Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis

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Abstract

BACGROUND Depression is common in people with Alzheimer's disease (AD) affecting overall outcomes and decreasing quality of life. Although depression in AD is primarily treated with antidepressants, there are few randomised controlled trials (RCTs) assessing efficacy and results have been conflicting.

OBJECTIVES To systematically review evidence on efficacy of antidepressant treatments for depression in AD.

METHODS Systematic review and meta-analysis of double blind RCTs comparing antidepressants *v.* placebo for depression in AD. We searched MEDLINE, CINAHL, EMBASE, PsycINFO, the Cochrane Controlled Trials Register and on line national and international registers. Primary outcomes were treatment response and depressive symptoms. Secondary outcomes were cognition, acceptability and tolerability. Risk of bias was also assessed.

RESULTS Seven studies met inclusion criteria. Three compared sertraline with placebo; one compared both sertraline and mirtazapine to placebo; imipramine, fluoxetine and clomipramine were evaluated in one study each. In terms of response to treatment (6 studies, 297 patients treated with antidepressants and 223 with placebo), no statistically significant difference between antidepressants and placebo was found (odds ratio (OR) 1.95, 95% CI 0.97-3.92). We found no significant drug-placebo difference for depressive symptoms (5 studies, 311 patients, SMD -0.13; 95% CI -0.49 to 0.24). Overall quality of the evidence was moderate because of methodological limitations in studies and the small number of trials.

CONCLUSION Despite the importance of depression in people with AD, few RCTs are available on efficacy of antidepressants, limiting clear conclusions of their potential role. There is a need for further high quality RCTs.

Declarations of interest

None.

Introduction

Alzheimer's disease (AD) is a primary neurodegenerative dementia and is one of the leading causes of disability in older people [1,2]. While progressive cognitive impairment is the hallmark of the illness, neuropsychiatric symptoms affect almost all patients and are persistent [3,4]. Depression is one of the most common neuropsychiatric symptoms in AD, associated with institutionalisation [5], and mortality [6,7]. Up to 50% of AD patients experience depression or clinically significant depressive symptoms during the course of the disease [8]. Major depressive disorder affects approximately 20% to 30% of people with AD [9,10], and personal or family history of depression [11], and younger age at onset of dementia are risk factors [12]. Depressive symptoms are more common than clinical depression [13,14], and are highly persistent [10]. Depression and depressive symptoms increase the risk of behavioural disturbance and accelerate functional decline [15].

Antidepressants remain the mainstay of treatment for AD patients with depression. This is driven by a lack of alternative treatment options and a perception that antidepressants are effective in this population [16]. In line with a recent clinical review of the literature [17], there does not appear to be clear evidence from systematic reviews and meta-analyses to support this practice. Several randomised controlled trials (RCTs) testing antidepressants versus placebo have produced conflicting results [18-22]. In an antidepressants withdrawal study, patients with neuropsychiatric symptoms showed a worsening of depressive symptoms compared to those who continued treatment [23].

There is conflicting evidence on the effects of antidepressants on cognition, with some studies reporting a beneficial effect [24-26] and some harmful [27]. Psychological therapies have also

been studied for depression in AD, with a systematic review reporting that current evidence is limited due to the small number of trials and varying approaches used [28].

Use of antidepressants in AD is associated with significant side-effects including hyponatraemia [29], cardiotoxicity [30] and increased bleeding tendency [27,31,32]. Effectiveness of antidepressants in AD has been evaluated by narrative reviews [33], whereas quantitative reviews and meta-analyses have examined effectiveness in all types of dementia but have not included latest studies conducted [34,35]. In this review, we investigated efficacy and acceptability by conducting a comprehensive, recent, worldwide review of the literature of antidepressants for depression in AD.

Methods

We searched major health databases such as MEDLINE, EMBASE, CINHAL, PsycINFO and the Cochrane library for ongoing trials, as well as national and international trial registers, to March 2016. We searched for all depression AD RCTs with additional search terms (including each antidepressant as a separate term, see Appendix 1 for the full search strategy). We scanned the reference lists of all included studies and 82 reviews in the area of depression in AD and other dementias.

Inclusion criteria were: (1) RCTs comparing any single antidepressants with placebo, (2) people with a diagnosis of AD, (3) patients with a diagnosis of depression as confirmed by either Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria [36] or either disease-specific criteria [14] or a validated rating scale for depression in older people. Validated scales included those used in both clinical and research settings in old age psychiatry [37], such as the Hamilton Depression Rating Scale (HDRS/HAM-D) [38], the Montgomery Asberg Depression Rating Scale (MADRS) [39], and the Cornell Scale for Depression in Dementia [40].

