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Prevention of major depressive disorder relapse and recurrence with second-generation antidepressants: A systematic review and meta-analysis

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Abstract

Objective—To review data on the efficacy and effectiveness of second-generation antidepressants for preventing major depression relapse and recurrence during continuation and maintenance phase treatment, respectively.

Methods—MEDLINE®, EMBASE, and PsychLit; the Cochrane Library; and the International Pharmaceutical Abstracts were searched from January 1980 through April 2007 for reviews, randomized controlled trials, meta-analyses, and observational studies. Two persons independently reviewed abstracts and full text articles using a structured data abstraction form to ensure consistency in appraisal and data extraction.

Findings—Four comparative trials and 23 placebo controlled trials that addressed relapse or recurrence prevention were included. Results of comparative trials have not demonstrated statistically significant differences between duloxetine and paroxetine, fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine. Pooled data for the class of second-generation antidepressants compared with placebo suggest a relatively large effect size that persists over time. The number needed to treat to prevent one additional relapse or recurrence is 5 (95% CI 4 to 6). Differences in the length of open-label treatment prior to randomization, drug type, and trial duration did not affect pooled estimates of relapse rates ($P = 0.716$, $P = 0.507$, and $P = 0.480$,

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respectively). Across all trials, 7% of patients randomized to active treatment and 5% of patients randomized to placebo discontinued treatment because of adverse events.

Conclusions—This review demonstrates the overall benefits of continuation- and maintenance-phase treatment of major depression with second-generation antidepressants, and stresses the need for additional studies on comparative differences among drugs.

Keywords

Antidepressant; major depressive disorder; prevention; relapse; recurrence

INTRODUCTION

Antidepressants commonly are used as first-line treatment for major depressive disorder (MDD). On average, approximately 60% of patients respond to acute-phase treatment with second-generation antidepressants such as bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine (1). Once a patient demonstrates an appropriate response to an antidepressant, ongoing treatment is recommended.

Treatment guidelines for MDD (2,3) suggest an acute-phase treatment duration of 6 to 12 weeks. For patients who demonstrate an adequate response (usually defined as remission) to acute-phase treatment, continuation-phase treatment of 4 to 9 months is recommended. The goal of continuation-phase treatment is enduring absence of depressive symptoms so the patient's episode can be considered completely resolved. Effective continuation-phase treatment prevents *relapse* - the return of depressive symptoms during the current depressive episode. Following successful continuation-phase treatment, a maintenance-phase treatment to prevent *recurrence* of a new, distinct episode is considered. For those with a history of recurrent MDD, maintenance-phase treatment can frequently last for years.

To date, two reviews have systematically assessed relapse prevention during continuation and maintenance treatment (4,5). However, these reviews included all antidepressants rather than just second-generation antidepressants; they are also limited by the dates of their literature searches (searches censored at 1987 (4) and 2000 (5) and therefore do not include more recent studies). A more recent review by Zimmerman and colleagues (2007) focused on second-generation antidepressants, although the intent of this review was to illustrate how conclusions differ between extension and placebo substitution trials. Because second-generation drugs are now the most frequently prescribed antidepressants, our goal was to evaluate systematically data on the efficacy of second-generation antidepressants for maintaining remission and to assess this evidence in light of their tolerability during ongoing treatment.

We conducted a systematic review and meta-analysis of comparative and placebo-controlled evidence for 12 second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine). We refer to these agents collectively as antidepressants. The key questions for this review were:

1. For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining remission (i.e., preventing relapse or recurrence)?
2. For adults with depressive syndrome, what is the overall effect size for active treatment compared with placebo, and is the effect size persistent over time?

METHODS

Key Questions

Key questions designed to address efficacy, effectiveness, and tolerability of antidepressants for maintaining remission guided our work. The key questions were formulated through a public process involving the public, the US Scientific Resource Center for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ), and various stakeholder groups. The AHRQ provided funding for the initial review, although the current update and analysis was unfunded.

Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, PsychLit, and the International Pharmaceutical Abstracts. Our searches covered 1980 through April 2007. We manually searched reference lists of relevant review articles and letters to the editor. Additionally, we hand-searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the US Food and Drug Administration (FDA).

Study Selection

Two persons independently reviewed titles and abstracts. We included head-to-head trials comparing one antidepressant to another, as well as placebo-controlled trials. Studies included adult inpatients and outpatient populations with depressive illness with demonstrated response or remission to treatment. Head-to-head trials were included if they reported relapse or recurrence rates, regardless of whether participants were randomized following successful acute or continuation-phase treatment (i.e., extension versus randomized substitution). For the purpose of our meta-analysis, inclusion criteria were more stringent for placebo-controlled evidence; only studies that randomized participants after demonstrating either an acute-phase response or lack of relapse during the continuation phase were included (i.e., randomized placebo substitution trials).

Data Abstraction

Trained reviewers abstracted data from each study; a senior reviewer read each abstracted article and evaluated completeness of data extraction. We recorded intention-to-treat results if available.

Quality and Strength Assessment

We assessed the internal validity (quality) of trials based on predefined criteria from the US Preventive Services Task Force (ratings: good-fair-poor) (6) and the National Health Service Centre for Reviews and Dissemination (7). Elements of internal validity assessment included randomization, allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis, and overall and differential loss to followup. Discrepancies in quality assessment were resolved by discussion and, when necessary, consultation with a third-party.

Data Synthesis

We qualitatively summarized all studies. For placebo-controlled trials – the majority of the included studies – we also conducted quantitative analyses. We calculated the relative risk of loss of response for active treatment compared with placebo. The primary outcome measure was defined as loss of response or remission (i.e., continuation-phase relapse or maintenance-phase recurrence); in most trials this was defined as an increase in the Hamilton Depression rating scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) above a

predefined cut-off point. We conducted relative risk meta-analysis of relapse rates for trials stratified by duration of followup: less than 1 year and 1 year or more. Risk difference meta-analyses were used to calculate numbers needed to treat (NNT) overall and for each time period.

Trials with multiple placebo comparisons were included in the analysis. For example, in trials that compared multiple dosing arms to a single placebo group, the dosing arms were combined for a single comparison as long as doses were within the range of approved doses. In trials that compared one or more drug to placebo, each drug-placebo comparison was included as an observation, but the sample size of the placebo group was reduced proportionately to the number of comparisons so as not to over-represent the placebo group. For each meta-analysis, we tested for heterogeneity of treatment effects using I^2 statistics. We report the results of the more conservative random effects models (8). To estimate possible publication bias, we used funnel plots, Beggs adjusted rank correlation test, and the Egger regression approach (9,10). However, because these tests have low statistical power when the number of trials is small (11), undetected bias may still be present.

