Pharmacologic treatment of depression in multiple sclerosis

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[Intervention Review]

Pharmacologic treatment of depression in multiple sclerosis

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ABSTRACT

Background

Depression is a common problem in patients with multiple sclerosis (MS). It is unclear which pharmacologic treatment is the most effective and the least harmful.

Objectives

To investigate the efficacy and tolerability of pharmacologic treatments for depression in patients with MS.

Search methods

We searched the Cochrane Multiple Sclerosis Group's Trials Register (June 2010), reference lists of relevant articles and conference proceedings. Regulatory agencies were used as additional sources of information on adverse effects.

Selection criteria

Adequately and quasi-randomized controlled blinded or unblinded trials in children and adults with MS. Experimental intervention: pharmacologic treatments for depression without restrictions regarding dose, route of administration, frequency, or duration. Control intervention: placebo treatment or no treatment.

Data collection and analysis

Two teams of reviewers independently assessed trial quality and extracted data. We contacted study authors for additional information. We collected adverse effects from the trials.

Information about study population, type of intervention, outcome measures, and study design were extracted from the selected studies. Trial quality was evaluated with the criteria: randomization, allocation concealment, blinding, handling of incomplete outcome data, freedom from selective reporting and freedom from other bias.

The impact of missing data on the study results was explored with sensitivity analyses comparing the results from the analyses of study completers with those from best- and worst-case scenarios.

Main results

Two trials (70 participants) were included. One trial (28 participants) compared treatment with desipramine for five weeks to placebo. The other trial (42 participants) compared treatment with paroxetine for twelve weeks to placebo. Both trials had a significant number of patients lost to follow-up or with missing outcome measurements.

There was a trend towards efficacy of both treatments compared to placebo, but this difference was not statistically significant except for one outcome. Confidence intervals were wide in all analyses and our sensitivity analysis showed that the missing data may have had an important effect in both trials, with large differences between best-case and worst-case scenarios for all assessed outcomes.

Both treatments were associated with adverse effects, with significantly more patients treated with paroxetine suffering from nausea or headache. Given the difference in trial duration and type of drug, we decided not to perform a meta-analysis.

Authors' conclusions

Both desipramine and paroxetine show a trend towards efficacy in depression in MS the short term, but both treatments were associated with adverse effects, with significantly more patients treated with paroxetine suffering from nausea or headache. Further clinical research on the treatment of depression in MS is clearly needed. Future trials should address the efficacy and tolerability in the long term and compare antidepressant treatments head-to-head.

PLAIN LANGUAGE SUMMARY

Drug treatment for depression in multiple sclerosis

Many patients with multiple sclerosis (MS) suffer from depression. In this review we summarized studies of antidepressant drug treatments in patients with MS. We found two studies that met the inclusion criteria of methodological quality, comprising of a total of 70 participants: one (28 participants) reported the effects of desipramine, the other (42 participants) the effects of paroxetine. The two studies showed no improvement of depression with both treatments in the short term (five/twelve weeks). Adverse effects, such as nausea or headache occurred frequently. Further studies on drug treatment of depression in MS with a longer duration are clearly needed, as the results may be affected by the small size of participants and by the fact that many participants did not complete the studies.

BACKGROUND

Depression is a common problem in patients with multiple sclerosis (MS) (Siegert 2005). The prevalence of major depression in patients with multiple sclerosis is higher than in both the general population and patients with other chronic diseases (Patten 2005). Several factors may account for the development of depression in MS. Depression may be the result of the psychological burden of having a chronic disease with an unpredictable course. On the other hand, the ongoing structural damage in the central nervous system (CNS) of patients with MS may also lead to depressive symptoms (Siegert 2005). Given these considerations, it is uncertain whether depression in patients with MS should be treated as in the general population, or whether it requires a different approach.

While pharmacologic treatment can be effective in patients with MS, it is uncertain which pharmacologic treatment for depression is the most effective and least harmful in patients with MS. A systematic review of all relevant randomized controlled trials is the best way to resolve this uncertainty.

OBJECTIVES

To investigate the efficacy and tolerability of pharmacologic treatments for depression in patients with MS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials on pharmacologic antidepressive treatment in patients with MS. Double-blind, single-blind or unblinded trials were included. Adequately randomized and quasi randomized trials were included, non-randomized trials were excluded. Individual patient data were included if available.

Types of participants

Children and adults with a diagnosis of definite MS according to the Poser (Poser 1983) or McDonald (McDonald 2001) diagnostic criteria, who suffer from depression (either diagnosed by a psychiatrist or defined as a score suggesting depression on a validated depression scale).

Types of interventions

Experimental intervention: pharmacologic treatments for depression without restrictions regarding dose, route of administration, frequency, or duration. Control intervention: placebo treatment or no treatment. Treatment of all randomized patients (in both experimental and control groups) with psychotherapy during the trial was no exclusion criterium, trials with psychotherapy as the control condition were excluded.

Types of outcome measures

Primary outcomes

Any improvement of depression, as measured with one of the following depression scales:

- Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960)
- Beck Depression Inventory (BDI) (Beck 1961)
- Zung Self-Rating Depression Scale (Zung SDS) (Zung 1965)
- Symptoms Checklist 90 [Depression Subscale] (SCL-90) (Derogatis 1973)
- Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977)
- Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979)
- The Hospital Anxiety and Depression Scale [Depression Subscale] (HADS) (Zigmond 1983)
- Inventory of Depressive Symptomatology (IDS) (Rush 1986)
- Major Depression Inventory (MDI) (Bech 2001)

Secondary outcomes

The tolerability of the pharmacologic treatments were investigated by identifying:
1. The total number of patients experiencing any adverse effect of the treatment in question
2. The total number of patients experiencing any of following specific adverse effects of antidepressant treatment:
(a) Agitation/anxiety
(b) Constipation
(c) Diarrhoea
(d) Dry mouth
(e) Hypotension
(f) Insomnia
(g) Nausea
(h) Sleepiness/drowsiness
(j) Urinary problems
(k) Vomiting
(l) Death, suicide and suicidality
In order to identify any rare or unexpected adverse effects of the treatment in question, we collected all adverse effects data reported in the identified studies during the data extraction phase and discussed ways to summarise them post hoc.

Search methods for identification of studies

No language restrictions were applied to the search.

Electronic searches

The Trials Search Co-ordinator searched the Cochrane Multiple Sclerosis Group's Specialised Register (June 2010).
Keywords are listed in (Appendix 1).
Information on the Cochrane Multiple Sclerosis Group's Trials Register, and details of search strategies used to identify trials can be found in the 'Specialized Register' section within the Cochrane Multiple Sclerosis Group's module.

Searching other resources

(1) Checking reference tables of identified studies.
(2) Handsearching of published abstracts of conference proceedings.
(3) Personal communication with authors of identified studies and other researchers in the field.
Strategy (3) was used to identify unpublished or ongoing studies.
Regulatory agencies were additional sources of information for adverse effects:

- In the UK: Current Problems in Pharmacovigilance (www.mhra.gov.uk);
- In Australia: the Australasian Adverse Drug Reactions Bulletn (www.tga.gov.au/adr/aadrb.htm);

- In Europe: the European Public Assessment Reports from European Medicines Evaluation Agency (www.emea.eu);
- In the US: Food and Drug Administration FDA Medwatch (www.fda.gov/medwaTCH).

Data collection and analysis

Selection of studies

The titles and abstracts of publications identified by the above search strategy were assessed independently for inclusion by two teams of reviewers (MK/JM, and AG/MU/JDK), the full text was selected for further assessment if the abstract suggested relevance.

Data extraction and management

Information about study population, type of intervention, outcome measures, and study design were extracted independently from the selected studies by two teams of reviewers (MK/MU/AG, and JM/JDK) on a data extraction form. Results were extracted as raw numbers.

Assessment of risk of bias in included studies

The methodological quality of the studies was evaluated independently by two teams of reviewers (MK/JDK/AG and JM/MU) according to the guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). The criteria used in the assessment of methodological quality were (1) randomization, (2) allocation concealment, (3) blinding, (4) handling of incomplete outcome data, (5) freedom from selective reporting and (6) freedom from other bias.

Measures of treatment effect

For dichotomous outcome measures, treatment effects are expressed as odds ratios with their 95% confidence interval.
In this review we did not perform meta-analysis, if meta-analysis is to be performed in future versions of this review, studies will be summarized using a fixed-effect model. Studies with dichotomous outcomes will summarized using the Mantel-Haenszel fixed-effect model, and the odds ratio will be used as summary statistic. Studies with continuous outcomes will be summarized with the inverse variance method and the weighted mean difference will be given as summary statistic.

Dealing with missing data

The impact of missing data on the study results was explored with a sensitivity analysis comparing the results from the analyses of study completers with those from best- and worst-case scenarios. In the best-case scenario, all missing data from the treatment group were included as having shown a treatment effect, while those missing from the placebo group were included as having shown no effect. In the worst-case scenario missing data from the treatment group were included as having shown no treatment effect, while those missing from the placebo group were included as having shown a treatment effect.

Assessment of heterogeneity

Statistical heterogeneity among the identified studies is tested for with the chi-squared test. Significant heterogeneity among the studies is addressed by either refraining from performing a meta-analysis altogether (in the case of serious heterogeneity), or by excluding one or a small minority of heterogenous studies. Heterogeneity is explored by investigating the influence of subgroups (men vs. women, adults vs. children, progressive vs. non-progressive MS).

Assessment of reporting biases

Publication bias is assessed with Funnel plots as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

RESULTS

Description of studies

Results of the search

The search strategy yielded a total of 1217 citations (MEDLINE: 617, EMBASE 539, CINAHL: 5, CENTRAL: 50, Handsearching: 6). Two teams of reviewers (MK/JDK and AG/JM/MU) perused titles and abstracts for relevance and independently excluded 1215 citations. All excluded studies did not meet the inclusion criteria. Two studies were included in this review. Our search of additional resources yielded no further results. Our search of regulatory agency databases yielded no additional information on adverse effects. There were no disagreements regarding study inclusion or exclusion between the two teams or between individual team members.

Included studies

Ehde and colleagues (Ehde 2008) screened 349 patients with MS recruited from the Western MS Center at the University of Washington, through flyers sent to local neurologists and through regional MS support groups. Patients were eligible to participate in

the study if they were 18 years or older, had a diagnosis of MS confirmed by a neurologist or an MS trained physiatrist and a diagnosis of major depressive disorder or dysthymia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First 1996). Patients were excluded if they had failed treatment with paroxetine in the past, were in psychotherapy, were taking psychotropic medications or more than 50mg or amitriptyline or equivalent for pain or sleep, had imminent suicidal ideation, were pregnant, nursing or not using effective contraception, had bipolar disorder or psychosis based on the SCID, had alcohol or drug-dependence based on the SCID, were participating in another drug trial, or had used corticosteroids within the two weeks prior to enrolment in the study. Forty-two patients met the study criteria and agreed to participate in the study and were randomized to receive either paroxetine (22 patients) or placebo (20 patients). The duration of the trial was 12 weeks. Patients were seen at enrolment, after six weeks and at study end, additional telephone contacts took place after 1, 2, 4, and 8 weeks. The dosage started at 10mg/day and was increased if tolerated to up to 40mg/day by the study psychiatrists. Patients were assessed with the CES-D and HAM-D scales and several other psychometric scales at enrolment, at six weeks and at 12 weeks. The HAM-D was used to measure the primary outcome measures: (1) a reduction of at least 50% of the HAM-D score between first and last assessments and (2) the number of patients with a score of 7 or less on the HAM-D scale at the last assessment. Secondary outcome measures were the difference between baseline and last assessment in the scores on the HAM-D and CES-D scale, on the Modified Fatigue Impact Scale (Fischer 1999), the Perceived Deficits Questionnaire (Sullivan 1990), the Satisfaction with Life Scale (Diener 1985), and the MOS 36-Item Short-Form Health Questionnaire (Ware 1992).