There were no restrictions in terms of participant characteristics, or class of antidepressants and studies in minor depression in Alzheimer's disease were considered eligible. Studies that compared 2 treatment groups with placebo were included as long as there were separate results reported on the effects of each of the antidepressants. Primary outcomes were response to treatment and mean depression scores between the treatment and placebo groups. Secondary outcomes were cognition, number of drop-outs, and number of adverse events. We used a random-effects model to represent overall estimate effects, and where appropriate, used standardised mean differences as not all studies used the same outcome measures of depression. Heterogeneity was assessed with the chi-squared test.

Two reviewers independently extracted data (VO, RN), and any disagreements were resolved with a third author (NT). We used Revman 5.3.5. for data analysis, and the Risk of Bias Tool as recommended by the Cochrane Handbook to assess risk of bias in the included studies, which was assessed independently (VO, RN) (on domains of sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting). Disagreement on quality of studies was low and was resolved by authors' consensus. We used the GRADE approach [41] to summarise overall quality of evidence. We identified a total of 3808 references through database searching and 13 additional references via other sources (reference lists of identified studies and reviews of the literature). After removal of duplicates and clearly irrelevant articles we retrieved 148 full text records. Irrelevant articles were those that were not directly relevant to the study of effectiveness of antidepressants in depression in older people with cognitive impairment and/or dementia. Of the 148 full text records, we excluded 109 as not relevant, leaving 38 full text references to be fully assessed for eligibility. A further 27 were excluded as not meeting criteria of this review (see Appendix Table 1 for details). We identified

one ongoing study [42] (DIADs-3) investigating the effectiveness of venlafaxine, and three trials which were terminated [43], or completed without published outputs or are of unknown status [44,45]. A total of 7 studies met the inclusion criteria. Figure 1 shows details of the search process.

Results

Antidepressants versus placebo

Three studies compared sertraline with placebo [19,21,46], one RCT compared both sertraline and mirtazapine to placebo [47]; imipramine [20], fluoxetine [22] and clomipramine [18] were examined in one study each.

Primary outcome

Response to treatment (dichotomous outcome)

Efficacy at 6-13 weeks and 24-39 weeks

Six studies (involving 520 patients) contributed data on short-term response [18,19,21,22,46,47]. There was no statistically significant difference on odds of response between antidepressants and placebo (OR 1.95, 95% confidence interval (CI) 0.97 to 3.92, p = 0.06) (see Figure 2). There was significant heterogeneity between studies (I^2 = 61%). Only two studies (involving 359 patients) contributed data on long-term response [46,47]. The odds of response did not differ between antidepressants and placebo (OR 1.08, 95% CI 0.69 to 1.69, p = 0.74, I^2 = 8%).

Mean depression scores (continuous outcome)

Efficacy at 6-13 weeks and 39 weeks

There were no statistically significant difference between antidepressants and placebo, with a standardised mean difference (SMD) of -0.13 (95% CI -0.49 to 0.24), five studies, 311 participants) (see Figure 3), with moderate heterogeneity between studies (I^2 = 50%) [19-22,47].

Only one study [47] contributed data on long-term response for mean depressive symptoms; mean difference (MD) of -0.00 (95% CI -1.77 to 1.77, 1 study, 150 participants).

Secondary outcomes

Cognition (MMSE scores) (continuous outcome)

Efficacy 6-13 weeks

Five studies [18-20,22,47] provided data for this outcome, showing no statistically significant difference between antidepressants and placebo, with a mean difference (MD) of 0.14 (95% CI -1.65 to 1.93, 251 participants, I^2 = 0%, Figure 4).

Acceptability: number of drop-outs (dichotomous outcome)

Efficacy 6-13 weeks and 24-39 weeks

At 6-13 weeks, similar numbers of patients dropped out of the intervention and control groups (OR 1.40, 95% CI 0.88 to 2.23, p = 0.15; seven studies, 523 participants, I^2 = 0%, Figure 5), with all studies contributing to the analyses [18-22,46,47]. Data from two studies [46,47] showed that there were no differences between the two groups on number of drop-outs for long-term response (OR 1.31, 95% CI 0.81 to 2.13, p = 0.27; 347 participants, I^2 = 15%).

Tolerability: number of adverse events (dichotomous outcome)

Efficacy 6-13 weeks and 39 weeks

Although more adverse events were reported by patients in the intervention group, there were no significant differences overall between the two groups (OR 1.91, 95% CI 0.92 to 3.96, p = 0.08; seven studies; [18-22,46,47] 632 patients, I^2 = 0%, Figure 6). One trial [47] contributed data on adverse events long-term (OR 1.30, 95% CI 0.67 to 2.54, p = 0.44; 326 participants), with no differences between the two groups.