As an additional means of comparing relapse rates for active treatment with those for placebo over time, we calculated weighted mean relapse rates for all reported time points across included trials. We plotted the weighted mean relapse rates for active treatment and placebo against time (weeks) and added a linear trend line for each group. A general linear model was used to test whether differences in relapse rates between active treatment and placebo were consistent over time.

The most common trial design was an open-label acute treatment phase of 6 to 15 weeks, followed by a randomized, double-blind, placebo-controlled continuation- and/or maintenance-phase for acute-phase responders or remitters. Because trials differed in the length of open-label treatment prior to randomization and the duration of treatment after randomization, we conducted a meta-regression to explore how heterogeneity in design impacted estimates of relative risk. Similarly, we used meta-regression to explore whether pooling antidepressants as a class was a reasonable approach. For simplicity, this analysis explored heterogeneity by comparing SSRI trials (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) to other second-generation antidepressant trials (e.g., bupropion, duloxetine, mirtazapine, nefazodone, trazodone, and venlafaxine).

To balance our assessment of benefits, we examined reported rates of adverse events and rates of loss to followup due to adverse events. We qualitatively compared the rates from included relapse/recurrence prevention studies with rates reported in acute-phase trials (1,12). We also conducted a relative risk meta-analysis for active treatment compared with placebo for both overall loss to followup and loss to followup due to adverse events. However, because of variability in study populations and in adverse event assessment and reporting among trials, caution should be taken in interpreting this evidence.

All statistical analyses were conducted using STATA 9.1 (StataCorp, 2005).

RESULTS

Our search identified 2,318 titles and abstracts (Appendix 1). Of these, we reviewed 902 full text articles and retained 29 articles describing 27 unique trials that addressed relapse or recurrence prevention (Table 1 and Table 2). The most common reason for exclusion was “wrong study design”; many of the excluded studies assessed acute-phase treatment. Included studies differed in their design (e.g., timing of randomization, eligibility criteria, etc.), although most studies randomized acute-phase responders or remitters to ongoing treatment with active drug or placebo. Most trials used a predefined cut-off point on a standardized scale (e.g., HAM-D or MADRS) to determine eligibility for randomization, although the cut-off point varied

among trials. Likewise, operational definitions for relapse and recurrence varied among trials. The majority of included trials were given a "fair" quality rating; they represent a broad range of methodological quality.

Comparative Trials

Four head-to-head trials (five publications) provide evidence of moderate strength that the overall efficacy of second-generation antidepressants for maintaining remission does not differ between drugs studied in these trials (Table 1)(13–17). Comparisons included duloxetine with paroxetine (17), fluoxetine with sertraline (13), fluvoxamine with sertraline (14,15), and trazodone with venlafaxine (16). Relapse rates did not differ significantly among trials. Although these trials reported relapse or recurrence rates, no comparative trial used a substitution design to randomize participants following successful acute or continuation treatment.

Placebo-Controlled Trials

Twenty-three RCTs provided placebo-controlled evidence to support the general efficacy of second-generation drugs for preventing relapse or recurrence in patients with depressive disorders (Table 2) (18–40). Twelve trials (13 placebo comparisons) were shorter than 1 year for the randomized followup (18–27,29,40). These trials provide consistent evidence in favor of active drug over placebo, with the majority representing the efficacy of relapse prevention. The unadjusted frequency of relapse was 22% for active treatment, compared with 42% for placebo. An additional 11 RCTs were 1 year or longer (28,30–39). These trials also provide consistent evidence in favor of active treatment over placebo, with the majority representing recurrence prevention during maintenance-phase treatment. The unadjusted frequency of relapse was 26% for active treatment, compared with 48% for placebo.

Meta-Analysis

Trials shorter than 1 year—Twelve trials were included in our relative risk meta-analysis of trials lasting less than 1 year after randomization (Figure 1): one on bupropion (18), three on citalopram (19,27,40), one on escitalopram (20), three on fluoxetine (21,22,29), and one each on mirtazapine (23), nefazodone (24), sertraline (25), and venlafaxine (26). The pooled relative risk of relapse was 0.54 (95% CI 0.46 to 0.62) and the NNT to prevent one additional relapse over a mean time of 8 months was 5 (95% CI: 4–6). Moderate heterogeneity was detected among these trials (I^2 = 47%). Tests for publication bias were not statistically significant.

Trials 1 year or longer—Eleven trials provided data points for followup of 1 year or more (Figure 2): one on citalopram (28), one on escitalopram (38), one on fluvoxamine (30), one on nefazodone (31), two on paroxetine (32,37), four on sertraline (33–35,39), and one on venlafaxine (36). Trials consistently favored active treatment over placebo for preventing relapse and/or recurrence, although differences were not always statistically significant. For example, during a 100-week comparison of sertraline 50-100mg/d to placebo, 45% of sertraline-treated participants and 54% of placebo-treated participants had a recurrence, but differences were not statistically significant (P=0.21) (35). The pooled relative risk of recurrence was consistent with our estimates of relapse for trials with shorter followup (RR = 0.56; 95% CI: 0.48–0.66) and the NNT to prevent one additional recurrence over a mean time of 16 months was 5 (95% CI: 4–6). As with the analysis of shorter trials, moderate heterogeneity was detected among the longer trials (I^2 = 30%). Tests for publication bias were not statistically significant.

Trend Analysis

To aid in assessing the risk of relapse or recurrence over time with active drug treatment compared with placebo, we calculated the weighted mean relapse/recurrence rates and plotted them over time (Figure 3). Although this plot demonstrates some inconsistencies in relapse and recurrence rates among trials, adding a linear trend to these data points demonstrates a relatively consistent difference between active drug and placebo. Comparing the linear trends using a general linear model revealed a statistically non-significant treatment by time interaction (P=0.59), supporting the conclusion that differences in pooled relapse/recurrence rates between active treatment and placebo persist over time.

Meta-Regression

Our meta-regression explored heterogeneity in included trials with regard to the duration of open-label treatment prior to randomization of responders, the length of the post-randomization phase, and drug type (SSRI or other second-generation antidepressant). None of these variables statistically significantly influenced our estimates of effect size ($P = 0.716$, $P = 0.480$, and $P = 0.507$ respectively).

