# RESEARCH PAPER

# Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis

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#### ABSTRACT

**Background** A wide variety of pharmacological agents are used in the management of neuropsychiatric symptoms, which are common in Alzheimer's disease (AD), but results from randomised controlled trials (RCTs) on the efficacy and safety of these agents are conflicting. **Objectives** To quantify the efficacy and safety of pharmacological treatment on neuropsychiatric symptoms in AD patients.

Methods Systematic review and meta-analysis of RCTs comparing pharmacological agents with placebo on Neuropsychiatric Inventory (NPI) and safety outcomes in AD patients with neuropsychiatric symptoms. **Results** Cholinesterase inhibitors (ChEls) and atypical antipsychotics improved NPI total scores (ChEIs: standardised mean difference (SMD) -0.12; 95% CI -0.23 to -0.02; atypical antipsychotics: SMD -0.21; 95% CI -0.29 to -0.12), but antidepressants (95% CI -0.35 to 0.37) and memantine (95% CI -0.27 to 0.03) did not. However, ChEIs and atypical antipsychotics increased risk of dropouts due to adverse events (ChEIs: risk ratio (RR) 1.64; 95% CI 1.12 to 2.42; atypical antipsychotics: RR 2.24; 95% CI 1.53 to 3.26) and on incidence of adverse events (ChEIs: RR 1.08; 95% CI 1.01 to 1.17; atypical antipsychotics: RR 1.17; 95% CI 1.05 to 1.31). For typical antipsychotics, no study was included. **Conclusions** ChEIs and atypical antipsychotics could improve neuropsychiatric symptoms in AD patients, but with bad safety outcomes.

#### INTRODUCTION

The global prevalence of dementia is as high as 24 million and has been predicted to quadruple by the year 2050. Alzheimer's disease (AD) is the most common form of dementia, accounting for an estimated 60%-80% of cases. In the USA alone, AD causes an estimated healthcare costs of \$172 billion per year.<sup>1</sup> It has been suggested that neuropsychiatric symptoms rather than cognitive dysfunction or functional impairment imposed the greatest burden on family caregivers, and predicted the caregivers' decisions to institutionalise patients with dementia. Therefore, interventions aimed at improving neuropsychiatric symptoms could have a tremendous impact on patients, caregivers and society. There are multiple classes of pharmacological agents in use for neuropsychiatric symptoms, including, but not limited to, cholinesterase inhibitors (ChEIs), antipsychotics, antidepressants, mood stabilisers and N-methyl-D-aspartate-receptor modulators. Some

clinical trials and meta-analyses<sup>2–7</sup> have evaluated the efficacy and safety of these drugs on neuropsychiatric symptoms, but have had conflicting findings. Thus, we performed a systematic review and meta-analysis to quantify the efficacy and safety of pharmacological interventions for neuropsychiatric symptoms in AD patients.

## METHODS Identification of trials

We systematically searched PubMed, EMBASE, the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews for reports published before December 2013. The search criteria combined three separate domains: condition (Alzheimer's disease or AD), intervention (cholinesterase inhibitors; donepezil; galantamine; rivastigmine; metrifonate; tacrine; antipsychotics; haloperidol; thioridazine; thiothixene; chlorpromazine; acetophenazine; clozapine; olanzapine; risperidone; quetiapine; aripiprazole; antidepressants; setraline; fluoxetine; citalopram; trazodone; mood stabilizers; valproate; carbamazepine; lithium; anticonvulsants; benzodiazepines; memantine; or psychotropic drugs) and symptoms (behavioral and psychological symptoms of dementia, BPSD, neuropsychiatric symptoms, behavior). Terms were searched in titles and abstracts. We retrieved English-language articles for review, and also collected additional references from bibliographies of reviews, original research articles and other articles of interest.

#### Study selection and data extraction

Two investigators independently reviewed all pertinent articles using predetermined inclusion criteria. Trials were selected for inclusion if they met all of the following criteria: (1) double-blind, placebocontrolled, randomised controlled trials (RCTs); (2) the design of the trial was either parallel or crossover; for a crossover trial, it had a washout period greater than 1 week; (3) patients enrolled were diagnosed as probable or possible AD according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition or the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; (4) studies compared any medicine at any dose with placebo, with any treatment durations; and (5) neuropsychiatric outcomes were measured with the most common neuropsychiatric scales-



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To cite: Wang J, Yu J-T, Wang H-F, et al. J Neurol Neurosurg Psychiatry Published Online First: [please include Day Month Year] doi:10.1136/jnnp-2014-308112 Neuropsychiatric Inventory (NPI) (NPI-10 or NPI-12) or Neuropsychiatric Inventory-Nursing Home version (NPI-NH).

For each trial, two reviewers were blinded to the authors and journal, and independently abstracted data. The mean change of NPI total scores and SDs for the mean change were extracted. For SDs that were not reported directly, we sought them from the authors or calculated them from SEs, CIs or p values that relate to the difference between means in two groups according the Cochrane Handbook for Systematic Reviews of to Interventions. Studies were excluded if the mean change of NPI total scores were not available. Moreover, if there were duplicate publications from the same population, only one of the trials that reported the mean change of NPI total score and SD was included, others were excluded. Besides the sample size, mean age, sex, race, treatment regimen, discontinuations and adverse events were also collected. Wherever possible, outcomes from the intention-to-treat (ITT) population were used and, if not possible, observed case or per protocol outcomes were extracted. Discrepancies in the collected data were discussed and if consensus was not reached, a third reviewer was the final arbitrator.

#### **Statistical analysis**

Meta-analyses were performed using Review Manager V.5.2 software. Combining the NPI-10, NPI-12 and NPI-NH scales in an overall summary estimate, we calculated standardised mean differences (SMDs) and 95% CIs for changes from baseline for continuous data. For dichotomous dropouts and adverse events, we conducted an analysis of the risk ratio (RR), absolute risk differences with 95% CI and p values to assess the safety of the study drug. A random effect model was applied to assess the effect sizes for each treatment–placebo comparison in our study. In dose-ranging trials with multiple treatment groups, we combined treatment groups by weighting the effects for each subgroup by its sample size according to the Cochrane Handbook for Systematic Reviews of Interventions.

The degree of heterogeneity was assessed by visual inspection, and by a  $\chi^2$  test combined with the I<sup>2</sup> method. An  $\alpha$  error p<0.20 and an I<sup>2</sup>>50% were regarded as indicators of heterogeneity of outcomes. To establish the robustness of the outcome, we excluded studies in which the SDs were absent or estimated, or ITT analysis was not used, to conduct sensitivity analyses. Subgroup analyses were performed based on different medicines if there were more than three trials for same one. We also assessed the risk of bias according to Cochrane criteria. Publication bias was evaluated using STATA12.0 software with Begg's test method and funnel plots were presented. In addition, we applied GRADE Profiler 3.6 to assess quality of the included trials according to the GRADE criteria. All analyses were two-tailed, with 5% risk of a type I error ( $\alpha$  of 0.05).

#### RESULTS

# Literature search findings and characteristics of included trials

The results of the search process are depicted in the flow chart (figure 1). Of 2035 articles identified, 32 met all review criteria, including 15 ChEIs trials,<sup>8–22</sup> six atypical antipsychotic trials,<sup>23–28</sup> two antidepressant trials,<sup>29 30</sup> one mood stabiliser trial<sup>31</sup> and eight memantine trials.<sup>32–39</sup> All studies were randomised, double-blind, placebo-controlled trials and were performed mainly in North American and European countries. Baseline characteristics were similar between intervention and placebo groups in all the trials. Among the 32 included studies, three was randomised crossover design trials, and the others were randomised parallel trials. In all, 16 trials compared with one fixed-dose of medicine and placebo, and 16 were dose ranging. Among these dose-ranging studies, five used more than one dose compared with a single placebo group.

The 32 trials included 6812 patients in medicine treatment group and 4844 participants in placebo treatment group. The mean ages of patients in medicine treatment groups ranged from 73.3 to 85.6 years. The mean baseline MMSE scores ranged from 4.5 to 21.2. The detail characteristics of these studies and populations were listed in online supplementary table \$1.

#### **Bias risk assessment**

Although all included trials were randomised, double-blinded and placebo-controlled, specification of randomisation and allocation concealment methods were different from each other. The randomisation was conducted according to a computerised randomisation schedule among nine trials, 11 reports specified the varied methods of randomisation and the other 12 reports did not give detail information, although they were noted randomisation. Twenty-one studies explicitly



**Figure 1** Flowchart of randomised controlled trials (RCTs) included and excluded in the meta-analysis. NPI, Neuropsychiatric Inventory; VD, vascular dementia.

Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Meandom, 55% CI         PL Andom, 55% CI           Black tal.         2007         -1.01         16.46         176         3.31         16.56         167         0.09         0.01         0.02         0.01<		Medicine		Placebo				Std. Mean Difference	Std. Mean Difference	
1.11 Chils vs Placebe         Black et al. 2007       -1.91 16.45 176       -3.31 16.56 167       9.0%       -0.08 [-0.13, 0.30]         Broady et al. 2006       -0.9 11.63 226       0.0 9, 90 220       0.08 [-0.13, 0.30]       -0.14 [-0.28, 0.01]         Perdiman et al. 2001       -4.61 13.3 144       7.133 15.7 55       4.2%       -0.04 [-0.28, 0.02]         Homes et al. 2006       -2.0 8 8.22       98 0.79       8.56 103       6.5%       -0.22 [-0.60, 0.04]         Homes et al. 2006       -2.0 8 8.22       98 0.79       8.56 103       6.5%       -0.22 [-0.60, 0.04]         Kaufer et al. 1988       0.0 1 0 23       3.84 10.44 135       8.1%       -0.24 [-0.20, 0.08]         Kaufer et al. 2001       -0.3 10.87 261       0.5 7.21 125       8.0%       -0.08 [-0.20, 0.13]         Not estimable       -0.33 10.27 261       0.5 7.21 125       8.0%       -0.01 [-0.23, 0.00]         Reskind et al. 2001       -2.3 12.62 013       -2.4 12.62 0.003); P = 67%       -0.14 [-0.34, 0.05]         Tentot et al. 2001       -3.3 12.45 12.9 7.13       7.2%       -0.31 [-0.27, 0.00]         Winblad et al. 2001       -6.23 7.24 f59       -3.7 10.3 47 7.0%       -0.31 [-0.34, 0.05]         Berogeneity: Tau"o 0.03; Chi = 36.23, df = 12 (P = 0.0003); P = 0.59; P = 0.000       -0.31 [-0.34, 0.05] <t< td=""><td>Study or Subgroup</td><td>Mean</td><td>SD</td><td>Total</td><td>Mean</td><td>SD</td><td>Total</td><td>Weight</td><td>IV, Random, 95% Cl</td><td>IV, Random, 95% Cl</td></t<>	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Black et al. 2007 Forday et al. 2006 Forday et al. 2007 Forday et al. 2006 Forday et al. 2007 Forday et al. 2008 Forday	1.1.1 ChEls vs Placebo									
Brodsky et al. 2005       -0.9       1.1.8       326       0.6       9.68       320       9.5%       -0.1.4 [-0.29, 0.01]         Courting et al. 2001       -4.8       13.3       144       1       13.3       148       7.5%       -0.02 [-0.05, 0.08]         Horman et al. 2007       -3.68       17.3       13.7       7.3%       -0.01 [-0.20, 0.28]       -0.01 [-0.20, 0.28]         Johannsen et al. 2006       -2.08       8.22       99       0.78       8.66       103       6.5%       -0.32 [-0.60, 0.08]         Marter et al. 2006       -2.08       8.22       99       0.79       8.66       103       6.5%       -0.22 [-0.60, 0.08]         Lyketsos et al. 2004       0       0       0       0       0       0       0       0.20 [-0.20, 0.09]         Tantot et al. 2001       -0.3       10.87       261       0.5       7.21       126       8.0%       0.01 [-0.20, 1.01]         Subtotal (9%, C)       -0.3       10.37       261       0.5       7.21       126       8.0%       0.01 [-0.20, 0.03]         Vinblad et al. 2001       -0.3       10.37       201       2.21       12.6       0.00 [-0.20, 0.03]       0.12 [-0.33, 0.02]         Subtotal (9%, C)	Black et al, 2007	-1.91	16.45	176	-3.31	16.56	167	8.0%	0.08 [-0.13, 0.30]	
Countrey et al. 2004 -4.8 10.3 283 -6.7 10.3 283 9.2% 0.19 [0.02.0.35] Holmes et al. 2001 -2.3 10.24 41 3.3 15.57 55 4.2% -0.42 [0.65.0.19] Holmes et al. 2001 -2.3 10.24 41 3.3 15.57 55 4.2% -0.42 [0.65.0.19] Holmes et al. 2006 -2.0 8.22 90 70 8.94 10.41 135 8.1% -0.22 [0.50.0.06] Kaufer et al. 198 0.33 10.41 273 3.84 10.41 135 8.1% -0.32 [0.50.0.06] Kaufer et al. 198 0.33 10.41 273 3.84 10.41 135 8.1% -0.32 [0.50.0.06] Hore et al. 198 0.33 10.41 273 3.84 10.41 135 8.1% -0.32 [0.50.0.06] Hore et al. 198 0.3 10.41 273 3.84 10.41 135 8.1% -0.32 [0.50.0.06] Hore et al. 198 0.0 0 0 0 0 0 0 Not estimable Reskind et al. 2001 -2.3 19.28 10.3 125 10.5 6.05 0.05 Hore et al. 198 0.3 10.41 273 3.84 10.41 135 4.00 +0.75 18.81 102 10.7% -0.14 [0.39, 0.11] Heterogeneity: Tau" = 0.02; Ch" = 35.29, df = 12 (P = 0.0003); P = 67% Test for overall effect .2 = 3.77 18.1 20.3 129 20.2% -0.14 [0.34, 0.05] De Deyn et al. 2005 -1.12 18.81 106 -9.75 18.81 102 10.7% -0.31 [0.64, 0.01] Heterogeneity: Tau" = 0.02; Ch" = 35.29, df = 12 (P = 0.0003); P = 67% Test for overall effect .2 = 3.27 15.1 10.01 18.3 125 12.3% -0.31 [0.64, 0.01] Suttorat (95% C) -2.37 7.24 159 -3.7 10.3 47 7.0% -0.31 [0.64, 0.01] Heterogeneity: Tau" = 0.02; Ch" = 35.29, df = 12 (P = 0.0003); P = 0.59; P =	Brodaty et al,2005	-0.9	11.36	326	0.6	9.96	320	9.5%	-0.14 [-0.29, 0.01]	
Feldman et al.2001 Howard et al.2004 Howard et al.2007 1.25 40 2.23 Cauter et al.2004 Howard et al.2007 1.15 40 2.20 1.24 Howard et al.2007 1.15 40 2.20 1.24 Howard et al.2007 1.15 40 2.20 1.25 1.12 40 2.20 Heterogeneity. Not applicable Finkel et al.2008 Heterogeneity. Not applicable Finkel et al.2007 Heterogeneity. Not applicable Finkel et al.2007 Heterogeneity. Not applicable Finkel et al.2007 Heterogeneity. Not applicable Heterogeneity.	Courtney et al, 2004	-4.8	10.3	283	-6.7	10.3	283	9.2%	0.18 [0.02, 0.35]	
Holmes et al. 2004 Howard et al. 2007 Holmsen et al. 2006 Hole at al. 2007 Hole at al. 2007 Hole at al. 2007 Hole at al. 2008 Hole	Feldman et al,2001	-4.6	13.3	144	1	13.3	146	7.5%	-0.42 [-0.65, -0.19]	
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Lyketsos et al. 2004 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Kaufer et al,1998	0.83	10.41	273	3.84	10.41	135	8.1%	-0.29 [-0.50, -0.08]	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Lyketsos et al, 2004	0	0	0	0	0	0		Not estimable	
Reskind et al., 1999       0	Morris et al,1998	1.15	10.83	273	3.9	10.83	135	8.1%	-0.25 [-0.46, -0.05]	
Rockwood et al. 2001 -0.3 10.87 261 0.5 7.21 125 8.0% -0.08 [-0.27, 0.03] Tariot et al. 2001 -2.3 19.28 103 -4.9 19.5 105 6.6% 0.13 [-0.14, 0.13] Winblad et al. 2006 -3.8 12.45 128 -2.11 120 5 120 7.1% -0.14 [-0.39, 0.11] Subtrat (95% C) -1.2 19.28 103 -4.9 19.5 105 6.6% 0.13 [-0.14, 0.39, 0.11] Heterogeneity Tar = 0.02; ChP = 26.26 2927 Test for overall effect 2 = 2.37 ( $P = 0.003$ ); $P = 67\%$ Test for overall effect 2 = 2.37 ( $P = 0.003$ ); $P = 67\%$ Test for overall effect 2 = 2.37 ( $P = 0.02$ ) Hittage 12,006 -115 18.18 106 -4.75 18.81 102 10.1% -0.06 [-0.35, 0.20] De Deyn et al. 2006 -15.43 17.32 131 -10.01 18.83 125 12.3% De Deyn et al. 2006 -16.43 17.32 131 -10.01 18.83 125 12.3% Sutter et al. 2007 -16.9 18.18 366 -13 16.4 121 17.7% -0.16 [-0.37, 0.04] Street et al. 2008 -16.43 17.32 131 -10.01 18.83 125 12.3% Sutter et al. 2008 -7.3 20.2 94 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Street et al. 2008 -7.16 15.4 85 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutter et al. 2008 -7.16 15.4 85 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutter et al. 2008 -7.16 15.4 85 -7 (P = 0.59); P = 0% Test for overall effect Z = 4.65 ( $P = 0.00001$ ) <b>1.13</b> Antidepressants vs Placebo Hierogeneity: Tar <sup>2</sup> = 0.03; ChP = 1.5.8, df = 1.6 -0.21); P = 35% Test for overall effect Z = 2.34 ( $P = 0.02$ ) <b>1.14</b> Mood stabilizers vs Placebo Hierogeneity: Not applicable Test for overall effect Z = 2.34 ( $P = 0.02$ ) <b>1.14</b> Mood stabilizers vs Placebo Packine et al. 2007 1.25 112 3 18.0 12.2 13 15.8 17 13.0% Dest [0.16, 1.76] Dest [0.20, 0.10] Dest [0.16, 1.76] Dest [0.21, 0.22] Dest [0.25, 0.10] Dest [0.16, 1.76] Dest [0.20, 0.10] Dest [0.16, 1.76] Dest [0.20, 0	Raskind et al,1999	0	0	0	0	0	0		Not estimable	
Tariot et al. 2000 Tariot et al. 2000 Tariot et al. 2001 Vinbla et al. 2006 -3.8 12.45 23 19.28 227 2211 12.05 120 7.18 -0.14 [0.39, 0.11 -0.14 [0.39, 0.11 -0.14 [0.39, 0.11 -0.12 [0.23, 0.02] Heterogeneity: Tau <sup>2</sup> 0.02; Chi <sup>2</sup> = 36.29, df = 12 (P = 0.0003); P = 67% Test for overall effect Z = 2.37 (P = 0.02) <b>1.1.2</b> Applical antipsychotics vs Placebo De Deyn et al. 2004 -15.3 15.84 100 $-9.75$ 18.81 100 $-9.75$ 18.81 100 $-9.75$ 18.81 100 $-9.75$ 18.81 100 $-9.75$ 18.81 100 $-9.75$ $-0.25-0.34$ [0.68, 0.01] -0.35 [0.68, 0.01] -0.14 [0.34, 0.05] De Deyn et al. 2004 -15.3 15.84 100 $-15.3$ 15.84 100 $-17.5$ 18.81 100 $-17.5$ 18.81 100 $-17.5$ $-0.35$ [0.68, 0.01] -0.35 [0.68, 0.01] -0.55 (0.70] -0.55 (0.70] -0.50 (0.71] -1.3 Antidepressants ve Placebo Finkel et al. 2008 -1.45 (0.57) 18.57 18.52 13 100.0% 0.96 [0.16, 1.76] -0.56 (0.80, 0.32] -0.55 (0.81, 0.32] -0.55 (0.81, 0.32] -0.55 (0.81, 0.32] -0.55 (0.81, 0.32] -0.55 (0.81, 0.32] -0.55 (0.93, 0.32] -0.55 (0.93, 0.32] -0.55 (0.93, 0.32] -0.55 (0.93, 0.32] -0.55 (0.93, 0.32] -0.55 (0.94, 0.34] -0.55 (0.95, 0.32] -0.55 (0.94, 0.34] -0.55 (0.94, 0.34] -0.55	Rockwood et al,2001	-0.3	10.87	261	0.5	7.21	125	8.0%	-0.08 [-0.29, 0.13]	
Tariot et al. 2001 Virbid et al. 2006 Virbid et al. 2006 Virbid et al. 2007 1.12 Advices Placebo Bakchine et al. 2008 Virbid et al. 2007 1.12 Advices Placebo Bakchine et al. 2008 Virbid et al. 2007 1.12 Advices Placebo Bakchine et al. 2008 Virbid et al. 2007 1.13 Nutices Placebo Bakchine et al. 2007 1.15 Memantine vs Placebo Bakchine et al. 2008 Virbid et al. 2007 1.15 Memantine vs Placebo Bakchine et al. 2008 Virbid et al. 2007 1.15 Memantine vs Placebo Bakchine et al. 2008 Virbid et al. 200	Tariot et al,2000	0.42	11.87	692	2	11.3	286	10.0%	-0.13 [-0.27, 0.00]	
Winblad et al. 2006 -3.8 12.45 12.8 -2.1 12.05 120 7.1% -0.14 [-0.39, 0.11] Heterogeneity: Tau" = 0.02; Chi = 38.29, Gf = 12 (P = 0.0003); P = 67% Test for overall effect $Z = 2.37$ (P = 0.02) <b>1.1.2 Atypical antipsychotics vs Placebo</b> De Deyn et al. 2004 -16.13 15.94 520 -13.7 20.3 129 20.2% -0.14 [-0.34, 0.05] De Deyn et al. 2004 -16.13 15.94 520 -13.7 10.3 47 7.0% -0.08 [-0.37, 0.04] Mintzer et al. 2004 -16.13 15.94 520 -13.7 10.3 47 7.0% -0.08 [-0.37, 0.04] Site et al. 2005 -16.23 7.24 159 -3.7 10.3 47 7.0% -0.38 [-0.64, 0.01] Site et al. 2008 -16.43 17.32 131 -10.01 18.83 125 12.3% -0.38 [-0.64, 0.01] Sutzer et al. 2008 -7.3 20.2 94 -4.2 20 142 10.2% -0.40 [-0.67, 0.13] Sutzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.3 12.2 0 54 -57 12 120 72.6% -0.32 [-0.29, 0.12] <b>1.1.3 Antidepressants vs Placebo</b> Heterogeneity: Tau" = 0.00; Chi" = 5.8, df = 7 (P = 0.59); P = 0% Test for overall effect $Z = 4.65$ (P = 0.0001) <b>1.1.3 Antidepressants vs Placebo</b> Hermann et al. 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotat (95% C) <b>1.1.4 Mood stabilizers vs Placebo</b> Hermann et al. 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.05 [0.16, 1.76] Heterogeneity: Tau" = 0.03; Chi" = 1.54, df = 1 (P = 0.21); I" = 35% Test for overall effect $Z = 2.34$ (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008 -1.45 122 -5.13 15.8 187 130.0% 0.96 [0.16, 1.76] Destines on et al. 2008 -1.45 5201 2.1 18.22 201 3.2% -0.21 [-0.40, 0.03] Heterogeneity: Not applicable Test for overall effect $Z = 2.34$ (P = 0.002) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008 -1.4 15.52 201 2.1 18.2 201 3.2% -0.21 [-0.40, 0.03] Heterogeneity: Not applicable Test for overall effect $Z = 0.35$ (H = 7 (P = 0.0002); P = 75% Test for overall effect $Z = 0.35$ (H = 0.02) Subtotat (95% C) Heterogeneity: Tau" = 0.04; Chi" =	Tariot et al,2001	-2.3	19.28	103	-4.9	19.5	105	6.6%	0.13 [-0.14, 0.41]	
Subtotal (95% C) $2927 = 2211 = 100.0\%$ $-0.12 [-0.23, -0.02]$ Heterogeneity: Tau" = 0.02; Chi <sup>2</sup> = 36.29, Gri 12 (P = 0.0003); P = 67% Test for overall effect: Z = 2.37 (P = 0.02) 1.1.2 Alypical antipsychotics vs Placebo De Deyn et al. 2005 -11.2 18.81 106 -9.75 18.81 102 10.1% -0.08 [-0.35, 0.20] Mintzer et al. 2005 -11.2 18.81 106 -9.75 18.81 102 10.1% -0.08 [-0.35, 0.20] Mintzer et al. 2006 -1.64.3 17.2 131 -1.00 11.83 122 3% -0.35 [-0.64, 0.01] Strem et al. 2006 -1.16 15.4 86 -4.2 20 142 10.2% -0.04 [-0.64, 0.01] Subtra et al. 2008 -1.16 15.4 86 -4.2 20 142 10.2% -0.04 [-0.64, 0.01] Subtra et al. 2008 -1.16 15.4 86 -4.2 20 142 10.2% -0.04 [-0.64, 0.01] Subtra et al. 2008 -1.16 15.4 86 -4.2 20 142 10.2% -0.04 [-0.64, 0.01] Heterogeneity: Tau" = 0.00; Chi <sup>2</sup> = 5.6 g. d <sup>2</sup> = 7 (P = 0.59); P = 0% Test for overall effect: Z = 4.65 (P < 0.00001) 1.1.3 Antidepressants vs Placebo Hermann et al. 2007 1.25 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% C) 1 14 18 140 100.% 0.96 [0.16, 1.76] Meterogeneity: Tau" = 0.03; Chi <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect: Z = 2.03 (P = 0.97) 1.1.4 Mood stabilizers vs Placebo Hermann et al. 2007 1.25 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% C) 1 14 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Tau" = 0.03; Chi <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect: Z = 2.34 (P = 0.02) 1.1.5 Memantine vs Placebo Hermann et al. 2007 1.25 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect: Z = 2.34 (P = 0.02) 1.1.5 Memantine vs Placebo Hermann et al. 2008 1.1 42 (S = 5.13 15.8 187 13.0% 0.96 [0.16, 1.76] De 50.90, 5.0, 10 11.1 2, 202 3.7 14 201 13.2% 0.016 [0.21] 1.02, 0.02] Hermann et al. 2008 1.1 42 (S = 2.17 (S = 1.33% 0.015 [0.00, 0.01] Prosteinsson et al. 2008 1.1 126, 20 (27 (P = 0.0002); P = 75% Test for overall effect: Z = 1.52 (P = 0.01) Hermann et al. 2007 1 15.6 178 1.13 35 1172 1.28% Test for overall effect: Z = 1.52 (P	Winblad et al, 2006	-3.8	12.45	128	-2.1	12.05	120	7.1%	-0.14 [-0.39, 0.11]	
Heterogeneity: Tau" = 0.02; Chi" = 38.29, df = 12 (P = 0.0003); P = 67% Test for overall effect $Z = 2.37$ (P = 0.02) <b>1.1.2 Atypical antipsychotics vs Placebo</b> De Deyn et al, 2004 - 16.13 15.94 520 - 13.7 20.3 129 20.2% De Deyn et al, 2004 - 16.13 15.94 520 - 13.7 20.3 129 20.2% De Deyn et al, 2004 - 16.13 15.94 520 - 13.7 10.3 47 7.0% De Deyn et al, 2005 - 15.9 18.18 366 - 13 16.4 121 17.7% Site et al, 2000 - 6.23 7.24 159 - 3.7 10.3 47 7.0% De 16.83 12.00 - 6.23 7.24 159 - 3.7 10.3 47 7.0% De 16.83 12.00 - 6.23 7.24 159 - 3.7 10.3 47 7.0% De 16.83 12.00 - 7.1 8.1 100 - 4.2 20 142 10.2% De 10.40 (D.07, 0.13) Suttzer et al, 2008 - 7.3 20.2 94 - 4.2 20 142 11.4% De 15.04.0.011 Suttzer et al, 2008 - 7.1 8.1 100 - 4.2 20 142 11.4% De 15.04.0.011 Suttzer et al, 2008 - 7.1 8.1 100 - 4.2 20 142 11.4% De 15.04.0.011 Suttzer et al, 2008 - 7.1 8.5 124 - 6.5 12 120 72.6% Test for overall effect $Z = 4.65$ (P - 0.0001) <b>1.1.3 Antidepressants vs Placebo</b> Hermann et al, 2007 12.5 18.39 14 - 5.77 18.52 13 100.0% De 36 [0.16, 1.76] Heterogeneity: Tau" = 0.03; Chi" = 1.54, df = 1 (P = 0.21); IP = 35% Test for overall effect $Z = 2.34$ (P = 0.02) <b>1.1.4 Mood stabilizers vs Placebo</b> Hermann et al, 2008 - 1.45 8.57 318 - 2.73 8.57 152 13.3% De 36 [0.16, 1.76] De 36 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect $Z = 2.34$ (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al, 2008 1.1 4.25, 201 7.1 18.52 13 100.0% De 36 [0.16, 1.76] De stand 2016 1.1 2.5, 201 7.1 18.52 13.1 00.0% De 36 [0.16, 1.76] De stand 2016 0.21; P = 10.02 df = 4.7 P = 0.0002); P = 75% Test for overall effect $Z = 1.53$ (P = 0.03) Test for overall effect $Z = 1.53$ (P = 0.03) Test for overall effect $Z = 1.53$ (P = 0.04) F = 60.15, Test for overall effect $Z = 1.53$ (P = 0.03) Test for overall effect $Z = 1.53$ (P = 0.04) F = 60.15, Test for overall effect $Z = 1.53$ (P = 0.03)	Subtotal (95% Cl)			2927			2111	100.0%	-0.12 [-0.23, -0.02]	-
