M, Bosi M, Mundo E. Short-term intravenous citalopram augmentation in partial/nonresponders with major depression: a randomized placebo-controlled study. *Int Clin Psychopharmacol* 2008;23(4):198-202.

45. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol* 1996;16(4):307-14.

46. Montgomery SA, Loft H, Sanchez C, Reines EH, Papp M. Escitalopram (S-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. *Pharmacol Toxicol* 2001;88(5):282-6.

47. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358(3):252-60.

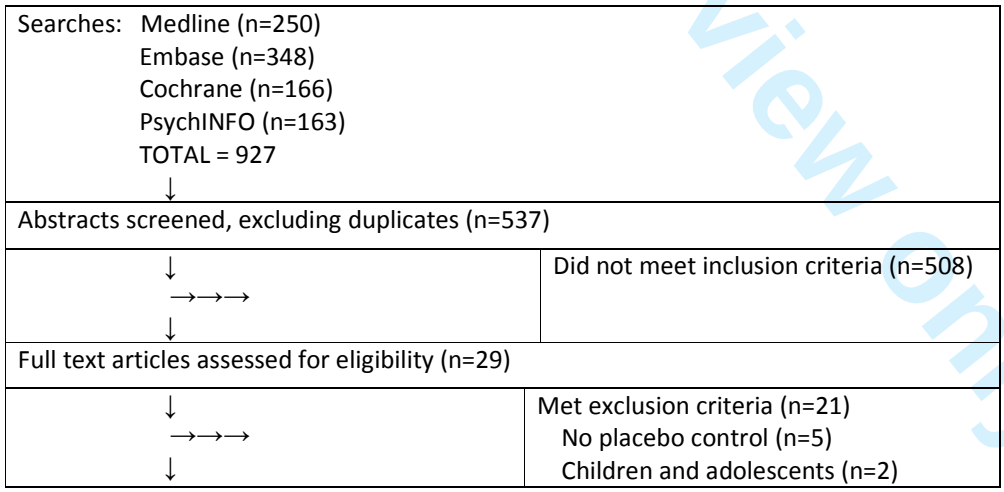
48. Montgomery SA, Pedersen V, Tanghoj P, Rasmussen C, Rioux P. The optimal dosing regimen for citalopram--a meta-analysis of nine placebo-controlled studies. *Int Clin Psychopharmacol* 1994;9 Suppl 1:35-40.

49. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. *CNS Spectr* 2002;7(4 Suppl 1):40-4.

50. Parker NG, Brown CS. Citalopram in the treatment of depression. *Ann Pharmacother* 2000;34(6):761-71.

APPENDIX

Figure 1. Summary of the article selection process



	Treatment resistant (n=2) Medically ill (n=9) Relapse prevention (n=2) Data reported in larger trial (n=1)
Articles included in this review (n=8)	

Table 1. Risk of bias in included studies

Study	Random sequence generation	Allocation concealment	Blind participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective reporting
Burke 2002	Unclear	Unclear	Low	Unclear	Low	High
Feighner 1999	Unclear	Unclear	Low	Unclear	Low	High
Frank 2004	Unclear	Unclear	Low	Unclear	Low	High
Gastpar 2006	Low	Unclear	Low	Unclear	Low	High
Lepola 2003	Unclear	Unclear	Low	Unclear	Low	High
Mendels 1999	Unclear	Unclear	Unclear	Unclear	Low	High
Montgomery 1992	Unclear	Unclear	Low	Unclear	High	High
Stahl 2000	Unclear	Unclear	Low	Unclear	Low	High

Deleted: ¶

Deleted: Table 1. Characteristics of included studies ¶ ¶ Study ... [25]

Deleted: 2

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Formatted: Line spacing: single

Deleted: ¶ Study ... [26]

Page 6: [1] Deleted 6/11/2011 9:56:00 PM

provided outcome data for all 16 participants. The intention-to-treat samples in the remaining studies were defined as randomized patients who took at least one dose of study medication and had at least one post-baseline outcome assessment.

Page 6: [2] Deleted 6/11/2011 9:57:00 PM

provided remission rates for both placebo and citalopram groups. Three of the studies [24 29 30] did not provide response rates and two of the studies [25 29] did not provide data on changes in outcome measures compared to baseline. All studies except one

Page 6: [3] Deleted 6/13/2011 10:02:00 PM

Baseline characteristics of patients in included studies are described in Table 3.

Page 7: [4] Deleted 6/13/2011 11:43:00 PM

making it difficult to compare his results to other studies.