Adverse Events

The most common adverse event documented in continuation- and maintenance-phase studies was headache, followed by nausea (weighted mean incidence = 15.5% and 7.4% respectively). Compared with the incidence of adverse events in acute-phase studies (1,41), the relative incidence of these events during long-term treatment was slightly lower. Based on 22 trials that provided sufficient data, loss to followup in general and loss to followup because of adverse events represented an average of 50% and 7%, respectively, of patients randomized to active treatment and 68% and 4%, respectively, of patients randomized to placebo. Based on data pooled from 17 placebo-controlled trials, the relative risk of dropping out for any reason was statistically significantly lower for active treatment than for placebo (RR = 0.75; 95% CI 0.69 to 0.83). Data pooled from 18 placebo-controlled trials demonstrated that loss to followup because of adverse events was not statistically significantly different between active treatment and placebo (RR = 1.42; 95% CI: 0.92–2.20).

DISCUSSION

We systematically assessed the efficacy and tolerability of second-generation antidepressants for the prevention of relapse and recurrence during treatment in the continuation- and maintenance-phases of major depression. Only a small number of trials directly compared one antidepressant to another. Results of these trials did not demonstrate statistically significant differences between duloxetine and paroxetine (17), fluoxetine and sertraline (13), fluvoxamine and sertraline (14,15), and trazodone and venlafaxine (16) for preventing relapse or recurrence. Although results are relatively consistent, we consider the strength of comparative evidence to be moderate because additional studies could change our conclusions. Pooled data for second-generation antidepressants as a class compared with placebo suggest a relatively large effect size that persists over time, reflecting high strength evidence for continued treatment beyond the acute phase. The NNT to prevent one additional relapse or recurrence is in the range of four to six patients.

The tolerability profile of continuation- and maintenance-phase treatment is fair to good. In clinical trials, 7% of patients randomized to active treatment and 5% of patients randomized to placebo discontinued continuation- or maintenance-phase treatment because of adverse events. Although loss to followup was high (i.e., 50% and 68% for active drug and placebo, respectively), the relative risk of discontinuing treatment because of adverse events did not differ significantly between active treatment and placebo. Overall loss to followup in acute-

phase studies has been estimated at approximately 24% (12), which is considerably lower than our estimates from continuation- and maintenance-phase studies. Our estimates likely are high because of longer trial duration, the preventive aim of this treatment, and misclassification of clinical endpoints (i.e., relapse or recurrence) as loss to followup.

Current practice guidelines for MDD recommend continuation-phase treatment for 4 to 9 months for patients who demonstrate an adequate response to acute-phase treatment (2,3). For patients with recurrent MDD, maintenance treatment is recommended. Our systematic review and meta-analysis provide relatively strong support for these guidelines. Based on the consistency of effect sizes over time, our review illustrates stable benefits of active treatment over placebo for up to 2 years of treatment. Although our analysis was able to demonstrate continued benefits of drug treatment over time, we were not able to draw inferences as to the most appropriate duration of antidepressant treatment. We identified only one RCT that compared relapse rates for differing lengths of antidepressant treatment (21), but the sample size of the longest treatment arm in this trial may have been insufficiently powered. Still, fluoxetine was shown to be more efficacious than placebo for up to 38 weeks (i.e., approximately 9 months) in this trial. More research is needed to determine the most appropriate length of therapy.

In a well-conducted systematic review of relapse prevention with first- and second-generation antidepressants in depressive disorders, Geddes and colleagues (2003) reported a 70% reduction in the odds of relapse for patients continuing antidepressant treatment compared with patients discontinuing treatment. The effect sizes reported in this analysis were “similar for all classes of antidepressants,” (5) but such unadjusted indirect comparisons may not be valid. To explore this further, we used data reported in the Geddes et al. review and converted their odds ratio to a relative risk -- namely, 0.45 for active drug compared with placebo (95% CI 0.41 – 0.49) and 0.41 specifically for second-generation antidepressants compared with placebo (95% CI 0.35 – 0.48). The confidence intervals for the relative risk of relapse that we calculated for only second-generation antidepressants (less than 1 year, 0.46 – 0.62; 1 year or longer, 0.48 – 0.66) overlapped this relative risk estimate from the Geddes et al. study, and our analysis included nearly twice as many trials of newer antidepressants.

Even though a small number of comparative studies found no statistically significant differences between second-generation antidepressants, we are unable to draw firm conclusions as to whether one drug may be better than another for long-term treatment. These comparative trials were extension trials and did not re-randomize patients to continuation or maintenance treatment, but rather gave patients the option to continue on with their blinded acute-phase treatment. This trial design has been shown to produce overall lower relapse rates, but larger differences between active treatment and placebo than placebo substitution trials that randomizes participants at the time of successful acute- or continuation-phase completion (42). For this reason, we limited our meta-analyses to placebo substitution trials. Although this does not answer the question of whether the extension or placebo-substitution design provides a more accurate assessment of the benefits of drug treatment, we believe our results provide strong evidence for the benefits of continuing versus discontinuing antidepressant treatment after successful acute- or continuation-phase treatment.

Although it is tempting to draw inferences about one drug compared with another by indirectly comparing effect sizes among placebo-controlled trials (e.g., figure 1–figure 2), we caution against such inferences because included trials differed in design and because unadjusted comparisons may be inaccurate. Adjusted indirect comparisons usually agree with results of head-to-head comparisons, but only when the trials being indirectly compared are similar (43). Because of differences in trial design and in operational definitions (e.g., definition of relapse or recurrence) used by investigators, we chose not to conduct adjusted indirect

comparisons. More research is needed to verify whether second-generation antidepressants differ in relapse rates.

Our analysis is limited in other ways. The primary problem is the quantity and quality of available evidence addressing our question. Only a handful of comparative studies have been published, making it difficult to generalize about one drug compared with any other. Furthermore, the number of placebo-controlled trials is insufficient to make adjusted indirect comparisons. Evidence for some drugs was limited to a single study. Although we conducted a meta-regression to explore heterogeneity, data were insufficient to assess all important differences among trials. One important distinction that we could not address is whether presenting with a history of a single episode versus recurrent episodes made a difference in relapse or recurrence rates. Because this is a primary decision point for psychiatrists in deciding whether to continue with maintenance-phase treatment, more work is needed in this area.