Individual patient data was sought and kindly provided by the study authors.

All 20 patients randomized to placebo treatment finished the study, while 5 (23%) of the 22 patients randomized to paroxetine were lost to follow-up before the trial ended in week 12. Three patients (1 in the placebo and 2 in the paroxetine group) had no baseline HAM-D score, and nine patients (1 in the placebo group, 3 in the paroxetine group, and the 5 patients lost to follow-up) had no HAM-D score at study end. Due to the loss to follow-up and missing baseline and follow-up HAM-D scores, 6 of 22 patients (27%) in the paroxetine group and 2 of 20 patients (10%) in the placebo group could not be analysed for their HAM-D scores. CES-D scores were available for 17 patients from the paroxetine group and all 20 patients from the placebo group.

Seven patients (35%) in the placebo group and 12 (55%) in the paroxetine group developed at least one adverse effect. The most common adverse effects in the placebo group were headache in 2 (10%), and nausea and sexual dysfunction in 1 patient each. The most common adverse effects in the paroxetine group were nausea in 11 (50%) patients, headache and dry mouth in 9 (41%), and sexual dysfunction in 5 (23%). Two patients from the paroxetine group withdrew from the study due to adverse effects.

Schiffer and co-workers (Schiffer 1990) invited patients with a diagnosis of definite multiple sclerosis according to the Poser diagnostic criteria (Poser 1983) who met the research diagnostic criteria for definite major depressive disorder (Endicott 1979) to participate in a randomized placebo controlled trial. The duration of the trial was five weeks, all patients who remained in the study for at least two weeks were included in the analyses. Patients were assessed with the BDI and HAM-D scales at each weekly visit. Of the 39 patients invited over a three year period, six refused to participate and one was excluded because he had already started antidepressant treatment elsewhere. Thirty-two patients were randomized to either desipramine or placebo. Four patients were excluded within the first week after randomization: two because they decided against taking medication (although adverse events had not been the reason) and two others because they were found not to have definite multiple sclerosis. It is not known to which group these four excluded patients had been randomized. Twenty-eight patients were included in the analyses: 14 patients received desipramine, and 14 received placebo. The daily dose of desipramine was increased during the first week from 75mg to 150mg or to the highest dose permitted by adverse effects. The dose was also adjusted according to serum levels of desipramine that were evaluated in the second week of the trial. Dose adjustments were also made for the patients who received placebo. All patients received psychotherapy in addition to the drug treatment. The primary outcome of the trial was an assessment of clinical improvement of depression by the blinded primary therapist.

Individual patient data are given in the published manuscript.

Eight patients (5 (36%) from the desipramine group and 3 (21%) from the placebo group) were lost to follow-up before the trial ended in week 5.

Seven patients (50%) in the placebo group and 12 (86%) in the desipramine group developed at least one adverse effect. The most commonly reported adverse effects were postural hypotension, dry mouth and constipation, other adverse effects were jitteriness, edema, dizziness and rash. More detailed data on adverse effects are not reported.

Risk of bias in included studies

Both studies had a large number of patients lost to follow-up and missing outcome measurements, which puts them at a high risk of attrition bias. We defined a loss to follow-up of more than 10% of patients as suggestive of a high risk of bias (for details see 'risk of bias' tables Characteristics of included studies and Figure 1 and Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

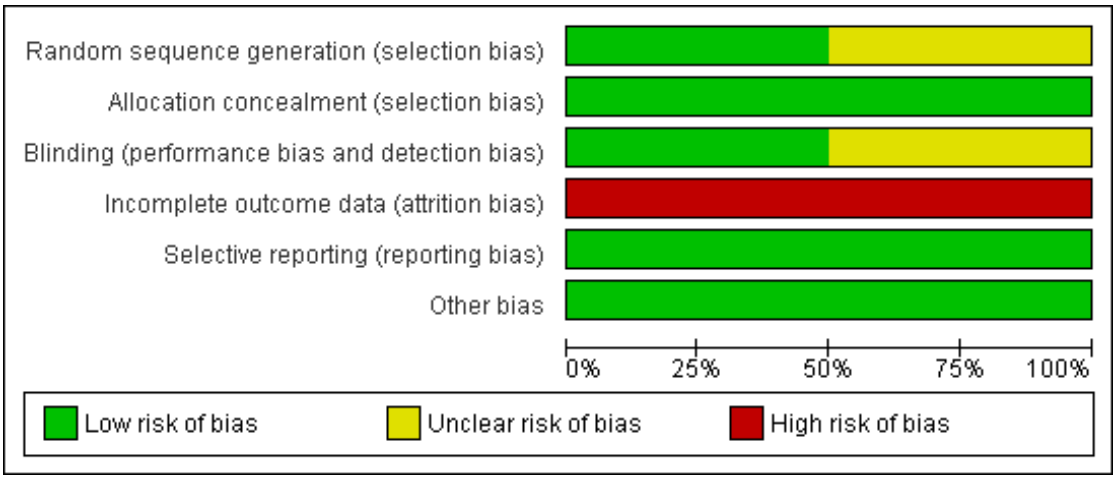
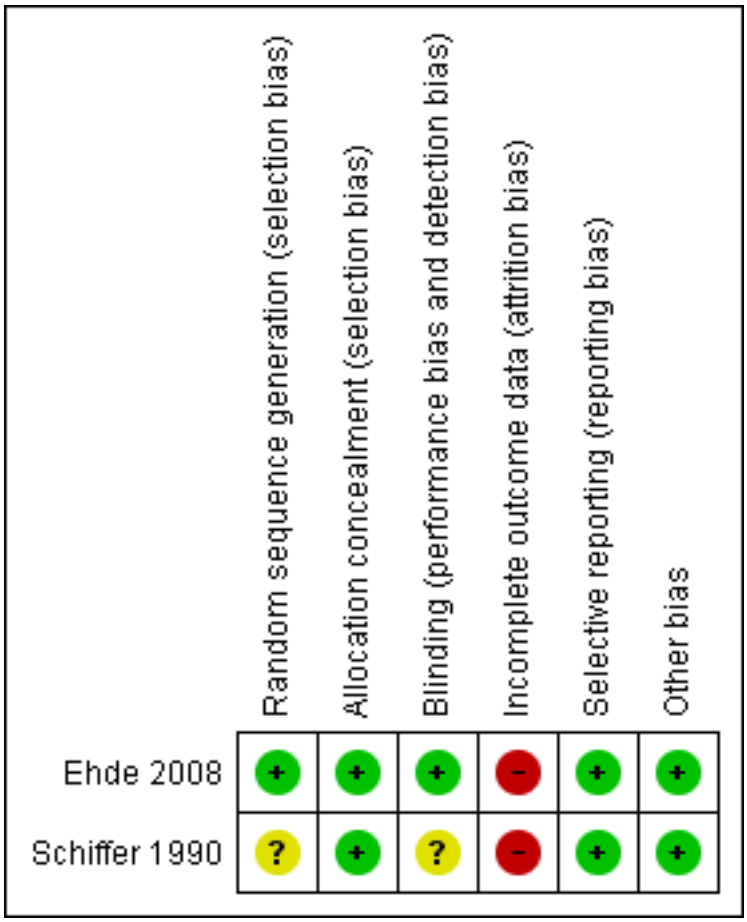


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

In both trials, a considerable (see above) number of patients was lost to follow-up or had missing outcome measurements. Both trials used intermediate observations to overcome this problem: Schiffer (Schiffer 1990) included everybody in the end analysis who participated for at least two of the five weeks of trial duration, and Ehde (Ehde 2008) carried intermediate measurements forward to replace the measurement at the end of the trial. In our opinion, both methods are inappropriate for dealing with missing data.

We decided to perform an analysis of study completers, and to estimate the effect of the missing data in these two trials by including a sensitivity analysis with best-case and worst-case scenarios.

Due to the differences between the trials in trial duration and type of medication, we decided not to perform a meta-analysis.

Desipramine (Analysis 1.1; Figure 3; Analysis 1.2; Figure 4; Analysis 1.3; Figure 5; Analysis 1.4; Figure 6;) as well as paroxetine (Analysis 2.1; Figure 7; Analysis 2.2; Figure 8; Analysis 2.3; Figure 9; Analysis 2.4; Figure 10) treatment of depression in MS showed a trend towards efficacy, but the confidence intervals were wide and neither intervention had a statistically significant effect on all outcomes. This is probably due to the small size of both trials. Patients treated with paroxetine were significantly more likely to drop to a HAM-D score of 7 or lower after 12 weeks of treatment (OR 4.68, 95% confidence interval 1.04 - 21.04, p=0.04, Analysis 2.2; Figure 8).

Figure 3. Forest plot of comparison: 1 Desipramine versus placebo, outcome: 1.1 Reduction of HAM-D score by at least 50% at five weeks.

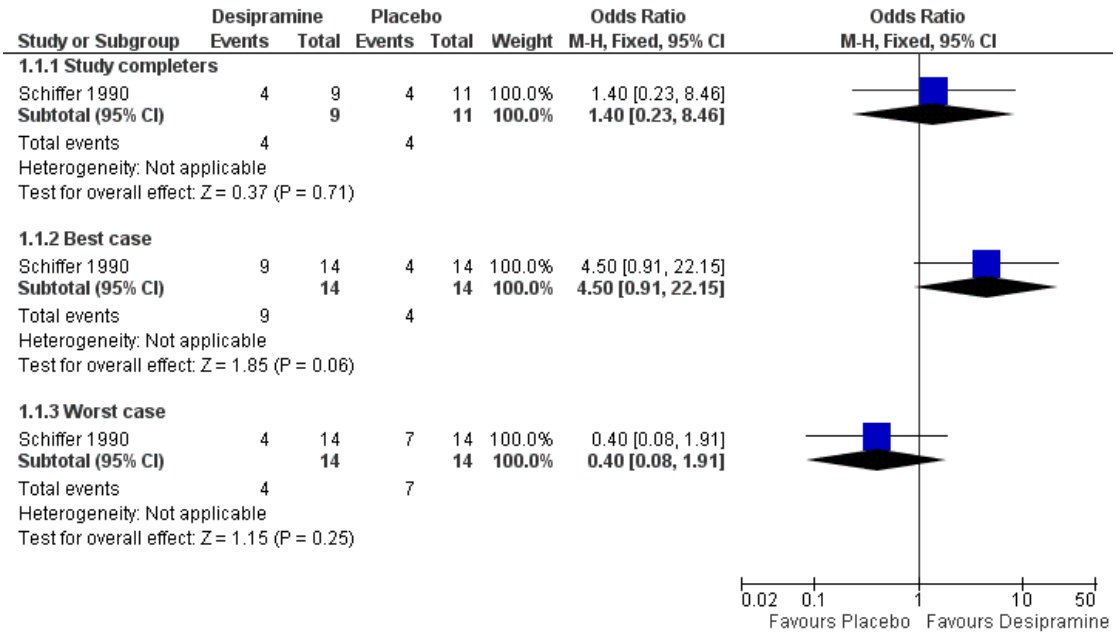


Figure 4. Forest plot of comparison: 1 Desipramine versus placebo, outcome: 1.2 Reduction of HAM-D score to 7 or lower at five weeks.