Test for overall effect: $Z = 2.37$ (P = 0.02) <b>1.1.2 Atypical antipsychotics vs Placebo</b> De Deyn et al. 2006 -16.13 15.94 520 -13.7 20.3 129 20.2% -0.14 [-0.34, 0.05] De Deyn et al. 2005 -11.2 18.81 106 -9.75 18.81 102 10.1% -0.08 [+0.37, 0.04] Mintzer et al. 2000 -6.23 7.24 159 -3.7 10.3 47 7.0% -0.31 [+0.64, 0.01] Strein et al. 2008 -11.6 15.4 85 -4.2 20 142 11.0% -0.15 [+0.40, 0.01] Stutzer et al. 2008 -11.6 15.4 85 -4.2 20 142 11.0% -0.15 [+0.40, 0.11] Stutzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.0% -0.15 [+0.40, 0.11] Stutzer et al. 2008 -7.3 120.2 94 -4.2 20 142 11.0% -0.15 [+0.40, 0.11] Stutzer et al. 2008 -7.3 120.2 94 -4.2 20 142 11.0% -0.15 [+0.40, 0.11] Stutzer et al. 2008 -7.3 1561 950 100.0% -0.15 [+0.41, 0.11] Stutzer et al. 2008 -7.1 18.1 100 -4.2 20 142 11.0% -0.15 [+0.41, 0.11] Stuttot et gloS% C1) -1561 950 100.0% -0.29 [-0.8] Test for overall effect Z = 4.85 (P < 0.0001) <b>1.13 Antidepressants vs Placebo</b> Heterogeneity: Tau" = 0.03 (Ch <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 35% Test for overall effect Z = 0.3 (P = 0.97) <b>1.14 Mood stabilizers vs Placebo</b> Heterogeneity: Not applicable Test for overall effect Z = 2.34 (P = 0.02) <b>1.15 Memantine vs Placebo</b> Heterogeneity: Not applicable Test for overall effect Z = 2.34 (P = 0.02) <b>1.16 Memantine vs Placebo</b> Bakchine et al. 2006 -1.4 1 65.8 201 2.1 16.82 202 13.2% -0.21 [-0.4, 0.34] Fow stal, 2006 -1.4 1 65.8 201 2.1 16.82 202 13.2% -0.31 [-0.4, 0.04] Porsteins not et al.2006 -1.4 1 65.8 201 2.1 16.82 202 13.2% -0.31 [-0.4, 0.04] Posteins not et al.2006 -1.4 1 65.8 201 2.1 16.82 202 13.2% -0.31 [-0.4, 0.04] Posteins et al.2006 -1.4 1 65.8 201 2.1 16.82 202 13.2% -0.31 [-0.4, 0.04] Posteins not et al.2006 -1.4 1 65.8 201 2.1 16.82 202 13.2% -0.31 [-0.4, 0.04] Posteins et al.2006 -1.4 15.5 17.8 1.1 13.85 17.2 12.8% -0.01 [-0.27, 0.03] Heterogeneity: Tau" = 0.04; Ch <sup>2</sup> = 2.8.6, df = 7 (P = 0.0002); P = 75% Test for overall effect Z = 1.53 (P = 0.13) Heterogeneity: Tau" = 0.04; Ch <sup>2</sup> = 2.8.6, df = 7 (P = 0.0002); P = 7	Heterogeneity: Tau <sup>2</sup> = 0.02	2; Chi <del>"</del> = 3	36.29, d	f = 12 (f	P = 0.00	03); I² =	67%			
1.1.2 Atypical antipsychotics vs Placebo         De Deyn et al. 2004       -16.13       15.94       520       -13.7       20.3       129       20.2%       -0.14 [-0.34, 0.05]         De Deyn et al. 2005       -15.2       18.1       106       -9.75       18.8       102       10.1%       -0.08 [+0.35, 0.20]         Mintzer et al. 2000       -16.33       17.2       159       57.7       10.3       47       7.0%       -0.31 [+0.64, 0.01]         Street et al. 2008       -7.18.1       100       +4.2       20       14.2       10.2%       -0.40 [+0.67, -0.01]         Sultzer et al. 2008       -7.3       20.2       94       -4.2       20       14.2       10.2%       -0.31 [+0.64, 0.01]         Sultzer et al. 2008       -7.3       20.2       94       -4.2       20       14.2       10.1%       -0.15 [+0.40, 0.11]         Sultzer et al. 2008       -7.3       20.7       15.0       950       100.0%       -0.21 [+0.29, 0.12]       -0.21 [+0.29, 0.12]         Heterogeneity. Tau*= 0.03; ChP= 1.54, df= 1 (P = 0.21); P = 35%       140       100.0%       0.96 [0.16, 1.76]       0.97 [+0.40, 0.34]         Heterogeneity. Not applicable       14       13       100.0%       0.96 [0.16, 1.76]       0.36 [0.16, 0.36] <td>Test for overall effect: Z = :</td> <td>2.37 (P =</td> <td>0.02)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Test for overall effect: Z = :	2.37 (P =	0.02)							
<b>1.1.2</b> Atypical antipsycholics vs Placebo De De per at al 2006 - 16.13 15.94 520 - 13.7 20.3 129 20.2% - 0.14 [-0.34, 0.05] De Deyn et al 2005 - 11.2 18.81 106 - 9.75 18.81 102 10.1% - 0.08 [-0.35, 0.04] Mintzer et al 2000 - 6.23 7.24 159 - 3.7 10.3 47 7.0% - 0.31 [-0.64, 0.01] Streim et al 2008 - 16.43 17.32 131 - 10.01 18.83 125 12.3% - 0.35 [-0.60, 0.11] Sutzer et al 2008 - 11.6 15.4 85 - 4.2 20 142 11.0% - 0.15 [-0.40, 0.11] Sutzer et al 2008 - 71 18.1 100 - 4.2 20 142 11.0% - 0.15 [-0.40, 0.11] Sutzer et al 2008 - 71 18.1 100 - 4.2 20 142 11.0% - 0.15 [-0.40, 0.11] Sutzer et al 2008 - 71 18.1 100 - 4.2 20 142 11.0% - 0.15 [-0.40, 0.11] Sutzer et al 2008 - 71 18.1 100 - 4.2 20 142 11.0% - 0.15 [-0.40, 0.11] Suttotal (95% CI) - 1561 - 40.01) <b>1.1.3</b> Antidepressants vs Placebo Finkel et al - 2004 - 4.7 17.6 124 - 6.5 12 120 72.6% - 0.12 [-0.13, 0.37] Lyketsos et al 2003 - 8.9 17.5 24 - 3.7 17.5 20 27.4% - 0.29 [-0.80, 0.31] Heterogeneity: Tau" = 0.03; Chi" = 1.54, df = 1 (P = 0.21); I" = 35% Test for overall effect Z = 0.33 (P = 0.97) <b>1.1.4</b> Mood stabilizers vs Placebo Hermann et al, 2007 12.5 18.39 14 - 5.77 18.52 13 100.0% - 0.96 [0.16, 1.76] Subtotal (95% CI) - 144 13 100.0% - 0.96 [0.16, 1.76] Subtotal (95% CI) - 14.54, df = 1 (P = 0.21); I" = 35% Test for overall effect Z = 2.34 (P = 0.02) <b>1.5</b> Menantine vs Placebo Hermons et al, 2003 - 1.45 8.57 318 - 2.73 8.57 152 13.3% - 0.15 [-0.04, 0.34] Fox et al, 2003 - 1.45 8.57 318 - 2.73 8.57 152 13.3% - 0.15 [-0.04, 0.34] Fox et al, 2003 - 1.45 8.57 318 - 2.73 8.57 152 13.3% - 0.01 [-0.22, 0.20] Peskind et al, 2006 - 1.4 16.58 201 2.1 16.82 202 13.2% - 0.21 [-0.40, 0.01] Peskind et al, 2006 - 1.4 16.58 201 2.1 16.82 202 13.2% - 0.21 [-0.40, 0.01] Peskind et al, 2006 - 1.4 16.58 126 13.7 13 13.3 100.0% - 0.31 [-0.40, 0.02] Peskind et al, 2006 - 1.4 16.58 126 13.7 14 201 13.2% - 0.30 [-0.50, 0.01] Prove tet al, 2007 1 16.5 178 11.4 13.65 172 12.8% - 0.01 [-0.22, 0.20] Peskind et al, 2006 - 1.4 16.59 126 3.8 16.06 126 11.7% - 0.2										
De Deyn et al 2004 -16.13 15.94 520 -13.7 20.3 129 20.2% -0.14 $+0.34, 0.051$ De Deyn et al 2005 -11.2 18.81 106 -9.75 18.81 102 10.1% -0.08 $+0.35, 0.201$ Mintzer et al, 2007 -15.9 18.18 366 -13 16.4 121 17.7% -0.16 $+0.37, 0.04$ Street et al, 2008 -18.43 17.32 131 -10.01 18.83 125 12.3% -0.35 $+0.64, 0.011$ Streit et al, 2008 -71.8 1.1 100 -4.2 20 142 10.2% -0.44 $+0.67, 0.131$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 $+0.41, 0.111$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 $+0.41, 0.111$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 $+0.41, 0.111$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 $+0.41, 0.111$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 $+0.41, 0.111$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 142 11.4% -0.15 $+0.40, 0.111$ Sutzer et al, 2008 -7.1 8.1 100 -4.2 20 72.6% 0.12 $+0.13, 0.371$ Heterogeneity. Tau" = 0.03; Ch"= 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect Z = 4.65 (P < 0.00001) 1.1.3 Antidepressants vs Placebo Heterogeneity. Tau" = 0.03; Ch"= 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect Z = 0.33 (P = 0.97) 1.1.4 Mood stabilizers vs Placebo Heterogeneity. Not applicable Test for overall effect Z = 2.34 (P = 0.02) 1.1.5 Memantine vs Placebo Bakchine et al, 2006 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.15 $ -0.04, 0.34 $ For stal, 2001 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.058 $ -0.3, 0.28 $ Peskind et al, 2005 -1.44 16.58 201 2.1 16.82 202 13.2% 0.015 $ -0.04, 0.03 $ Porsteinsson et al, 2008 -1.45 8.57 73 8.27 152 12.3% 0.015 $ -0.04, 0.03 $ Porsteinson et al, 2003 -1.45 112 202 3.7 14 201 13.2% -0.21 $ -0.40, 0.01 $ Porsteinson et al, 2003 0.5 15.76 126 3.8 16.06 126 11.7% 0.03 $ -0.21  -0.45, 0.04 $ Heterogeneity. Tau" = 0.04; Ch"= 28.28, df = 7 (P = 0.0002); P = 75% Test for overall effect Z = 1.53 (P = 0.13) Fator et al, 2007 1 16.5 178 1.1 13.65 172 12.8% Test for overall effect Z = 1.60 20 df = 4 (P = 0.04) B = 60.1%	1.1.2 Atypical antipsycho	tics vs P	lacebo							-
De Deyn et al, 2005 -11.2 18.81 106 -9.75 18.81 102 10.1% -0.18 [-0.35, 0.20] Mintzer et al, 2000 -6.23 7.24 169 -3.7 10.3 47 7.0% -0.18 [-0.37, 0.04] Streim et al, 2008 -16.43 17.32 131 -10.01 18.83 125 12.3% -0.33 [-0.64, 0.01] Sutzer et al, 2008 -11.6 15.4 85 -4.2 20 142 11.0% -0.15 [-0.41, 0.11] Sutzer et al, 2008 -7 18.1 100 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al, 2008 -7 18.1 100 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al, 2008 -7 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al, 2008 -7 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al, 2008 -7 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al, 2008 -7 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al, 2004 -4.7 17.6 124 -6.5 12 120 72.6% -0.29 [-0.80, 0.31] Lyketos et al, 2003 -8.9 17.5 24 -3.7 17.5 20 27.4% -0.29 [-0.80, 0.31] Lyketos et al, 2003 -8.9 17.5 24 -3.7 17.5 20 27.4% -0.29 [-0.80, 0.31] Heterogeneity. Tau" = 0.03; Ch" = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect Z = 0.03; Ch = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect Z = 0.03; Ch = 0.97) 1.1.4 Mod stabilizers vs Placebo Hermann et al, 2007 12.5 18.39 14 -5.77 18.52 13 100.0% -0.66 [0.16, 1.76] Heterogeneity. Nat applicable Test for overall effect Z = 2.34 (P = 0.02) 1.1.5 Meanmine vs Placebo Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.66 [0.98, 0.32] Postiental effect Z = 2.34 (P = 0.02) 1.1.5 Meanmine vs Placebo Bakchine et al, 2003 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.66 [0.98, 0.32] Postiental effect Z = 1.53 (P = 0.02) 1.1.5 Meanmine vs Placebo Bakchine et al, 2003 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.21 [-0.40, 0.01] Postelinson et al, 2003 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.21 [-0.40, 0.01] Postelinson et al, 2003 -1.45 8.57 318 -2.73 8.57 152 -1.32% -0.21 [-0.40, 0.01] Postelinson et al, 2003 -1.45 8.57 318 -2.73 8.57 152 -1.32% -0.21 [-0.40, 0.01] Postelinson et al, 2003 -1.45 178 1.1 13.65 172 12.8% -0.21 [-0.40, 0.01] Postelinson et al,	De Deyn et al,2004	-16.13	15.94	520	-13.7	20.3	129	20.2%	-0.14 [-0.34, 0.05]	
$\begin{array}{llllllllllllllllllllllllllllllllllll$	De Deyn et al,2005	-11.2	18.81	106	-9.75	18.81	102	10.1%	-0.08 [-0.35, 0.20]	
Streit et al. 2000 - 6.23 7.24 199 - 3.7 10.3 47 7.0% - 0.31 [-0.64, 0.01] Streit et al. 2008 -16.43 17.52 131 -10.01 18.83 125 12.3% -0.35 [-0.60, -0.11] Sutzer et al. 2008 -1.16 15.4 85 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 8.1 100 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 8.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 8.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sutzer et al. 2008 -7.1 7.5 124 -6.5 12 120 72.6% -0.21 [-0.29, -0.12] Heterogeneity: Tau <sup>2</sup> = 0.03; Ch <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect: Z = 0.03; P = 0.07) 1.1.4 Mood stabilizers vs Placebo Hermann et al. 2007 12.5 18.39 14 -5.77 18.52 13 100.0% -0.96 [0.16, 1.76] Sutotal (95% Ci) 144 58.57 318 -2.73 8.57 152 13.3% -0.15 [-0.40, 0.34] Fox et al. 2002 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.66 [-0.98, -0.32] Heterogeneity: Not applicable Test for overall effect: Z = 2.34 (P = 0.02) 1.1.5 Menantine vs Placebo Bakchine et al. 2008 -1.4 15.68 201 2.1 16.82 202 13.2% -0.56 [-0.98, -0.32] Peskind et al. 2003 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.66 [-0.98, -0.32] Peskind et al. 2006 -1.4 15.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, -0.01] Porsteinsson et al.2001 -1.4 15.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, -0.01] Prosteinson et al.2003 -1.12 20 2.7 7 13 25.2 216 13.4% -0.03 [-0.16, 0.22] Reisberg et al. 2003 -0.5 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.45, 0.04] Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75% Test for overall effect: Z = 1.53 (P = 0.13) Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75% Test for overall effect: Z = 1.53 (P = 0.13)	Mintzer et al, 2007	-15.9	18.18	366	-13	16.4	121	17.7%	-0.16 [-0.37, 0.04]	
Streim et al. 2008 -16.43 17.32 131 -10.01 18.83 125 12.3% -0.35 [-0.60, -0.11] Sultzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.0% -0.15 [-0.41, 0.11] Sultzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.0% -0.15 [-0.41, 0.11] Sultzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.0% -0.15 [-0.40, 0.11] Sultzer et al. 2008 -7.1 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Subtotal (95% C)) 1561 950 100.0% -0.21 [-0.29, -0.12] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect $Z = 4.65$ (P < 0.00001) 1.1.3 Antidepressants vs Placebo Finkel et al, 2004 -4.7 17.6 124 -6.5 12 120 72.6% 0.12 [-0.13, 0.37] Lyketsos et al, 2003 -8.9 17.5 24 -3.7 17.5 20 27.4% -0.29 [-0.99, 0.31] Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect $Z = 0.03$ (Ch = 0.97) 1.1.4 Mood stabilizers vs Placebo Hermann et al, 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% C)) 144 13 100.0% 0.96 [0.16, 1.76] Heterogeneily: Not applicable Test for overall effect $Z = 2.34$ (P = 0.02) 1.15 Memantine vs Placebo Bakchine et al, 2008 -1.4 45 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Fox et al, 2003 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.08 [-0.13, 0.28] Hermann et al, 2006 -1.4 4 16.58 201 2.1 16.82 202 13.2% -0.21 [-0.45, 0.04] Prostein scone et al, 2003 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.15 [-0.04, 0.34] Peskind et al, 2006 -1.4 16.58 201 2.1 16.82 202 13.2% -0.01 [-0.45, 0.04] Prostein scone et al, 2003 0.5 15.76 128 3.8 16.06 126 11.7% -0.21 [-0.45, 0.04] Prostein scone et al, 2003 0.5 15.76 128 3.8 16.06 126 11.7% -0.21 [-0.45, 0.04] Prostein scone et al, 2004 -0.1 11.2 202 3.7 14 201 13.2% -0.03 [-0.50, -0.10] Van Dyck et al, 2007 1 18.5 178 1.1 13.65 172 12.8% -0.01 [-0.22, 0.20] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 2.8.26, df = 7 (P = 0.004); P = 75% Test for overall effect $Z = 1.53$ (P = 0.13) Favours (Placebol)	Street et al,2000	-6.23	7.24	159	-3.7	10.3	47	7.0%	-0.31 [-0.64, 0.01]	
Sultzer et al. 2008 -11.6 15.4 85 -4.2 20 142 10.2% -0.40(-0.67, -0.13) Sultzer et al. 2008 -7.3 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sultzer et al. 2008 -7 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sultzer et al. 2008 -7 18.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect $Z = 4.65$ (P < 0.00001) <b>1.1.3 Antidepressants vs Placebo</b> Finkel et al. 2004 -4.7 17.6 124 -6.5 12 120 72.6% -0.29 [-0.89, 0.31] Lyketsos et al. 2003 -8.9 17.5 24 -3.7 17.5 20 27.4% -0.29 [-0.89, 0.31] Uktostal (95% Cl) -1448 140 100.0% -0.96 [0.16, 1.76] Subtotal (95% Cl) -1448 140 100.0% -0.96 [0.16, 1.76] Subtotal (95% Cl) -144 13 100.0% -0.96 [0.16, 1.76] Subtotal (95% Cl) -145 8.57 318 -2.73 8.57 152 13.3% -0.15 [-0.04, 0.34] Hermann et al. 2007 12.5 18.39 14 -5.77 18.52 13 100.0% -0.96 [0.16, 1.76] Subtotal (95% Cl) -145 8.57 318 -2.73 8.57 152 13.3% -0.15 [-0.04, 0.34] Hermann et al. 2007 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.65 [-0.98, 0.32] Hermann et al. 2008 -1.4 16.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, 0.01] Presteinesson et al. 2008 -1.4 16.58 201 2.1 16.82 202 13.2% -0.30 [-0.40, 0.21 [-0.40, 0.01] Presteinesson et al. 2000 -1.4 11.2 202 3.7 14 201 13.2% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.21] Hermann et al. 2007 -1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.40, 0.20] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 20.20, df = 7 (P = 0.004); P = 75% Test for	Streim et al, 2008	-16.43	17.32	131	-10.01	18.83	125	12.3%	-0.35 [-0.60, -0.11]	