This review confirms the benefits of continuation- and maintenance-phase treatment of major depression with second-generation antidepressants. Our review supports current clinical practice guidelines. Additionally, our meta-regression provides some evidence that the efficacy of different types of second-generation antidepressants does not differ in clinically significant ways, although more research is needed to confirm this conclusion. Given that ongoing treatment can prevent a relapse or recurrence for approximately one in five patients, clinicians should continue to encourage treatment beyond the acute phase and work with patients to find the most suitable drug.

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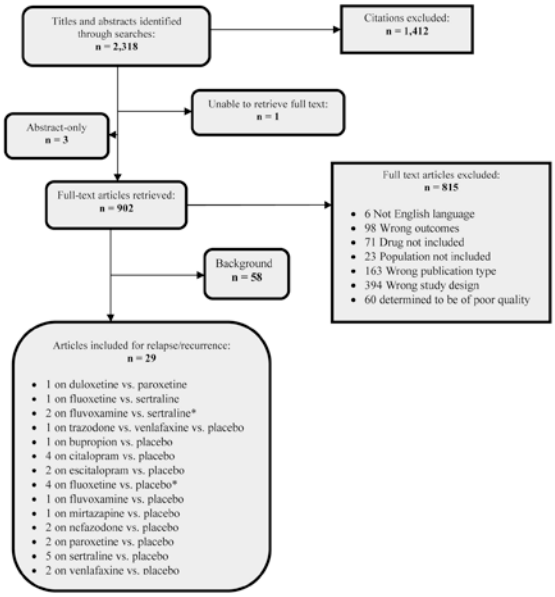
REFERENCES

1. Hansen RA, Gartlehner G, Lohr KN, et al. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Annals of Internal Medicine 2005;143:415–426. [PubMed: 16172440]
2. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. American Journal of Psychiatry 2000;157:1–45.
3. Depression guideline panel. Depression in primary care: Volume 2, Treatment of major depression. AHCPR publication No. 93-0550. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1993.
4. Loonen AJ, Peer PG, Zwanikken GJ. Continuation and maintenance therapy with antidepressive agents. Meta-analysis of research. Pharmaceutisch Weekblad Scientific Edition 1991;13:167–175. [PubMed: 1834986]
5. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003;361:653–661. [PubMed: 12606176]
6. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. American Journal of Preventive Medicine 2001;20:21–35. [PubMed: 11306229]
7. Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4. 2nd edition. York, United Kingdom: 2001.
8. Egger, M.; Smith, GD.; Altman, DG. Systematic Reviews in Health Care. 2nd edition. 2001.

9. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101. [PubMed: 7786990]
10. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. British Medical Journal 1997;315:629–634. [PubMed: 9310563]
11. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. Journal of Clinical Epidemiology 2000;53:1119–1129. [PubMed: 11106885]
12. Gartlehner G, Hansen RA, Carey TS, et al. Discontinuation rates for selective serotonin reuptake inhibitors and other second-generation antidepressants in outpatients with major depressive disorder: a systematic review and meta-analysis. International Clinical Psychopharmacology 2005;20:59–69. [PubMed: 15729080]
13. Van Moffaert M, Bartholome F, Cosyns P, et al. A controlled comparison of sertraline and fluoxetine in acute and continuation treatment of major depression. Human Psychopharmacology 1995;10:393–405.
14. Franchini L, Gasperini M, Perez J, et al. A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. Journal of Clinical Psychiatry 1997;58:104–107. [PubMed: 9108811]
15. Franchini L, Gasperini M, Zanardi R, et al. Four-year follow-up study of sertraline and fluvoxamine in long-term treatment of unipolar subjects with high recurrence rate. Journal of Affective Disorders 2000;58:233–236. [PubMed: 10802132]
16. Cunningham LA, Borison RL, Carman JS, et al. A comparison of venlafaxine, trazodone, and placebo in major depression. Journal of Clinical Psychopharmacology 1994;14:99–106. [PubMed: 8195464]
17. Perahia DG, Wang F, Mallinckrodt CH, et al. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. European Psychiatry 2006;21:367–378. [PubMed: 16697153]
18. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. Biological Psychiatry 2002;51:753–761. [PubMed: 11983189]
19. Robert P, Montgomery SA. Citalopram in doses of 20–60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. International Clinical Psychopharmacology 1995;10 (Suppl 1):29–35. [PubMed: 7622809]
20. Rapaport MH, Bose A, Zheng H. Escitalopram continuation treatment prevents relapse of depressive episodes. Journal of Clinical Psychiatry 2004;65:44–49. [PubMed: 14744167]
21. Reimherr FW, Amsterdam JD, Quitkin FM, et al. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. American Journal of Psychiatry 1998;155:1247–1253. [PubMed: 9734550]
22. Schmidt ME, Fava M, Robinson JM, et al. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. Journal of Clinical Psychiatry 2000;61:851–857. [PubMed: 11105738]
23. Thase ME, Nierenberg AA, Keller MB, et al. Efficacy of mirtazapine for prevention of depressive relapse: a placebo-controlled double-blind trial of recently remitted high-risk patients. Journal of Clinical Psychiatry 2001;62:782–788. [PubMed: 11816867]
24. Feiger AD, Bielski RJ, Bremner J, et al. Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. International Clinical Psychopharmacology 1999;14:19–28. [PubMed: 10221638]
25. Doogan DP, Caillard V. Sertraline in the prevention of depression. British Journal of Psychiatry 1992;160:217–222. [PubMed: 1540762]
26. Simon JS, Aguiar LM, Kunz NR, et al. Extended-release venlafaxine in relapse prevention for patients with major depressive disorder. Journal of Psychiatric Research 2004;38:249–257. [PubMed: 15003430]
27. Hochstrasser B, Isaksen PM, Koponen H, et al. Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. British Journal of Psychiatry 2001;178:304–310. [PubMed: 11282808]