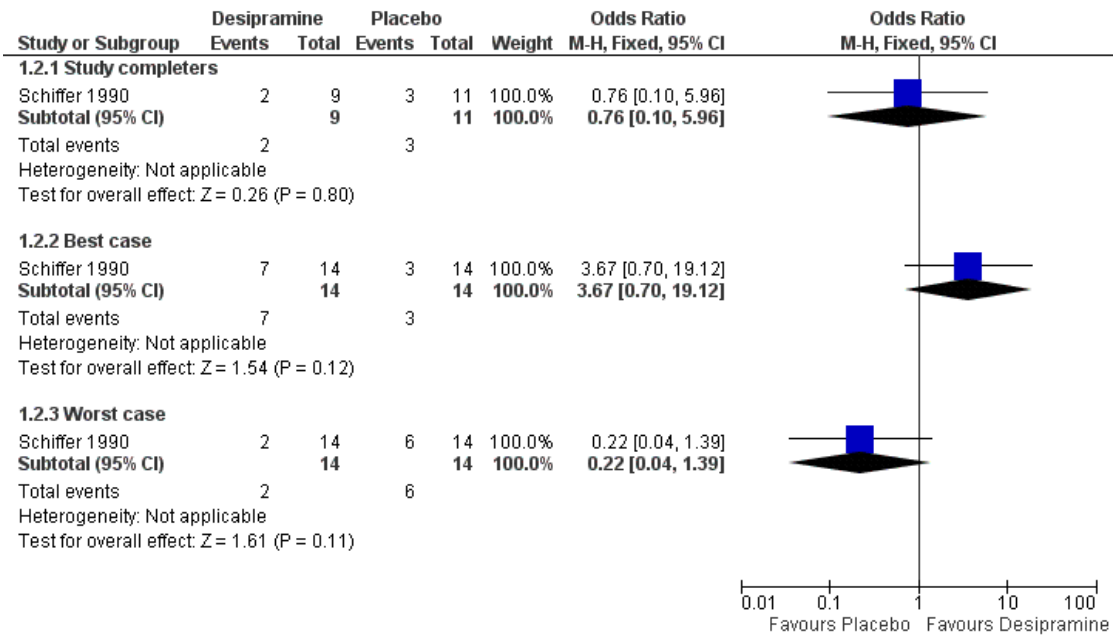


Figure 5. Forest plot of comparison: 1 Desipramine versus placebo, outcome: 1.3 Any reduction of HAM-D score at five weeks.

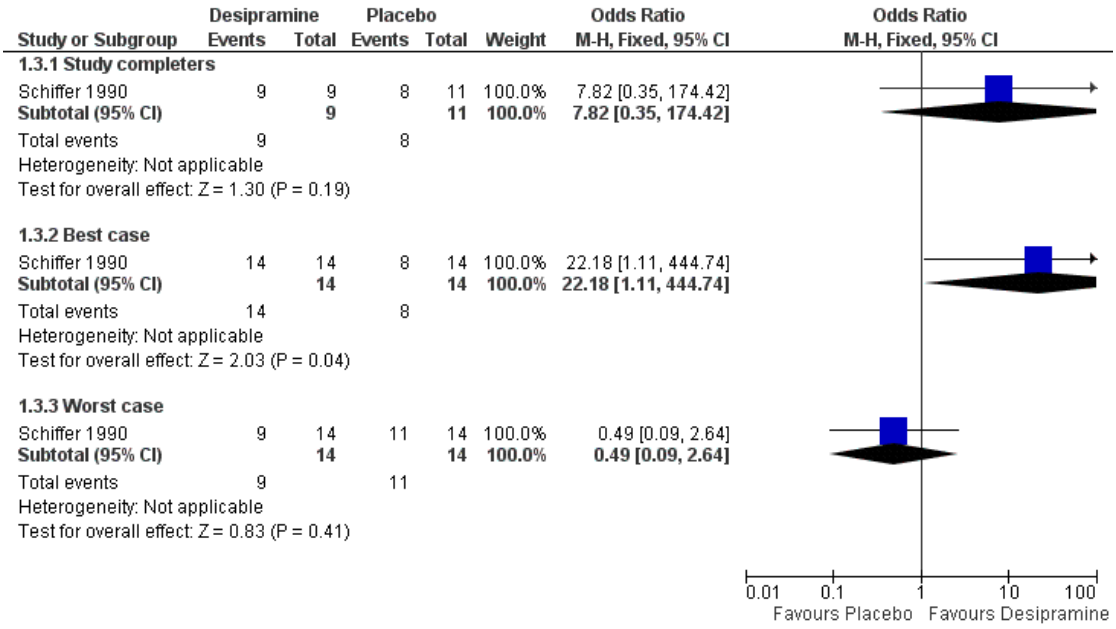


Figure 6. Forest plot of comparison: 1 Desipramine versus placebo, outcome: 1.4 Any reduction of BDI score at five weeks.

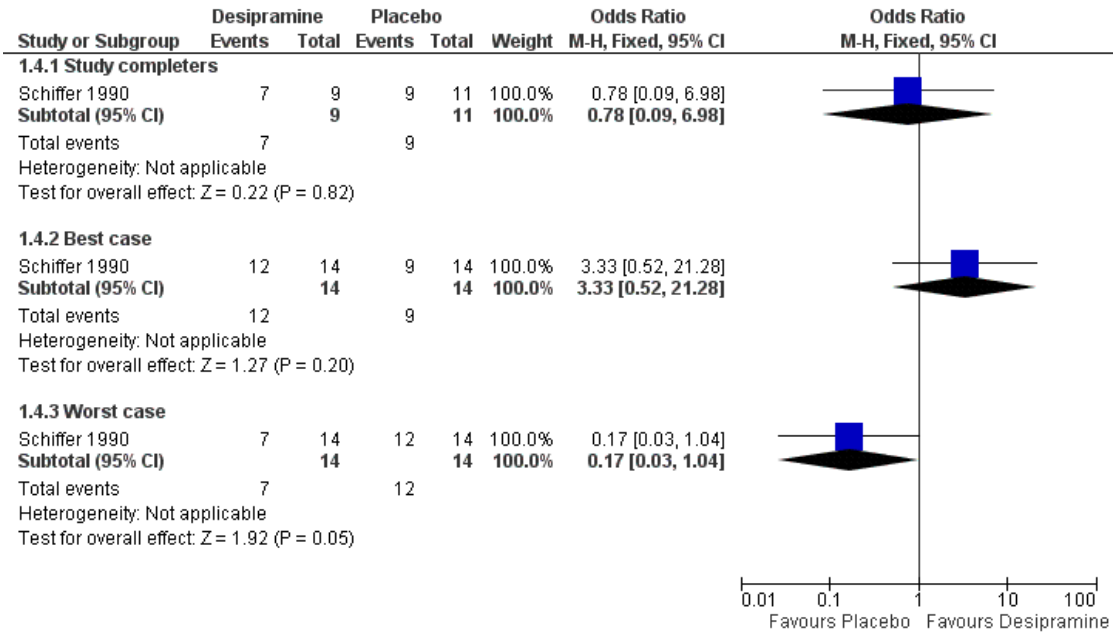


Figure 7. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.1 Reduction of HAM-D score by at least 50% at twelve weeks.

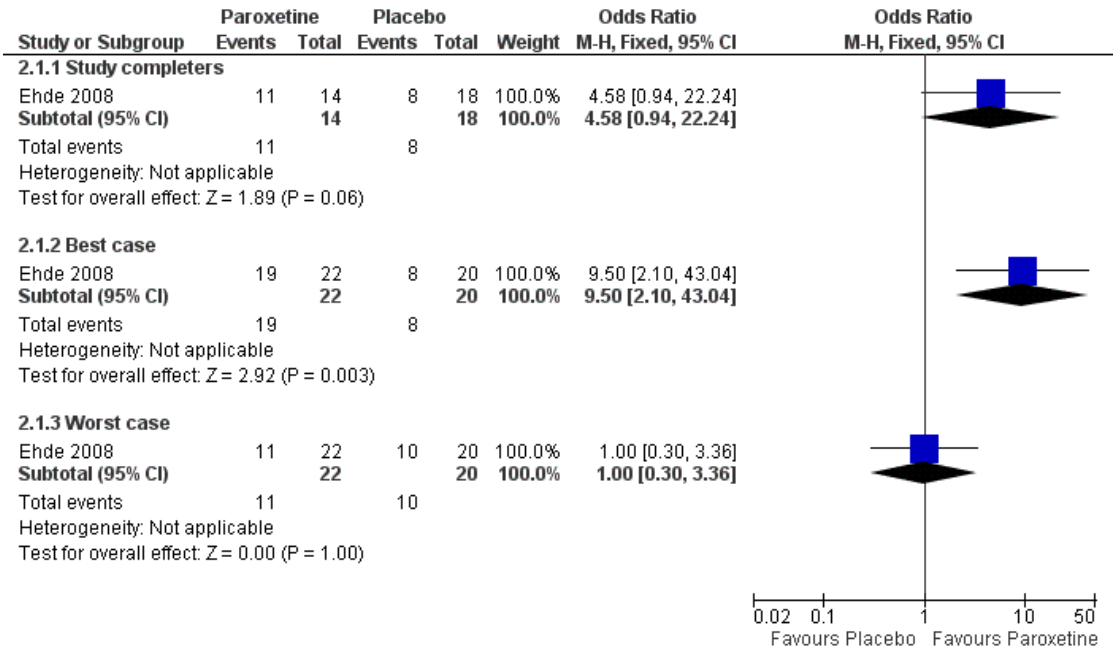


Figure 8. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.2 Reduction of HAM-D score to 7 or lower at twelve weeks.

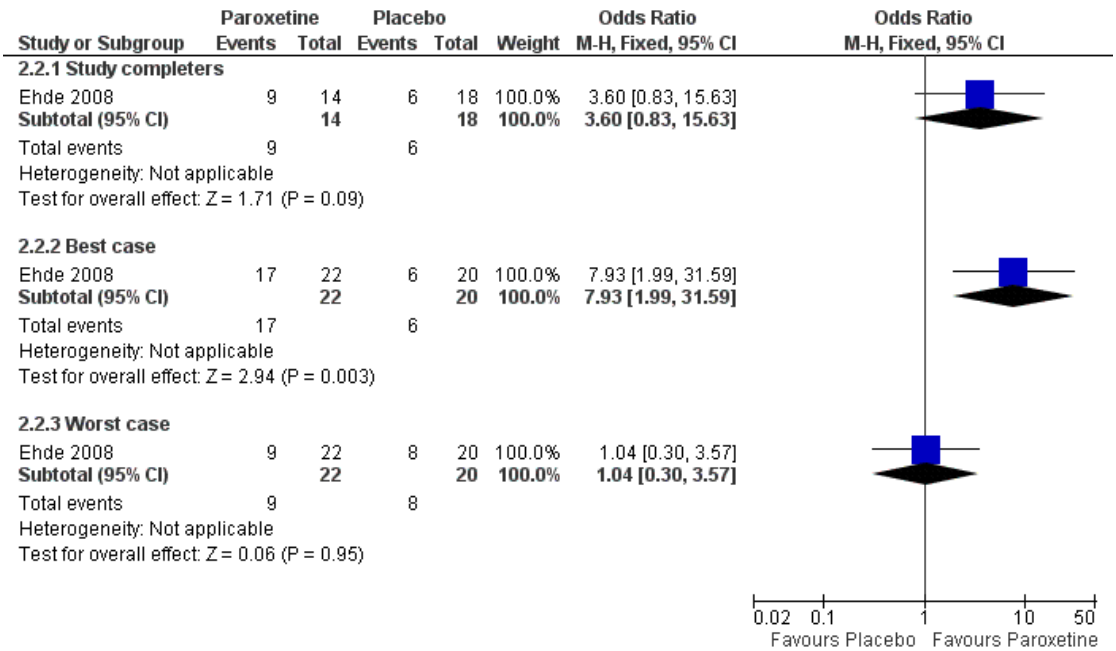


Figure 9. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.3 Any reduction of HAM-D score at twelve weeks.