Risk of bias and overall quality of evidence

Figure 7 shows authors' judgements about each risk of bias item presented as percentages across all included studies. As can be seen from the graph, bias was detected predominantly in the domains of sequence generation and blinding of outcome, limitations applicable to earlier studies. Using the GRADE approach, the overall quality of evidence was judged as moderate indicative of a possibility that a new trial added to the meta-analysis could change the estimate of the effect (see Appendix Figure 8).

Discussion

We found that the overall evidence of effectiveness for antidepressants in people with AD is small, with only a few clinical trials conducted to date. Our pooled meta-analysis (6 RCTs, 297 patients treated with antidepressants and 223 with placebo) failed to show significant differences between antidepressants and placebo for response to treatment. Although the overall difference between antidepressants and placebo failed to reach accepted levels of statistical significance, the analysis trended towards treatment response (p=0.06), with the smaller trials contributing a positive effect of antidepressants. Although our overall analyses were negative, we cannot fully rule out a possible clinical advantage of antidepressants because of the paucity of RCTs. As most studies to date except for the Banerjee *et al.*, (2011) trial have been small, we conclude that further research is required to definitively confirm or refute effectiveness.

Data from five studies from 311 participants (147 treated with antidepressants and 164 with placebo) showed that antidepressants were not superior to placebo in terms of depressive symptoms. For continuous scores, the majority of studies used the Hamilton Depression Rating Scale for Depression (HRSD) [38] which has not been validated for use in patients with Alzheimer's disease, whilst the remaining studies used the Cornell Scale for Depression in Dementia (CSDD) [40]. No research evidence or consensus exists as to what constitutes a

clinically meaningful difference in depressive symptoms between drug and placebo treatment in AD. The National Institute for Health and Clinical Excellence requires a difference of at least three points as a criterion for clinically significant change in depression in the general population [48].

When we examined other outcomes we found no significant differences in drop-out between antidepressants and placebo, and no differences in effect on cognition. For tolerability, although more adverse events were reported in the antidepressant group, there were no significant differences.

Risk of bias analyses showed that although all included studies were double blind RCTs, there was evidence of unclear risk in some domains, mostly within the earlier studies. Based on the GRADE system, we were able to classify the overall quality of evidence as 'moderate' for both treatment response and depressive symptoms, because of methodological limitations and the limited number of trials.

This review followed guidelines set out by the Cochrane Collaboration [49]. We used a comprehensive and sensitive strategy to identify all RCTs reported in the literature, and selection of studies, data extraction, and assessments of risk of bias were independently conducted by two authors. However, there are limitations to our review. Identified RCTs were heterogeneous with regards to participants selected and the type of treatments involved, as the class of antidepressant differed and in two of the trials not all participants had major depression. Duration of exposure to antidepressants also differed and the majority of RCTs contributing data to the meta-analysis had fewer than 50 participants. It was not possible to test for publication bias which may have influenced the results.

Implications for practice and research

The small number of studies and the variations in terms of type of antidepressant tested make it difficult to draw conclusions about the effectiveness of pharmacological treatments for depression in people with AD. There is a need for further well-designed multicentre RCTs which adhere to high standards of methodology and reporting and include diagnostically homogenous populations and large samples. The lack of evidence base makes it difficult to use this research to inform evidence-based policy about whether antidepressants are effective in treating depression in people with Alzheimer's disease.

Interaction effects may have contributed to the results of this review such as type of antidepressant, dose and severity of depressive symptoms and should be investigated in future research. Results of our review suggest that the pathophysiology of depression in AD may be different to that of primary depression, as indicated by lack of evidence of pathological changes in monoaminergic nuclei in people with AD [50,51], and may therefore explain lack of efficacy of conventional antidepressant treatments. An alternative hypothesis to underlying deficits in monoamine neurotransmitters includes deficits in glutamatergic transmission, which has led to a call for further research in identifying biomarkers and treatments for depression in AD that extent beyond the monoaminergic hypothesis [52].

Despite the limited and contradictory evidence regarding efficacy of antidepressants in AD, they are still commonly prescribed. David *et al.*, (2016) reported a significant increase in prescribing rates from 26% in 2010 to 31% in 2014 [53], and similar rates have been seen in other studies [54,55]. It is possible that attempts to reduce use of antipsychotics in people with dementia have contributed to this. Given evidence that apathy is a co-morbid factor of depression in AD [56], associated with different outcomes, it will be important for future studies to report

whether people with clinically significant symptoms of apathy are excluded from antidepressants trials research.