28. Klysner R, Bent-Hansen J, Hansen HL, et al. Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. British Journal of Psychiatry 2002;181:29–35. [PubMed: 12091260]
29. Gilaberte I, Montejo AL, de la Gandara J, et al. Fluoxetine in the prevention of depressive recurrences: a double-blind study. Journal of Clinical Psychopharmacology 2001;21:417–424. [PubMed: 11476126]
30. Terra JL, Montgomery SA. Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. International Clinical Psychopharmacology 1998;13:55–62. [PubMed: 9669185]
31. Gelenberg AJ, Trivedi MH, Rush AJ, et al. Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. Biological Psychiatry 2003;54:806–817. [PubMed: 14550680]
32. Montgomery SA, Dunbar G. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. International Clinical Psychopharmacology 1993;8:189–195. [PubMed: 8263317]
33. Keller MB, Kocsis JH, Thase ME, et al. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. Journal of the American Medical Association 1998;280:1665–1672. [PubMed: 9831997]
34. Lepine JP, Caillard V, Bisserbe JC, et al. A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. American Journal of Psychiatry 2004;161:836–842. [PubMed: 15121648]
35. Wilson KC, Mottram PG, Ashworth L, et al. Older community residents with depression: long-term treatment with sertraline. Randomised, double-blind, placebo-controlled study. British Journal of Psychiatry 2003;182:492–497. [PubMed: 12777339]
36. Montgomery SA, Entsuah R, Hackett D, et al. Venlafaxine versus placebo in the preventive treatment of recurrent major depression. Journal of Clinical Psychiatry 2004;65:328–336. [PubMed: 15096071]
37. Reynolds CF 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. New England Journal of Medicine 2006;354:1130–1138. [PubMed: 16540613]
38. Kornstein SG, Bose A, Li D, et al. Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. Journal of Clinical Psychiatry 2006;67:1767–1775. [PubMed: 17196058]
39. Lustman PJ, Clouse RE, Nix BD, et al. Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Archives of General Psychiatry 2006;63:521–529. [PubMed: 16651509]
40. 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. International Clinical Psychopharmacology 1993;8:181–188. [PubMed: 8263316]
41. Gartlehner, G.; Hansen, RA.; Thieda, P., et al. Comparative effectiveness of pharmacologic treatment of depression. (Prepared by RTI-UNC under Contract No. 290-02-0016, TO #7). Rockville, MD: Agency for Healthcare Research and Quality; 2006 Apr. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm
42. Zimmerman M, Posternak MA, Ruggero CJ. Impact of study design on the results of continuation studies of antidepressants. Journal of Clinical Psychopharmacology 2007;27:177–181. [PubMed: 17414242]
43. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. British Medical Journal 2003;326:472. [PubMed: 12609941]

Appendix 1: Results of Literature Search for Prevention of Relapse and Recurrence



* Multiple articles published for a single trial

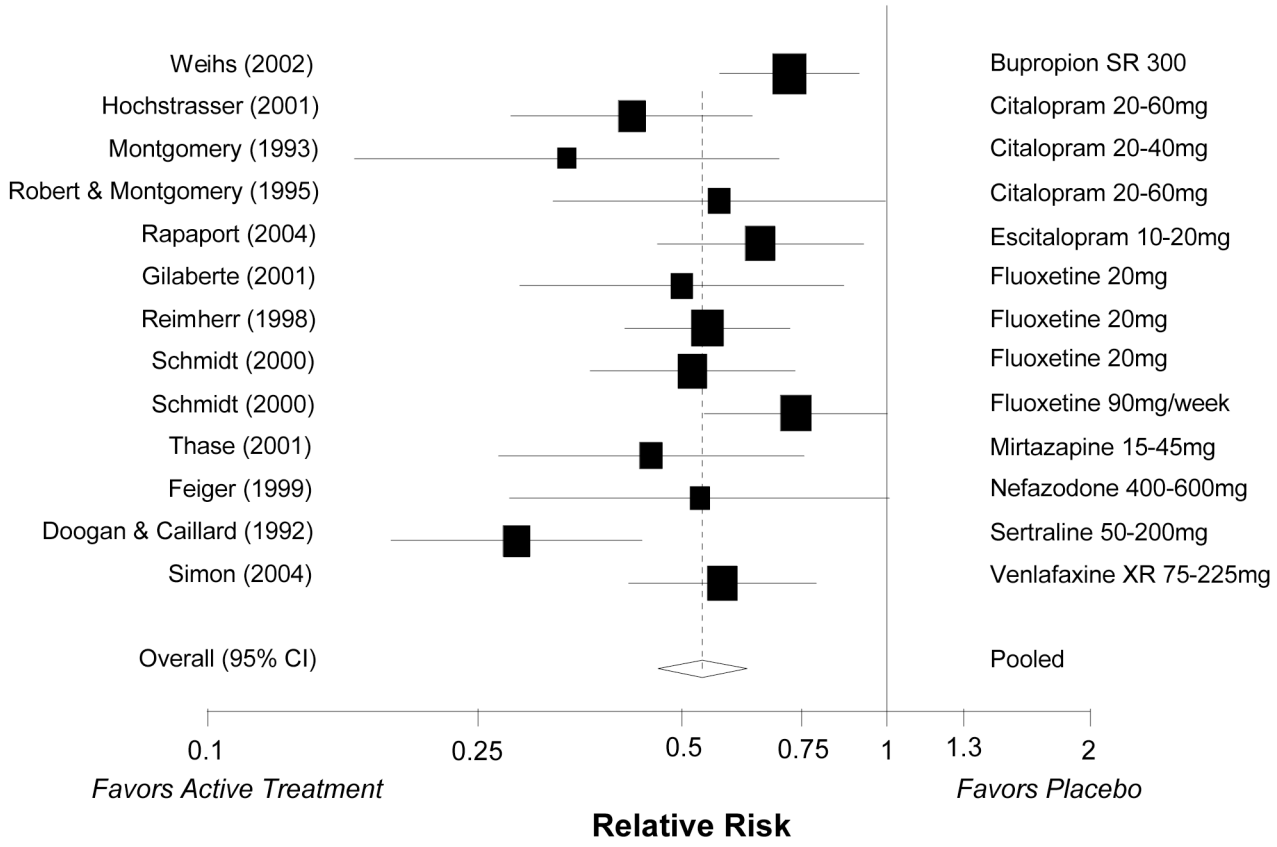


Figure 1.
Meta-analysis of placebo-controlled trials with less than 1 year of double-blinded randomized followup for relapse or recurrence prevention