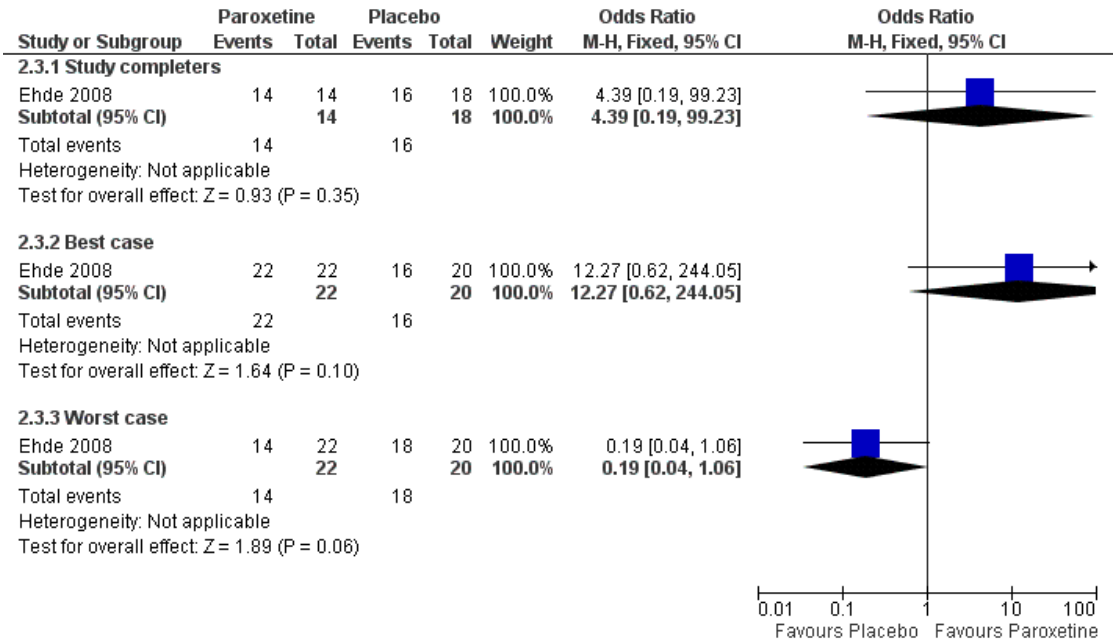
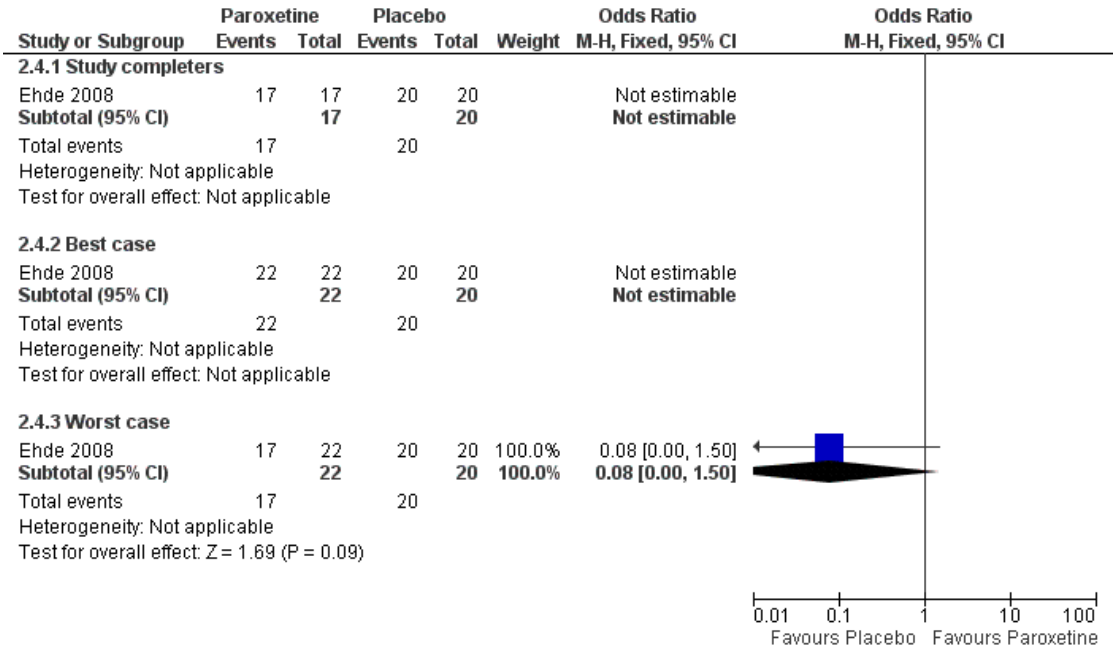


Figure 10. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.4 Any reduction of CES-D score at twelve weeks.



Our sensitivity analysis showed that missing data had an important influence in both trials, with large differences between best-case and worst-case scenarios for every outcome.

Both treatments were associated with adverse effects (Analysis 1.5; Figure 11; Analysis 2.5; Figure 12; Analysis 2.6; Figure 13; Analysis 2.7; Figure 14; Analysis 2.8; Figure 15; Analysis 2.9; Figure 16). The analysis of the number of patients with at least one adverse effect showed a non-significant trend towards more adverse effects than on placebo for both desipramine (OR 6.0; 95% confidence interval: 0.97 - 37.3; p=0.05; Analysis 1.5; Figure 11) and paroxetine (OR 2.23; 95% confidence interval 0.64 - 7.74; p=0.21; Analysis 2.5; Figure 12). Significantly more patients on paroxetine than on placebo suffered from nausea (OR 15.83; 95% confidence interval: 1.79 - 139.92; p=0.01 ; Analysis 2.7; Figure 14) or headache (OR 7.5; 1.39 - 40.43; p=0.02; Analysis 2.8; Figure 15).

Figure 11. Forest plot of comparison: 1 Desipramine versus placebo, outcome: 1.7 Number of patients with at least one side effect.

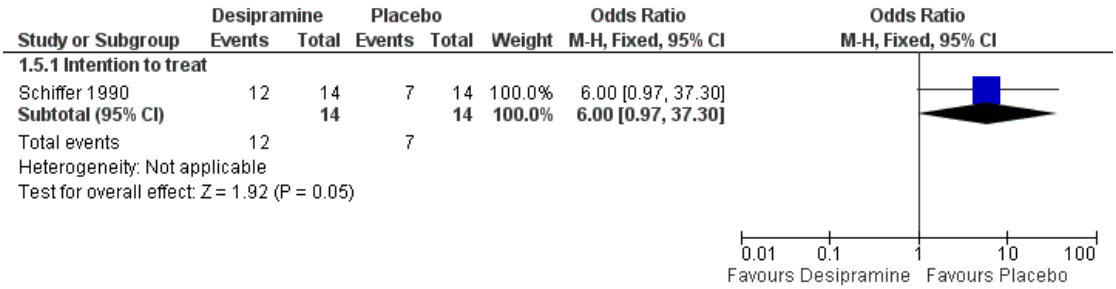


Figure 12. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.5 Number of patients with at least one side effect.

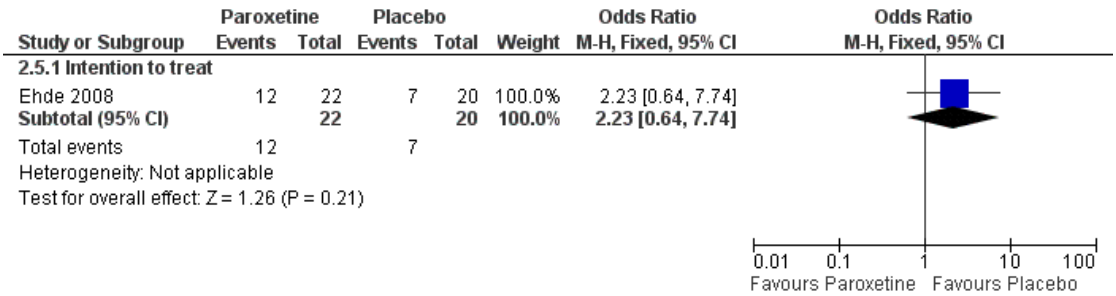


Figure 13. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.6 Number of patients with dry mouth.

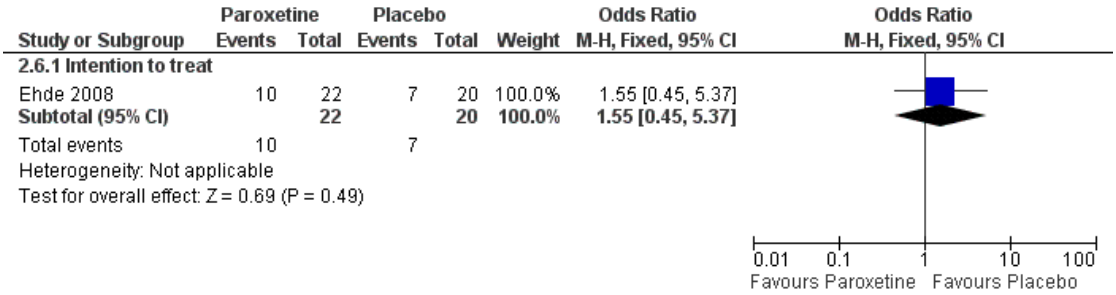


Figure 14. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.7 Number of patients with nausea.

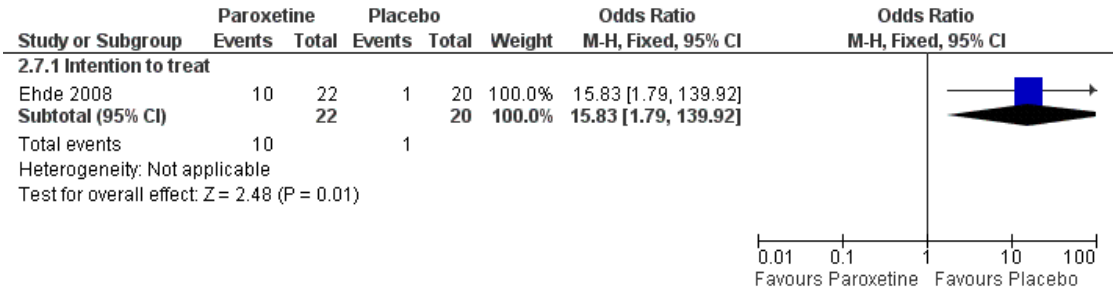


Figure 15. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.8 Number of patients with headache.