Sultzer et al. 2008 -7.3 20.2 94 -4.2 20 142 11.0% -0.15 [-0.41, 0.11] Sultzer et al. 2008 -7.1 81.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Sultzer et al. 2008 -7.1 81.1 100 -4.2 20 142 11.4% -0.15 [-0.40, 0.11] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect $Z = 4.65$ (P < 0.00001) 1.1.3 Antidepressants vs Placebo Finkel et al. 2004 -4.7 17.5 124 -6.5 12 120 72.6% 0.12 [-0.13, 0.37] Lyketsos et al. 2003 -8.3 17.5 24 -3.7 17.5 20 27.4% -0.29 [-0.89, 0.31] Subtotal (95% CI) -148 -148 -140 100.0% 0.96 [0.16, 1.76] Heterogeneity: Tau <sup>2</sup> = 0.03; Ch <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect $Z = 0.03$ (P = 0.97) 1.1.4 Mood stabilizers vs Placebo Hermann et al. 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect $Z = 2.34$ (P = 0.02) 1.15 Mematine vs Placebo Bakchine et al. 2008 -1.4 5 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Hermann et al. 2008 -1.4 16.58 201 2.1 16.82 202 13.2% -0.65 [-0.98, -0.32] Hermann et al. 2008 -1.4 16.58 201 2.1 16.82 202 13.2% -0.65 [-0.98, -0.32] Hermann et al. 2008 -1.4 16.58 201 2.1 16.82 202 13.2% -0.31 [-0.04, 0.04] Porsteinsson et al. 2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.16, 0.28] Hermann et al. 2007 1 16.5 178 1.1 13.65 172 12.2% -0.01 [-0.22, 0.04] Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75% Test for overall effect $Z = 1.53$ (P = 0.13) Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75% Test for overall effect $Z = 1.53$ (P = 0.13) Test for overall effect $Z = 1.53$ (P = 0.03)	Sultzer et al,2008	-11.6	15.4	85	-4.2	20	142	10.2%	-0.40 [-0.67, -0.13]	
Subtotal (95% CI) $-7$ 18.1 100 $-4.2$ 20 142 11.4% $-0.15 [0.40, 0.11]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect Z = 4.65 (P < 0.00001) <b>1.1.3 Antidepressants vs Placebo</b> Finkel et al. 2004 $-4.7$ 17.6 124 $-6.5$ 12 120 72.6% $0.12 [-0.13, 0.37]$ Lyketos et al. 2003 $-8.9$ 17.5 24 $-3.7$ 17.5 20 27.4% $-0.29 [-0.89, 0.31]$ Subtotal (95% CI) $148$ 140 100.0% Test for overall effect Z = 0.03; Ch <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect Z = 0.03 (P = 0.97) <b>1.1.4 Mood stabilizers vs Placebo</b> Hetrman et al. 2007 12.5 18.39 14 $-5.77$ 18.52 13 100.0% $0.96 [0.16, 1.76]$ Subtotal (95% CI) $14$ 13 100.0% $0.96 [0.16, 1.76]$ Heterogeneity: Not applicable Test for overall effect Z = 2.34 (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008 $-1.45$ 8.57 318 $-2.73$ 8.57 152 13.3% $0.15 [-0.04, 0.34]$ Fox et al. 2012 $-18.7$ 16 72 $-8.3$ 16 77 $9.4\%$ $-0.65 [-0.98, -0.22]$ Herman et al. 2008 $-1.4$ 16.58 201 2.1 16.82 202 13.2% $-0.21 [-0.40, 0.01]$ Presteindes al. 2008 $-1.4$ 16.58 201 2.1 16.32 202 13.2% $-0.21 [-0.40, 0.01]$ Presteinesson et al. 2008 $-1.1$ 12.5.2 217 0.3 25.2 216 13.4% $0.03 [-0.16, 0.22]$ Herman et al. 2004 $-0.1$ 11.2 202 3.7 14 201 13.2% $-0.01 [-0.22, 0.01]$ Presteinesson et al. 2007 1 1 16.5 176 136 1.17 13.0% $-0.01 [-0.22, 0.20]$ Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75% Test for overall effect Z = 1.53 (P = 0.13) Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75% Test for overall effect Z = 1.53 (P = 0.13) Heterogeneity: Tau <sup>2</sup> = 0.04; Ch <sup>2</sup> = 28.26, df = 7 (P = 0.002); P = 75%	Sultzer et al,2008	-7.3	20.2	94	-4.2	20	142	11.0%	-0.15 [-0.41, 0.11]	
Subtrate (95% C1) 1561 950 100.0% $-0.21[-0.29, -0.12]$ Heterogeneity: Tar $^{2} = 0.00$ ; Chi <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect. Z = 4.65 (P < 0.00001) <b>1.13 Antidepressants vs Placebo</b> Finklet et al, 2004 -4.7 17.6 124 -6.5 12 120 72.6% $-0.29$ [-0.89, 0.31] Subtrati (95% C1) 148 140 100.0% $0.01 [-0.35, 0.37]$ Heterogeneity: Tar $^{2} = 0.03$ ; Ch <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect. Z = 0.03 (P = 0.97) <b>1.1.4 Mood stabilizers vs Placebo</b> Herrmann et al, 2007 12.5 18.39 14 -5.77 18.52 13 100.0% $0.96 [0.16, 1.76]$ Heterogeneity: Not applicable Test for overall effect. Z = 2.34 (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% $0.15 [-0.04, 0.34]$ Fox et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% $0.15 [-0.4, 0.34]$ Fox et al, 2008 -1.4 18.58 201 2.1 16.82 202 13.2% $-0.21 [-0.40, -0.01]$ Peskind et al, 2008 -1.4 18.58 201 2.1 18.20 202 13.2% $-0.21 [-0.40, -0.01]$ Presteinsson et al, 2008 -1.4 18.58 201 2.1 18.80 127 12.8% $-0.21 [-0.40, -0.01]$ Presteinsson et al, 2008 -1.4 18.58 201 2.1 18.80 12 12 13.2% $-0.21 [-0.40, -0.01]$ Presteinsson et al, 2008 -1.4 18.58 201 2.1 18.80 127 12.2.8% $-0.21 [-0.40, -0.01]$ Presteinse et al, 2008 -1.4 18.58 201 2.1 18.80 127 12.8% $-0.30 [-0.50, -0.10]$ Presteinsen et al, 2008 -1.4 18.58 201 2.1 18.30 133 100.0% $-0.12 [-0.27, 0.03]$ Heterogeneity: Tar $^{2} = 0.04$ ; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); P = 75% Test for overall effect. Z = 1.53 (P = 0.13) Favours [Medicine] Favours [Placebo]	Sultzer et al,2008	-7	18.1	100	-4.2	20	142	11.4%	-0.15 [-0.40, 0.11]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.58, df = 7 (P = 0.59); P = 0% Test for overall effect: Z = 4.65 (P < 0.00001) <b>1.1.3 Antidepressants vs Placebo</b> Finkel et al. 2004 -4.7 17.6 124 -6.5 12 120 72.6% 0.12 [-0.13, 0.37] Lyketsos et al.2003 -8.9 17.5 24 -3.7 17.5 20 27.4% -0.29 [-0.89, 0.31] Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect: Z = 0.03 (P = 0.97) <b>1.1.4 Mood stabilizers vs Placebo</b> Hermann et al. 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtrotal (95% Cl) 14 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Tot applicable Test for overall effect: Z = 2.34 (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Fox et al.2008 -1.4 18.58 201 2.1 18.82 15.8 187 13.0% 0.08 [-0.13, 0.28] Peskind et al.2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.16, 0.22] Reisberg et al. 2003 0.5 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.40, -0.01] Tariot et al.2004 -0.1 11.2 202 3.7 14 201 13.2% -0.30 [-0.50, -0.10] Van Dyck et al.2007 1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.50, -0.10] Van Dyck et al.2007 1 16.5 178 1.1 13.65 172 12.8% -0.30 [-0.50, -0.10] Subtrotal (95% Cl) 1496 1333 100.0% -0.12 [-0.27, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); P = 75% Test for overall effect: Z = 1.53 (P = 0.13) Test for subgroup differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04)  E = 60.1%	Subtotal (95% CI)			1561			950	100.0%	-0.21 [-0.29, -0.12]	-
Test for overall effect: $Z = 4.85$ (P < 0.00001) 1.1.3 Antidepressants vs Placebo Finkel et al: 2004 -4.7 17.6 124 -6.5 12 120 72.6% Lyketsos et al: 2003 -8.9 17.5 24 -3.7 17.5 20 27.4% 1.2 [-0.13, 0.37] Lyketsos et al: 2003 -8.9 17.5 24 -3.7 17.5 20 27.4% 1.2 [-0.13, 0.37] -0.29 [-0.89, 0.31] 0.01 [-0.35, 0.37] 1.1.4 Mood stabilizers vs Placebo Hermann et al: 2007 12.5 18.39 14 -5.77 18.52 13 100.0% Subtotal (95% CI) 14 13 100.0% 1.1.5 Menantine vs Placebo Backnine et al: 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% Fox et al: 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% Fox et al: 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% Peskind et al: 2008 -1.44 16.58 201 2.1 16.82 202 13.2% Porsteinsson et al: 2008 -1.44 16.58 201 2.1 16.82 202 13.2% Posteins et al: 2008 -1.44 16.58 201 2.1 16.82 202 13.2% Posteins et al: 2008 -1.44 16.58 201 2.1 16.82 102 11.7% Posteins et al: 2008 -1.44 16.58 201 2.1 16.82 102 11.7% Posteins et al: 2008 -1.4 16.58 201 2.1 16.82 11.7% Posteins et al: 2008 -1.4 16.58 201 2.1 16.82 102 11.2% Posteins et al: 2008 -1.4 16.58 201 2.1 16.82 11.7% Posteins et al: 2008 -1.4 16.58 201 2.1 16.82 11.7% Posteins et al: 2008 -1.4 16.58 201 2.1 16.82 11.7% Posteins et al: 2008 -1.4 16.58 201 2.1 16.82 11.7% Posteins et al: 2009 -1.4 16.58 201 2.1 16.82 11.7% Posteins et al: 2009 -1.4 16.58 1.78 1.1 13.55 172 12.8% Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 13.2% Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 13.2% Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et al: 2004 -0.1 11.2 202 3.7 14 201 2.2 0.20 Posteins et a	Heterogeneity: Tau <sup>2</sup> = 0.00	]; Chi <sup>2</sup> = !	5.58, df:	= 7 (P =	: 0.59); P	*= 0%				
<b>1.1.3 Antidepressants vs Placebo</b> Finkel et al., 2004 $-4.7$ 17.6 124 $-6.5$ 12 120 72.6% Lyketsos et al.2003 $-8.9$ 17.5 24 $-3.7$ 17.5 20 27.4% Subtotal (95% C) 148 140 100.0% Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect: $Z = 0.03$ (Chi <sup>2</sup> = 1.64, df = 1 (P = 0.21); P = 35% Test for overall effect: $Z = 0.03$ (Chi <sup>2</sup> = 1.64, df = 1 (P = 0.21); P = 35% Test for overall effect: $Z = 0.03$ (Chi <sup>2</sup> = 1.64, df = 1 (P = 0.21); P = 35% Test for overall effect: $Z = 0.03$ (Chi <sup>2</sup> = 0.97) <b>1.1.4 Mood stabilizers vs Placebo</b> Hermann et al. 2007 12.5 18.39 14 $-5.77$ 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% C) 144 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect: $Z = 2.34$ (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008 $-1.45$ 8.57 318 $-2.73$ 8.57 152 13.3% Fox et al.2012 $-18.7$ 16 72 $-8.3$ 16 77 9.4% -0.65 [-0.98, 0.32] Porsteinson et al.2008 $-1.4$ 16.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, -0.01] Porsteinson et al.2008 $-1.4$ 16.58 201 2.1 1 6.82 202 13.2% -0.21 [-0.40, -0.01] Porsteinson et al.2008 $-1.4$ 16.58 201 2.1 1 6.82 202 13.2% -0.21 [-0.40, -0.01] Porsteinson et al.2008 $-1.4$ 16.58 201 2.1 1 6.82 $-0.01 [-0.22, 0.02]$ Reisberg et al. 2003 $0.5$ 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.45, 0.04] -0.21 [-0.45, 0.04] -0.21 [-0.27, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); P = 75% Test for overall effect: $Z = 1.53$ (P = 0.13) Test for overall effect: $Z = 1.53$ (P = 0.13) Test for subproven differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04) E = 601 5%	Test for overall effect: $Z = -$	4.65 (P <	0.0000	1)						
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Finder et al., 2004 -4.7 17.6 124 -6.5 12 120 72.6% $0.12 \{0.13, 0.3\}$ Lyketsos et al.2003 -8.9 17.5 24 -3.7 17.5 20 27.4% $0.22 \{0.38, 0.3\}$ Subtotal (95% CI) 148 140 100.0% $0.01 [-0.35, 0.37]$ Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 1.54, df = 1 (P = 0.21); I <sup>2</sup> = 35% Test for overall effect $Z = 0.03$ (P = 0.97) 1.1.4 Mood stabilizers vs Placebo Hermann et al. 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% CI) 14 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect: $Z = 2.34$ (P = 0.02) 1.1.5 Memantine vs Placebo Bakchine et al. 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Fox et al.2012 -18.7 16 72 -8.3 16 77 9.4% -0.65 [-0.98, 0.32] Hermann et al.2013 -3.9 15.64 182 -5.13 15.8 187 13.0% 0.08 [-0.13, 0.28] Peskind et al.2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.16, 0.40] Persteins on et al.2008 1.1 25.2 217 0.3 25.2 216 13.2% -0.21 [-0.40, -0.01] Particles and 1.1 2.2 22 3.7 14 201 13.2% -0.21 [-0.40, -0.01] Tariot et al.2007 1 18.5 178 1.1 13.66 172 12.8% -0.01 [-0.22, 0.03] Heterogeneity: Chi <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.002); I <sup>2</sup> = 75% Test for overall effect: $Z = 1.53$ (P = 0.12) Test for overall effect: $Z = 1.53$ (P = 0.02) df = 4 (P = 0.04) I <sup>2</sup> = 60.1%	1.1.5 Antidepressants vs	Placebo	470				400	70.00		
$\begin{array}{c} \text{LyRelsUs P(a1,2003)}{1.16} & -6.3 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 17.5 & 24 & -3.7 & 100.0\% & 0.01 [-0.35, 0.37] \\ \hline \text{Heterogeneity: Tau"= 0.03; Ch"= 1.54, df= 1 (P = 0.21); P = 35\% \\ \hline \text{Test for overall effect: } Z = 0.03 (P = 0.97) \\ \hline \textbf{1.1.4 Mood stabilizers vs Placebo \\ \text{Herrmann et al, 2007 } 12.5 & 18.39 & 14 & -5.77 & 18.52 & 13 & 100.0\% & 0.96 [0.16, 1.76] \\ \text{Heterogeneity: Not applicable} \\ \hline \text{Test for overall effect: } Z = 2.34 (P = 0.02) \\ \hline \textbf{1.1.5 Memantine vs Placebo} \\ \hline \textbf{Bacchine et al, 2008 } -1.45 & 8.57 & 318 & -2.73 & 8.57 & 152 & 13.3\% \\ \text{Herrmann et al, 2013 } -3.9 & 15.64 & 182 & -5.13 & 15.8 & 187 & 13.0\% \\ \text{Peskind et al, 2006 } -1.4 & 16.58 & 201 & 2.1 & 16.82 & 202 & 13.2\% \\ \text{Persteinsson et al, 2003 } 1.1 & 25.2 & 217 & 0.3 & 25.2 & 216 & 13.4\% \\ \text{Porsteinsson et al, 2003 } 0.5 & 15.76 & 126 & 3.8 & 16.06 & 126 & 11.7\% \\ \text{Van Dyck et al, 2007 } 1 & 16.5 & 178 & 1.1 & 13.65 & 172 & 12.8\% \\ \text{Test for overall effect: } Z = 1.63 (P = 0.02) \\ \hline \text{Test for overall effect: } Z = 1.63 (P = 0.04); Ch"= 28.26 & df= 7 (P = 0.0002); P = 75\% \\ \hline \text{Test for overall effect: } Z = 1.53 (P = 0.13) \\ \hline \end{array}$	Finkel et al, 2004	-4.7	17.6	124	-6.5	12	120	72.6%	0.12[-0.13, 0.37]	
Subtotal (95% Cl) = 1.54, df = 1 (P = 0.21); P = 35% Test for overall effect: $Z = 0.03$ (Ch <sup>2</sup> = 1.53, df = 1 (P = 0.21); P = 35% Test for overall effect: $Z = 0.03$ (P = 0.97) <b>1.1.4 Mood stabilizers vs Placebo</b> Herrmann et al, 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect: $Z = 2.34$ (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Herrmann et al, 2013 -3.9 15.64 182 -5.13 15.8 187 19.4% -0.65 [-0.98, -0.32] Herrmann et al, 2006 -1.4 18.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, -0.01] Posteinsson et al, 2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.16, 0.22] Reisberg et al, 2003 0.5 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.45, 0.04] Tariot et al, 2004 -0.1 11.2 202 3.7 14 201 13.2% -0.30 [-0.50, -0.10] Van Dyck et al, 2007 1 18.5 178 1.1 13.65 172 12.8% -0.01 [-0.22, 0.20] Subtotal (95% Cl) 1496 1333 100.0% -0.12 [-0.27, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); I <sup>2</sup> = 75% Test for overall effect: $Z = 1.53$ (P = 0.13) Test for subgroup differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04) I <sup>2</sup> = 60.1%	Lyketsos et al,2003	-8.9	17.5	149	-3.7	17.5	20	27.4%	-0.29 [-0.89, 0.31]	
Heterogeneity: Tau <sup>2</sup> = 0.03 ( $P = 0.97$ ) <b>1.1.4</b> Mood stabilizers vs Placebo Herrmann et al, 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% CI) 14 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect: Z = 2.34 ( $P = 0.02$ ) <b>1.1.5</b> Memantine vs Placebo Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.65 [-0.04, 0.34] Fox et al, 2012 -18.7 16 72 -8.3 16 77 9.4% -0.65 [-0.98, -0.32] Herrmann et al, 2006 -1.4 16.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, -0.01] Posteinsson et al, 2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.16, 0.22] Reisberg et al, 2003 0.5 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.40, -0.01] Porsteinsson et al, 2003 0.5 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.40, -0.01] Partie et al, 2004 -0.1 11.2 202 3.7 14 201 13.2% -0.01 [-0.22, 0.20] Subtotal (95% CI) 1496 1333 100.0% -0.12 [-0.27, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 ( $P = 0.002$ ); $P = 75\%$ Test for overall effect: Z = 1.53 ( $P = 0.13$ ) Test for subgroup differences: Chi <sup>2</sup> = 10.02 df = 4 ( $P = 0.04$ ) $P = 60.1\%$				148	0.0434.15	- 250	140	100.0%	0.01[-0.35, 0.37]	
<b>1.1.4 Mood stabilizers vs Placebo</b> Herrmann et al, 2007       12.5       18.39       14       -5.77       18.52       13       100.0%       0.96       [0.16, 1.76]         Subtotal (95% cl)       14       13       100.0%       0.96       [0.16, 1.76]         Heterogeneity: Not applicable       14       13       100.0%       0.96       [0.16, 1.76]         Test for overall effect: $Z = 2.34$ (P = 0.02)       14       13       100.0%       0.96       [0.16, 1.76]         Heterogeneity: Not applicable       18.7       18       -2.73       8.57       152       13.3%       0.15       [0.04, 0.34]         Fox et al, 2012       -18.7       16       72       -8.3       16       77       9.4%       -0.65       [-0.98, -0.32]       -0.65         Herrmann et al, 2006       -1.4       16.58       201       2.1       16.82       202       13.2%       -0.21       [-0.40, -0.01]       0.22       -0.21       [-0.45, 0.04]         Peskind et al, 2006       1.1       2.22       3.7       14       201       13.2%       -0.30       [-0.22, 0.20]       -0.31       [-0.45, 0.04]       -0.31       [-0.45, 0.04]       -0.31       [-0.45, 0.04]       -0.31       [-0.5, -0.2	Heterogeneity: I au* = 0.0.	3; Chin = 1	1.54, di:	= 1 (P =	0.21);1	-= 35%				
1.1.4 Mood stabilizers vs Placebo         Herrmann et al, 2007       12.5       18.39       14       -5.77       18.52       13       100.0%       0.96       [0.16, 1.76]         Subtotal (95% Cl)       14       13       100.0%       0.96       [0.16, 1.76]       0.96       [0.16, 1.76]         Heterogeneity: Not applicable       Test for overall effect: $Z = 2.34$ (P = 0.02)       0.96       [0.16, 1.76]       0.96       [0.16, 1.76]         1.1.5 Memantine vs Placebo       Bakchine et al. 2008       -1.45       8.57       318       -2.73       8.57       152       13.3%       0.15       [-0.04, 0.34]         Fox et al, 2012       -18.7       16       72       -8.3       16       77       9.4%       -0.05       -0.02        -0.21       -0.01       0.30       0.096       [0.16, 1.76]       -0.65       -0.02        -0.21       -0.01       -0.21       -0.01       0.32       -0.21       -0.25       0       0	lest for overall effect: $\angle = 1$	0.03 (P =	0.97)							
Herrmann et al, 2007 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Subtotal (95% Cl) 12.5 18.39 14 -5.77 18.52 13 100.0% 0.96 [0.16, 1.76] Heterogeneity: Not applicable Test for overall effect: $Z = 2.34$ (P = 0.02) 1.1.5 Memantine vs Placebo Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Fox et al, 2012 -18.7 16 72 -8.3 16 77 9.4% -0.65 [-0.98, -0.32] Herrmann et al, 2003 -1.44 18.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, 0.01] Porsteinsson et al, 2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.13, 0.28] Peskind et al, 2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.60, 0.01] Porsteinsson et al, 2008 1.1 25.2 217 0.3 25.2 216 13.4% 0.03 [-0.50, 0.01] Tariot et al, 2004 -0.1 11.2 202 3.7 14 201 13.2% -0.30 [-0.50, 0.01] Van Dyck et al, 2007 1 16.5 178 1.1 13.66 172 12.8% -0.01 [-0.22, 0.20] Subtotal (95% Cl) 1496 1333 100.0% -0.12 [-0.27, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); I <sup>2</sup> = 75% Test for overall effect: $Z = 1.53$ (P = 0.13) Test for subproup differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04) I <sup>2</sup> = 60.1%	1 1 4 Mood stabilizors vs	Diacobo								
Hermann et al, 2007       12.5       16.33       14       -5.77       18.52       13       100.0%       0.96 [0.16, 1.76]         Heterogeneity: Not applicable       14       13       100.0%       0.96 [0.16, 1.76]         Test for overall effect: $Z = 2.34$ (P = 0.02)       1.1.5       Memantine vs Placebo         Bakchine et al, 2008       -1.45       8.57       318       -2.73       8.57       152       13.3%       0.15 [-0.04, 0.34]         Fox et al, 2012       -18.7       16       72       -8.3       16       77       9.4%       -0.65 [-0.98, -0.32]         Herrmann et al, 2013       -3.9       15.64       182       -5.13       15.8       187       13.0%       0.08 [-0.13, 0.28]         Peskind et al, 2006       -1.4       16.58       201       2.1       16.22       202       13.2%       -0.21 [-0.45, 0.04]         Porsteinsson et al, 2003       1.5       15.76       12.6       3.8       16.06       126       11.7%       -0.21 [-0.45, 0.04]         Tariot et al, 2004       -0.1       11.2       202       3.7       14       201       13.2%       -0.01 [-0.22, 0.20]         Van Dyck et al, 2007       1       16.5       178       133       100.0%	Lermonn et el 2007	125	10.00	1.4	E 77	10 50	10	100.00	0.06 (0.16, 1.76)	
Subtract (95% Cf) Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.02); P <sup>2</sup> = 75% Test for overall effect: Z = 1.53 (P = 0.13) 1.15 Memantine vs Placebo Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% -0.15 [-0.04, 0.34] -0.65 [-0.98, -0.32] -0.65 [-0.92, 0.65 [-0.98, -0.32]	Subtotal (95% Cl)	12.5	10.39	14	-5.77	10.52	13	100.0%	0.96 [0.16, 1.76]	
Test for overall effect: $Z = 2.34$ (P = 0.02) <b>1.1.5 Memantine vs Placebo</b> Bakchine et al, 2008 -1.45 8.57 318 -2.73 8.57 152 13.3% 0.15 [-0.04, 0.34] Fox et al, 2012 -18.7 16 72 -8.3 16 77 9.4% -0.65 [-0.98, -0.32] Herrmann et al, 2013 -3.9 15.64 182 -5.13 15.8 187 13.0% 0.08 [-0.13, 0.28] Peskind et al, 2006 -1.4 16.58 201 2.1 16.82 202 13.2% -0.21 [-0.40, -0.01] Porsteinsson et al, 2003 0.5 15.76 126 3.8 16.06 126 11.7% -0.21 [-0.45, 0.04] Tariot et al, 2004 -0.1 11.2 202 3.7 14 201 13.2% -0.030 [-0.50, -0.10] Van Dyck et al, 2007 1 16.5 178 1.1 13.65 172 12.8% -0.01 [-0.22, 0.20] Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); I <sup>2</sup> = 75% Test for overall effect: $Z = 1.53$ (P = 0.13) Test for subparuum differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04) I <sup>2</sup> = 60.1%	Hotorogonoiti: Not onnline	hla		14			15	100.0%	0.30 [0.10, 1.70]	
<b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008       -1.45       8.57       318       -2.73       8.57       152       13.3%       0.15 [-0.04, 0.34]         Fox et al. 2012       -18.7       16       72       -8.3       16       77       9.4%       -0.65 [-0.98, -0.32]         Herrmann et al.2013       -3.9       15.64       182       -5.13       15.8       187       13.0%       0.08 [-0.13, 0.28]         Peskind et al.2006       -1.4       16.58       201       2.1       16.82       202       13.2%       -0.21 [-0.40, 0.01]         Porsteinsson et al.2008       1.1       25.2       216       13.4%       0.03 [-0.16, 0.22]       -7.74       -7.74       -0.32       -0.21 [-0.45, 0.04]       -7.74       -7.74       -0.21 [-0.45, 0.04]       -7.75       -7.75       -7.75%       -0.31 [-0.22, 0.20]       -0.12 [-0.27, 0.03]       -0.12 [-0.27, 0.03]       -0.12 [-0.27, 0.03]       -0.5       -0.5       -0.25 0.5       -0.25 0.5       Favours [Placebo]       Favours [Placebo]         Test for overall effect: Z = 1.53 (P = 0.13)	Test for everall effect: 7 - 7		0.02							
<b>1.1.5 Memantine vs Placebo</b> Bakchine et al. 2008 $-1.45$ 8.57       318 $-2.73$ 8.57       152       13.3% $-0.15$ [ $-0.04$ , $0.34$ ]         Fox et al.2012 $-18.7$ 16       72 $-8.3$ 16       77       9.4% $-0.65$ [ $-0.98$ , $-0.32$ ]         Herrman et al.2013 $-3.9$ 15.64       182 $-5.13$ 15.8       187       13.0% $0.08$ [ $-0.13$ , $0.28$ ]         Peskind et al.2006 $-1.4$ 16.58       201       2.1       16.82       202       13.2% $-0.21$ [ $-0.45$ , $0.01$ ]         Porsteinsson et al.2008       1.1       25.2       217       0.3       25.2       216       13.4% $0.03$ [ $-0.16$ , $0.22$ ]         Reisberg et al.2004 $-0.1$ 11.2       202       3.7       14       201       13.2% $-0.01$ [ $-0.22$ , $0.20$ ]         Van Dyck et al.2007       1       16.5       172       12.8% $-0.01$ [ $-0.27$ , $0.03$ ] $-0.12$ [ $-0.27$ , $0.03$ ]         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = $0.0002$ ); P = 75%       Test for overall effect: Z = 1.53 (P = $0.13$ ) $-0.5 -0.25$ $0$ $0.25$ $0.5$ Favours [Medicine]       Favours [Placebo]	Test for overall effect. $Z = 1$	2.34 (F =	0.02)							
Bakchine et al, 2008       -1.45       8.57       318       -2.73       8.57       152       13.3%       0.15 [-0.04, 0.34]         Fox et al, 2012       -18.7       16       72       -8.3       16       77       9.4%       -0.65 [-0.98, -0.32]         Herrmann et al, 2006       -1.4       16.82       201       2.1       16.82       202       13.2%       -0.21 [-0.40, -0.01]         Porsteinsson et al, 2008       1.1       25.2       217       0.3       25.2       216       13.4%       0.03 [-0.16, 0.22]         Reisberg et al, 2003       0.5       15.76       126       3.8       16.06       126       11.7%       -0.21 [-0.45, 0.04]         Tariot et al, 2004       -0.1       11.2       202       3.7       14       201       13.2%       -0.30 [-0.50, -0.10]         Van Dyck et al, 2007       1       16.5       178       1.1       13.65       172       12.8%       -0.01 [-0.22, 0.20]         Subtotal (95% Cl)       1496       1333       100.0%       -0.12 [-0.27, 0.03]       -0.5       -0.25       0       0.25       0.5         Favours [Medicine]       Favours [Placebo]       Favours [Placebo]       Favours [Placebo]       -0.5       -0.25       0 <td>1 1 5 Memantine vs Place</td> <td>aho</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	1 1 5 Memantine vs Place	aho								
Bachime et al, 2000       11.83       0.57       316       72       10.33       10.10 $[0.09, 0.03]$ Fox et al, 2012       18.7       16       72       -8.3       16       77       9.4%       -0.65 $[0.09, 0.03]$ Herrmann et al, 2003       -1.4       16.58       201       2.1       18.82       202       13.2%       -0.21 $[0.09, 0.03]$ Perskind et al, 2008       -1.4       16.58       201       2.1       18.82       202       13.2%       -0.21 $[0.09, 0.02]$ Perskind et al, 2008       -1.4       16.52       217       0.3       25.2       216       13.4%       0.03 $[0.16, 0.04, 0.01]$ Porsteinsson et al, 2008       1.1       25.2       216       13.4%       0.03 $[0.16, 0.02, 0.01]$ Tariot et al, 2004       -0.1       11.2       202       3.7       14       201       13.2%       -0.01 $[0.22, 0.20]$ Van Dyck et al, 2007       1       16.5       178       1.1       13.65       172       12.8%       -0.01 $[0.22, 0.20]$ Subtotal (95% CI)       1496       1333       100.0%       -0.12 $[0.27, 0.03]$ $-0.5$	Rekehing et al. 2009	-1 45	9.67	210	-2.72	9.67	152	12 206	0 15 60 04 0 241	
Herrman et al. 2013       -3.9       15.64       182       -5.13       15.8       187       13.0%       -0.05 [-0.33, -0.32]         Peskind et al. 2006       -1.4       16.58       201       2.1       16.82       202       13.2%       -0.21 [-0.40, -0.01]         Porsteinsson et al. 2008       1.1       2.52       217       0.3       25.2       216       13.4%       0.03 [-0.16, 0.22]         Reisberg et al.       2003       0.5       15.76       12.6       3.8       16.06       126       11.7%       -0.21 [-0.45, 0.04]         Tariot et al.2004       -0.1       11.2       202       3.7       14       201       13.2%       -0.01 [-0.22, 0.20]         Van Dyck et al.2007       1       16.5       178       1.1       13.65       172       12.8%       -0.01 [-0.22, 0.20]         Van Dyck et al.2007       1       16.5       178       1.3       100.0%       -0.12 [-0.27, 0.03]         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); P <sup>2</sup> = 75%       -0.5       -0.25       0       0.25       0.5         Test for overall effect: Z = 1.53 (P = 0.13)       Test for overall effect: Z = 1.0.02       df= 4 (P = 0.04)  E = 60.1%       Favours [Placebo]       Favours [Placebo] <td>Eavet al 2012</td> <td>10.7</td> <td>16</td> <td>72</td> <td>-2.73</td> <td>16</td> <td>77</td> <td>0.4%</td> <td>0.13[-0.04, 0.34]</td> <td></td>	Eavet al 2012	10.7	16	72	-2.73	16	77	0.4%	0.13[-0.04, 0.34]	
The final metric algo 15 10 10 10 10 10 10 10 10 10 10 10 10 10	Herrmann et al 2012	-10.7	15.64	102	-6.13	16.9	197	12.0%	0.09 [-0.30, -0.32]	
Perskind et al., 2000       -1.4       16.53       201       2.1       16.20       13.2%       -0.21 [-0.40, -0.01]         Porsteinsson et al, 2008       1.1       25.2       216       13.4%       0.03 [-0.16, 0.22]         Reisberg et al, 2003       0.5       15.76       126       3.8       16.06       126       11.7%       -0.21 [-0.45, 0.04]         Tariot et al, 2004       -0.1       11.2       202       3.7       14       201       13.2%       -0.30 [-0.50, -0.10]         Van Dyck et al, 2007       1       16.5       178       1.1       13.65       172       12.8%       -0.01 [-0.22, 0.20]         Subtotal (95% CI)       1496       1333       100.0%       -0.12 [-0.27, 0.03]       -0.12 [-0.27, 0.03]         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); I <sup>2</sup> = 75%       Test for overall effect: Z = 1.53 (P = 0.13)       -0.5       -0.25       0       0.25       0.5         Favours [Medicine]       Favours [Placebo]       Favours [Placebo]       Favours [Placebo]       -0.5       -0.25       0       5	Renmann et al 2013	-3.9	10.04	201	-5.13	10.0	202	13.0%	0.08 [-0.13, 0.28]	
Poisterinsson et al. 2003       1.1       2.17       0.3       2.02       13.4%       0.03       [0.10, 0.22]         Reisberg et al. 2003       0.5       15.76       126       3.8       16.06       126       11.7%       -0.03       [0.45, 0.04]         Tariot et al.2004       -0.1       11.2       202       3.7       14       201       13.2%       -0.03       [0.45, 0.04]         Van Dyck et al.2007       1       16.5       178       1.1       13.65       172       12.8%       -0.01       [0.22, 0.20]         Subtotal (95% Cl)       1496       1333       100.0%       -0.12       [-0.27, 0.03]         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); I <sup>2</sup> = 75%       -0.12       [-0.27, 0.03]         Test for overall effect: Z = 1.53 (P = 0.13)       -0.12       [-0.25, -0.25, 0, 0.25, 0.5]         Favours [Placebo]	Peskinu et al 2006	-1.4	26.2	201	2.1	26.02	202	13.270	-0.21 [-0.40, -0.01]	
Tariot et al.,2004       -0.1       11.2       202       3.7       14       201       11.7%       -0.30 [-0.50, -0.10]         Van Dyck et al,2007       1       16.5       178       1.1       13.2%       -0.01 [-0.22, 0.20]         Subtotal (95% Cl)       1496       1333       100.0%       -0.12 [-0.27, 0.03]         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); i <sup>2</sup> = 75%       -0.12 [-0.27, 0.03]         Test for overall effect: Z = 1.53 (P = 0.13)       -0.5       -0.25       0       0.25       0.5         Favours [Medicine]       Favours [Placebo]       Favours [Placebo]       -0.5       -0.25       0       -0.5	Poisternsson et al.,2008	1.1	20.2	100	0.3	20.Z	100	13.470	0.03 [-0.10, 0.22]	
The subgroup differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04)   <sup>2</sup> = 60.1% Test for subgroup differences: Chi <sup>2</sup> = 10.02 df = 4 (P = 0.04)   <sup>2</sup> = 60.1%	Tariat at al 2004	0.5	10.70	202	3.8	10.00	120	10.7%	-0.21 [-0.45, 0.04]	
Variable Ref al, 2007       1       10.5       17.6       17.2       12.8%       -0.01 [-0.22, 0.20]         Subtotal (95% (1)       1496       1333       100.0%       -0.12 [-0.27, 0.03]         Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 28.26, df = 7 (P = 0.0002); I <sup>2</sup> = 75%       -0.12 [-0.27, 0.03]       -0.12 [-0.27, 0.03]         Test for overall effect: Z = 1.53 (P = 0.13)       -0.5       -0.25       0       0.25       0.5         Fest for subgroup differences: Chi <sup>2</sup> = 10.02       df = 4 (P = 0.04)       I <sup>2</sup> = 60.1%       Favours [Medicine]       Favours [Placebo]	Ven Dunk et al 2007	-0.1	10.5	170	3.7	10 65	170	13.2%	-0.30 [-0.50, -0.10]	
$\begin{array}{c} \text{Heterogeneity: Tau^2 = 0.04; Chi^2 = 28.26, df = 7 (P = 0.0002); I^2 = 75\% \\ \text{Test for overall effect: } Z = 1.53 (P = 0.13) \\ \end{array}$	Subtotal (05% CI)	1	10.5	1406	1.1	13.05	1333	100.0%	-0.01 [-0.22, 0.20]	
Test for subgroup differences: Chi2 = 10.02 df = 4 (P = 0.04) I2 = 60.1%	Hotorogonoity Tour - 0.0	1. Chiz - 1	~ ac oc	f = 7 /P	- 0 000	2)-12-7	1333	100.070	-0.12[-0.27, 0.03]	-
Test for subgroup differences: Chi2= 10.02 df= 4 (P = 0.04) I2= 60.1%	Test for overall effect: 7 - 1	+, UHF≓. 1.62 (P –	20.20,0 0.12)	- 7 (P	- 0.000	z), i*= /	3.20			
Test for subgroup differences: Chi2 = 10.02, df = 4 (P = 0.04), I2 = 60.1%	restion overall ellect. Z =	1.55 (F =	0.13)							
-0.5 -0.25 0 0.25 0.5 Test for subgroup differences: Chit= 10.02, df= 4 (P = 0.04), It= 60.1% Favours [Medicine] Favours [Placebo]										
Test for subgroup differences: Chi2 = 10.02, df = 4 (P = 0.04), I2 = 60.1%. Favours [Medicine] Favours [Placebo]										-0.5 -0.25 0 0.25 0.5
	Test for subgroup differen	ces: Chi <sup>a</sup>	<sup>2</sup> = 10.03	df= 4	(P = 0.0)	4)   <sup>2</sup> =	60.1%			Favours (Medicine) Favours (Placebo)

Figure 2 Forest plot of efficacy of various drugs on the Neuropsychiatric Inventory scale in Alzheimer's disease patients. Data type: continuous; effect measure: standardised mean difference; analysis model: random effects; statistical method: inverse variance.

mentioned use of placebo and drug tablets or capsules that were visually identical for allocation concealment; no adequate details were provided in the others. Moreover, in most (28) trials, efficacy outcomes were analysed by ITT data with the last observation carried forward methods for minimising effects of attrition bias. Finally, small sample size, crossover and multi-arm studies may produce other bias. Begg's test indicated that there was no significant publication bias, and funnel plots were presented in online supplementary figure S1. The quality of reports of all included studies was appraised with GRADE, and the outcome was listed in online supplementary table S2.

#### Efficacy

#### Cholinesterase inhibitors

Fifteen RCTs of various ChEIs (eight for donepezil, four for galantamine and three for metrifonate) with neuropsychiatric symptom outcomes have been selected, with seven of the 15 studies reporting statistically significant benefit. Twelve trials

reported data from the ITT analysis, with three trials reporting data only from the completed subjects analysis. For two trials,<sup>17 22</sup> the SDs for the mean change of NPI total scores were not available, but the results still suggested that ChEIs significantly benefited behavioural disturbances of AD patients compared with placebo (p < 0.05). We conducted meta-analyses with the other 13 trials. The summary meta-analysis also indicated that ChEIs improved neuropsychiatric symptoms on NPI scale compared with placebo (SMD -0.12; 95% CI -0.23 to -0.02) (figure 2). Here, we detected a substantial heterogeneity  $(I^2=67\%)$ , which may be explained by the different subtype of medicine, characteristics of populations, such as the mean age, race, baseline MMSE, and so on, and the treatment duration. In sensitivity analyses excluding studies that did not use ITT analysis method (SMD -0.14; 95% CI -0.25 to -0.03) or the only one long-term trial (SMD -0.15; 95% CI -0.24 to -0.06), we could still observe the improvement effect. However, when excluding studies that used estimated SDs, the significant benefit disappeared (95% CI -0.23 to 0.02). No significant publication

Figure 3 Forest plot of efficacy of donepezil and galantamine on the Neuropsychiatric Inventory scale in Alzheimer's disease patients in subgroup analyses. Data type: continuous; effect measure: standardised mean difference; analysis model: random effects; statistical method: inverse variance.

	Medicine Placebo						Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.1.1 donepezil vs place	ebo								
Black et al, 2007	-1.91	16.45	176	-3.31	16.56	167	9.6%	0.08 [-0.13, 0.30]	
Courtney et al, 2004	-4.8	10.3	283	-6.7	10.3	283	11.0%	0.18 [0.02, 0.35]	
Feldman et al,2001	-4.6	13.3	144	1	13.3	146	9.0%	-0.42 [-0.65, -0.19]	<u>← </u>
Holmes et al,2004	-2.9	10.24	41	3.3	15.57	55	5.0%	-0.45 [-0.86, -0.04]	←→────
Howard et al,2007	-3.56	17.73	128	-3.78	17.75	131	8.7%	0.01 [-0.23, 0.26]	
Johannsen et al,2006	-2.08	8.92	99	0.79	8.96	103	7.7%	-0.32 [-0.60, -0.04]	←
Tariot et al,2001	-2.3	19.28	103	-4.9	19.5	105	7.9%	0.13 [-0.14, 0.41]	
Winblad et al, 2006	-3.8	12.45	128	-2.1	12.05	120	8.5%	-0.14 [-0.39, 0.11]	
Subtotal (95% CI)			1102			1110	67.3%	-0.09 [-0.27, 0.08]	
Heterogeneity: Tau <sup>2</sup> = 0.	05; Chi²	= 28.80	), df = 7	(P = 0.0	0002); P	<sup>2</sup> = 76%			
Test for overall effect: Z =	= 1.05 (F	P = 0.29	)						
2.1.2 galantamine vs pla	acebo								
Brodaty et al.2005	-0.9	11.36	326	0.6	9.96	320	11.3%	-0.14 [-0.29, 0.01]	
Rockwood et al.2001	-0.3	10.87	261	0.5	7.21	125	9.5%	-0.08 [-0.29, 0.13]	
Tariot et al.2000	0.42	11.87	692	2	11.3	286	11.8%	-0.13 [-0.27, 0.00]	
Subtotal (95% CI)			1279			731	32.7%	-0.13 [-0.22, -0.03]	◆
Heterogeneity: Tau <sup>2</sup> = 0.	00: Chi²	= 0.22.	df = 2 (	P = 0.9	$(1):  ^2 = 0$	%		• / •	
Test for overall effect: Z =	= 2.68 (F	P = 0.00	7)						
Total (95% CI)			2381			1841	100.0%	-0.10 [-0.21, 0.02]	•
Heterogeneity: Tau <sup>2</sup> = 0.	02: Chi <sup>2</sup>	= 30.73	df = 1	0 (P = 0)	0006):	$1^2 = 67^{\circ}$	*		
Test for overall effect: Z =	= 1.66 (F	P = 0.10	)				•		-0.5 -0.25 0 0.25 0.5
Test for subgroup differences: $Chi^2 = 0.10$ , $df = 1$ (P = 0.75), $l^2 = 0.5$								Favours (Medicine) Favours (Placebo)	

bias was detected (continuity corrected z=0.62, Pr > |z|=0.537) (see online supplementary figure S1A).

In donepezil subgroup, we did not detected significant effects on neuropsychiatric symptoms (95% CI –0.27 to 0.08) (heterogeneity:  $I^2=76\%$ ). While in galantamine subgroup, our meta-analysis result indicated that galantamine could significantly improve behavioural disturbances of AD patients (SMD –0.13; 95% CI –0.22 to –0.03) (heterogeneity:  $I^2=0\%$ ) (figure 3).

#### Atypical antipsychotics

Atypical antipsychotics, also known as second-generation antipsychotics, include clozapine, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole. Six RCTs completely met our inclusion criteria and were selected in our meta-analysis. Of these, one study<sup>23</sup> used three different drugs and compared them with placebo respectively. Thus, we extracted data from it three times, forming eight comparisons. Five comparisons reported positive results. With these trials, our summary meta-analysis showed significant improvement on NPI total score in patients treated with atypical antipsychotics compared with placebo (SMD -0.21; 95% CI -0.29 to -0.12). The heterogeneity among the pooled study was mild ( $I^2=0\%$ ). The improvement on NPI scale was also significant in sensitivity analysis excluding studies that used estimated SDs (SMD -0.26; 95% CI -0.39 to -0.13). Begg's test did not detect significant publication bias (continuity corrected z=0.62, Pr>|z|=0.536) (see online supplementary figure S1B).

In subgroup analyses, the results suggested that olanzapine significantly benefited on behaviour symptoms of AD patients (SMD -0.18; 95% CI -0.31 to -0.04) (heterogeneity: I<sup>2</sup>=0%). In aripiprazole subgroup, we also detected significant improvement on NPI scale (SMD -0.20; 95% CI -0.35 to -0.05) (heterogeneity: I<sup>2</sup>=17%) (figure 4).

#### Antidepressants

Antidepressants include, but not limited to, sertraline, fluoxetine, citalopram and trazodone. Only two RCTs on sertraline were selected in our study. Both of them were randomised, placebo-controlled, parallel, 12-week, flexible-dose clinical trials. One study included 24 AD patients in sertraline group and 20 AD patients in placebo group. The other study enrolled 124 patients and 120 patients in drug and placebo groups, respectively. Neither of the two trials found significant differences in NPI total scores between sertraline and placebo groups over time. In consistent, the result of our meta-analysis did not detect significant differences on changes of NPI scales between the two groups (95% CI -0.35 to 0.37) (heterogeneity:  $I^2=35\%$ ).

#### Mood stabilisers

Only one eligible RCT was included in our study. It was a randomised, double-blind, placebo-controlled, crossover trial of valproate in institutionalised AD patients. The trial only included 14 patients in valproate group and 13 patients in placebo group. Treatment duration lasted 6 weeks, with a 2-week washout period. The result did not find significant differences on the changes of NPI total scores between valproate and placebo groups (p=0.075), but it suggested a trend that valproate treatment might worsen the NPI total score compared with placebo. The small sample size limited the credibility of the result.

#### Other drugs

Memantine, an N-methyl-D-aspartate receptor antagonist, has been approved in the USA for the treatment of moderate to severe AD. Eight RCTs including 1496 patients in memantine group and 1333 patients in placebo group reported NPI measures. No significant behavioural benefit was observed on NPI total score in our meta-analysis (95% CI -0.27 to 0.03). There was large heterogeneity among pooled memantine studies  $(I^2 = 75\%)$ . Although all trials were RCTs and treated patients with memantine 20 mg daily, the characteristics of populations differed from each other, such as the mean age, race, baseline MMSE and so on. Besides, the treatment duration ranged from 12 to 28 weeks. These discrepancies may explain the large heterogeneity. No significant publication bias was observed in Begg's test (continuity corrected z=1.36, Pr>|z|=0.174) (see online supplementary figure S1C). In sensitivity analyses, we still did not find significant benefit of memantine on neuropsychiatric symptoms after excluding studies that used estimated SDs (95% CI -0.27 to 0.01) or did not use ITT analysis method (95% CI -0.31 to 0.00).

For typical antipsychotics, benzodiazepines and other drugs, we did not search any study that met our inclusion criteria completely.

In addition, we conducted a meta-analysis to assess the efficacy of pharmacological treatment on neuropsychiatric symptoms in patients with any diagnosis of dementia. We also broadened the neuropsychiatric outcomes to include either NPI or the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale. The characteristics of additional



**Figure 4** Forest plot of efficacy of olanzapine and aripiprazole on the Neuropsychiatric Inventory scale in Alzheimer's disease patients in subgroup analyses. Data type: continuous; effect measure: standardised mean difference; analysis model: random effects; statistical method: inverse variance.

	Medici	ine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 ChEls vs Placebo							
Black et al, 2007	59	176	40	167	11.0%	1.40 [1.00, 1.97]	
Brodaty et al,2005	75	326	54	320	11.4%	1.36 [1.00, 1.87]	
Courtney et al, 2004	0	0	0	0		Not estimable	5 m
Feldman et al,2001	23	144	20	146	7.9%	1.17 [0.67, 2.03]	5.7 5 5
Holmes et al,2004	6	41	10	55	4.3%	0.80 [0.32, 2.04]	
Howard et al,2007	13	128	19	131	6.6%	0.70 [0.36, 1.36]	
Johannsen et al,2006	11	99	20	103	6.4%	0.57 [0.29, 1.13]	
Kaufer et al,1998	0	0	0	0		Not estimable	
Lyketsos et al, 2004	0	0	0	100	0.400	Not estimable	
Morris et al, 1998	58	213	16	135	8.4%	1.79[1.07, 3.00]	
Raskind et al, 1999	31	177	14	405	7.0%	1.09 [0.61, 1.94]	
Rockwood et al,2001	450	201	12	125	1.1%	3.43 [1.95, 6.04]	
Tariot et al 2000	103	102	40	200	0.20%	0.72 (0.42, 1.65)	
ranuletal,2001	19	103	21	105	8.3%	0.72[0.43, 1.21]	
Subtotal (95% Cl)		2548	21	1780	100.0%	1 23 [0 98 1 55]	
Total events	567	2340	200		100.070	1.25 [0.50, 1.55]	
Heterogeneity: Tau <sup>2</sup> = 0.09	Chi² = 2	9 1 2 d	f = 11 (P :	= 0 002	): IF = 629	*	
Test for overall effect: $Z = 1$	79 (P = 0	1.071		- 0.002	// = 02		
		,					
1.1.2 Atypical antipsychoti	ics vs Pla	acebo					
De Devn et al.2004	146	520	38	129	3.3%	0.95 [0.71, 1.29]	
De Devn et al.2005	18	106	18	102	0.8%	0.96 [0.53, 1.74]	
Mintzer et al, 2007	147	366	56	121	5.7%	0.87 [0.69, 1.09]	
Street et al.2000	43	159	11	47	0.9%	1.16 [0.65, 2.06]	
Streim et al, 2008	110	131	109	125	29.6%	0.96 [0.87, 1.06]	
Sultzer et al,2008	80	100	121	142	20.9%	0.94 [0.83, 1.06]	
Sultzer et al.2008	77	94	121	142	21.8%	0.96 (0.86, 1.08)	<b></b>
Sultzer et al, 2008	66	85	121	142	16.9%	0.91 [0.80, 1.04]	
Subtotal (95% CI)		1561		950	100.0%	0.94 [0.89, 1.00]	◆
Total events	687		595				
Heterogeneity: Tau <sup>2</sup> = 0.00	Chi <sup>2</sup> = 1	.53, df	= 7 (P = 0	.98); I²	= 0%		
Test for overall effect: Z = 2	.06 (P = 0	0.04)					
1.1.3 Antidepressants vs I	Placebo						
Finkel et al, 2004	22	124	23	120	85.9%	0.93 [0.55, 1.57]	
Lyketsos et al,2003	3	24	5	20	14.1%	0.50 [0.14, 1.84]	
Subtotal (95% CI)		148		140	100.0%	0.85 [0.52, 1.38]	
Liotal events	25	74 46.	_ 1 /D _ 0	201112	- 00		
Test for sucrell effect: 7 = 0		.74, ur: ) = 4 \	= 1 (P = 0	.39), 1-	= 0%		
Test for overall effect. $Z = 0$	.00 (F = 0	.51)					
1.1.4 Memantine vs Place	ho						
Bakchine et al. 2008	47	31.8	14	152	9 N %	1 60 (0 91 - 2 82)	
Fox et al 2012	19	72	23	77	10.3%	0.88 (0.53, 1.48)	
Herrmann et al 2013	31	182	32	187	12.4%	1 00 (0.63, 1.46)	
Peskind et al 2006	36	201	35	202	13.5%	1 03 [0 68 1 58]	
Porsteinsson et al 2008	23	217	25	216	9.8%	0.92 [0.54 1.56]	
Reisberg et al. 2003	29	126	42	126	14.3%	0.69 (0.46, 1.03)	
Tariot et al.2004	30	202	51	201	14.2%	0.59 (0.39, 0.88)	
van Dyck et al.2007	44	178	46	172	16.6%	0.92 [0.65, 1.32]	
Subtotal (95% CI)		1496		1333	100.0%	0.89 [0.73, 1.08]	
Total events	259		268				
Heterogeneity: Tau <sup>2</sup> = 0.03	Chi² = 1	0.56, d	f=7(P=	0.16);1	²= 34%		
Test for overall effect: Z = 1	.18 (P = 0	).24)	-				
							Favours (Medicine) Favours (Placebo)
Test for subaroup difference	es: Chi <sup>z</sup> :	= 5.66	df = 3 P	= 0.13	$ ^2 = 47.0$	)%	

Figure 5 Forest plot of safety of various drugs on all-caused dropouts in Alzheimer's disease patients. Data type: dichotomous; effect measure: risk ratio; analysis model: random effects; statistical method: Mantel–Haenszel.

	Medic	ine	Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.5.1 Donepezil							
Black et al, 2007	59	176	40	167	11.0%	1.40 [1.00, 1.97]	-
Courtney et al, 2004	0	0	0	0		Not estimable	15
Feldman et al,2001	23	144	20	146	7.9%	1.17 [0.67, 2.03]	- y
Holmes et al,2004	6	41	10	55	4.3%	0.80 [0.32, 2.04]	12
Howard et al,2007	13	128	19	131	6.6%	0.70 [0.36, 1.36]	
Johannsen et al,2006	11	99	20	103	6.4%	0.57 [0.29, 1.13]	• • • • • • • • • • • • • • • • • • • •
Tariot et al,2001	19	103	27	105	8.3%	0.72 [0.43, 1.21]	
winblad et al,2006	33	128	21	120	8.8%	1.47 [0.91, 2.40]	
Subtotal (95% CI)		819		827	53.2%	0.99 [0.74, 1.32]	
Total events	164		157				
Heterogeneity: Tau <sup>2</sup> = 0.	.07; Chi <sup>2</sup> =	: 11.60	, df = 6 (P	= 0.07	); I <sup>z</sup> = 48%	6	
Test for overall effect: Z	= 0.10 (P	= 0.92)					
1.5.2 Galantamine							
Brodaty et al,2005	75	326	-54	320	11.4%	1.36 [1.00, 1.87]	
Lyketsos et al, 2004	0	0	0	0		Not estimable	
Rockwood et al,2001	86	261	12	125	7.7%	3.43 [1.95, 6.04]	
Tariot et al,2000	153	692	46	286	11.6%	1.37 [1.02, 1.85]	
Subtotal (95% CI)		1279		731	30.8%	1.75 [1.10, 2.76]	
Total events	314		112				
Heterogeneity: Tau <sup>2</sup> = 0.	.13; Chi <sup>2</sup> =	9.07,	df = 2 (P =	= 0.01);	l² = 78%		
Test for overall effect: Z	= 2.37 (P	= 0.02)					
1.5.3 Metrifonate							
Kaufer et al,1998	0	0	0	0		Not estimable	
Morris et al,1998	58	273	16	135	8.4%	1.79 [1.07, 3.00]	
Raskind et al, 1999	31	177	14	87	7.6%	1.09 [0.61, 1.94]	
Subtotal (95% CI)		450		222	16.0%	1.42 [0.87, 2.32]	
Total events	89		30				
Heterogeneity: Tau <sup>2</sup> = 0.	.05; Chi <sup>2</sup> =	= 1.61.	df = 1 (P =	= 0.20);	I <sup>2</sup> = 38%		
Test for overall effect: Z	= 1.41 (P	= 0.16)	`				
		,					
Total (95% CI)		2548		1780	100.0%	1.23 [0.98, 1.55]	
Total events	567		299				
Heterogeneity: Tau <sup>2</sup> = 0.	.09; Chi <sup>2</sup> =	: 29.12	df = 11 (	P = 0.0	02); I <sup>2</sup> = 6	2%	
Test for overall effect: Z	= 1.79 (P	= 0.07)					U.5 U.7 1 1.5 2
Test for subaroup differences: Chi² = 4.76. df = 2 (P = 0.09). l² = 57.9%							Favours (Medicine) Favours (Placebo)

**Figure 6** Forest plot of safety of donepezil, galantamine and metrifonate on all-caused dropouts in Alzheimer's disease patients in subgroup analyses. Data type: dichotomous; effect measure: risk ratio; analysis model: random effects; statistical method: Mantel–Haenszel.

studies in this part of meta-analysis were listed in online supplementary table S3. Our results showed that ChEIs and atypical antipsychotics significantly improved neuropsychiatric symptoms compared with placebo (ChEIs, SMD -0.11; 95% CI -0.20 to -0.01; atypical antipsychotics, SMD -0.18; 95% CI -0.27 to -0.09), while antidepressants and memantine did not (antidepressants, 95% CI -0.35 to 0.37; memantine, 95% CI -0.27 to 0.01) (see online supplementary figure S2). More detailed information is available in online supplementary appendix 1.

#### Safety

#### All-cause dropouts

In overall meta-analyses on safety, there were no significant differences in the number of dropouts caused by any reason between any medicine treatment group and placebo treatment group (ChEIs: 95% CI 0.98 to 1.55; atypical antipsychotics: 95% CI 0.89 to 1.00; antidepressants: 95% CI 0.52 to 1.38; memantine: 95% CI 0.73 to 1.08) (figure 5). In donepezil and metrifonate subgroups, we observed similar results (donepeil: 95% CI 0.74 to 1.32; metrifonate: 95% CI 0.87 to 2.32). However, in the galantamine subgroup, the number of allcaused dropouts was significantly higher in galantamine treated group than in placebo treated group (RR 1.75; 95% CI 1.10 to 2.76) (figure 6).

#### Adverse events-caused dropouts

In ChEIs treated group, the number of withdrawals due to adverse events was significantly higher than in placebo treated group (RR 1.64; 95% CI 1.12 to 2.42) (figure 7). In atypical antipsychotics group, the number of adverse events caused dropouts was also higher (RR 2.24; 95% CI 1.53 to 3.26). But for antidepressants and memantine, we did not observe significant differences in the number of dropouts due to adverse events (antidepressants: 95% CI 0.52 to 1.94; memantine: 95% CI 0.71 to 1.38).

#### Adverse events

Adverse events were inconsistently mentioned in all trials. The common adverse events included but not limited to gastrointestinal symptoms (nausea, vomiting, diarrhoea, anorexia, etc), dizziness, headache, agitation, respiratory tract infection, asthenia, urinary tract infection and so on.

Patients in ChEIs and atypical antipsychotics groups experienced more adverse events than in placebo group (ChEIs: RR 1.08; 95% CI 1.01 to 1.17; atypical antipsychotics: RR 1.17; 95% CI 1.05 to 1.31) (figure 8). For memantine, no significant difference was detected in adverse events between memantine and placebo groups (95% CI 0.99 to 1.13).

In the additional meta-analysis of safety of pharmacological treatment in patients with any type of dementia, ChEIs increased the risk of all-caused dropouts (RR 1.34; 95% CI 1.14 to 1.58) (see online supplementary figure S3) and adverse events (RR 1.10; 95% CI 1.04 to 1.18) (see online supplementary figure S4); both ChEIs (RR 1.74; 95% CI 1.33 to 2.27) and atypical antipsychotics (RR 1.99; 95% CI 1.50 to 2.63) increased risk of dropouts due to adverse events (see online

	Medici	ine	Place	bo		Risk Ratio	Bisk Batio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.2.1 ChEls vs Placebo							
Black et al., 2007	34	176	18	167	127%	1 79 (1 05 3 05)	<b>_</b>
Brodaty et al 2005	24	326	15	320	11.7%	1.57 [0.84, 2.94]	
Courtney et al. 2004	0	0	0	0		Not estimable	
Feldman et al 2001	12	144	9	146	9.4%	1.35 (0.59, 3.11)	
Holmes et al 2004	3	41	ň	55	1.6%	9 33 (0 50 175 85)	
Howard et al 2007	- 0	n	ñ	0		Notestimable	
Johannsen et al 2006	1	99	2	103	2.3%	0.52 (0.05, 5.65)	<→
Kaufer et al 1998	'n	ñ	ñ		2.0 /0	Not estimable	
Lyketsos et al. 2004	ŏ	ō	õ	ō		Not estimable	
Morris et al 1998	34	273	6	135	9.3%	2 80 [1 21 6 51]	
Raskind et al. 1999	19	177	8	87	9.9%	1.17 [0.53, 2.56]	
Rockwood et al.2001	66	261	5	125	9.0%	6.32 [2.61.15.30]	
Tariot et al 2000	55	692	20	286	13.2%	1.14 [0.69, 1.86]	
Tariot et al 2001	11	103	19	105	10.9%	0.59 (0.30, 1.18)	
winblad et al 2006	20	128		120	10.0%	2.34 [1.07, 5.12]	
Subtotal (95% CI)		2420	-	1649	100.0%	1.64 [1.12, 2.42]	
Total events	279		110				
Heterogeneity: $Tau^2 = 0.23$	$3^{\circ}$ Chi <sup>2</sup> = 2	5 59 dt	= 10 (P =	= 0 004	$1 \cdot 1^2 = 61^{\circ}$	*	
Test for overall effect: $Z = 2$	2.51 (P = 0)	0.000,000					
		,					
1.2.2 Atypical antipsychol	tics vs Pla	icebo					
De Devn et al 2004	43	520	5	129	11.3%	2 1 3 10 86 5 281	
De Devn et al 2005	10	106	7	102	11.0%	1 37 [0 54 3 47]	
Mintzer et al. 2007	62	366	16	121	20.3%	1 28 [0 77 2 13]	
Street et al 2000	19	159	2	47	5.8%	2 81 [0 68 11 62]	
Streim et al. 2008	17	131	10	125	14 4 %	1 62 [0.00, 11.02]	
Sultzer et al 2008	15	94	7	142	121%	3 24 [1 37 7 64]	<b>_</b>
Sultzer et al 2008	24	100	- 7	142	13.1%	4 97 [2 19 10 96]	<b>_</b>
Sultzer et al 2008	15	85	- 7	142	12.1%	3 58 [1 52 8 43]	<b>_</b>
Subtotal (95% CI)		1561	•	950	100.0%	2 24 [1 53 3 26]	
Total events	205		61	000	100.070	2.24 [ 1.55, 5.26]	
Heterogeneity: Tau <sup>2</sup> = 0.13	200 2: Chi <sup>2</sup> = 1:	176 dt	= 7 (P =	0 1 1 1 1	<sup>2</sup> = 40%		
Test for overall effect: $7 = 7$	117 (P < 1	0.0001		0.11),1	- 40 /0		
restion overall ellect. Z = -	+.17 ( 0						
1 2 3 Antidenressants vs	Diacebo						
Finkel et al. 2004	15	124	15	120	96 7%	0 97 10 50 1 991	
Lyketeoe et al 2004	10	24	10	20	4 204	2 62 (0.30, 1.03)	← → →
Subtotal (95% Cl)		148		140	100.0%	1 01 [0 52 1 94]	
Total events	16	140	16	140	100.070	1.01 [0.52, 1.54]	
Hotorogonoity Tous - 0.00		24 df-	- 1 / 0 - 0	661-18	- 0%		
Test for overall effect: 7 - 0	), CIII = 0.	.34, ui - 1 00\	- 1 (F - 0	.50), 1	- 0 %		
restion overall ellect. Z = 0	5.05 (F = C						
1.2.4 Memantine vs Place	bo						
Rekehing at al. 2009	29	210	a	162	Q / 96	2 22 10 94 5 271	
Eavet al 2012	20	72	10	77	9.470 11 004	2.23 [0.94, 3.27]	
Horrmonn of al 2012	15	102	10	107	10.0%	1 64 (0 71 2 24)	
Reckind of al 2006	10	201	10	202	11 204	1.04 [0.71, 3.34]	
Perstaineeen et al 2009	19	201	17	202	10.070	0.76 (0.29 1, 4.00)	
Poichard at al. 2002	13	126	22	100	12.170	0.70 [0.36, 1.93]	
Tariot at al 2004	13	202	22	201	12.2%	0.09 [0.31, 1.12]	
van Dyck at al 2007	10	170	20	170	15.970		
san Dyck et al,2007 Subtotal (95% Cl)	22	1/06	∠3	1332	100.0%		
Total quanta	1.40	1490	1 7 4	1555	100.0%	0.99 [0.7 1, 1.38]	
Hotorogonoity Tou3 - 0.11	140	261 -4	131	0.063	3 - 400		
Toot for overall effect: 7 - 0		0.04, UI	- 7 (F =	0.00), 1	- 40%		
restror overall ellect. Z = t	J.04 (F = U						
							0.2 0.5 1 2 5
Test for subaroup differen	ces: Chi <sup>z</sup> :	= 11.61	. df = 3 (i	P = 0.0	09), I <sup>2</sup> = 7	4.2%	Favours (Medicine) Favours (Placebo)

Figure 7 Forest plot of safety of various drugs on adverse events-caused dropouts in Alzheimer's disease patients. Data type: dichotomous; effect measure: risk ratio; analysis model: random effects; statistical method: Mantel–Haenszel.

supplementary figure S5). For memantine, we did not detect any significant bad safety outcomes.

#### DISCUSSION

Among the various drugs in use for the treatment of neuropsychiatric symptoms, we found that ChEIs and atypical antipsychotics have convincing evidence of benefit for neuropsychiatric symptoms, but with certain adverse effects. For antidepressants and memantine, we did not observe significant benefit for neuropsychiatric symptoms, even though without significant adverse effects.

So far, two meta-analyses<sup>2</sup> <sup>3</sup> have demonstrated that ChEIs show benefit for neuropsychiatric symptoms, which is consistent with the results of our study. For memantine, one meta-analysis<sup>4</sup> found that it improved behaviour symptoms while two<sup>4</sup> <sup>6</sup> did not demonstrate that. In addition, donepezil,<sup>4</sup> galantamine<sup>5</sup> and metrifonate<sup>7</sup> were all proved to have significant effect on neuropsychiatric symptoms in early studies. However, in current meta-analysis, only galantamine was verified beneficial for neuropsychiatric symptoms. For atypical antipsychotics and anti-depressants, no other meta-analyses have been published. The

inclusion criteria for different studies are not completely identical; therefore, the results are different. For example, in study of Gauthier *et al*,<sup>6</sup> they enrolled patients with moderate to severe AD, while in our study, we enrolled patients with any severity of AD. Moreover, our meta-analysis excluded trials in which data of the mean change of NPI scores from baseline in drug and placebo groups were not available, and included studies published in recent years. All these may impact the results of the study.

The strengths of this study include the inclusion of the lately published trials, which were not (or not entirely) included in previous reviews. Moreover, we applied widely used meta-analytic techniques to calculate the non-reported data such as SDs, thus, minimising missing data. Furthermore, we assessed the quality of the included trials, and presented a summary table of the outcomes. Finally, we analysed the effect and safety of almost all common drugs that were clinically used to treat neuropsychiatric symptoms. Our findings of the significant improvement in neuropsychiatric scales in AD patients treated with ChEIs, atypical antipsychotics are important, because neuropsychiatric problems are common in AD,

	Medici	ne	Place	bo		Risk Ratio	Risk Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Random, 95% Cl
1.3.1 ChEls vs Placebo						······································	
Black et al. 2007	140	176	117	167	12.6%	1 14 (1 00 1 29)	
Brodaty et al 2005	235	326	224	320	14.5%	1.03 (0.93, 1.14)	
Courtney et al. 2004	0	0	0	0		Not estimable	
Feldman et al 2001	120	144	117	146	13.7%	1 04 (0 93 1 16)	
Holmes et al 2004						Not estimable	
Howard et al 2007	20	128	15	131	1.3%	1 36 (0 73 2 55)	<b>_</b>
Johannsen et al 2006		99	10	103	0.7%	0.83 (0.34, 2.02)	<→
Kaufer et al.1998	Ō	0	0	0		Not estimable	
Lyketsos et al. 2004	Ō	Ō	ō	Ō		Not estimable	
Morris et al.1998	Ō	Ō	Ō	Ō		Not estimable	
Raskind et al. 1999	Ō	Ō	ō	Ō		Not estimable	
Rockwood et al.2001	225	261	79	125	11.3%	1.36 [1.18, 1.57]	
Tariot et al.2000	531	692	206	286	15.7%	1.07 (0.98, 1.16)	+
Tariot et al.2001	99	103	102	105	17.9%	0.99 (0.94, 1.04)	-
winblad et al.2006	105	128	91	120	12.2%	1.08 (0.95, 1.23)	
Subtotal (95% CI)		2057		1503	100.0%	1.08 [1.01, 1.17]	◆
Total events	1483		961			• / •	
Heterogeneity: Tau <sup>2</sup> = 0.01	: Chi <sup>2</sup> = 21	6.74. d	f = 8 (P =	0.0008	$1^2 = 70^9$	8	
Test for overall effect: $Z = 2$	16 (P = 0)	0.03)					
		,					
1.3.2 Atypical antipsychot	ics vs Pla	icebo					
De Devn et al.2004	0	0	0	0		Not estimable	
De Devn et al 2005	Ō	Ō	ō	Ō		Not estimable	
Mintzer et al, 2007	Ō	Ō	ō	Ō		Not estimable	
Street et al 2000	Ō	Ō	ō	Ō		Not estimable	
Streim et al, 2008	16	131	17	125	3.0%	0.90 (0.47, 1.70)	←
Sultzer et al 2008	71	100	83	142	35.0%	1.21 [1.01, 1.46]	
Sultzer et al.2008	62	85	83	142	33.9%	1.25 [1.03, 1.51]	
Sultzer et al.2008	59	94	83	142	28.1%	1.07 (0.87, 1.32)	
Subtotal (95% CI)		410		551	100.0%	1.17 [1.05, 1.31]	
Total events	208		266				
Heterogeneity: Tau <sup>2</sup> = 0.00	: Chi <sup>2</sup> = 1.	99. df:	= 3 (P = 0	.58): I <sup>2</sup>	= 0%		
Test for overall effect: Z = 2	2.84 (P = 0)	0.005)	•				
1.3.3 Antidepressants vs	Placebo						
Finkel et al, 2004	0	0	0	0		Not estimable	
Lyketsos et al.2003	Ō	ō	ō	Ō		Not estimable	
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not applica	ble						
Test for overall effect: Not a	applicable						
	•••						
1.3.4 Memantine vs Place	bo						
Bakchine et al, 2008	178	318	78	152	9.1%	1.09 [0.91, 1.31]	
Fox et al.2012	0	0	0	0		Not estimable	
Herrmann et al.2013	138	182	136	187	15.3%	1.04 [0.92, 1.18]	
Peskind et al 2006	120	201	111	202	10.1%	1.09 [0.92, 1.29]	
Porsteinsson et al.2008	176	217	142	216	15.9%	1.23 (1.10, 1.39)	
Reisberg et al, 2003	106	126	109	126	17.8%	0.97 (0.88, 1.08)	— <b>—</b>
Tariot et al.2004	158	202	156	201	17.5%	1.01 (0.91, 1.12)	_ <b>+</b>
van Dyck et al. 2007	131	178	125	172	14.4%	1.01 (0.89. 1.15)	_ <b>--</b>
Subtotal (95% CI)		1424		1256	100.0%	1.06 [0.99, 1.13]	◆
Total events	1007	-	857				
Heterogeneity: Tau <sup>2</sup> = 0.00	: Chi <sup>2</sup> = 1	1.17. d	f=6(P=	0.08): I	<sup>2</sup> = 46%		
Test for overall effect: Z = 1	.63 (P = 0	1.10)	- v				
		,					
							U.S. U.7 1 1.5 2
Test for subaroup differen	ces: Chi⁼÷	= 2.61.	df = 2 (P	= 0.27)	$  ^2 = 23.4$	1%	Favours (Medicine) Favours (Placebo)

Figure 8 Forest plot of safety of various drugs on adverse events in Alzheimer's disease patients. Data type: dichotomous; effect measure: risk ratio; analysis model: random effects; statistical method: Mantel–Haenszel.

and are major contributors to loss of autonomy, morbidity and need for nursing home placement.

Several limitations to our meta-analysis restrict the interpretation of our results. First, the NPI seems to be the most comprehensive scale and is thought to be more sensitive to change than some other scales; therefore, it has been widely used to appraise the neuropsychiatric symptoms. However, there are still some studies that did not apply it, especially studies performed before the generation of the NPI scale. This causes some trials to be excluded from our study. Second, some of our included trials excluded participants receiving psychotropic medicines, while some trials allowed, and even demanded, the use of medicines such as ChEIs and other drugs in their study. The use of such medicines may have an impact on our results. In addition, as mentioned above, AD is progressive, and patients declined at progressive different stages of severity, which may also influence our results when pooling data. Finally, very few trials were included for typical antipsychotics, antidepressants and mood stabilisers. Therefore, no convincing conclusions can be drawn regarding the efficacy of these drugs for neuropsychiatric symptoms.

Despite some limitations, we believe that our results are the first attempt to quantitatively synthesise the efficacy and safety of various of medicines for neuropsychiatric symptoms of AD patients, suggesting a mild to moderate benefit in neuropsychiatric outcomes from ChEIs and antipsychotics. Our meta-analysis results indicate that for AD patients who have neuropsychiatric disturbances, ChEIs and atypical antipsychotics may be considered as a therapeutic option. However, it is notable that the decision to use these medicines needs to be considered in light of the adverse effects, cost and feasibility. As recommended,<sup>40</sup> for AD patients with neuropsychiatric symptoms, excluding the medical and environmental factors, non-pharmacological interventions should be attempted before moving to drug therapy. If non-pharmacological interventions do not work, drug therapy should be used to manage neuropsychiatric symptoms. For patients with symptoms of depression or anxiety, selective serotonin reuptake inhibitors, such as antidepressants, are advised for treating the symptoms patients exhibit. For patients without symptoms of depression or anxiety, combining with the goal of minimising adverse effects, ChEIs are first recommended for well tolerated, and then atypical antipsychotics. Typical antipsychotics are not recommended

because there is less evidence of benefit and more adverse effects compared with atypical antipsychotics.

Overall, our meta-analysis results indicate a benefit in neuropsychiatric symptoms for AD patients from ChEIs and atypical antipsychotics. Future researches should focus more on neuropsychiatric outcomes. It is important to continue efforts to perform high-quality trials of non-pharmacological treatments in combination with drug therapy, and the safety evaluation of the drugs cannot be ignored.

**Contributors** JTY and LT designed the analysis. JW, HFW, XFM, CW and CCT collected and abstracted the data. JW and HFW carried out the statistical analysis. JW and JTY drafted the manuscript. All authors analysed and interpreted the data and critically revised the manuscript for important intellectual content. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official view of their institutions or any other party. JTY and LT have full access to all of the data and take full responsibility for the data, analyses and interpretation. All authors reviewed and approved the final report.

#### Competing interests None.

**Ethics approval** In accordance with NRES and MRC guidance, this study does not require ethics approval as it does not directly involve human participants. The data used in the systematic review and meta-analysis have come from studies which have previously satisfied regulatory requirements and been peer reviewed.

Provenance and peer review Not commissioned; externally peer reviewed.

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# Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis

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