Response rates for citalopram were not significantly superior to placebo in other studies. Montgomery *et al.*

Page 7: [5] Deleted 6/13/2011 11:39:00 PM

reported no significant difference in response rates, without publishing the data to support this finding. There was also no significant difference in response rates in the study by: Frank *et al.*

Page 7: [6] Deleted 6/13/2011 11:39:00 PM

, which used a small sample and may not have had sufficient power to detect a difference; and Lepola *et al.*

Page 7: [7] Deleted 6/13/2011 11:39:00 PM

, which relied on observed cases to assess response.

Page 7: [8] Deleted 6/11/2011 10:06:00 PM

Change from baseline. Change from baseline scores are set out in Table 5. Five studies [23 24 26 28 30] reported significant improvement in depression scores with citalopram, relative to placebo. Montgomery *et al.* also reported depression scores in the citalopram group to be significantly superior to placebo, but did not provide the actual data for this comparison. Lepola *et al.* [27 52] found no statistically significant difference in score improvements between the two groups, and Frank *et al.*

Page 7: [9] Deleted 6/11/2011 10:06:00 PM

provided no information on this outcome measure.

Meta-analysis of change from baseline scores

Page 7: [10] Deleted 6/10/2011 2:53:00 AM

had a small but significant improvement in their baseline HAM-D scores, relative to

Page 8: [11] Deleted 6/14/2011 10:39:00 AM

Citalopram is not significantly better than placebo in producing remission of MDD in adults, according to two studies reporting this outcome measure. Citalopram may be significantly better than placebo in producing a response in MDD, but this is inconclusive, as five studies reported statistically significant differences in response between the two groups, and three did not. The use of inconsistent definitions of "response" in these studies complicates evaluation of this outcome. Most of the studies were probably too brief to adequately assess remission and response rates in patients with MDD, as longer trials are necessary to adequately assess the effect of citalopram on these outcome variables[53 54].

Meta-analysis of standardised mean differences in the change from baseline HAM-D scores indicates that there is a small but statistically significant improvement in symptom scores with citalopram treatment, relative to placebo. However, statistically significant improvement does not necessarily point to a clinically significant benefit for patients with MDD. Using a medium effect size of 0.5 as a cut-off for clinical significance adopted by NICE

Page 8: [12] Deleted 6/10/2011 1:10:00 AM

, treatment with citalopram may produce a small but not clinically-significant improvement in symptoms of MDD

Page 8: [13] Deleted 6/10/2011 1:10:00 AM

. Clinical advantage of citalopram is more likely to be evident in patients with severe MDD similar to those recruited in these studies; those with mild to moderate MDD often have a smaller response to antidepressant treatment[56 57].

Improvement, response or remission?

The studies reviewed in this paper focus on the change from baseline scores as the main outcome variable. Focus on this outcome measure has been criticised by Keller

Page 8: [14] Deleted 6/14/2011 10:43:00 AM

as satisfying industry and research imperatives rather than clinical needs.
Demonstration of statistically significant improvement in scores of citalopram-treated patients may be sufficient to fulfil regulatory requirements for drug registration, and may provide interim data in longer trials.
Statistical measure of improvement, however, may not help clinicians assess whether citalopram would be of benefit for MDD, a disorder with a "dynamic and changeable" symptomatic course.

Page 8: [15] Deleted 6/14/2011 10:43:00 AM

Response is more clinically-meaningful than improvement, as a measure of symptom amelioration, but may still be of limited value in clinical settings, for instance, when deciding whether to alter treatment. Furthermore, response is a relative measure, with the degree of improvement necessary for a "response" being influenced by baseline symptom severity. As Nierenberg

Page 8: [16] Deleted **6/14/2011 11:26:00 AM**

points out, patients with severe depression scoring 32 on HAM-D would achieve response with the score falling to 16, but this lower rating may still be sufficiently high for them to be considered depressed.

The most clinically-helpful measure is remission, but most studies reviewed here do not provide remission rates for MDD. The study authors may be reluctant to provide these data because only 20% to 30% of patients treated with selective serotonin reuptake inhibitors achieve remission during short-term therapy [6 60]. As Keller

Page 8: [17] Deleted **6/14/2011 11:29:00 AM**

points out, higher remission rates may be achieved by administering drugs in greater doses, using a flexible dosing regime, with augmentation strategies and for longer periods

Page 8: [18] Deleted **6/14/2011 11:29:00 AM**

. However, such a treatment approach may not fit the objectives of industry-sponsored trials designed to demonstrate the efficacy and safety of a specific drug. In the absence of data on remission rates favouring citalopram, preference may be given to other drugs with superior remission rates, relative to placebo, when treating MDD[62 63].