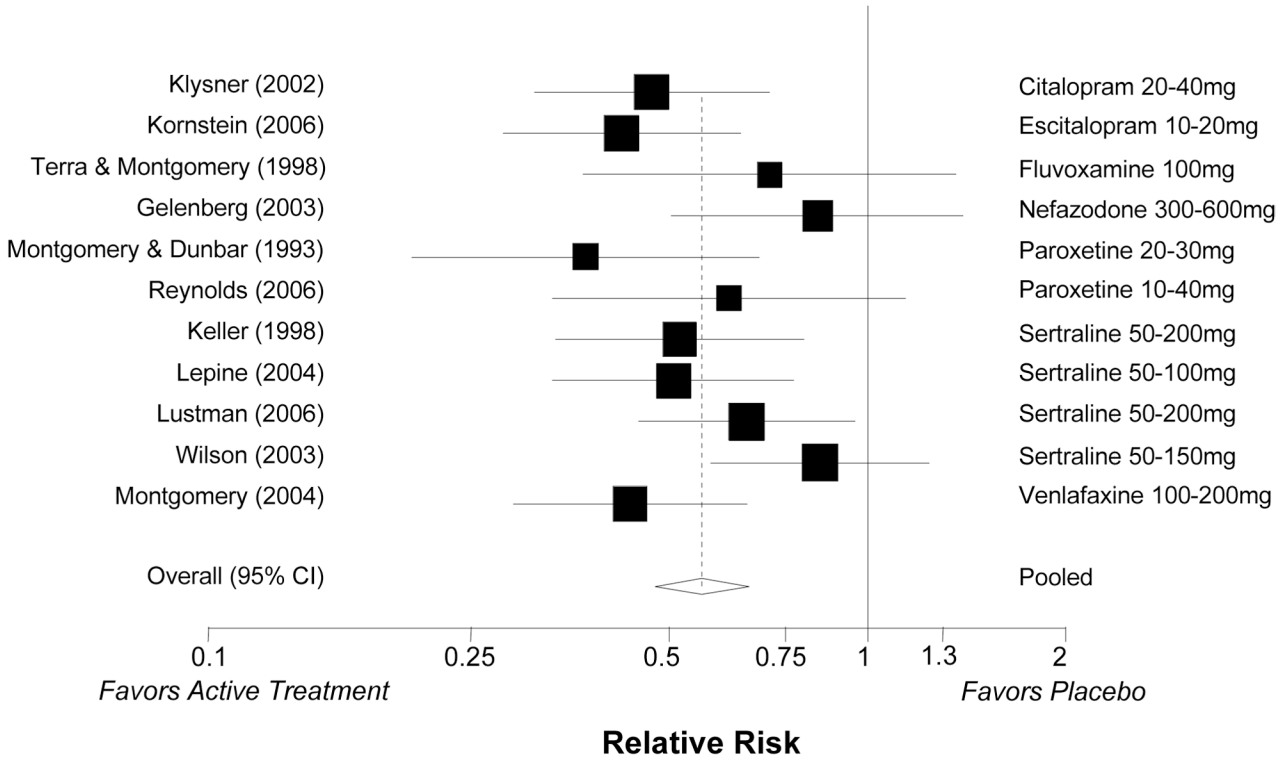


Figure 2.
Meta-analysis of placebo-controlled trials with 1 year or more of double-blinded randomized followup for relapse or recurrence prevention

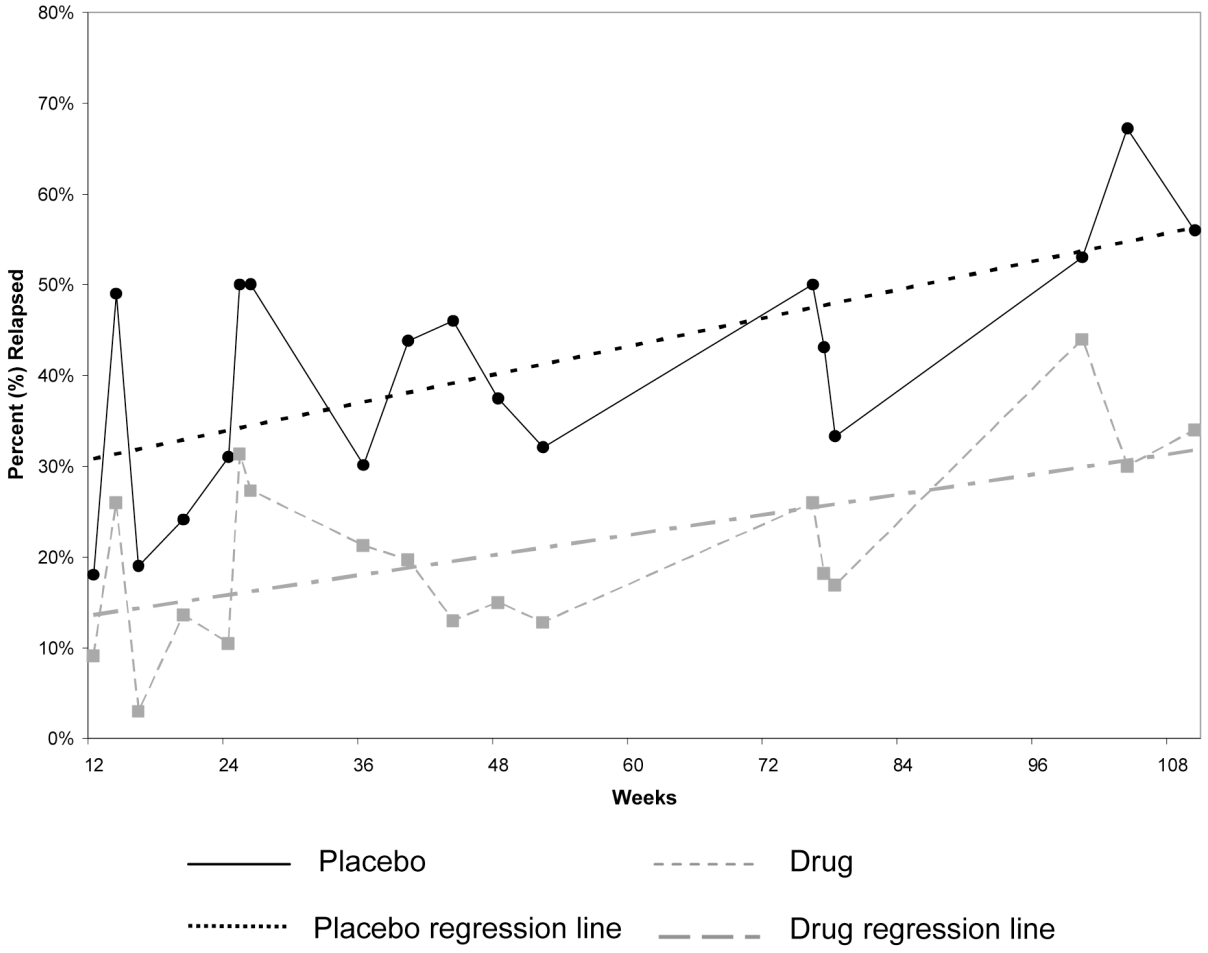


Figure 3.
Weighted mean relapse frequency by length of followup
P= 0.59 for test of difference in relapse rates for drug versus placebo over time