To conclude, this is an up-to-date, methodologically rigorous meta-analysis on the efficacy of antidepressants for depression in patients with AD including all available trials. We found no clear evidence to support the efficacy of antidepressants for treating depression in AD. These findings do not mean that people with severe depression and AD should not be treated with antidepressants. Given this review is limited by a paucity of trials, small studies overall and variation in patients recruited, further RCTs are needed to confirm the effects of antidepressants in AD.

Conflicts of Interest:

There are no known conflicts of interest.

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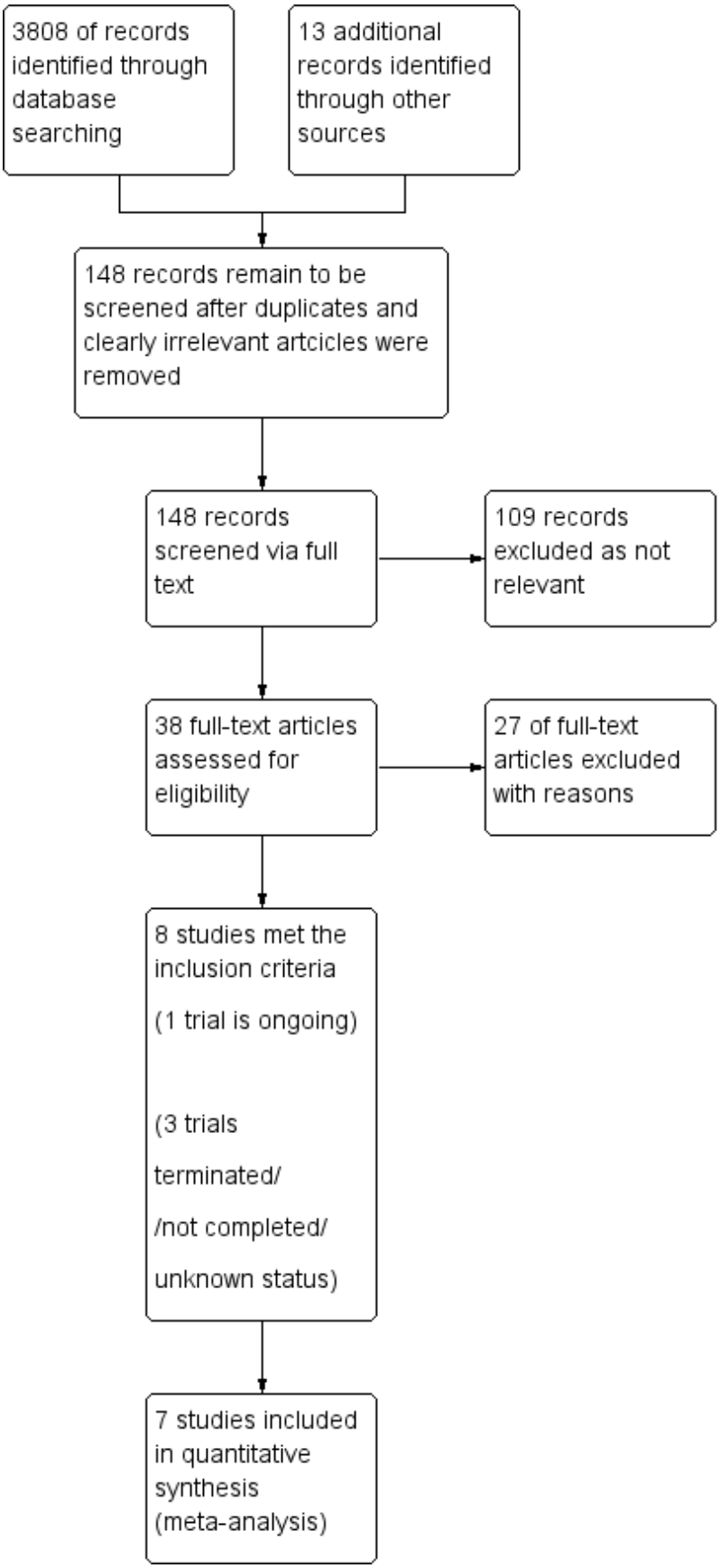
3808 of records identified through database searching
13 additional records identified through other sources
148 records remain to be screened after duplicates and clearly irrelevant artcicles were removed
148 records screened via full text
109 records excluded as not relevant
38 full-text articles assessed for eligibility
27 of full-text articles excluded with reasons
8 studies met the inclusion criteria
(1 trial is ongoing)
(3 trials terminated/ /not completed/ unknown status)
7 studies included in quantitative synthesis (meta-analysis)