Bias

Inadequate description of research methodology in the included studies raises apprehension of bias. There was little information in the reviewed papers about the methods used to generate random sequences

Page 8: [19] Deleted **6/14/2011 1:00:00 PM**

and blind participants, clinicians and evaluators

Page 8: [20] Deleted **6/14/2011 1:00:00 PM**

. Such information is essential for evaluating trial integrity, and while the absence of this information does not in itself establish bias, it can cause doubt in the audience about the validity of published results. For instance, Moncrieff

Page 8: [21] Deleted **6/14/2011 1:00:00 PM**

, after highlighting the methodological shortcomings in antidepressant trials, questioned the effectiveness of antidepressants.

Industry sponsorship of the reviewed studies adds to the apprehension of bias. Industry-sponsored research may be influenced by "potentially massive financial gains" associated with research demonstrating drug effectiveness

Page 8: [22] Deleted **6/14/2011 1:00:00 PM**

. The desire to show a drug to be more effective than its comparator, or the belief that it is so, may be described as a "wish bias" in antidepressant research

Page 8: [23] Deleted 6/14/2011 1:00:00 PM

. This "wish" for a particular outcome in drug research can be contrasted with the objective, dispassionate stance that scientific research demands.

Page 8: [24] Deleted 6/14/2011 2:52:00 PM

I estimated the effectiveness of citalopram, relative to placebo, as Hedges' *g* of 0.27 in this meta-analysis of five published studies. This result

Page 13: [25] Deleted 6/13/2011 9:26:00 PM

Table 1. Characteristics of included studies

Study	Female (%)	Mean age (range) in years	Sample[(a)] (total[(b)]) placebo	Sample[(a)] (total[(b)]) citalopram	Completers [(c)] (%)	Citalopram dose (mg)	Treatment (weeks)	Treatment setting (O)utpatient (I)npatient
Burke 2002	61	40 (18-65)	119 (122)	125 (125)	76	40	8	O
Feighner 1999	60	39 (18-65)	129 (n/p)	521 (n/p)	67	10-60	6	O
Frank 2004	50	40 (29-50)	8 (8)	8 (8)	100	20	4	O
Gastpar 2006	69	49 (18-74)	130 (n/p)	127 (n/p)	95	20	6	O
Lepola 2003	69-72	44 (18-65)	154 (n/p)	159 (n/p)	93	20-40	8	O
Mendels 1999	32-35	43 (18-65)	91 (91)	89 (89)	54	20-80	4	O
Montgomery 1992	69	44 (18-70)	50 (65)	105 (134)	86	20,40	6	O and I
Stahl 2000	58	38 (18-60)	107 (108)	103 (107)	40	20-60	24	O?

Note: [(a)] participants included in outcome evaluation; [(b)] total randomized population; [(c)] proportion of participants completing the study; (n/p) data not published

Page 13: [26] Deleted 6/11/2011 9:34:00 PM

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Sponsor?
Burke 2002	?	?	+	+	-	Forest
Feighner 1999	?	?	+	+	-	Lundbeck
Frank 2004	?	?	+	+	-	Forest
Gastpar 2006	+	?	+	+	-	None
Lepola 2003	?	?	+	+	-	Lundbeck
Mendels 1999	?	?	?	+	-	Pfizer
Montgomery 1992	?	?	+	-	-	Lundbeck
Stahl 2000	?	?	+	+	-	Forest

Note: (+) criterion addressed; (-) criterion not addressed; (?) unclear whether the criterion has been addressed

Table 3. Baseline mean scores in included studies

Study	HAM-D placebo	HAM-D citalopram	MADRS placebo	MADRS citalopram	CGI-S placebo	CGI-S citalopram
Burke 2002	25.8	25.9[(c)]	29.5	29.2	4.2	4.3
Feighner 1999	24.6	24.6[(b)]	27.1	27.5	4.3	4.3
Frank 2004	n/p	n/p[(b)]	-	-	-	-
Gastpar 2006	22	21.8[(a)]	-	-	92.3% [(d)]	92.9% [(d)]
Lepola 2003	-	-	28.7	29.2	4.22	4.3
Mendels 1999	24.1	23.9[(a)]	-	-	4.7	4.6
Montgomery 1992	n/p	n/p[(a)]	n/p	n/p	n/p	n/p
Stahl 2000	26.4	26.5[(b)]	31.1	32.4	4.32	4.38