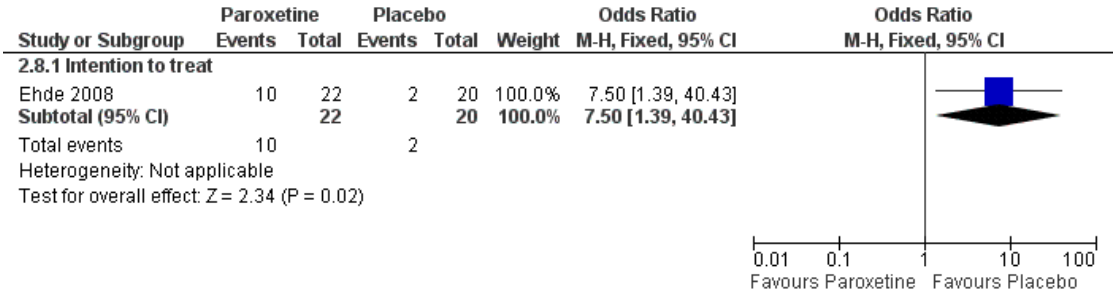
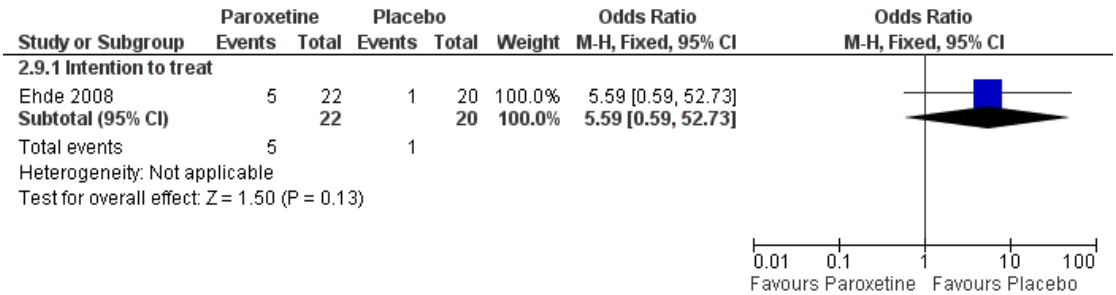


Figure 16. Forest plot of comparison: 2 Paroxetine versus placebo, outcome: 2.9 Number of patients with sexual dysfunction.



DISCUSSION

Given the relevance of the problem of depression in MS, it was somewhat unexpected to find only two small trials addressing its pharmacological treatment. The small size of the trials translates into wide confidence intervals and a relatively low reliability of the results.

Both trials included a considerable number of patients who were either lost to follow-up before the end of the trial or for whom outcome measurements were missing. This problem of missing data is the more important because of the small size of the trials. In order to estimate the effect the missing data had on the results, we performed a sensitivity analysis with best-case and worst-case scenarios. This analysis showed that the results of both trials may be highly influenced by the missing data, as there were large differences between the best-case and worst-case scenarios for all outcomes.

Desipramine as well as paroxetine show a trend toward efficacy for depression in MS, but confidence intervals are wide and there were no statistically significant differences between verum and placebo for all but one outcome (Analysis 2.2; Figure 8). On the other hand, both treatments were associated with more adverse effects than placebo, with significantly more patients on paroxetine than on placebo developing nausea (Analysis 2.7; Figure 14) or headache (Analysis 2.8; Figure 15).

AUTHORS' CONCLUSIONS

Implications for practice

The current literature suggests that the pharmacological treatment of depression in MS with desipramine or paroxetine may be effective in the short term, although adverse effects are common. At present no further evidence-based recommendations can be given.

Implications for research

Further clinical research on the pharmacologic treatment depression in MS is clearly necessary and should address the efficacy and tolerability of antidepressants in the longer term. It would be helpful if such trials included head-to-head comparisons between antidepressants.

REFERENCES

References to studies included in this review

Ehde 2008 ***{published and unpublished data}***
Ehde DM, Kraft GH, Chwastiak L, Sullivan MD, Gibbons LE, Bombardier CH, et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. *General Hospital Psychiatry* 2008;**30**:40–8.

Schiffer 1990 ***{published data only}***
Schiffer RB, Wineman NM. Antidepressant pharmacotherapy of depression associated with multiple sclerosis. *American Journal of Psychiatry* 1990;**147**:1493–97.

Additional references

Bech 2001
Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *Journal of Affective Disorders* 2001;**66** (2-3):159–64.

Beck 1961
Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;**12**(1):561–71.

Derogatis 1973
Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. *Psychopharmacology Bulletin* 1973;**9**(1):13–28.

Diener 1985
Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. *Journal of Personality Assessment* 1985;**49**:71–5.

Endicott 1979
Endicott J, Spitzer RL. Use of the Research Diagnostic Criteria and the Schedule for Affective Disorders and Schizophrenia to study affective disorders. *American Journal of Psychiatry* 1979;**136**:52–6.

First 1996
First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. American Psychiatric Press, Inc., 1996.

Fischer 1999
Fischer JS, La Rocca NG, Miller DM, Ritvo PG, Andrews H, Paty D. Recent developments in the assessment of quality of life in MS. *Multiple Sclerosis* 1999;**5**:251–9.

Hamilton 1960
Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 1960;**23**(1):56–62.

Higgins 2008
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Wiley & Sons, Ltd., 2008.

McDonald 2001
McDonald WI, Compston A, Edan G. Recommended diagnostic criteria for MS: Guidelines from the International

Panel on the diagnosis of multiple sclerosis. *Annals of Neurology* 2001;**50**:121–7.

Montgomery 1979
Montgomery SA, Asberg M. A new depression scale, designed to be sensitive to change. *British Journal of Psychiatry* 1979;**134**:382–92.

Patten 2005
Patten SB, Beck CA, Williams JVA, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. *Neurology* 2003;**61**(11):1524–7.

Poser 1983
Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for Multiple Sclerosis: guidelines for research proposals. *Annals of Neurology* 1983;**13**:227–31.

Radloff 1977
Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measures* 1977;**1**:385–401.

Rush 1986
Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger JE, Burns CT. The Inventory of Depressive Symptomatology (IDS): Preliminary findings. *Psychiatry Research* 1986;**18**:65–87.

Siegert 2005
Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. *Journal of Neurology, Neurosurgery, and Psychiatry* 2005;**76**(4):469–75.

Sullivan 1990
Sullivan JJ, Egdley K, Dehoux E. A survey of multiple sclerosis: Part 1. Perceived cognitive problems and compensatory strategy use. *Canadian Journal of Rehabilitation* 1990;**4**:99–105.

Ware 1992
Ware JE, Sherbourne CD. The MOS 36-item short-form health survey. *Medical Care* 1992;**30**:473–83.

Zigmond 1983
Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica* 1983;**67**(6): 361–70.

Zung 1965
Zung WWK. A self-rating depression scale. *Archives of General Psychiatry* 1965;**12**(1):63–70.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ehde 2008

Methods	Double-blind randomized placebo-controlled single-center trial
Participants	Patients eighteen years or older with both a diagnosis of MS confirmed by a neurologist or MS-trained physiatrist and a diagnosis of major depressive disorder or dysthymia
Interventions	Up to 40mg/day of paroxetine or placebo
Outcomes	Number of patients with a reduction of at least 50% in HAM-D scores, number of patients with a HAM-D score of seven or lower, number of patients with reduced scores on the HAM-D and CES-D scales, difference between baseline and final scores on the Modified Fatigue Impact Scale, the Perceived Deficits Questionnaire, the Satisfaction with Life Scale, and the MOS 36-Item Short-Form Health Questionnaire
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by randomization table in blocks of ten with a computerized random number generator. Patients were stratified according to whether they had depression or depression and dysthymia
Allocation concealment (selection bias)	Low risk	The allocation sequence was not generated by the trial authors but by the University of Washington Investigational Drug Service using a computerized random number generator
Blinding (performance bias and detection bias) All outcomes	Low risk	The placebo capsules were similar in appearance to the paroxetine capsules. Patients and researchers were blinded to the allocated treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% of study participants were lost to follow-up, which suggests a high risk of attrition bias An intention to treat analysis was performed with all study participants with the last observation carried forward for those with missing data; a separate analysis was performed with study completers. In our

		opinion, this method is inappropriate for dealing with missing data
Selective reporting (reporting bias)	Low risk	There was no concern that outcomes were reported selectively
Other bias	Low risk	The study appeared free of other problems that could put it at a high risk of bias

Schiffer 1990

Methods	Double-blind randomized placebo-controlled single center trial
Participants	Patients with a diagnosis of both MS and depression according to pre-defined criteria
Interventions	Up to 200mg/day of desipramine or placebo
Outcomes	Main outcome measure: blinded assessment of clinical improvement by the primary therapist, secondary outcomes: scores on the HAM-D and BDI scales
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomized with a pre-randomized schedule, no further information is given
Allocation concealment (selection bias)	Low risk	The randomization sequence was generated by the hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Unclear risk	While the clinical judgements of the primary therapist are described as blinded, it is unclear whether the investigators administering the rating scales were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% of study participants were lost to follow-up, which suggests a high risk of attrition bias Only study completers were included in the analyses. In our opinion, this method is inappropriate for dealing with missing data
Selective reporting (reporting bias)	Low risk	There was no concern that outcomes were reported selectively

Other bias	Low risk	The study appeared free of other problems that could put it at a high risk of bias

DATA AND ANALYSES

Comparison 1. Desipramine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of HAM-D score by at least 50% at five weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Study completers	1	20	Odds Ratio (M-H, Fixed, 95% CI)	1.4 [0.23, 8.46]
1.2 Best case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	4.5 [0.91, 22.15]
1.3 Worst case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.4 [0.08, 1.91]
2 Reduction of HAM-D score to 7 or lower at five weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Study completers	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.10, 5.96]
2.2 Best case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	3.67 [0.70, 19.12]
2.3 Worst case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.39]
3 Any reduction of HAM-D score at five weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Study completers	1	20	Odds Ratio (M-H, Fixed, 95% CI)	7.82 [0.35, 174.42]
3.2 Best case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	22.18 [1.11, 444.74]
3.3 Worst case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.64]
4 Any reduction of BDI score at five weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Study completers	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.09, 6.98]
4.2 Best case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	3.33 [0.52, 21.28]
4.3 Worst case	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 1.04]
5 Number of patients with at least one adverse effect	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Intention to treat	1	28	Odds Ratio (M-H, Fixed, 95% CI)	6.0 [0.97, 37.30]

Comparison 2. Paroxetine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of HAM-D score by at least 50% at twelve weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Study completers	1	32	Odds Ratio (M-H, Fixed, 95% CI)	4.58 [0.94, 22.24]
1.2 Best case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	9.5 [2.10, 43.04]
1.3 Worst case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.36]
2 Reduction of HAM-D score to 7 or lower at twelve weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Study completers	1	32	Odds Ratio (M-H, Fixed, 95% CI)	3.6 [0.83, 15.63]
2.2 Best case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	7.93 [1.99, 31.59]
2.3 Worst case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.30, 3.57]