Figure 1: Flow diagram of the review

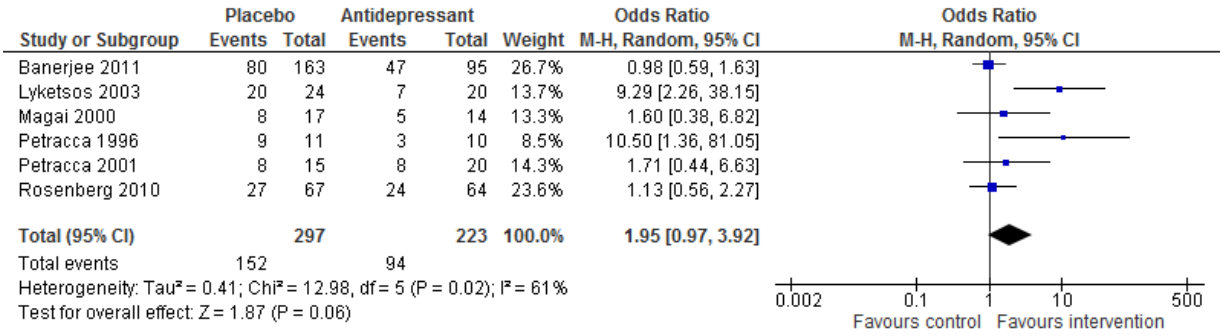

Figure 2. Forest plot of comparison of antidepressants versus placebo: Response to treatment (6-13 weeks)

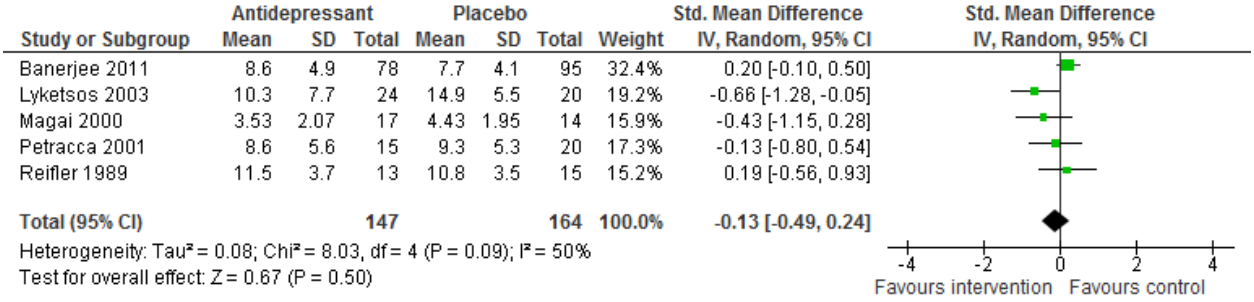

Figure 3. Forest plot of comparison of antidepressants versus placebo: Mean depression scores (6-13 weeks)

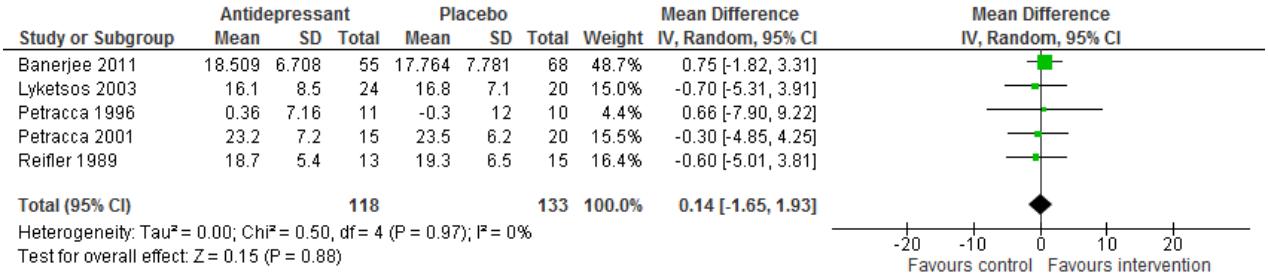

Figure 4. Forest plot of comparison of antidepressants versus placebo: Cognition MMSE scores (6-13 weeks)