Note: [(a)] HAMD-17 scale; [(b)] HAMD-21 scale; [(c)] HAMD-24 scale; [(d)] percentage of patients rated as moderately, markedly or severely ill; (n/p) data not published; (-) measurement scale not utilised

Table 4. Outcome measures: response or remission

Study	Response placebo (%)	Response citalopram (%)	Response criteria	Remission placebo (%)	Remission citalopram (%)	Remission criteria
Burke 2002	27.7	45.6[(b)]	50% improvement on MADRS	n/p	n/p	n/p
Feighner 1999	n/p	n/p[(a)]	50% improvement on MADRS	n/p	n/p	n/p
Frank 2004	50	63	50% reduction in HAMD score	n/p	n/p	n/p
Gastpar 2006	39.2	55.9[(b)]	HAMD <10 or 50% improvement	n/p	n/p	n/p
Lepola 2003	48.2	52.6 [(c)]	50% improvement on MADRS	n/p	42.8 [(c)]	MADRS < 12
Mendels 1999	47	81[(a)]	Very much or much improved on CGI-I	n/p	n/p	n/p
Montgomery 1992	n/p	n/p	50% improvement on MADRS or HAMD	n/p	n/p	n/p
Stahl 2000	n/p	n/p[(b)]	50% improvement on HAMD	28	45	HAMD-17 <8

Note: [(a)] significantly different from placebo, p<0.05; [(b)] significantly different from placebo, p<0.01; [(c)] observed cases only; (n/p) data not published

Table 5. Outcome measures: change from baseline on HAM-D, MADRS and CGI-S scales

Study	HAM-D placebo	HAM-D citalopram	MADRS placebo	MADRS citalopram	CGI-S placebo	CGI-S citalopram
Burke 2002	-7.6	-9.9[(a)]	-9.4	-12.0[(a)]	-0.8	-1.2[(a)]
Feighner 1999	-9.3	-11.2[(a)]	-9.4	-12.7[(b)]	-1.1	-1.4[(a)]
Frank 2004	n/p	n/p	-	-	-	-
Gastpar 2006	-9.0	-11.4[(b)]	-	-	-34.4% [(c)]	-51.7%[(b)(c)]
Lepola 2003	-	-	-12.1	-13.6	-1.42 [(e)]	-1.58 [(e)]
Mendels 1999	-6.95	-9.43[(a)]	-	-	n/p	n/p[(a)]
Montgomery 1992	n/p	n/p[(a)(d)]	n/p	n/p[(a)(d)]	n/p	n/p [(a)(d)]
Stahl 2000	-10.0	-14.5[(b)]	-11.1	-18.0[(b)]	-1.2	-1.8[(b)]

Note: [(a)] significantly different from placebo, p<0.05; [(b)] significantly different from placebo, p<0.01; [(c)] Decrease in the percentage of patients rated as moderately, markedly or severely ill; [(d)] significant only for citalopram 40mg; [(e)] data from Lepola (2004); (n/p) data not published; (-) scale not utilized

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

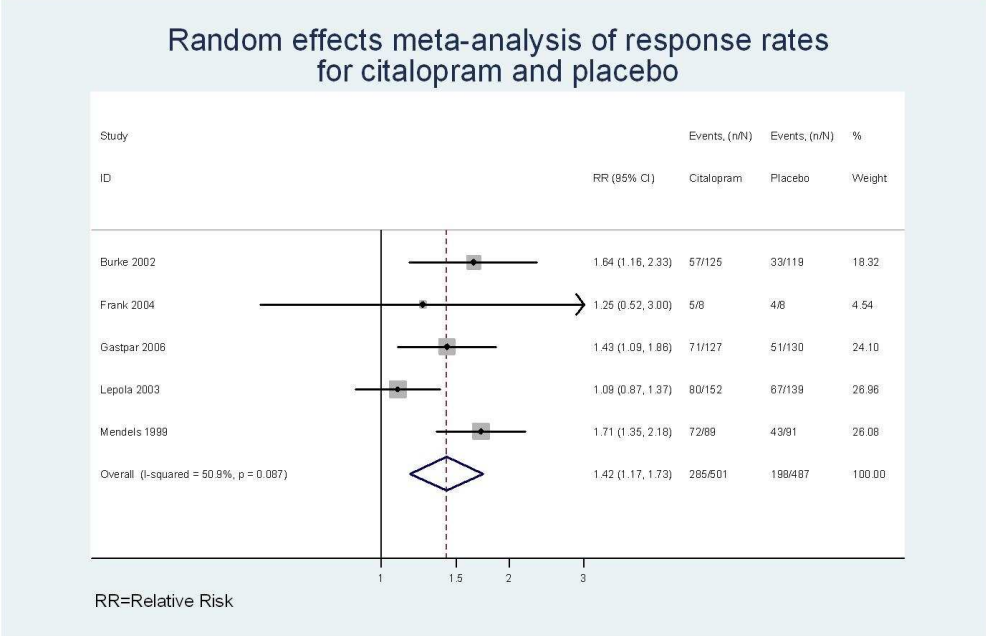


Figure 2
369x240mm (96 x 96 DPI)