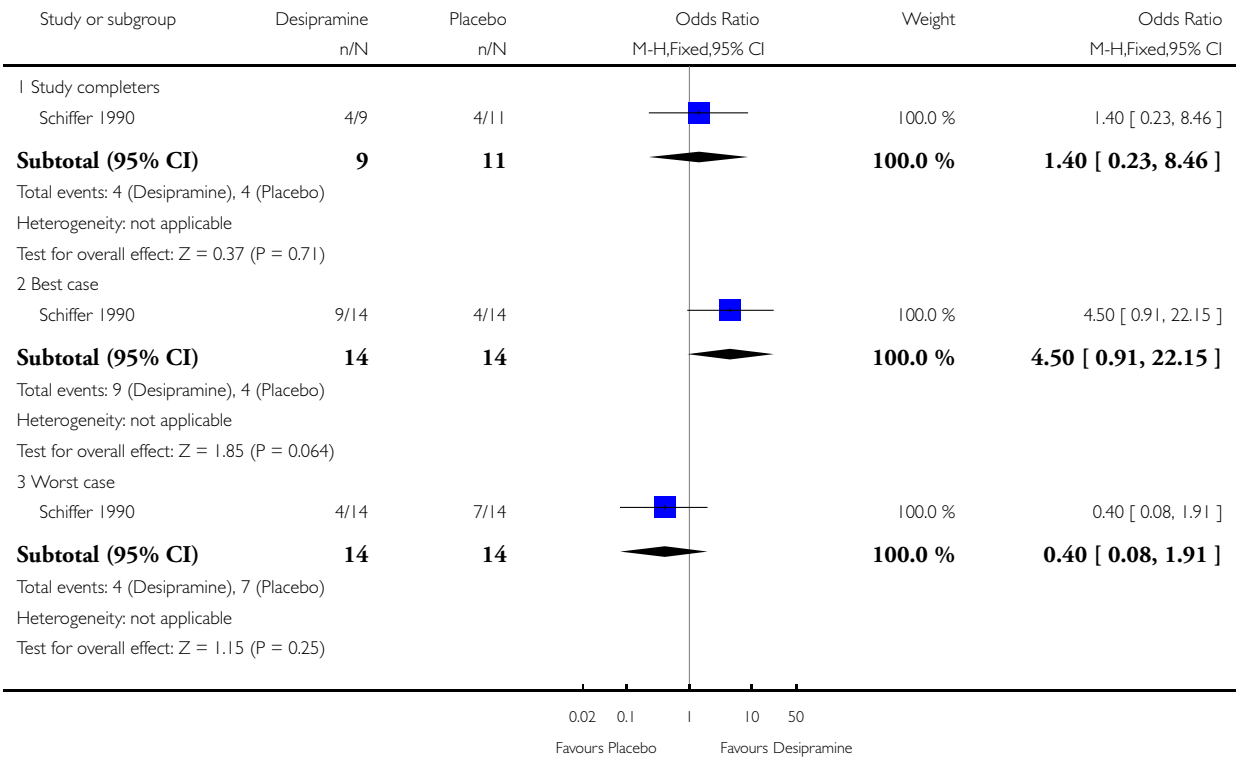
3 Any reduction of HAM-D score at twelve weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Study completers	1	32	Odds Ratio (M-H, Fixed, 95% CI)	4.39 [0.19, 99.23]
3.2 Best case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	12.27 [0.62, 244.05]
3.3 Worst case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 1.06]
4 Any reduction of CES-D score at twelve weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Study completers	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Best case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Worst case	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.50]
5 Number of patients with at least one adverse effect	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Intention to treat	1	42	Odds Ratio (M-H, Fixed, 95% CI)	2.23 [0.64, 7.74]
6 Number of patients with dry mouth	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Intention to treat	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.45, 5.37]
7 Number of patients with nausea	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Intention to treat	1	42	Odds Ratio (M-H, Fixed, 95% CI)	15.83 [1.79, 139.92]
8 Number of patients with headache	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Intention to treat	1	42	Odds Ratio (M-H, Fixed, 95% CI)	7.5 [1.39, 40.43]
9 Number of patients with sexual dysfunction	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Intention to treat	1	42	Odds Ratio (M-H, Fixed, 95% CI)	5.59 [0.59, 52.73]

Analysis 1.1. Comparison 1 Desipramine versus placebo, Outcome 1 Reduction of HAM-D score by at least 50% at five weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 1 Desipramine versus placebo

Outcome: 1 Reduction of HAM-D score by at least 50% at five weeks

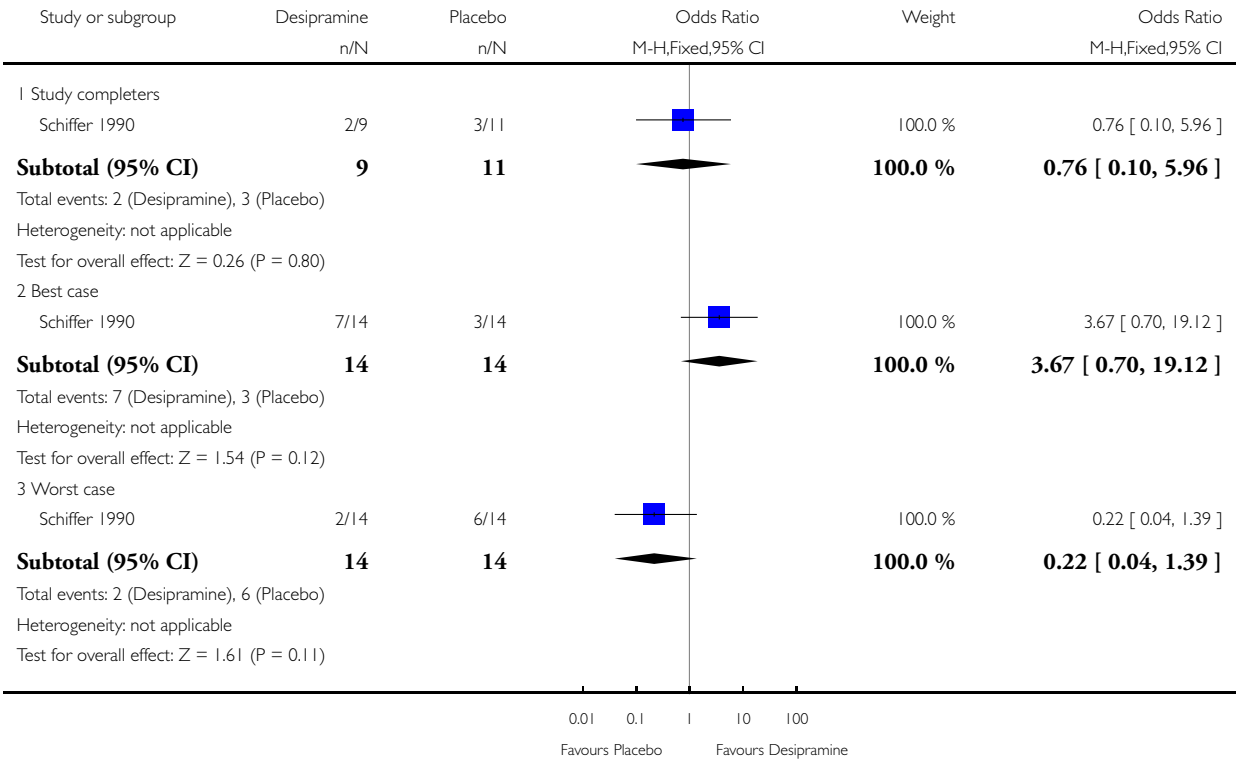


Analysis 1.2. Comparison 1 Desipramine versus placebo, Outcome 2 Reduction of HAM-D score to 7 or lower at five weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 1 Desipramine versus placebo

Outcome: 2 Reduction of HAM-D score to 7 or lower at five weeks



Analysis 1.3. Comparison 1 Desipramine versus placebo, Outcome 3 Any reduction of HAM-D score at five weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 1 Desipramine versus placebo

Outcome: 3 Any reduction of HAM-D score at five weeks

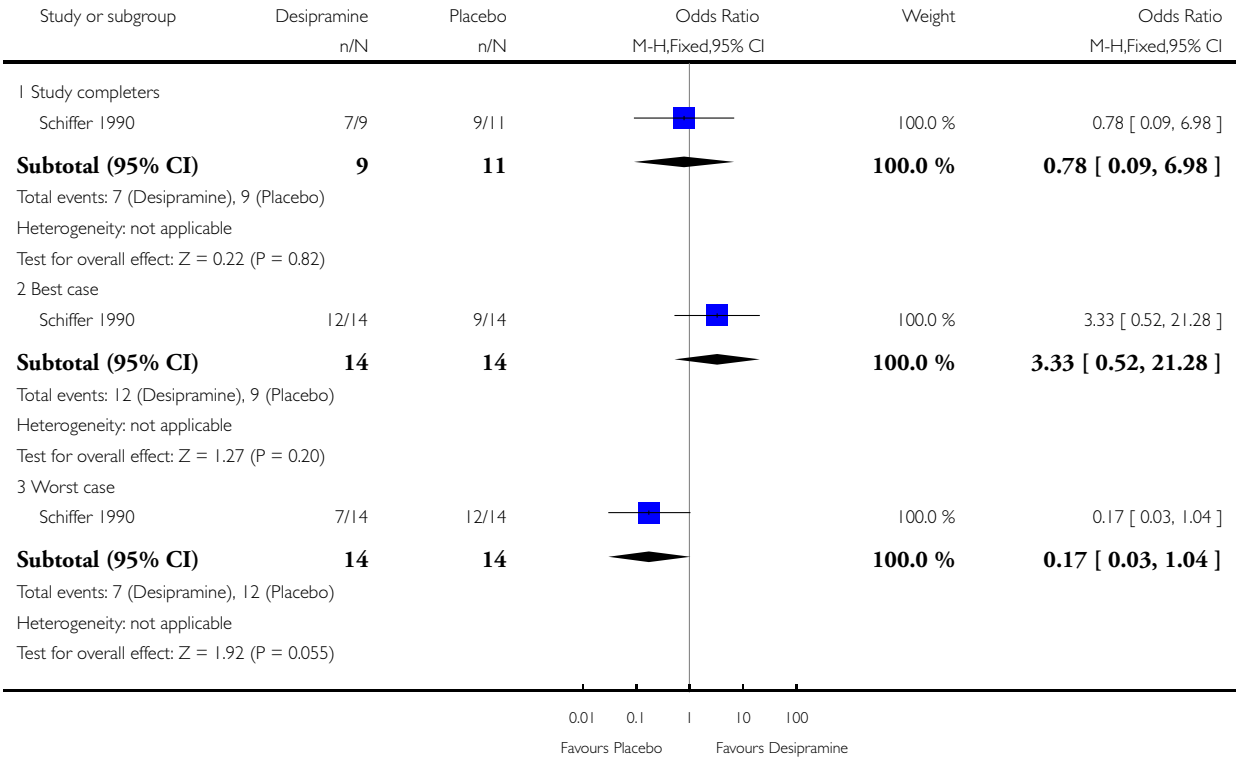
Study or subgroup	Desipramine n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Study completers					
Schiffer 1990	9/9	8/11		100.0 %	7.82 [0.35, 174.42]
Subtotal (95% CI)	**9**	**11**		**100.0 %**	**7.82 [0.35, 174.42]**
Total events: 9 (Desipramine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
2 Best case					
Schiffer 1990	14/14	8/14		100.0 %	22.18 [1.11, 444.74]
Subtotal (95% CI)	**14**	**14**		**100.0 %**	**22.18 [1.11, 444.74]**
Total events: 14 (Desipramine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.03 (P = 0.043)					
3 Worst case					
Schiffer 1990	9/14	11/14		100.0 %	0.49 [0.09, 2.64]
Subtotal (95% CI)	**14**	**14**		**100.0 %**	**0.49 [0.09, 2.64]**
Total events: 9 (Desipramine), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					