Table 1

Comparative studies reporting relapse or recurrence rates during continuation or maintenance treatment

Study	Depressive severity eligibility criteria for relapse or recurrence assessment phase	Phase	Duration (weeks)	N	Recurrent depression N (%)	Comparison and dose (mg/d)	Relapse or recurrence N (%)		Quality rating
Perahia et al., 2006	≥30% reduction in HAM-D total score	Acute	8	93	NR	Duloxetine 80	NA		Fair
				102	NR	Duloxetine 120	NA		
				96	NR	Paroxetine 20	NA		
				99	NR	Placebo	NA		
		Continuation	24	71	NR	Duloxetine 80	6 (9)		
				81	NR	Duloxetine 120	12 (15)	*P*=NR	
				70	NR	Paroxetine 20	2 (3)		
				70	NR	Placebo	11 (16)		
Van Moffaert et al., 1995	≥ 50% reduction in MADRS or HAM-D, or HAM-D < 10 and CGI-I ≤ 2	Acute	8	82	25 (30)	Fluoxetine 20–40	NA		Fair
				83	23 (28)	Sertraline 50–100	NA		
		Continuation	24	56	-	Fluoxetine 20–40	7 (13)	*P*=NR (ns)	
				49	-	Sertraline 50–100	5 (10)		
Franchini et al., 1997; Franchini et al., 2000	Absence of DSM-IV depressive symptoms; absence of functional impairment; HAM-D < 8	Acute	NR	NR	NR	NR	NA		Fair
		Continuation	16	NR	NR	NR	NA		
		Maintenance (2 year)	104	32	32 (100)	Fluvoxamine 200	6 (19)	*P*=0.88	
				32	32 (100)	Sertraline 100	7 (22)		
		Maintenance (4 year)	208	25	-	Fluvoxamine 200	5 (20)	*P*=0.92	
				22	-	Sertraline 100	3 (14)		
Cunningham et al., 1994	CGI-I ≤ 2	Acute	6	77	209 (93)[†]	Trazodone 150–400	NA		Fair
				72		Venlafaxine 75–200	NA		
				76		Placebo	NA		
		Continuation / Maintenance	52	30	-	Trazodone 150–400	4 (13)	*P*=NR (ns)	
				37	-	Venlafaxine 75–200	3 (8)		
				29	-	Placebo	4 (14)		

MADRS: Montgomery-Asberg Depression Rating Scale

HAM-D: Hamilton rating scale for depression

CGI-I: Clinical Global Impression of Improvement

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition

NA: not applicable

NR: not reported

NS: not significant

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Table 2

Placebo-controlled, randomized, relapse or recurrence prevention studies

Study	Depressive severity eligibility criteria for randomization	Phase	Duration (weeks)	N	Recurrent depression N (%)	Comparison and dose (mg/d)	Relapse or recurrence N (%)		Quality rating
Weihs et al., 2002	CGI-I ≤ 2	Acute	8	816	816 (100)	Bupropion SR 300	NA		Fair
		Continuation	44	210	-	Bupropion SR 300	78 (37)		
				213	-	Placebo	111 (52)	*P*=0.004	
Montgomery et al., 1993	MADRS ≤ 12	Acute	6	NR	NR	Citalopram 20–40	NA		Fair
		Continuation	24	48	-	Citalopram 20	4 (8)		
				57	-	Citalopram 40	7 (12)	*P*<0.02*	
				42	-	Placebo	13 (31)		
Robert & Montgomery, 1995	MADRS ≤ 12	Acute	8	391	NR	Citalopram 20–60	NA		Fair
		Continuation	24	152	-	Citalopram 20–60	21 (14)		
				74	-	Placebo	18 (24)	*P*=0.04	
Hochstrasser et al., 2001	MADRS ≤ 11	Acute	6–9	427	427 (100)	Citalopram 20–60	NA		Fair
		Continuation	16	327	-	Citalopram 20–60	NA		
		Maintenance	48	132	-	Citalopram 20–60	24 (18)		
				137	-	Placebo	59 (43)	*P*<0.001	
Klysner et al., 2002	MADRS ≤ 11	Acute	8	230	35 (15)	Citalopram 20–40	NA		Fair
		Continuation	16	172	-	Citalopram 20–40	NA		
		Maintenance	48	60	-	Citalopram 20–40	19 (32)		
				61	-	Placebo	41 (67)	*P*=NR	
Kornstein et al., 2006	MADRS ≤ 12	Acute	8	131	NR	Citalopram 20–60	NA		Fair
				129	NR	Fluoxetine 20–80			
				128	NR	Paroxetine 20–50			
				127	NR	Sertraline 50–200			
		Continuation	18	234	-	Escitalopram 10–20	NA		
		Maintenance	52	73	-	Escitalopram 10–20	20 (27)		
				66	-	Placebo	43 (65)	*P*=NR	