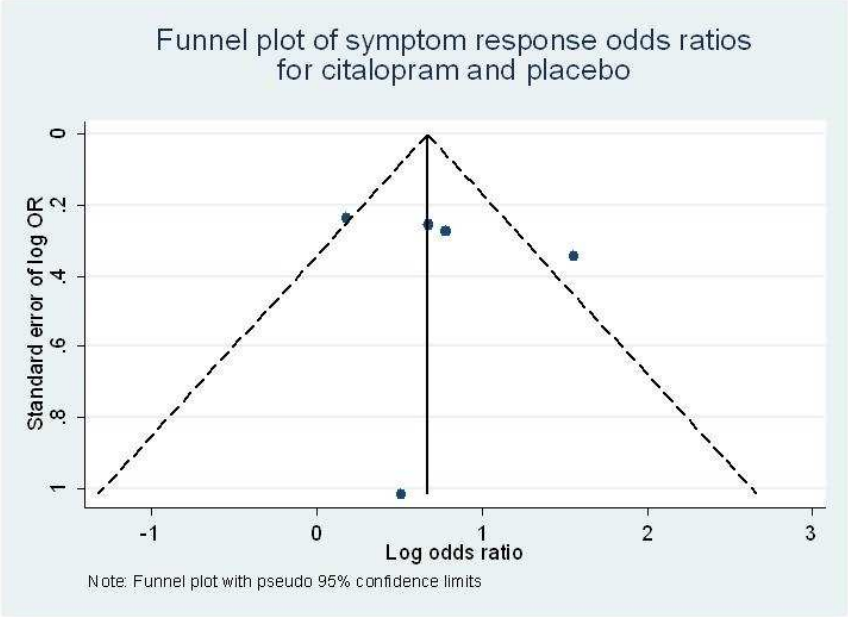


Figure 3
222x139mm (96 x 96 DPI)

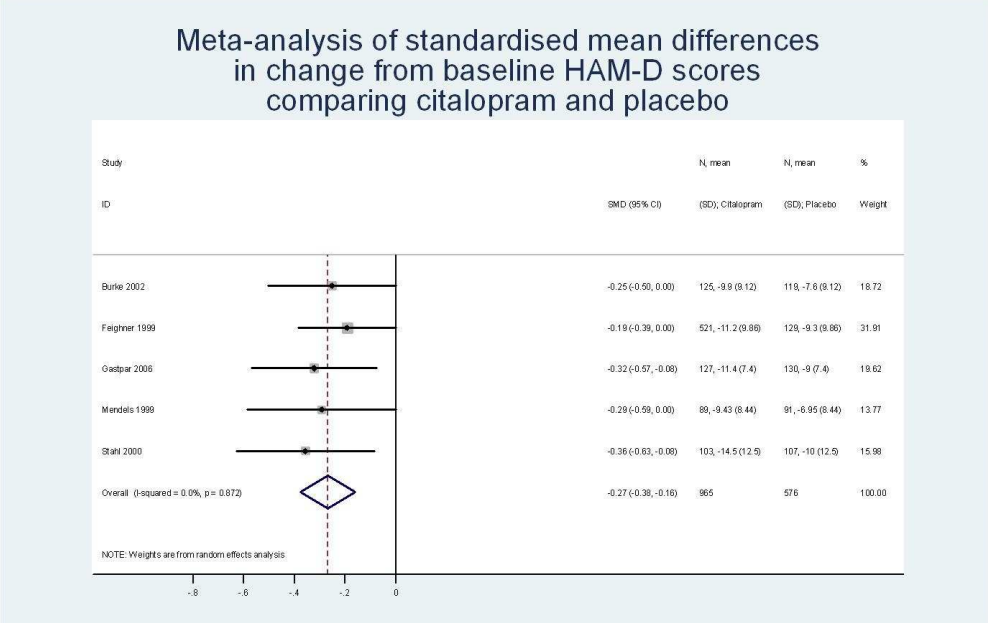


Figure 4
368x235mm (96 x 96 DPI)