Analysis 1.4. Comparison 1 Desipramine versus placebo, Outcome 4 Any reduction of BDI score at five weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 1 Desipramine versus placebo

Outcome: 4 Any reduction of BDI score at five weeks

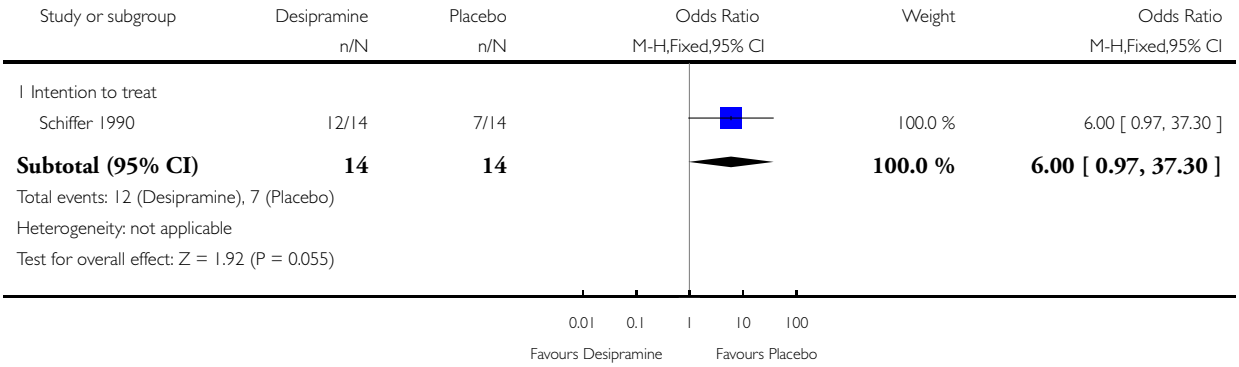


Analysis 1.5. Comparison 1 Desipramine versus placebo, Outcome 5 Number of patients with at least one adverse effect.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 1 Desipramine versus placebo

Outcome: 5 Number of patients with at least one adverse effect

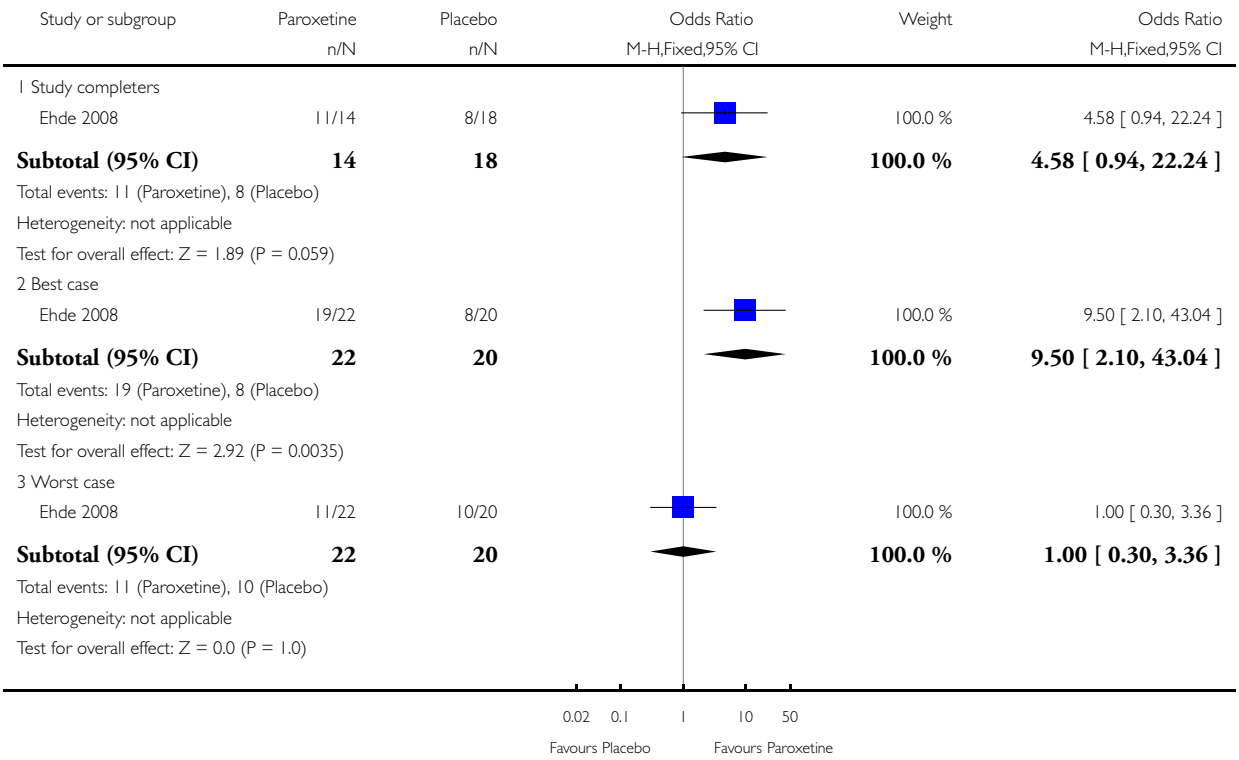


Analysis 2.1. Comparison 2 Paroxetine versus placebo, Outcome 1 Reduction of HAM-D score by at least 50% at twelve weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 1 Reduction of HAM-D score by at least 50% at twelve weeks

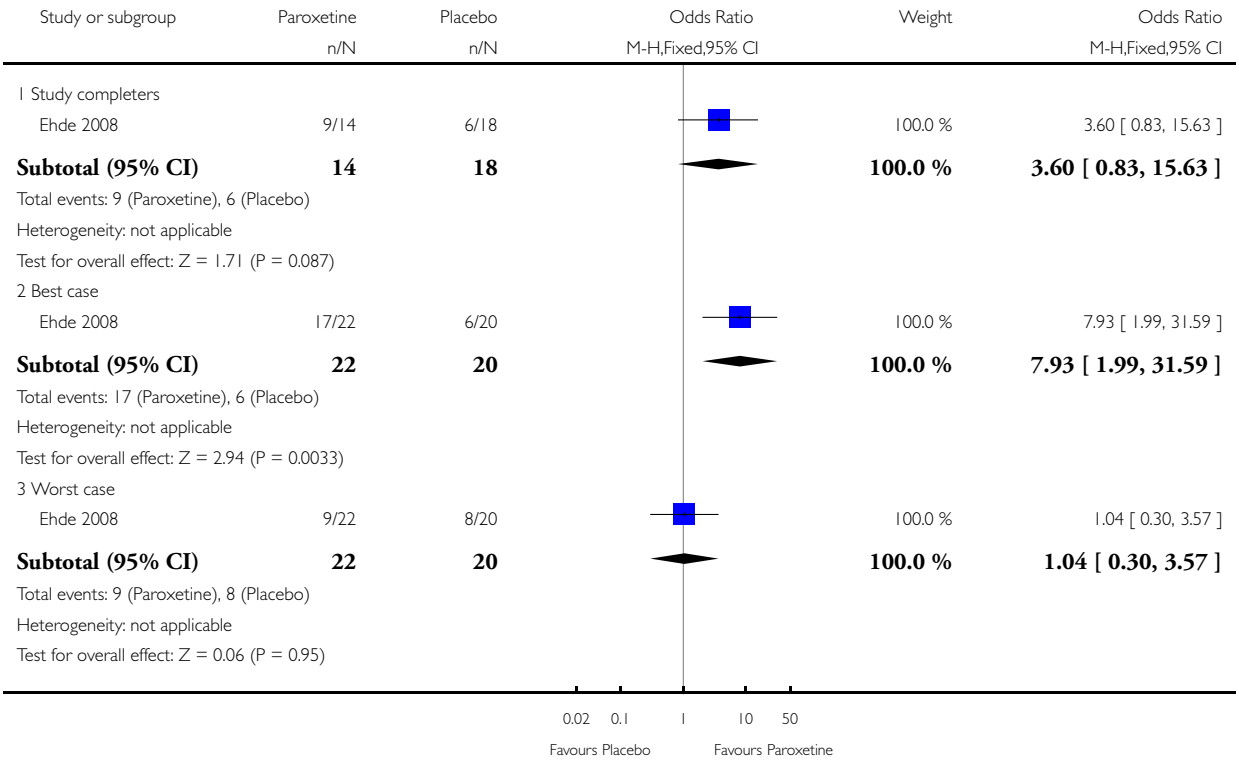


Analysis 2.2. Comparison 2 Paroxetine versus placebo, Outcome 2 Reduction of HAM-D score to 7 or lower at twelve weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 2 Reduction of HAM-D score to 7 or lower at twelve weeks

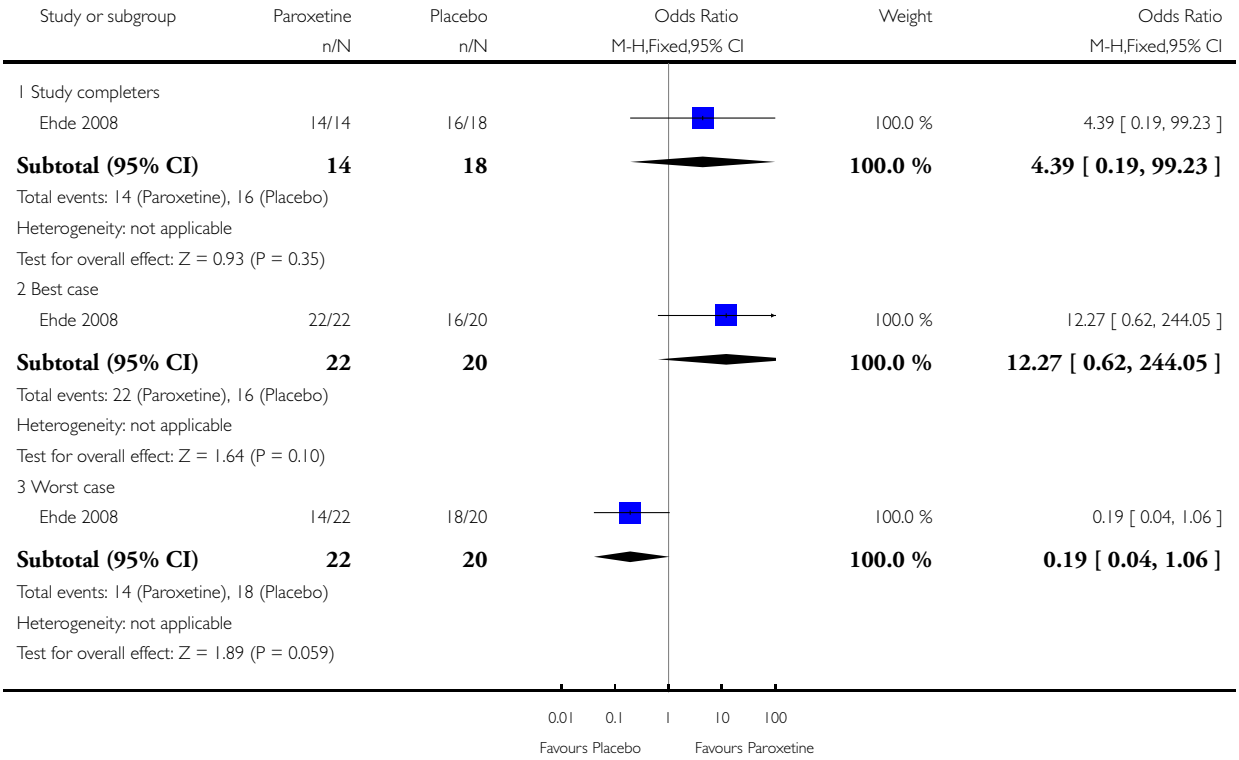


Analysis 2.3. Comparison 2 Paroxetine versus placebo, Outcome 3 Any reduction of HAM-D score at twelve weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 3 Any reduction of HAM-D score at twelve weeks