Study	Depressive severity eligibility criteria for randomization	Phase	Duration (weeks)	N	Recurrent depression N (%)	Comparison and dose (mg/d)	Relapse or recurrence N (%)		Quality rating
Rapaport et al., 2004	MADRS ≤ 12	Acute	8	502	331 (66)	Escitalopram 10–20	NA		Fair
		Continuation	36	181	-	Escitalopram 10–20	47 (26)	*P*=0.01	
				93	-	Placebo	37 (40)		
Reimherr et al., 1998	Absence of DSM-III depressive symptoms; HAM-D < 7	Acute	12–14	839	NR	Fluoxetine 20	NA		Fair
		Continuation	14	299	-	Fluoxetine 20	77 (26)	*P*<0.001	
				95	-	Placebo	46 (49)		
		Continuation†	38	105	-	Fluoxetine 20	9 (9)	*P*<0.04	
				52	-	Placebo	12 (23)		
		Continuation†	50	28	-	Fluoxetine 20	3 (11)	*P*=0.54	
				34	-	Placebo	6 (16)		
Schmidt et al., 2000	Absence of DSM-IV depressive symptoms, and CGI-S ≤ 2, and HAM-D ≤ 9	Acute	13	932	NR	Fluoxetine 20	NA		Fair
		Continuation	25	189	143 (76)	Fluoxetine 20	49 (26)		
				190	137 (72)	Fluoxetine 90/week	70 (37)	*P*<0.01*	
				122	80 (66)	Placebo	61 (50)		
Gilaberte et al., 2001	Absence of DSM-III depressive symptoms, and CGI-S ≤ 2, and HAM-D ≤ 8	Acute	8	253	253 (100)	Fluoxetine 20–40	NA		Fair
		Continuation	24	179	-	Fluoxetine 20–40	NA		
		Maintenance	52	70	-	Fluoxetine 20	14 (20)	*P*=0.01	
				70	-	Placebo	28 (40)		
Terra & Montgomery, 1998	CGI-S ≤ 2, and MADRS < 12	Acute	6	436	436 (100)	Fluvoxamine 100	NA		Fair
		Continuation	18	283	-	Fluvoxamine 100	NA		
		Maintenance	52	110	-	Fluvoxamine 100	14 (13)	*P*<0.001	
				94	-	Placebo	33 (35)		
Thase et al., 2001	CGI-S ≤ 2, and HAM-D ≤ 7	Acute	8–12	410	211 (52)	Mirtazapine	NA		Fair
		Continuation	40	76	-	Mirtazapine 15–45	15 (20)	*P*=0.001	
				80	-	Placebo	35 (44)		
Feiger et al., 1999	HAM-D ≤ 10	Acute	16	467	NR	Nefazodone 400–600	NA		Fair
		Continuation	36	65	81 (62)†	Nefazodone 400–600	1 (2)	*P*=0.009	
				66		Placebo	12 (18)		

Study	Depressive severity eligibility criteria for randomization	Phase	Duration (weeks)	N	Recurrent depression N (%)	Comparison and dose (mg/d)	Relapse or recurrence N (%)		Quality rating
Gelenberg et al., 2003	≥ 50% reduction in HAM-D	Acute	12	681	681 (100)	Nefazodone 300–600	NA		Fair
		Continuation	16	269	-	Nefazodone 300–600	NA		
		Maintenance	52	76	-	Nefazodone 300–600	23 (30)	*P*=0.043	
				84	-	Placebo	40 (48)		
Montgomery & Dunbar, 1993	HAM-D ≤ 8	Acute	8	172	172 (100)	Paroxetine 20–30	NA		Fair
		Continuation / Maintenance	52	68	-	Paroxetine 20–30	11 (16)	*P*<0.01	
				67	-	Placebo	29 (43)		
Reynolds et al., 2006	HAM-D score of 0 to 10 for 3 consecutive weeks, plus 16 weeks of stable continuation	Acute	NR	195	88 (45)	Paroxetine 10–40	NA		Fair
		Continuation	16	151	NR	Paroxetine 10–40	NA		
		Maintenance‡	110	35	15 (43)	Paroxetine 10–40	12 (34)	*P*=0.06	
				18	7 (39)	Placebo	10 (56)		
Doogan & Caillard, 1992	≪ Response was satisfactory and both patient and investigator agreed »	Acute	8	480	306 (69)	Sertraline 50–200	NA		Fair
		Continuation	44	185	-	Sertraline 50–200	24 (13)	*P*<0.001	
				110	-	Placebo	48 (46)		
Keller et al., 1998	CGI-I ≤ 2 and HAM-D ≤ 7 or ≥ 50% reduction in HAM-D, as well as HAM-D ≤ 15, CGI-I ≤ 2, and CGI-S ≤ 3	Acute	12	309	145 (47)	Sertraline 50–200	NA		Fair
		Continuation	16	209	-	Sertraline 50–200	NA		
		Maintenance	76	77	-	Sertraline 50–200	5 (6)	*P*=0.002	
				84	-	Placebo	19 (23)		
Lepine et al., 2004	Absence of “depressed mood” and “markedly diminished interest” according to DSM-IV, and ≤ 2 of other 7 DSM-IV criteria, and ≤ 2 for sum of first two MADRS items	Continuation	≥ 16	371	371 (100)	≠ Sertraline	NA		Good
		Remission Stability	8	371	-	Placebo	NA		
		Maintenance	72	189	-	Sertraline 50–100	32 (17)	*P*=0.002	
				99	-	Placebo	33 (33)		
Lustman et al., 2006	4 consecutive twice-monthly BDI scores of 9 or less	Acute	16	351	351 (100)	Sertraline 50–200	NA		Good
		Maintenance	52	79	79 (100)	Sertraline 50–200	27 (34)	*P*=NR	
				73	73 (100)	Placebo	38 (52)		
Wilson et al., 2003	≥ 50% reduction in HAM-D	Acute	8	318	NR	Sertraline 50–200	NA		Fair
		Continuation	16–20	254	NR	Sertraline 50–200	NA		

Study	Depressive severity eligibility criteria for randomization	Phase	Duration (weeks)	N	Recurrent depression N (%)	Comparison and dose (mg/d)	Relapse or recurrence N (%)		Quality rating
		Maintenance	100	56	16 (29)	Sertraline 50–150	25 (45)	*P*=0.21	
				57	15 (26)	Placebo	31 (54)		
Simon et al., 2004	CGI-S ≤ 3 and HAM-D ≤ 10	Acute	8	490	NR	Venlafaxine XR 75–225	NA		Fair
		Continuation	26	161	-	Venlafaxine XR 75–225	45 (28)	*P*<0.001	
				157	-	Placebo	82 (52)		
Montgomery et al., 2004	HAM-D≤12 at day 56 with no HAM-D ≥ 20 and no two consecutive HAM-D > 10	Acute / Continuation	26	495	495 (100)	Venlafaxine 100–200	NA		Fair
		Maintenance	52	109	-	Venlafaxine 100–200	24 (22)	*P*<0.001	
				116	-	Placebo	64 (55)		

MADRS: Montgomery-Asberg Depression Rating Scale

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DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition

NA: not applicable

NR: not reported

NS: not significant

*Active treatment vs. placebo

†Not included in meta-analysis; compared with placebo switchers in the specified time interval

‡Paroxetine plus clinical management and placebo plus clinical management groups only; psychotherapy groups excluded