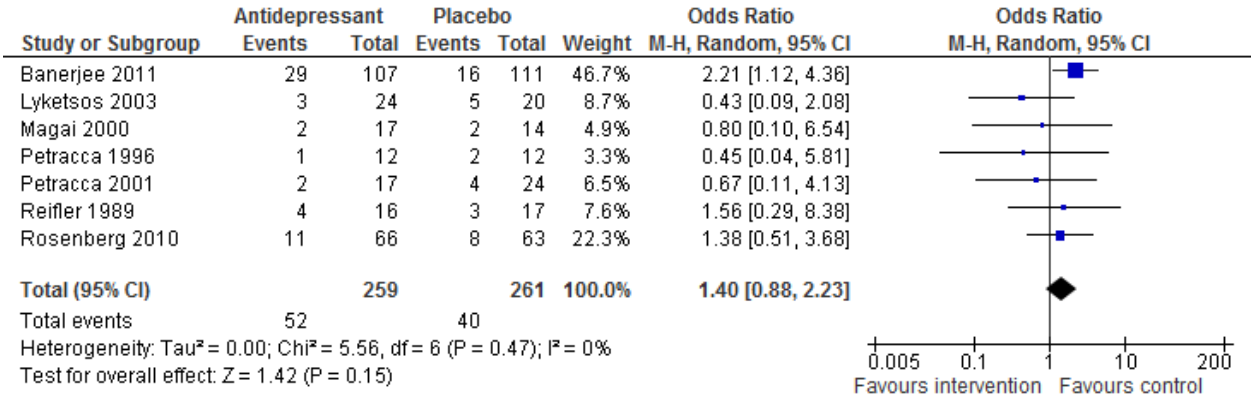

Figure 5. Forest plot of comparison of antidepressants versus placebo: Acceptability Number of drop-outs (6-13 weeks)

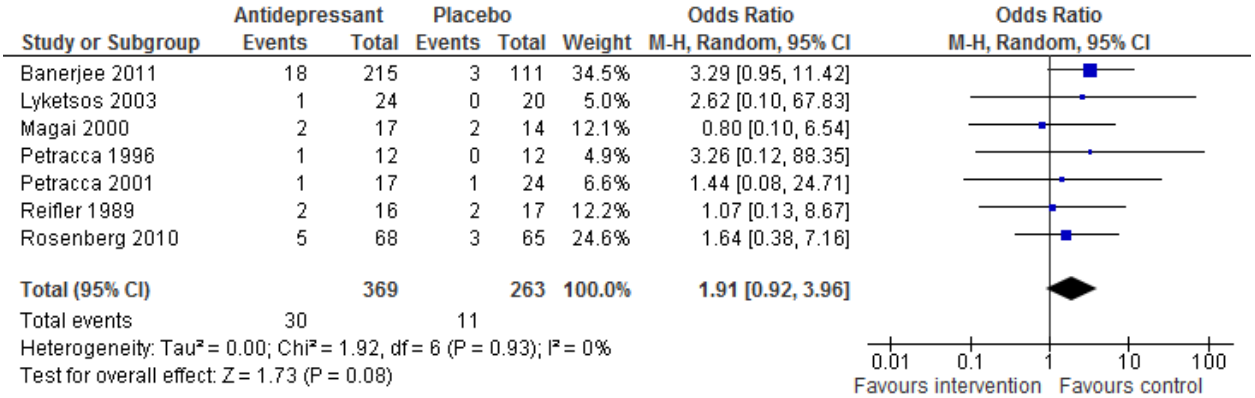

Figure 6. Forest plot of comparison of antidepressants versus placebo: Tolerability Number of adverse events (6-13 weeks)

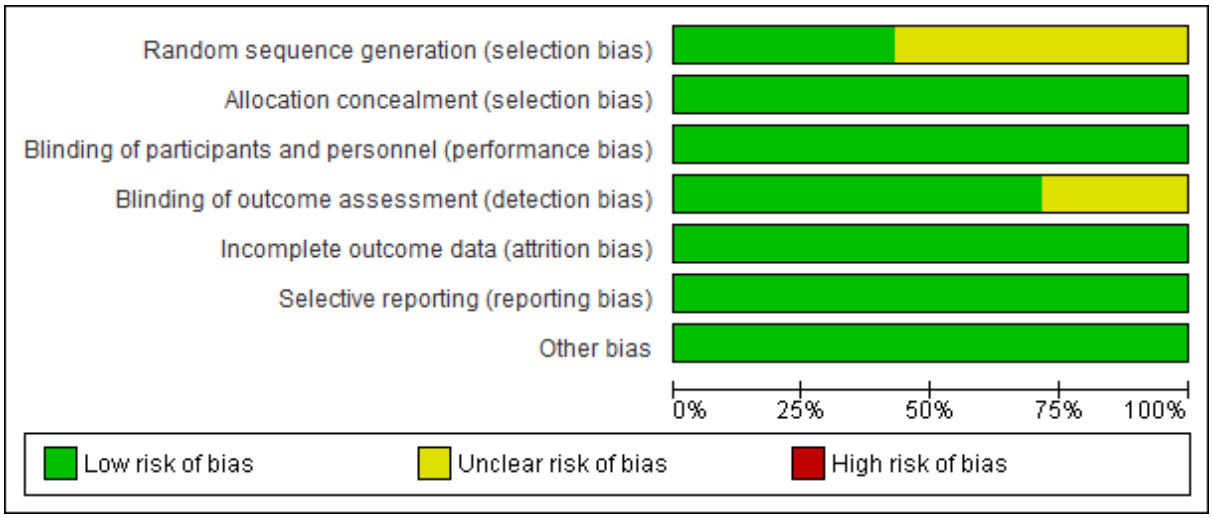

Figure 7. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Appendix 1 Supplementary file

Search strategy

1. Alzheimer*.mp.
2. AD.mp.
3. exp Alzheimer Disease/
4. Dement*.mp.
5. exp Dementia/
6. exp Dementia/
7. anti-depres*.mp.
8. antidepres*.mp.
9. exp Antidepressive Agents/
10. citalopram.mp.
11. exp Citalopram/
12. escitalopram.mp.
13. paroxetine.mp.
14. exp Paroxetine/
15. fluoxetine.mp.
16. exp Fluoxetine/
17. fluvoxamine.mp.
18. exp Fluvoxamine/
19. trazodone.mp.
20. exp Trazodone/
21. nefazodone.mp.
22. venlafaxine.mp.
23. duloxetine.mp.
24. reboxetine.mp.
25. bupropion.mp.
26. exp Bupropion/
27. amoxapine.mp.
28. exp Amoxapine/
29. amitriptyline.mp.
30. exp Amitriptyline/
31. nortriptyline.mp.
32. exp Nortriptyline/
33. desipramine.mp.
34. exp Desipramine/
35. trimipramine.mp.

36. exp Trimipramine/
37. imipramine.mp.
38. exp Imipramine/
39. protriptyline.mp.
40. exp Protriptyline/
41. doxepin.mp.
42. exp Doxepin/
43. clomipramine.mp.
44. exp Clomipramine/
45. mirtazapine.mp.
46. mianserin.mp.
47. exp Mianserin/
48. moclobemide.mp.
49. exp Moclobemide/
50. phenelzine.mp.
51. exp Phenelzine/
52. tranylcypromine.mp.
53. exp Tranylcypromine/
54. SSRI*.mp.
55. selective serotonin reuptake inhibitor.mp.
56. TCA*.mp.
57. depress*.mp.
58. dysthymi*.mp.
59. adjustment disorder*.mp.
60. mood disorder*.mp.
61. affective disorder.mp.
62. affective symptom*.mp.
63. exp Depression/
64. exp Depressive Disorder, Major/
65. exp Depressive Disorder/
66. exp Dysthymic Disorder/
67. exp Alzheimer Disease/ or exp Dementia/
68. (behavioural and psychological symptoms of dementia).mp.
69. neuropsychiatric symptom*.mp.
70. NPS.mp.
71. exp Behavioral Symptoms/
72. exp Psychomotor Agitation/

73. randomized controlled trial.pt.

74. controlled clinical trial.pt.

75. randomized.ab.

76. randomised controlled trial.tw.

77. placebo.ab.

78. random*.ab.

79. drug therapy.fs.

80. randomly.ab.

81. trial.ab.

82. 1 or 2 or 3 or 4 or 5 or 6

83. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56

84. 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72

85. 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81

86. 82 and 83 and 84 and 85

87. limit 86 to humans

Table 1 Characteristics of Excluded Studies

1	Rozzini 2010	Not a RCT, observational study on the use of SSRIs on cognition in patients with AD of which some were depressed
2	Mowla 2007	Double-blind placebo-controlled RCT of fluoxetine in mild to moderate AD, patients with major or minor depression were excluded
3	de Vasconcelos 2007	Double-blind placebo-controlled RCT study of venlafaxine for depression in dementia, no separate data available for patients with AD
4	Rao 2006	Not a RCT, open label treatment study of escitalopram for depression in AD
5	Finkel 2004	Double-blind placebo-controlled RCT on efficacy of sertraline in people with AD and behavioural disturbances, patients with AD were not depressed and those with psychiatric disorders were excluded
6	Oslin 2003	Double blind controlled trial of venlafaxine versus sertraline in depressed nursing home residents, no placebo arm or separate data for patients with AD
7	Moretti 2002	Study on efficacy of SSRIs in patients with AD, randomisation unclear. Patients with AD were not depressed and those with psychiatric disorders were excluded
8	Lanctot 2002	Double-blind placebo-controlled cross-over RCT of sertraline in nondepressed patients with severe probable AD and behavioural disturbances, those with major depression were excluded
9	Raji 2001	Not a RCT, report on three case studies on the use of mirtazapine in the treatment of depression in AD
10	Streim 2000	Double-blind RCT of nortriptyline in nursing home residents with depression (of which some had dementia), no placebo arm and no separate data available for patients with AD
11	Karlsson 2000	Double-blind RCT on efficacy of citalopram compared to mianserin in depressed patients with or without dementia, no placebo arm and no separate data for patients with AD
12	Katona 1998	Double-blind RCT comparing paroxetine with imipramine in depressed patents with dementia, no placebo arm and no separate data for patients with AD
13	Trappler 1998	Not a RCT, open label trial on use of SSRIs (fluoxetine, sertraline, and paroxetine) in depressed nursing home residents of which some had AD
14	Pfeiffer 1997	Not a RCT, open label study on use of venlafaxine in depressed patients with AD
15	Taragano 1997	Double-blind RCT of fluoxetine vs. amitriptyline in the treatment of major depression in AD, no placebo arm
16	Roth 1996	Double-blind placebo-controlled RCT of moclobemide in older people with dementia and/or depression, no separate data available for patients with AD
17	Volicer 1994	Not a RCT, report on case studies on use of sertraline in people with advanced AD and depression
18	Fuchs 1993	Double-blind placebo-controlled RCT of the effect of maprotiline in patients with dementia and mild depression, no separate data for patients with AD, excluded patients in need of antidepressant therapy
19	Passeri 1993	Double-blind RCT of 5’-methlytetrahydrofolic acid (5'-MTHF) vs trazodone on depressive symptoms in normofolatemic older people with mild to moderate dementia and depression, no placebo arm or separate data for patients with AD
20	Nyth 1992	Double-blind placebo-controlled RCT of citalopram in depressed older people and/or dementia, no separate data available for patients with AD

21	Haupt 1991	Not a RCT, report on a case study on use of mianserine for treating depression in Alzheimer's Disease
22	Lawlor 1991	Double-blind placebo-controlled RCT crossover trial of meta-chlorophenylpiperasine in patients with moderate to severe AD, behavioural disturbances and levels of mild depression, patients did not meet criteria for major depression
23	Reynolds 1987	Not a RCT, open trial of nortriptyline in older people with depression and/or dementia, no separate data available for patients with AD
24	Jenike 1985	Not a RCT, report on case studies on use of standard antidepressants and monoamine oxidase inhibitors in depressed patients with AD
25	Mokhber 2014	Double-blind RCT of sertraline, venlafaxine, and desipramine in depressed patients with moderate AD, no placebo arm
26	Passeri 1987	Double-blind placebo-controlled RCT of minaprine in patients with AD and multi-infarct dementia (MID), patients were not depressed and those with a psychiatric illness were excluded
27	Mizukami 2006	Not a RCT, open label trial of milnacipran in treating depression in AD

Antidepressants compared to placebo for depression in Alzheimer's disease

Patient or population: Depression in Alzheimer's disease

Setting: Community and nursing home care

Intervention: Antidepressants

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality
		Without Antidepressants	**With Antidepressants**	**Difference**	
Treatment response assessed with: Depression rating scale or clinician-rated global impression of change scale Follow up: range 6 to 13 weeks № of participants: 520 (6 RCTs)	**OR 1.95** (0.97 to 3.92)	42.2%	**58.7%** (41.4 to 74.1)	**16.5% more** (0.7 fewer to 31.9 more)	⨁⨁⨁◯ MODERATE [1]
Mean Depression scores assessed with: Depression Rating Scales (Cornell Scale for Depression in Dementia – CSDD or Hamilton Depression Rating Scale –HAM-D) Follow up: range 6 to 13 weeks № of participants: 311 (5 RCTs)	-	-	-	SMD **0.13 fewer** (0.49 fewer to 0.24 more)	⨁⨁⨁◯ MODERATE [1]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Studies included few participants and events and evidence of inconsistency in whether there was an effect

Figure 8: Summary of findings table: antidepressants versus placebo for depression in Alzheimer's disease