Analysis 2.4. Comparison 2 Paroxetine versus placebo, Outcome 4 Any reduction of CES-D score at twelve weeks.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 4 Any reduction of CES-D score at twelve weeks

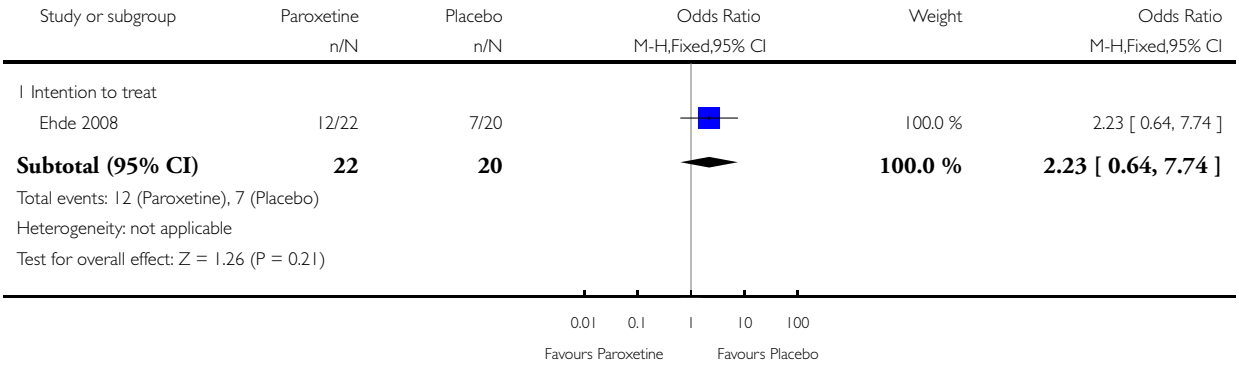
Study or subgroup	Paroxetine n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Study completers					
Ehde 2008	17/17	20/20			Not estimable
Subtotal (95% CI)	**17**	**20**			**Not estimable**
Total events: 17 (Paroxetine), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Best case					
Ehde 2008	22/22	20/20			Not estimable
Subtotal (95% CI)	**22**	**20**			**Not estimable**
Total events: 22 (Paroxetine), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Worst case					
Ehde 2008	17/22	20/20		100.0 %	0.08 [0.00, 1.50]
Subtotal (95% CI)	**22**	**20**		**100.0 %**	**0.08 [0.00, 1.50]**
Total events: 17 (Paroxetine), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.69 (P = 0.091)					

Analysis 2.5. Comparison 2 Paroxetine versus placebo, Outcome 5 Number of patients with at least one adverse effect.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 5 Number of patients with at least one adverse effect

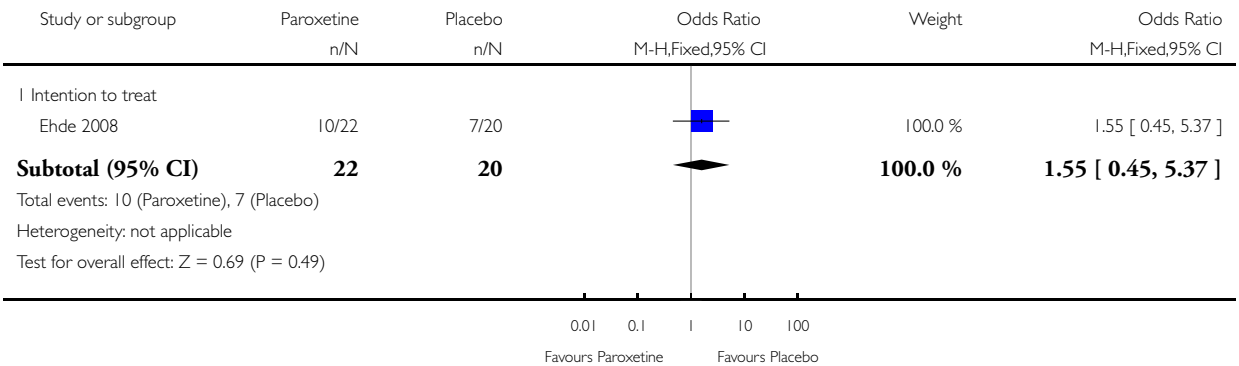


Analysis 2.6. Comparison 2 Paroxetine versus placebo, Outcome 6 Number of patients with dry mouth.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 6 Number of patients with dry mouth

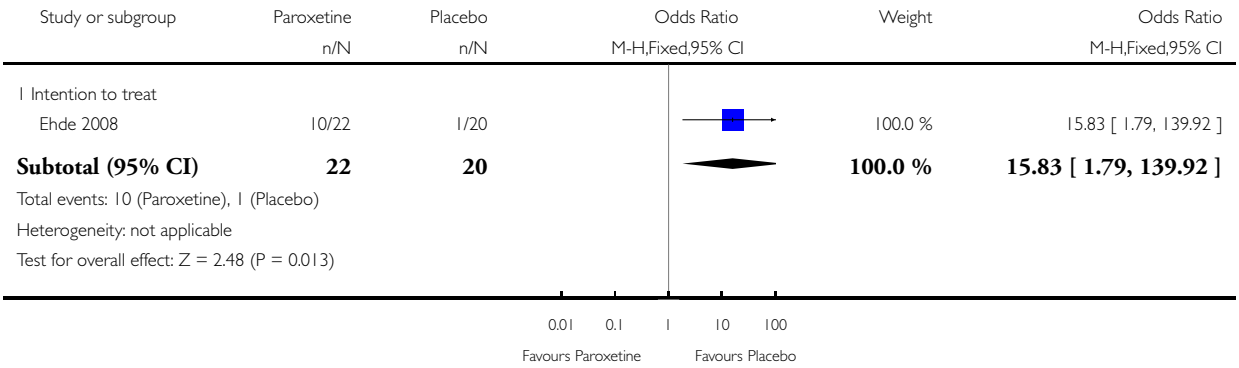


Analysis 2.7. Comparison 2 Paroxetine versus placebo, Outcome 7 Number of patients with nausea.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 7 Number of patients with nausea

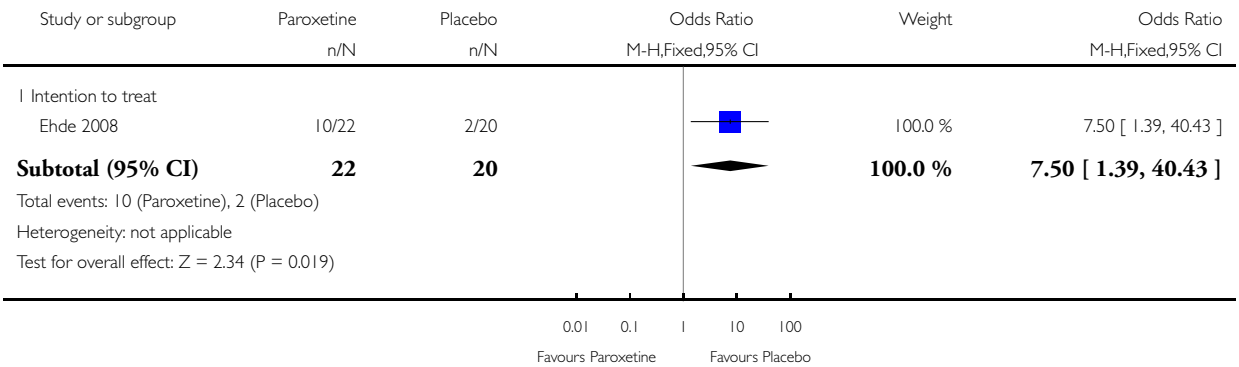


Analysis 2.8. Comparison 2 Paroxetine versus placebo, Outcome 8 Number of patients with headache.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 8 Number of patients with headache

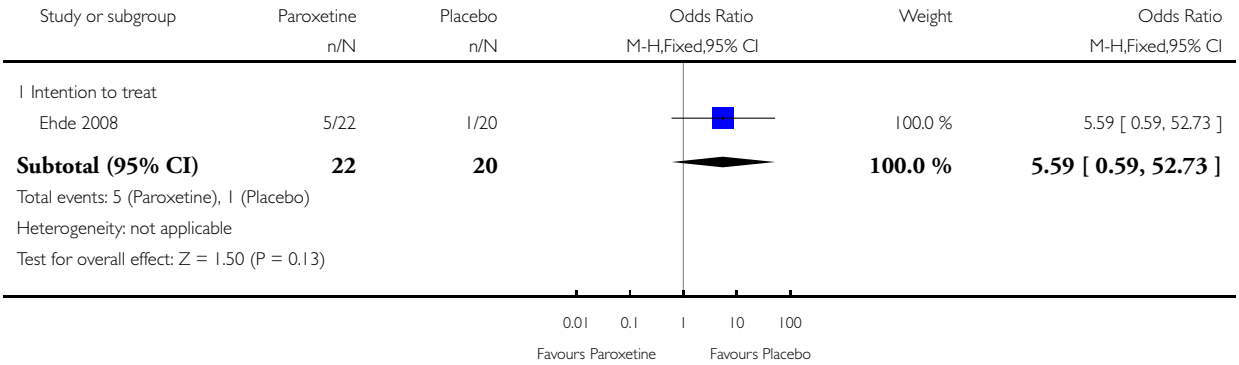


Analysis 2.9. Comparison 2 Paroxetine versus placebo, Outcome 9 Number of patients with sexual dysfunction.

Review: Pharmacologic treatment of depression in multiple sclerosis

Comparison: 2 Paroxetine versus placebo

Outcome: 9 Number of patients with sexual dysfunction



APPENDICES

Appendix 1. Keywords used in the systematic literature search

1. Depression
2. depress*
3. dysthym*
4. dysthymic disorder

WHAT'S NEW

Last assessed as up-to-date: 8 December 2010.

Date	Event	Description
8 April 2011	Amended	The section "Plain language summary" has been amended.

CONTRIBUTIONS OF AUTHORS

All authors cooperated in the literature search, data extraction, data analysis and in writing the review.

DECLARATIONS OF INTEREST

We declare we have no conflicts of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Depression [*drug therapy]; Desipramine [therapeutic use]; Multiple Sclerosis [*psychology]; Paroxetine [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans