# The effects of memantine on behavioral disturbances in patients with Alzheimer's disease: a meta-analysis

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**Background:** Memantine is effective in the treatment of behavioral disturbances in patients with Alzheimer's disease. It has not yet been fully determined which behavioral disturbances respond best to memantine.

Methods: We conducted a meta-analysis of memantine vs control (placebo or usual care) for the treatment of individual behavioral disturbances (delusion, hallucination, agitation/aggression, dysphoria, anxiety/phobia, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity/activity disturbances, nighttime disturbance/diurnal rhythm disturbances, and eating disturbances). Randomized controlled studies of memantine in patients with Alzheimer's disease were included in this study. To evaluate these outcomes, standardized mean difference (SMD), with 95% confidence intervals (95% CIs), based upon a random-effects model was evaluated in the meta-analysis.

Results: A total of 11 studies (n=4,261; memantine vs placebo: N=4, n=1,500; memantine + cholinesterase inhibitors [M+ChEIs] vs ChEIs: N=7, n=2,761) were included in the meta-analysis. Compared to control, memantine showed significant improvement in agitation/aggression (SMD=-0.11; 95% CIs =-0.20, -0.03; P=0.01;  $I^2=47\%$ ), delusion (SMD =-0.12; 95% CIs =-0.18, -0.06; P=0.0002;  $I^2=0\%$ ), disinhibition (SMD = -0.08; 95% CIs = -0.15, -0.00; P=0.04;  $I^2=0\%$ ), and nighttime disturbance/diurnal rhythm disturbances (SMD =-0.10; 95% CIs =-0.18, -0.02; P=0.02;  $I^2=36\%$ ). Memantine was also marginally superior to control in hallucination (SMD =-0.06; 95% CIs =-0.12, 0.01; P=0.07; I<sup>2</sup>=0%) and irritability/lability (SMD =-0.09; 95% CIs = -0.19, 0.01; P=0.07;  $I^2=42\%$ ). Memantine is similar to control in dysphoria, anxiety/ phobia, euphoria, apathy, and eating disturbance.

**Conclusion:** The meta-analysis suggest that memantine has benefits for the treatment of most of the behavioral disturbances in patients with Alzheimer's disease. Memantine does not deteriorate negative symptoms as behavioral disturbances in patients with Alzheimer's disease.

**Keywords:** memantine, Alzheimer's disease, behavioral disturbances, meta-analysis

### Introduction

Alzheimer's disease is a neurodegenerative disease. The percentage of people with Alzheimer's disease increases with age: 3% of people aged 65-74 years, 17% of people aged 75-84 years, and 32% of people aged 85 years and older have Alzheimer's disease.<sup>2</sup> It has an insidious onset, with gradual progression of cognitive symptoms and behavioral disturbances.1

There are the following four approved drugs for the treatment of Alzheimer's disease worldwide: memantine and three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine). 1 Memantine has been approved worldwide for treating

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moderate-to-severe Alzheimer's disease. It is postulated that memantine exerts its therapeutic effect through its action as a low-to-moderate affinity, noncompetitive (open channel), nonselective, voltage-dependent, *N*-methyl-D-aspartic acid (NMDA) receptor antagonist, which binds preferentially to NMDA receptor-operated calcium channels.<sup>3</sup> Memantine blocks the effects of sustained, pathologically elevated levels of glutamate, which could otherwise lead to neuronal dysfunction.<sup>4-6</sup> In addition, memantine may also upregulate NMDA receptor expression, causing activation in the presence of a strong stimulus.<sup>7</sup>

Our previous meta-analysis showed that memantine monotherapy was superior to placebo in cognitive impairment (standardized mean difference [SMD] =–0.27; 95% confidence intervals [95% CIs] =–0.39 to –0.14) and behavioral disturbances (SMD =–0.12; 95% CIs =–0.22 to –0.01).8 We did an additional meta-analysis to show that although there was a trend favoring the combination therapy with memantine and cholinesterase inhibitors compared to cholinesterase inhibitor monotherapy for treating cognitive impairment (SMD =–0.13; 95% CIs =–0.26 to 0.01), memantine was superior to placebo in behavioral disturbances (SMD =–0.13; 95% CIs =–0.24 to –0.02).9 Thus, there was evidence on the efficacy of memantine for cognitive impairment and behavioral disturbances on patients with Alzheimer's disease to date.

However, there are various symptoms of behavioral disturbances, such as delusion, hallucination, agitation/ aggression, dysphoria, anxiety/phobia, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity/ activity disturbances, nighttime disturbance/diurnal rhythm disturbances, and eating disturbances. 10 For example, although a drug, which has sedative effect, seems to be effective for positive symptoms, such as agitation and irritability, this drug seems to exasperate negative symptoms, such as apathy. 10 There has not been robust evidence on the efficacy of memantine for individual behavioral disturbances in patients with Alzheimer's disease. The effect size of antidementia drugs for individual behavioral disturbances in patients with Alzheimer's disease in randomized trials has been extremely small, due to the need to manage subscale scores of behavioral disturbance scale. Therefore, because a meta-analysis can increase the statistical power for group comparisons and can overcome the limitation of sample size in underpowered studies,11 we conducted a meta-analysis to achieve conclusive evidence for the efficacy of memantine on individual behavioral disturbances in patients with Alzheimer's disease.

### **Methods**

This meta-analysis was performed based upon the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (International prospective register of systematic reviews [PROSPERO]: CRD42017059245). We combined with the data from the studies of memantine monotherapy and the studies of combination therapy with memantine and cholinesterase inhibitors, because studies of the combination therapy included the patients who had several dementia symptoms at the baseline despite taking some cholinesterase inhibitors.

# Search strategy and inclusion criteria

To identify relevant studies, two of the authors (TK and SM) independently searched MEDLINE, Cochrane library, Scopus, and PsycINFO without language restrictions from the inception of their databases to April 25, 2017, using the following search strategy: ("Alzheimer Disease" [Mesh] OR "Alzheimer disease" OR "Alzheimer's disease") AND ("Memantine" [Mesh] OR "memantine") AND ("randomized" OR "random" OR "randomly"). The authors also searched ClinicalTrials.gov/), ISRCTN registry (https://www.isrctn.com/), and the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) to include randomized controlled trials as comprehensively as possible and to minimize the possibility of publication bias. Only randomized placebo- or usual care-controlled trials of memantine treatment in patients with Alzheimer's disease lasting  $\geq 2$  weeks were included. The studies that included more than 50% patients who received the combination therapy were classified as a combination therapy group in this study (Table 1). Two authors (TK and SM) independently assessed inclusion/exclusion criteria and selected the studies. The references of the included articles and review articles were also searched for citations of additional relevant published and unpublished studies, including conference abstracts.

# Data synthesis and outcome measures

The primary outcomes were individual behavioral disturbances as follows: delusion, hallucination, agitation/aggression, dysphoria, anxiety/phobia, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity/activity disturbances, nighttime disturbance/diurnal rhythm disturbances, and eating disturbances. Nine of 11 studies included in the meta-analysis used Neuropsychiatric Inventory, 13 and the other two studies 14,15 used the Behavioral Pathology in Alzheimer's Disease Rating Scale. 16 For three-arm (memantine 10 mg/day arm, memantine 20 mg/day arm, and placebo arm) studies, 17 we combined the data of the

memantine 10 mg/day arm with that of memantine 20 mg/day. For four-arm (memantine monotherapy arm, combination therapy with memantine and donepezil arm, donepezil monotherapy arm, and placebo arm) studies, 18 we combined the data of the memantine monotherapy arm with that of the combination therapy with memantine (ie, memantine group) and donepezil arm and the data of donepezil monotherapy arm with that of placebo arm (ie, non-memantine group).

### Data extraction

Two authors (TK and SM) independently extracted the data from the included studies. Where possible, we used intention-to-treat (ITT) or a full analysis set (FAS) population. When such data were unavailable, the results for observed case (OC) analysis were extracted from each study. When the data required for meta-analysis were missing, we contacted the investigators (or the industries) of the relevant study and requested unpublished data.

## Meta-analysis methods

The meta-analysis was conducted using Review Manager software. 19 The random-effects model was selected for this meta-analysis due to the potential heterogeneity across studies. To evaluate these outcomes, SMD, with 95% CIs, based upon a random-effects model, was evaluated in the meta-analysis. We assessed the methodological quality of the trials, according to the Cochrane risk-of-bias criteria in the Cochrane Handbook. 11 Study heterogeneity was tested using the  $I^2$  statistic, considering  $I^2 \ge 50\%$  to reflect considerable heterogeneity. 11 We did not find considerable heterogeneity with respect to all meta-analysis. To detect the confounding factors for the result of primary outcomes for efficacy, two subgroup analysis (including a test for subgroup differences) were performed for the following: severity of disease (mild-tomoderate vs moderate and moderate-to-severe) and therapeutic strategy (memantine monotherapy vs combination therapy with memantine and cholinesterase inhibitors). Finally, we utilized funnel plots to explore potential publication bias.

### Results

# Study characteristics

Of the 2,239 results obtained in our literature search, we excluded the following: 1,498 as duplicates, 693 after a review of the abstract or title review, and 28 articles after a review of the full text (22 review articles, four single-arm studies, and two same studies). We did not retrieve 10 studies by searching through the review articles and clinical trial registries (Figure S1). Although 30 studies were identified though the

literature search, only 11 studies (memantine monotherapy vs placebo: four studies, <sup>14,17,20,21</sup> n=1,500; combination therapy with memantine and cholinesterase inhibitors vs cholinesterase inhibitors: seven studies, <sup>15,18,22–26</sup> n=2,761) were included in the meta-analysis, since the other 20 studies did not report any available data for performing a meta-analysis.

The main characteristics of studies and patients are summarized in Table 1. The mean duration of the studies was 26.5 weeks (one study was 52 weeks, other studies were 24 weeks), the mean patient age was 76.3 years, and the percentage of males was 34.6%. Although one of the 11 studies was an open-label study (ie, not placebo-controlled study), <sup>22</sup> the other 10 studies were double-blinded, randomized, placebocontrolled trials. One study was a memantine extendedrelease study.23 The dose of memantine was 20 mg/day in all studies, other than Kitamura et al's<sup>17</sup> study (three arms: memantine 10 mg/day arm, memantine 20 mg/day arm, and placebo arm). The Howard et al's18 study used OC populations in their analysis. Because this study was a four-arm study (memantine monotherapy arm, combination therapy with memantine and donepezil arm, donepezil monotherapy arm, and placebo arm), 18 we combined the data of memantine monotherapy arm with that of combination therapy with memantine (ie, memantine group) and donepezil arm and data of donepezil monotherapy arm with that of placebo arm (ie, non-memantine group). Two studies were not sponsored by a pharmaceutical company. 18,22 Most of all studies included in the study excluded the patients who had psychiatric disorders other than Alzheimer's disease.

Evaluations on the methodological quality of the included studies were performed based upon the Cochrane risk-of-bias criteria and are shown in Figures S2 and S3.

# Results of the meta-analysis

Memantine showed significant improvement in agitation/ aggression (SMD =-0.11; 95% CIs =-0.20, -0.03; P=0.01, I<sup>2</sup>=47%; Figure 1), delusion (SMD =-0.12; 95% CIs =-0.18, -0.06; P=0.0002; I<sup>2</sup>=0%; Figure 2), disinhibition (SMD =-0.08; 95% CIs =-0.15, -0.00; P=0.04; I<sup>2</sup>=0%; Figure 3), and nighttime disturbance/diurnal rhythm disturbances (SMD =-0.10; 95% CIs =-0.18, -0.02; P=0.02; I<sup>2</sup>=36%; Figure 4) compared to control. Memantine was also marginally superior to control in hallucination (SMD =-0.06; 95% CIs =-0.12, 0.01; P=0.07; I<sup>2</sup>=0%; Figure 5) and irritability/lability (SMD =-0.09; 95% CIs =-0.19, 0.01; P=0.07; I<sup>2</sup>=42%; Figure 6). Memantine is similar to control in aberrant motor activity/activity disturbances, anxiety/phobia, apathy, dysphoria, eating disturbances, and euphoria

Table I Characteristics of included randomized controlled trials

Study, country, sponsorship	Total (n)	Methods: I. Study design 2. Duration 3. Analyzed population	Patients I. Diagnosis 2. Inclusion criteria 3. Study-defined disease severity 4. Mental disorder comorbidities 5. Concomitant drug	Age mean ± SD, years
<b>Monotherapy</b> Kitamura et al, <sup>17</sup> Japan, industry	315	I. DB-RCT 2. 24 weeks 3. FAS	<ol> <li>AD, DSM-IV, and NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 5–14, FAST 6a–7a</li> <li>Moderate to severe</li> <li>NR</li> <li>Not allowed concomitant drug use: AE, AP, APD, DON, MR, NMDARI, S/H, TD; allowed concomitant use within 2 weeks: BRO, LOR, RIL, TIA</li> </ol>	73.3±9.4
Nakamura et al, <sup>14</sup> Japan, industry	432	I. DB-RCT 2. 24 weeks 3. FAS	<ol> <li>AD, DSM-IV, and NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 5–14, FAST 6a–7a</li> <li>Moderate to severe</li> <li>Exclusion: severe psychiatric disorder other than probable AD</li> <li>Not allowed concomitant drug use: AE, AP, APD, DON, MR, NMDARI, S/H, TD; allowed concomitant use: BRO, LOR, RIL, TIA ≤150 mg/day</li> </ol>	74.6±8.4
Peskind et al, <sup>20</sup> USA, industry	403	I. DB-RCT 2. 24 weeks 3. ITT	<ol> <li>AD, NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 10-22</li> <li>Mild to moderate</li> <li>Exclusion: psychiatric disorder other than probable AD</li> <li>Allowed concomitant drug use: ADD, AH, AI, GB, GIN, OLA, RIS, TD, TOC</li> </ol>	77.5
van Dyck et al, <sup>21</sup> USA, industry	350	I. DB-RCT 2. 24 weeks 3. ITT	<ol> <li>AD, NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 5–14</li> <li>Moderate to severe</li> <li>Exclusion: psychiatric disorder other than probable AD</li> <li>Allowed concomitant drug use: AAPD, ADD, AH, AI, LAX, TD, TOC</li> </ol>	78.2
Combination thera	ру			
Araki et al, <sup>22</sup> Japan, nonindustry	37	I. O-RCT 2. 24 weeks 3. FAS	<ol> <li>AD, DSM-IV, and ICD-10</li> <li>HDS-R 3-16</li> <li>Moderate to severe</li> <li>NR</li> <li>NR</li> </ol>	78.8±7.7
Grossberg et al, <sup>23</sup> international, industry	677	I. DB-RCT 2. 24 weeks 3. ITT	<ol> <li>AD, DSM-IV-TR, and NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 3-14</li> <li>Moderate to severe</li> <li>Exclusion: DSM-IV Axis I disorder other than AD</li> <li>NR</li> </ol>	76.5
Herrmann et al, <sup>24</sup> Canada, industry	369	I. DB-RCT 2. 24 weeks 3. FAS	<ol> <li>AD, NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 5–15, NPI ≥13, NPI agitation/aggression score ≥1</li> <li>Moderate to severe</li> <li>Exclusion: psychiatric disorder other than probable AD</li> <li>Concomitant drug use: ADD 23.6%, ANX 3.3%, APD 22.2%</li> </ol>	74.9

Race (%)	Baseline cognitive function scales (mean ± SD)	Intervention, dose (mg/day)	n	Efficacy outcomes <sup>a</sup>
Japanese: 100	MMSE: 10.1±3.0; SIB: 71.1±17.8	MEM 20 mg (Fi) MEM 10 mg (Fi) PLA	100 107 108	MEM > PLA: FAST (20 mg), MMSE (20 mg), SIB (20 mg); MEM = PLA: ADCS-ADL19, CIBIC-Plus, FAST (10 mg), MMSE (10 mg), NPI10, SIB (10 mg)
Japanese: 100	MMSE: 9.9±3.0; SIB: 71.0±17.9	MEM 20 mg (Fi) PLA	221 211	MEM > PLA: Behave-AD, <b>SIB</b> ; MEM = PLA: <b>CIBIC-Plus</b> , FAST, MENFIS
Caucasian: 91.3, others: 8.7	ADAS-cog: 27.3; MMSE: 17.3	MEM 20 mg (Fi) PLA	201 202	MEM > PLA: <b>ADAS-cog</b> , CIBIC-Plus, NPI12; MEM = PLA: ADCS-ADL23
Caucasian: 80.9; others: 19.1	MMSE: 10.1; SIB: 76.4	MEM 20 mg (Fi)	178	MEM = PLA: <b>ADCS-ADL19</b> , BGP, CIBIC-Plus, FAST, NPI12, <b>SIB</b>
Japanese: 100	MMSE: 16.1	MEM 20 mg (Fi) + DON (100%, NR) DON (100%, NR)	19	MEM + DON > DON: CDT, CGI-I, MMSE, NPII0, ZBI; MEM + DON = DON: NIRS (mean of all channels)
Caucasian: 94.1; others: 5.9	MMSE: 10.8; SIB: 76.0	MEM-ER 28 mg (Fi) + ChEls (DON [69%, 8.0 mg], GAL [21%, 13.5 mg], RIV [9%, 6.8 mg])	342	MEM (ER) + ChEIs > PLA + ChEIs: CIBIC-Plus, NPI12, SIB, VFT; MEM (ER) + ChEIs = PLA + ChEIs: ADCS-ADL19
		PLA + ChEls (DON [63%, 7.8 mg], GAL [20%, 13.5 mg], RIV [12%, 6.8 mg]) MEM 20 mg (Fi) + ChEls	335 182	MEM + ChEls = PLA + ChEls:
	Japanese: 100  Japanese: 100  Caucasian: 91.3, others: 8.7  Caucasian: 80.9; others: 19.1  Japanese: 100	function scales (mean ± SD)  Japanese: 100 MMSE: 10.1±3.0; SIB: 71.1±17.8  Japanese: 100 MMSE: 9.9±3.0; SIB: 71.0±17.9  Caucasian: 91.3, ADAS-cog: 27.3; others: 8.7 MMSE: 17.3  Caucasian: 80.9; others: 19.1 SIB: 76.4  Japanese: 100 MMSE: 16.1  Caucasian: 94.1; MMSE: 10.8;	Japanese: 100   MMSE: 10.1±3.0; SIB: 71.1±17.8   MEM 20 mg (Fi) MEM 10 mg (Fi) PLA     Japanese: 100   MMSE: 9.9±3.0; SIB: 71.0±17.9   PLA     Japanese: 100   MMSE: 9.9±3.0; MEM 20 mg (Fi) PLA     Caucasian: 91.3, others: 8.7   MMSE: 17.3   MEM 20 mg (Fi) PLA     Caucasian: 80.9; MMSE: 17.3   MEM 20 mg (Fi) PLA     Caucasian: 80.9; others: 19.1   SIB: 76.4   MEM 20 mg (Fi)     Japanese: 100   MMSE: 16.1   MEM 20 mg (Fi) + DON (100%, NR)     DON (100%, NR)   DON (100%, NR)     Caucasian: 94.1; others: 5.9   SIB: 76.0   MEM-ER 28 mg (Fi) + ChEls (DON [63%, 8.8 mg])     PLA + ChEls (DON [63%, 7.8 mg], GAL [20%, 13.5 mg]	Japanese: 100   MMSE: 10.1±3.0; SIB: 71.1±17.8   MEM 20 mg (Fi)   100   107   108

(Continued)

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Table I (Continued)

Study, country, sponsorship	Total (n)	Methods: I. Study design 2. Duration 3. Analyzed population	Patients 1. Diagnosis 2. Inclusion criteria 3. Study-defined disease severity 4. Mental disorder comorbidities 5. Concomitant drug	Age mean ± SD years	
Howard et al, <sup>18</sup> UK, nonindustry	295	I. DB-RCT 2. 52 weeks 3. OC	<ol> <li>I. AD, NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 5–13</li> <li>Moderate to severe</li> <li>NR</li> <li>NR</li> </ol>	77.1±8.4	
Nakamura et al, <sup>15</sup> Japan, industry	546	I. DB-RCT 2. 24 weeks 3. FAS	<ol> <li>AD, DSM-IV-TR, and NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE I-14, SIB 30-85</li> <li>Moderate to severe</li> <li>Exclusion: severe psychiatric disorder other than probable AD</li> <li>Not allowed concomitant use: AP, APD, CD, GAL, MR, NMDARI, RIV, S/H, TD; allowed concomitant drug use: BRO, ESZ, LOR, RAM, RIL, SUV, TIA, ZOP</li> </ol>	78.5	
Porsteinsson et al, <sup>25</sup> USA, industry	433	I. DB-RCT 2. 24 weeks 3. ITT	<ol> <li>AD, NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 10–22</li> <li>Mild to moderate</li> <li>Exclusion: psychiatric disorder other than probable AD</li> <li>NR</li> </ol>	75.4	
Tariot et al, <sup>26</sup> USA, industry	404	I. DB-RCT 2. 24 weeks 3. ITT	<ol> <li>AD, NINCDS-ADRDA</li> <li>Age ≥50 years, MMSE 5–14</li> <li>Moderate to severe</li> <li>Exclusion: psychiatric disorder other than probable AD</li> <li>Concomitant drug use: ACE 37.0%, ASC 19.4%, CAL 11.4%, GB 13.6%, MV 39.2%, PAR 14.1%, TOC 62.3%</li> </ol>	75.5	

Note: <sup>a</sup>Primary outcomes in each study are given in bold.

Abbreviations: AA, African-American; AAPD, atypical antipsychotic drugs; ACE, acetylsalicylic acid; AD, Alzheimer disease; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADD, antidepressant drugs; AE, antiepileptics; AH, antihypertensives; AI, anti-inflammatories; ANX, anxiolytics; APD, antipsychotic drugs; AP, anti-Parkinson; ASC, ascorbic acid; BADLS, Bristol Activities of Daily Living Scale; Behave-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; BGP, Behavioral Rating Scale for Geriatric Patients; BRO, brotizolam; CAL, calcium; CD, cholinergic drugs; CDT, clock drawing test; CGBRS, Crichton Geriatric Behavioral Rating Scale; CGI-I, Clinical Global Impression-Improvement scale; ChEI, cholinesterase inhibitors; CIBIC-Plus, Clinician's Interview-based Impression of Change Plus Caregiver Input; CMAI, Cohen-Mansfield Agitation Inventory; DB-RCT, double-blind randomized controlled trial; DON, donepezil; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; TR, Text Revision; ER, extended release; ESZ, eszopiclone; FAS, full analysis set; FAST, functional assessment staging instrument; Fi, fixed dose; GAL, galantamine; GB, Ginkgo biloba; GHQ-I2, General Health Questionnaire 12; GIN, ginseng; HDS-R, Hasegawa's Dementia Scale-Revision; ICD-I0, International Classification Of Diseases, 10th edition; ITT, intention to treat; LAX, laxatives; LOR, lormetazepam; MEM, memantine; MENFIS, Mental Function Impairment Scale; MMSE, mini-mental state examination; MR, muscle relaxant; MV, multi-vitamins; n, number of patients; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NIRS, near-infrared spectroscopy; NMDARI, N-methyl-D-aspartate receptor inhibitor; NPI, Neuropsychiatric Inventory; NR, not reported; OC, observed case; OLA, olanzapine; O-RCT, openlabel randomized controlled trial; PAR, parace

(Figures 7–12). The data for individual behavioral disturbances scores were simulated with no publication bias.

### Subgroup analysis divided by therapeutic strategy

We did not find considerable heterogeneity with respect to all meta-analysis (Figures 1–12). We also did not find any significant subgroup differences in all subgroup analysis.

Delusion was the outcome, where memantine was superior to control in the monotherapy subgroup and the combination therapy subgroup (Figure 2). Agitation/aggression

and disinhibition were the outcomes, where memantine was superior to control in the combination therapy subgroup but not in the monotherapy subgroup (Figures 1 and 3).

### Subgroup analysis divided by the severity of disease

We also did not find considerable heterogeneity with respect to all meta-analysis (Figures 1–12). We also did not find any significant subgroup differences in all subgroup analysis. Although we found marginally subgroup differences in subgroup analysis divided by the severity of disease with

Male (%)	Race (%)	Baseline cognitive function scales (mean ± SD)	Drug, dose (mg/day)	n	Efficacy outcomes <sup>a</sup>
35	Caucasian: 95; AA: 3; others: 2	MMSE: 9.1±2.6	MEM 20 mg (Fi) + DON (50%, 10 mg)	149	MEM + DON = PLA + DON: BADLS, DEMQOL-proxy,
			PLA + DON (50%, 10 mg)	146	GHQ-12, MMSE, NPI12
27.2	Japanese: 100	MMSE: 10.8; SIB: 77.0	MEM 20 mg (Fi) + DON (100%, 6.9 mg)	273	MEM + DON = PLA + DON: Behave-AD, CGBRS, <b>SIB</b>
			PLA + DON (100%, 6.9 mg)	273	
47.8	NR	ADAS-cog: 27.4; MMSE: 16.8	MEM 20 mg (Fi) + ChEls (DON [71%, 9.5 mg], GAL [14%, 19.7 mg], RIV [15%, 9.2 mg])	217	MEM + ChEIs = PLA + ChEIs:  ADAS-cog, CIBIC-Plus,  ADCS-ADL, NPI12, MMSE
			PLA + ChEls (DON [63%, 8.9 mg], GAL [16%, 19.4 mg], RIV [20%, 10.0 mg])	216	
35.0	Caucasian: 91.3; others: 8.7	MMSE: 10.0; SIB: 79.0	MEM 20 mg (Fi) + DON (100%, 9.3 mg)	203	$\begin{split} & MEM + DON > PLA + DON; \\ & \mathbf{ADCS\text{-}ADL},  BGP,  CIBIC\text{-Plus}, \end{split}$
			PLA + DON (100%, 9.5 mg)	201	NPI12, <b>SIB</b>

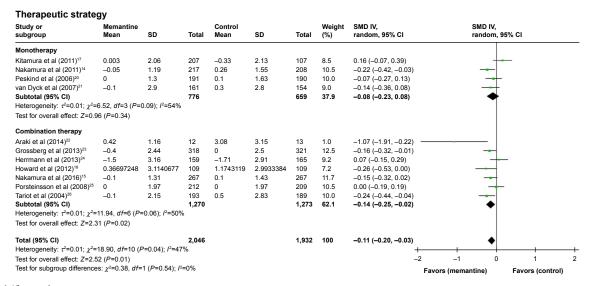


Figure I (Continued)

### Severity of disease Study or subgroup Memantine Mean Control Mean Weight (%) SMD IV, random, 95% CI SMD IV, random, 95% CI SD Total SD Total Mild-to-moderate Peskind et al (2006)20 1.3 1.97 191 212 0.1 1.63 190 10.0 -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) Porsteinsson et al (2008)25 0 209 10.5 0 1.97 Subtotal (95% CI) 403 399 20.5 -0.03 (-0.17, 0.11) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =0.23, df=1 (P=0.63); $I^2$ =0% Test for overall effect: Z=0.46 (P=0.65) Araki et al (2014)<sup>22</sup> Grossberg et al (2013)<sup>23</sup> 1.16 2.44 12 318 13 321 -1.07 (-1.91, -0.22) -0.16 (-0.32, -0.01) 0.42 3.08 3.15 1.0 2.5 12.5 -0.4 0 Herrmann et al (2013)<sup>24</sup> -1.5 3.16 159 109 -1.71 2.91 165 109 9.2 7.2 0.07 (-0.15, 0.29) -0.26 (-0.53, 0.00) Howard et al (2012)18 0.36697248 3.1140677 1.1743119 2.9933384 207 217 Kitamura et al (2011)17 0.003 2.06 -0.33 2.13 107 0.16 (-0.07, 0.39) -0.22 (-0.42, -0.03) Nakamura et al (2011)14 0.26 1.55 208 10.5 -0.051.19 Nakamura et al (2016)<sup>15</sup> -0.1 1.43 267 -0.15 (-0.32, 0.02) Tariot et al (2004)26 -0.1 2.15 193 0.5 2.83 189 10.0 -0.24 (-0.44, -0.04) -0.14 (-0.36, 0.08) van Dyck et al (2007)<sup>21</sup> -0.1 2.9 161 0.3 154 2.8 9.0 **Subtotal (95% CI)** Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =16.98, df=8 (P=0.03); $I^2$ =53% 1,643 1,533 79.5 -0.14 (-0.24, -0.03) Test for overall effect: Z=2.49 (P=0.01) Total (95% CI) 1,932 100 -0.11 (-0.20, -0.03) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =18.90, df=10 (P=0.04); $I^2$ =47% Test for overall effect: Z=2.52 (P=0.01) -1 Test for subgroup differences: $\chi^2$ =1.36, df=1 (P=0.24); $I^2$ =26.2% Favors (memantine) Favors (control)

 $\textbf{Figure I} \ \ \text{Forest plot of a gitation/aggression scores}.$ 

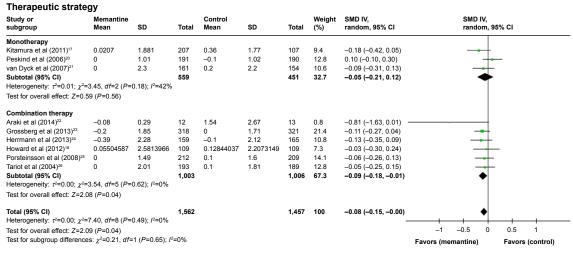
Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

Peskind et al $(2006)^{30}$	267 212 193 <b>1,270</b> 2,046	0.07 0.13 0.2 0.2 0.2 2.69 -0.1 -0.5 -0.11009174 0.1 -0.4 Control Mean	1.9 1.9 1.36 3 2.14 2.4 2.67 2.9006367 1.5 1.64 2.55	107 208 190 154 659 13 321 165 109 189 1,273 1,932 Total	7.2 10.8 9.7 8.0 35.7 16.3 8.3 5.6 10.8 9.8 64.3	-0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.23 (-0.43, -0.03) -0.12 (-0.35, 0.10) -0.17 (-0.28, -0.07)  Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.21) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)  -0.12 (-0.18, -0.06)  SMD IV, random, 95% CI	-0.5 -0.25 0 0.25 Favors (memantine) Favors (  SMD IV, random, 95% CI	+ 0.5 control
Nakamura et al (2011) <sup>14</sup> -0.15 1.68 Peskind et al (2006) <sup>20</sup> -0.1 1.27 van Dyck et al (2007) <sup>21</sup> -0.2 3.4 Subtotal (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =0.50, $d$ =3 ( $P$ =0.92); $I^2$ =0% Test for overall effect: $Z$ =3.23 ( $P$ =0.001) Combination therapy Araki et al (2014) <sup>22</sup> 0 0 Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Hermann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>16</sup> -0.1 1.16 Porsteinsson et al (2008) <sup>26</sup> -0.1 1.16 Porsteinsson et al (2008) <sup>26</sup> 0.2 2.02 Subtotal (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $d$ =5 ( $P$ =0.89); $I^2$ =0% Test for overall effect: $Z$ =2.20 ( $P$ =0.002) Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $d$ =9 ( $P$ =0.93); $I^2$ =0% Severity of disease Study or subgroup differences: $\chi^2$ =1.63, $d$ =1 ( $P$ =0.20); Severity of disease Positions of al (2008) <sup>26</sup> -0.1 1.4 Subgroup differences: $\chi^2$ =1.63, $d$ =1 ( $P$ =0.20); Distal et al (2006) <sup>20</sup> -0.1 1.27 Porsteinsson et al (2008) <sup>26</sup> -0.1 1.4 Subgroup differences: $\chi^2$ =1.63, $d$ =1 ( $P$ =0.11); $I^2$ =61% Test for overall effect: $Z$ =0.09 ( $P$ =0.33) Moderate-to-severe Araki et al (2014) <sup>22</sup> 0 0 0 Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Hermann et al (2011) <sup>23</sup> -0.42 6.85 4.85 Howard et al (2011) <sup>23</sup> -0.246 1.679	217 191 161 776 12 318 159 109 267 7212 193 1,270 2,046 Total	0.13 0.2 0.2 0.2 2.69 -0.1 -0.5 -0.11009174 0.1 0.4 Control Mean	1.9 1.36 3 2.14 2.4 2.67 2.9006367 1.5 1.64 2.55	208 190 154 659 13 321 165 109 267 209 189 1,273 1,932	10.8 9.7 8.0 35.7 16.3 8.3 5.6 13.6 10.8 9.8 64.3 100	-0.16 (-0.35, 0.03) -0.23 (-0.43, -0.03) -0.12 (-0.35, 0.10) -0.17 (-0.28, -0.07) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01) SMD IV, random, 95% CI	Favors (memantine) Favors (	
Peskind et al $(2006)^{90}$ —0.1 1.27 van Dyck et al $(2007)^{21}$ —0.2 3.4 Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =0.50, $df$ =3 ( $P$ =0.92); $I^2$ =0% Test for overall effect: $Z$ =3.23 ( $P$ =0.001)  Combination therapy  Araki et al $(2014)^{12}$ 0 0 0 Grossberg et al $(2013)^{23}$ —0.4 2.47 Hermann et al $(2013)^{24}$ —0.65 2.85 Howard et al $(2012)^{16}$ —0.27522936 2.956072* Nakamura et al $(2016)^{15}$ —0.1 1.16 Porsteinsson et al $(2008)^{25}$ —0.1 1.4 Tariot et al $(2004)^{26}$ —0.2 2.02 Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $df$ =5 ( $P$ =0.89); $I^2$ =0% Test for overall effect: $Z$ =2.20 ( $P$ =0.03)  Total (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $P$ =0.93); $I^2$ =0% Test for subgroup differences: $\chi^2$ =1.63, $df$ =1 ( $P$ =0.20);  Severity of disease  Study or subgroup differences: $\chi^2$ =1.63, $df$ =1 ( $P$ =0.20);  Severity of disease  Study or Subgroup differences: $\chi^2$ =1.63, $df$ =1 ( $P$ =0.21); $I^2$ =619 Test for overall effect: $I^2$ =0.01 1.27 Porsteinsson et al $I^2$ =0.08) $I^2$ =0.1 1.4 Subtotal (95% CI)  Heterogeneity: $I^2$ =0.02; $I^2$ =2.58, $I^2$ =1 ( $I^2$ =0.11); $I^2$ =619 Test for overall effect: $I^2$ =0.98 ( $I^2$ =0.33)  Moderate-to-severe  Araki et al $I^2$ =0.012 $I^2$ =0.04 2.47 Hermann et al $I^2$ =0.013 $I^2$ =0.246 2.956072* Kitamura et al $I^2$ =0.113 $I^2$ =0.246 2.956072* Kitamura et al $I^2$ =0.113 $I^2$ =0.246 2.956072* Kitamura et al $I^2$ =0.111 $I^2$ =0.246 1.679	191 161 776 12 318 159 109 267 212 193 1,270 2,046 Total	0.2 0.2 0.2 2.69 -0.1 -0.5 -0.11009174 0.1 -0.1 0.4 Control Mean	1.36 3 2.14 2.4 2.67 2.9006367 1.5 1.64 2.55	190 154 659 13 321 165 109 189 1,273 1,932	9.7 8.0 35.7 16.3 8.3 5.6 10.8 9.8 64.3	-0.23 (-0.43, -0.03) -0.12 (-0.35, 0.10) -0.17 (-0.28, -0.07)  Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)	Favors (memantine) Favors (	
van Dyck et al. (2007) <sup>21</sup>	161 776 12 318 159 109 267 212 193 1,270 2,046 Total	0.2  2.69 -0.1 -0.5 -0.11009174 0.1 -0.1 0.4  Control Mean	3 2.14 2.4 2.67 2.9006367 1.5 1.64 2.55	154 659 13 321 165 109 267 289 1,273 1,932	8.0 35.7 16.3 8.3 5.6 10.8 9.8 64.3 100	-0.12 (-0.35, 0.10) -0.17 (-0.28, -0.07)  Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.22) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)	Favors (memantine) Favors (	
Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =0.50, $dr$ =3 ( $P$ =0.92); $I^2$ =0%  Test for overall effect: $Z$ =3.23 ( $P$ =0.001)  Combination therapy  Araki et al (2014) <sup>22</sup> 0 0  Grossberg et al (2013) <sup>23</sup> -0.4 2.47  Hermann et al (2013) <sup>24</sup> -0.65 2.85  Howard et al (2013) <sup>25</sup> -0.1 1.16  Porsteinson et al (2008) <sup>26</sup> -0.1 1.4  Tariot et al (2004) <sup>26</sup> 0.2 2.02  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $dr$ =5 ( $P$ =0.89); $P$ =0%  Test for overall effect: $Z$ =2.20 ( $P$ =0.03)  Total (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.63, $dr$ =9 ( $P$ =0.93); $P$ =0%  Severity of disease  Study or subtomation when so D  Mild-to-moderate  Peskind et al (2006) <sup>26</sup> -0.1 1.27  Porsteinsson et al (2008) <sup>26</sup> -0.1 1.4  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $dr$ =1 ( $P$ =0.11); $P$ =619  Test for overall effect: $Z$ =0.98 ( $P$ =0.33)  Mid-to-moderate  Peskind et al (2008) <sup>26</sup> -0.1 1.4  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $dr$ =1 ( $P$ =0.11); $P$ =619  Test for overall effect: $Z$ =0.98 ( $P$ =0.33)  Moderate-to-severe  Araki et al (2014) <sup>22</sup> 0 0 0  Grossberg et al (2013) <sup>24</sup> -0.4 2.47  Hermann et al (2013) <sup>24</sup> -0.65 2.85  Howard et al (2011) <sup>27</sup> -0.27522936 2.956072:  Kitamura et al (2011) <sup>17</sup> -0.246 1.679	12 318 159 109 267 212 193 1,270 2,046 Total	2.69 -0.1 -0.5 -0.11009174 0.1 -0.1 0.4	2.14 2.4 2.67 2.9006367 1.5 1.64 2.55	13 321 165 109 267 209 1,273 1,932	16.3 8.3 5.6 13.6 10.8 9.8 64.3 100 Weight (%)	-0.17 (-0.28, -0.07)  Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)  -0.12 (-0.18, -0.06)  SMD IV, random, 95% CI	Favors (memantine) Favors (	
Heterogeneity: $r^2$ =0.00; $\chi^2$ =0.50, $df$ =3 ( $P$ =0.92); $I^2$ =0% Test for overall effect: $Z$ =3.23 ( $P$ =0.001)  Combination therapy  Araki et al (2014) $^{32}$ 0 0 0  Grossberg et al (2013) $^{33}$ -0.4 2.47  Herrmann et al (2013) $^{34}$ -0.65 2.85  Nakamura et al (2016) $^{15}$ -0.1 1.16  Porsteinsson et al (2008) $^{35}$ -0.1 1.4  Tariot et al (2004) $^{30}$ 0.2 2.02  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $df$ =5 ( $P$ =0.89); $I^2$ =0%  Test for overall effect: $Z$ =2.20 ( $P$ =0.03)  Total (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $P$ =0.93); $I^2$ =0%  Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Test for overall effect: $Z$ =0.11, $Z$ =0%  Mild-to-moderate  Peskind et al (2008) $Z$ =0.1 1.27  Porsteinsson et al (2008) $Z$ =0.1 1.4  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.02; $Z$ =2.58, $Z$ =1.61 ( $Z$ =0.11); $Z$ =619  Test for overall effect: $Z$ =0.98 ( $Z$ =0.33)  Moderate-to-severe  Araki et al (2014) $Z$ =0 0 0  Grossberg et al (2013) $Z$ =0.4 2.47  Herrmann et al (2012) $Z$ =0.27522936 2.956072:  Kitamura et al (2011) $Z$ =0.246 1.679	12 318 159 109 267 212 193 1,270 2,046 Total	-0.1 -0.5 -0.11009174 0.1 -0.1 0.4	2.4 2.67 2.9006367 1.5 1.64 2.55	13 321 165 109 267 209 189 1,273 1,932	16.3 8.3 5.6 13.6 10.8 9.8 <b>64.3</b>	Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)  SMD IV, random, 95% C1	Favors (memantine) Favors (	
Test for overall effect: Z=3.23 (P=0.001)  Combination therapy  Araki et al (2014) <sup>22</sup> 0 0 0  Grossberg et al (2013) <sup>23</sup> -0.45 2.85  Howard et al (2012) <sup>18</sup> -0.27522936 2.956072*  Nakamura et al (2016) <sup>18</sup> -0.1 1.16  Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4  Tariot et al (2004) <sup>26</sup> 0.2 2.02  Subtotal (95% CI)  Heterogeneity: τ²=0.00; χ²=1.65, df=5 (P=0.89); l²=0%  Test for overall effect: Z=2.20 (P=0.03)  Total (95% CI)  Heterogeneity: τ²=0.00; χ²=3.78, df=9 (P=0.93); l²=0%  Test for overall effect: Z=3.70 (P=0.0002)  Test for subgroup differences: χ²=1.63, df=1 (P=0.20);  Severity of disease  Study or Memantine  Wild-to-moderate  Peskind et al (2008) <sup>20</sup> -0.1 1.27  Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4  Subtotal (95% CI)  Heterogeneity: τ²=0.02; χ²=2.58, df=1 (P=0.11); l²=61%  Test for overall effect: Z=0.98 (P=0.33)  Moderate-to-severe  Araki et al (2014) <sup>22</sup> 0 0  Grossberg et al (2013) <sup>23</sup> -0.4 2.47  Hermann et al (2013) <sup>24</sup> -0.65 2.85  Howard et al (2012) <sup>18</sup> -0.27522936 2.956072*  Kitamura et al (2011) <sup>17</sup> -0.246 1.679  Kitamura et al (2011) <sup>17</sup> -0.246 1.679	318 159 109 267 212 193 <b>1,270</b> <b>2,046</b> Total	-0.1 -0.5 -0.11009174 0.1 -0.1 0.4	2.4 2.67 2.9006367 1.5 1.64 2.55	321 165 109 267 209 189 1,273 1,932	8.3 5.6 13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.29, 0.11) -0.12 (-0.18, -0.06)	Favors (memantine) Favors (	
Combination therapy  Araki et al. (2014) <sup>22</sup> 0 0  Grossberg et al. (2013) <sup>33</sup> -0.4 2.47  Herrmann et al. (2013) <sup>34</sup> -0.65 2.85  Howard et al. (2013) <sup>34</sup> -0.65 2.85  Howard et al. (2012) <sup>36</sup> -0.1 1.16  Porsteinsson et al. (2008) <sup>35</sup> -0.1 1.4  Tariot et al. (2004) <sup>36</sup> 0.2 2.02  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $d$ =5 ( $P$ =0.89); $P$ =0%  Test for overall effect: $Z$ =2.20 ( $P$ =0.03)  Total (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $d$ =9 ( $P$ =0.93); $P$ =0%  Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Severity of disease  Study or subgroup differences: $\chi^2$ =1.63, $d$ =1 ( $P$ =0.20);  Severity of disease  Peskind et al. (2006) <sup>30</sup> -0.1 1.27  Porsteinsson et al. (2008) <sup>35</sup> -0.1 1.4  Subtotal (95% CI)  Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $d$ =1 ( $P$ =0.11); $P$ =619  Test for overall effect: $Z$ =0.98 ( $P$ =0.33)  Moderate-to-severe  Araki et al. (2014) <sup>22</sup> 0 0  Grossberg et al. (2013) <sup>34</sup> -0.4 2.47  Hermann et al. (2013) <sup>34</sup> -0.45 2.85  Howard et al. (2012) <sup>48</sup> -0.65 2.85  Howard et al. (2012) <sup>49</sup> -0.27522936 2.956072*  Kitamura et al. (2011) <sup>17</sup> -0.246 1.679	318 159 109 267 212 193 <b>1,270</b> <b>2,046</b> Total	-0.1 -0.5 -0.11009174 0.1 -0.1 0.4	2.4 2.67 2.9006367 1.5 1.64 2.55	321 165 109 267 209 189 1,273 1,932	8.3 5.6 13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.29, 0.11) -0.12 (-0.18, -0.06)	Favors (memantine) Favors (	
Araki et al $(2014)^{12}$ 0 0 0 Grossberg et al $(2013)^{13}$ 0.4 2.47 Herrmann et al $(2013)^{13}$ 0.65 2.85 Howard et al $(2013)^{13}$ 0.27522936 2.956072: Alakamura et al $(2016)^{15}$ 0.1 1.16 Porsteinsson et al $(2008)^{25}$ 0.1 1.4 Tariot et al $(2004)^{25}$ 0.2 2.02 Subtotal (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $d$ =5 ( $P$ =0.89); $I^2$ =0% Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $d$ =9 ( $P$ =0.93); $I^2$ =0% Total (95% CI) Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $d$ =9 ( $P$ =0.93); $I^2$ =0% Severity of disease Study or subgroup differences: $\chi^2$ =1.63, $d$ =1 ( $P$ =0.20); Severity of disease Study or subgroup $\frac{1}{2}$ 0.1 1.27 Porsteinsson et al $(2008)^{20}$ 0.1 1.4 Subtotal (95% CI) Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $d$ =1 ( $P$ =0.11); $I^2$ =619; Test for overall effect: $Z$ =0.98 ( $P$ =0.33) Moderate-to-severe Araki et al $(2014)^{12}$ 0 0 Grossberg et al $(2013)^{13}$ 0.4 2.47 Herrmann et al $(2012)^{18}$ 0.65 2.85 Howard et al $(2012)^{18}$ 0.27522936 2.956072: Kitamura et al $(2011)^{17}$ 0.246 1.679	318 159 109 267 212 193 <b>1,270</b> <b>2,046</b> Total	-0.1 -0.5 -0.11009174 0.1 -0.1 0.4	2.4 2.67 2.9006367 1.5 1.64 2.55	321 165 109 267 209 189 1,273 1,932	8.3 5.6 13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.29, 0.11) -0.12 (-0.18, -0.06)	Favors (memantine) Favors (	
Grossberg et al (2013) <sup>33</sup> -0.4 2.47 -0.65 2.85 -0.65 2.85 -0.65 2.85 -0.672 -0.65 2.85 -0.672 -0.65 2.85 -0.672 -0.65 2.85 -0.672 -0.72 -0.7	318 159 109 267 212 193 <b>1,270</b> <b>2,046</b> Total	-0.1 -0.5 -0.11009174 0.1 -0.1 0.4	2.4 2.67 2.9006367 1.5 1.64 2.55	321 165 109 267 209 189 1,273 1,932	8.3 5.6 13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.29, 0.11) -0.12 (-0.18, -0.06)	Favors (memantine) Favors (	
Herrmann et al (2013) <sup>24</sup> -0.65 2.85 -0.27522936 2.955072*   Howard et al (2012) <sup>18</sup> -0.1 1.16   Porsteinsson et al (2016) <sup>18</sup> -0.1 1.4   Tariot et al (2024) <sup>28</sup> 0.2 2.02   Subtotal (95% CI)   Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $df$ =5 ( $F$ =0.89); $I^2$ =0%   Total (95% CI)   Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $df$ =5 ( $F$ =0.93); $I^2$ =0%   Total (95% CI)   Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $F$ =0.93); $I^2$ =0%   Total (95% CI)   Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $F$ =0.93); $I^2$ =0%   Total (95% CI)   Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $F$ =0.02);  Severity of disease   Study or   Severity of disease   Study or   Subgroup   Memantine   SD  Mild-to-moderate   Peskind et al (2006) <sup>20</sup> -0.1 1.27   Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4   Subtotal (95% CI)   Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $df$ =1 ( $F$ =0.11); $I^2$ =61%   Test for overall effect: $Z^2$ -0.98 ( $F^2$ -0.33)   Moderate-to-sever   Araki et al (2014) <sup>22</sup> 0 0 0   Grossberg et al (2013) <sup>23</sup> -0.4 2.47   Herrmann et al (2013) <sup>24</sup> -0.65 2.85   Howard et al (2012) <sup>18</sup> -0.27522936 2.956072:   Kitamura et al (2011) <sup>17</sup> -0.246 1.679	159 109 267 212 193 <b>1,270</b> <b>2,046</b> **Total	-0.5 -0.11009174 0.1 -0.1 0.4 Control Mean	2.67 2.9006367 1.5 1.64 2.55	165 109 267 209 189 1,273 1,932	8.3 5.6 13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01) -0.12 (-0.18, -0.06)	Favors (memantine) Favors (	
Howard et al $(2012)^{16}$	109 267 212 193 <b>1,270</b> <b>2,046</b> ************************************	-0.11009174 0.1 -0.1 0.4 Control Mean	2.9006367 1.5 1.64 2.55	109 267 209 189 1,273 1,932	5.6 13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.06 (-0.32, 0.21) -0.15 (-0.32, 0.02) -0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)  -0.12 (-0.18, -0.06)  SMD IV, random, 95% CI	Favors (memantine) Favors (	
Nakamura et al (2016) <sup>15</sup> -0.1 1.16 Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4 Traito et al (2004) <sup>26</sup> 0.2 2.02 Subtotal (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $dr$ =5 ( $P$ =0.89); $I^2$ =0% Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $dr$ =9 ( $P$ =0.93); $I^2$ =0% Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $dr$ =9 ( $P$ =0.93); $I^2$ =0% Total (95% CI) Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $dr$ =9 ( $P$ =0.93); $I^2$ =0% Test for overall effect: $Z$ =3.70 ( $P$ =0.0002) Test for subgroup differences: $\chi^2$ =1.63, $dr$ =1 ( $P$ =0.20);  Severity of disease Study or Memantine SD  Mild-to-moderate Peskind et al (2006) <sup>20</sup> -0.1 1.27 Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4 Subtotal (95% CI) Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $dr$ =1 ( $P$ =0.11); $I^2$ =619 Test for overall effect: $Z$ =0.98 ( $P$ =0.33)  Moderate-to-severe Araki et al (2014) <sup>22</sup> 0 0 Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>18</sup> -0.27522936 2.956072: Kitamura et al (2011) <sup>17</sup> -0.246 1.679	267 212 193 <b>1,270</b> <b>2,046</b> **2=38.6% Total	0.1 -0.1 0.4 Control Mean	1.5 1.64 2.55	267 209 189 1,273 1,932	13.6 10.8 9.8 <b>64.3</b> 100 Weight (%)	-0.15 (-0.32, 0.02) 0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01)  -0.12 (-0.18, -0.06)  SMD IV, random, 95% CI	Favors (memantine) Favors (	
Porsteinsson et al $(2008)^{26}$	212 193 <b>1,270</b> <b>2,046</b> Total	Control Mean	1.64 2.55 SD	209 189 1,273 1,932 Total	10.8 9.8 64.3 100 Weight (%)	0.00 (-0.19, 0.19) -0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01) -0.12 (-0.18, -0.06) SMD IV, random, 95% Cl	Favors (memantine) Favors (	
Tariot et al (2004) <sup>26</sup> 0.2 2.02 Subtotal (95% CI) Heterogeneity: $t^2$ =0.00; $\chi^2$ =1.65, $d$ =5 ( $P$ =0.89); $l^2$ =0% Total (95% CI) Heterogeneity: $t^2$ =0.00; $\chi^2$ =3.78, $d$ =9 ( $P$ =0.93); $l^2$ =0% Total (95% CI) Heterogeneity: $t^2$ =0.00; $\chi^2$ =3.78, $d$ =9 ( $P$ =0.93); $l^2$ =0% Total (95% CI) Test for overall effect: $Z$ =3.70 ( $P$ =0.0002) Test for subgroup differences: $\chi^2$ =1.63, $d$ f=1 ( $P$ =0.20); Severity of disease Study or Memantine Mean SD  Mild-to-moderate Peskind et al (2006) <sup>20</sup> -0.1 1.27 Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4 Subtotal (95% CI) Heterogeneity: $t^2$ =0.02; $\chi^2$ =2.58, $d$ f=1 ( $P$ =0.11); $l^2$ =619 Test for overall effect: $Z$ =0.98 ( $P$ =0.33)  Moderate-to-severe Araki et al (2014) <sup>22</sup> 0 0 0 Grossberg et al (2013) <sup>24</sup> -0.4 2.47 Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>16</sup> -0.27522936 2.956072: Kitamura et al (2011) <sup>17</sup> -0.246 1.679	193 1,270 2,046 2=38.6% Total	Control Mean	2.55 SD	189 1,273 1,932 Total	9.8 64.3 100 Weight (%)	-0.09 (-0.29, 0.11) -0.09 (-0.17, -0.01) -0.12 (-0.18, -0.06) SMD IV, random, 95% CI	Favors (memantine) Favors (	
Subtotal (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $dr$ =5 ( $P$ =0.89); $I^2$ =0% Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $dr$ =9 ( $P$ =0.93); $I^2$ =0% Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $dr$ =9 ( $P$ =0.93); $I^2$ =0% Test for overall effect: $Z$ =3.70 ( $P$ =0.0002) Test for overall effect: $Z$ =3.70 ( $P$ =0.0002)  Severity of disease Study or Subgroup Memantine Mean SD  Mild-to-moderate Peskind et al (2006) <sup>20</sup> -0.1 1.27 Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4 Subtotal (95% CI) Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $dr$ =1 ( $P$ =0.11); $I^2$ =619 Test for overall effect: $Z$ =0.98 ( $P$ =0.33) Moderate-to-sever  Araki et al (2014) <sup>22</sup> 0 0 Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>16</sup> -0.27522936 2.956072: Kitamura et al (2011) <sup>17</sup> -0.246 1.679	1,270 2,046 2=38.6% Total	Control Mean	<b>SD</b>	1,273 1,932 Total	64.3 100 Weight (%)	-0.09 (-0.17, -0.01) -0.12 (-0.18, -0.06) SMD IV, random, 95% CI	Favors (memantine) Favors (	
Heterogeneity: $r^2$ =0.00; $\chi^2$ =1.65, $df$ =5 ( $P$ =0.89); $I^2$ =0% Test for overall effect: Z=2.20 ( $P$ =0.03)  Total (95% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $P$ =0.93); $I^2$ =0% Test for overall effect: Z=3.70 ( $P$ =0.0002) Test for subgroup differences: $\chi^2$ =1.63, $df$ =1 ( $P$ =0.20);  Severity of disease  Study or Memantine Subgroup Mean SD  Mild-to-moderate Peskind et al (2006) $^{30}$ -0.1 1.27 Porsteinsson et al (2008) $^{30}$ -0.1 1.4  Subtotal (95% CI) Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $df$ =1 ( $P$ =0.11); $I^2$ =61% Test for overall effect: Z=0.98 ( $P$ =0.33)  Moderate-to-sever Araki et al (2014) $^{32}$ -0.4 2.47 Hermann et al (2013) $^{34}$ -0.65 2.85 Howard et al (2012) $^{40}$ -0.27522936 2.956072:  Kitamura et al (2011) $^{17}$ -0.246 1.679	2,046  2-38.6%  Total	Control Mean	1.36	1,932 Total	100 Weight (%)	-0.12 (-0.18, -0.06) SMD IV, random, 95% Cl	Favors (memantine) Favors (	
Test for overall effect: $Z=2.20$ ( $P=0.03$ )  Total (95% CI)  Heterogeneity: $z^2=0.00$ ; $\chi^2=3.78$ , $df=9$ ( $P=0.93$ ); $l^2=0\%$ Test for overall effect: $Z=3.70$ ( $P=0.0002$ )  Test for subgroup differences: $\chi^2=1.63$ , $df=1$ ( $P=0.20$ );  Severity of disease  Study or Memantine Mean SD  Mild-to-moderate  Peskind et al $(2006)^{20}$ — 0.1 1.27  Porsteinsson et al $(2008)^{25}$ — 0.1 1.4  Subtotal (95% CI)  Heterogeneity: $z^2=0.02$ ; $\chi^2=2.58$ , $df=1$ ( $P=0.11$ ); $l^2=61$ 9  Test for overall effect: $Z=0.98$ ( $P=0.33$ )  Moderate-to-severe  Araki et al $(2014)^{22}$ 0 0  Grossberg et al $(2013)^{24}$ — 0.4 2.47  Herrmann et al $(2012)^{16}$ — 0.65 2.85  Howard et al $(2012)^{16}$ — 0.27522936 2.956072:  Kitamura et al $(2011)^{17}$ — 0.246 1.679	<sup>12</sup> =38.6% <b>Total</b> 191	Mean 0.2	1.36	Total	Weight (%)	SMD IV, random, 95% CI	Favors (memantine) Favors (	
Heterogeneity: $r^2$ =0.00; $\chi^2$ =3.78, $d$ f=9 ( $P$ =0.93); $I^2$ =0% Test for overall effect: $Z$ =3.70 ( $P$ =0.0002) Test for subgroup differences: $\chi^2$ =1.63, $d$ f=1 ( $P$ =0.20); Severity of disease Study or Memantine Subgroup Memantine Subgroup Memantine Subgroup Nild-to-moderate Peskind et al ( $2006$ ) <sup>20</sup> -0.1 1.27 Porsteinsson et al ( $2008$ ) <sup>25</sup> -0.1 1.4 Subtotal (95% CI) Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $d$ f=1 ( $P$ =0.11); $I^2$ =61% Test for overall effect: $Z$ =0.98 ( $P$ =0.33) Moderate-to-severe Araki et al ( $2014$ ) <sup>22</sup> 0 0 Grossberg et al ( $2013$ ) <sup>23</sup> -0.4 2.47 Herrmann et al ( $2013$ ) <sup>24</sup> -0.5 2.85 Howard et al ( $2012$ ) <sup>26</sup> -0.27522936 2.956072: Kitamura et al ( $2011$ )17 -0.246 1.679	<sup>12</sup> =38.6% <b>Total</b> 191	Mean 0.2	1.36	Total	Weight (%)	SMD IV, random, 95% CI	Favors (memantine) Favors (	
Test for overall effect: Z=3.70 ( $P$ =0.0002) Test for overall effect: Z=3.70 ( $P$ =0.0002) Test for subgroup differences: $\chi^2$ =1.63, $df$ =1 ( $P$ =0.20);  Severity of disease  Study or Memantine SD  Mild-to-moderate Peskind et al (2006) <sup>20</sup> -0.1 1.27 Porsteinsson et al (2008) <sup>25</sup> -0.1 1.4  Subtotal (95% CI) Helterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $df$ =1 ( $P$ =0.11); $f^2$ =619 Test for overall effect: Z=0.98 ( $P$ =0.33)  Moderate-to-severe Araki et al (2014) <sup>22</sup> 0 0 Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>18</sup> -0.27522936 2.956072: Kitamura et al (2011) <sup>17</sup> -0.246 1.679	Total	Mean 0.2	1.36	190	9.7	random, 95% CI	Favors (memantine) Favors (	
Mild-to-moderate         1.27           Peskind et al (2006) <sup>20</sup> −0.1 1.4         1.27           Porsteinsson et al (2008) <sup>25</sup> −0.1 1.4         1.4           Subtotal (95% Ci)         1.4           Heterogeneity: $r^2$ =0.02; $\chi^2$ =2.58, $df$ =1 ( $P$ =0.11); $I^2$ =61%           Test for overall effect: $Z$ =0.98 ( $P$ =0.33)           Moderate-to-severe           Araki et al (2014) <sup>22</sup> 0 0 0           Grossberg et al (2013) <sup>23</sup> −0.4 2.47           Herrmann et al (2013) <sup>34</sup> −0.65 2.85           Howard et al (2012) <sup>18</sup> −0.27522936 2.956072°           Kitamura et al (2011) <sup>17</sup> −0.246 1.679	191	0.2	1.36	190	9.7	<u> </u>		
Peskind et al $(2006)^{30}$ -0.1 1.27 Porsteinsson et al $(2008)^{26}$ -0.1 1.4 Subtotal (95% C1)   Heterogeneity: $t^2$ =0.02; $\chi^2$ =2.58, $d$ f=1 ( $P$ =0.11); $l^2$ =61% Test for overall effect: $Z$ =0.98 ( $P$ =0.33)   Moderate-to-severe   Araki et al $(2014)^{22}$ 0 0 0 Grossberg et al $(2013)^{23}$ -0.4 2.47 Herrmann et al $(2013)^{24}$ -0.65 2.85 (Howard et al $(2012)^{18}$ -0.27522936 2.956072: Kitamura et al $(2011)^{17}$ -0.246 1.679						-0.23 (-0.43, -0.03)		
Porsteinsson et al (2008) <sup>25</sup>						0.20 ( 0.40, 0.00)		
Subtotal (95% CI)           Heterogeneity: r²=0.02; χ²=2.58, df=1 (P=0.11); l²=61%           Test for overall effect: Z=0.98 (P=0.33)           Moderate-to-severe           Araki et al (2014)²²         0         0           Grossberg et al (2013)²³         −0.4         2.47           Herrmann et al (2012)¹³         −0.6         2.85           Howard et al (2012)¹³         −0.27522936         2.956072²           Kitamura et al (2011)¹¹         −0.246         1.679	212	-0.1	1.04		10.8	0.00 (-0.19, 0.19)		
Test for overall effect: Z=0.98 (P=0.33)  Moderate-to-severe  Araki et al (2014) <sup>22</sup> 0 0  Grossberg et al (2013) <sup>23</sup> -0.4 2.47  Herrmann et al (2013) <sup>24</sup> -0.65 2.85  Howard et al (2012) <sup>18</sup> -0.27522936 2.956072 <sup>2</sup> Kitamura et al (2011) <sup>17</sup> -0.246 1.679	403			399	20.4	-0.11 (-0.33, 0.11)		
Araki et al (2014) <sup>22</sup> 0 0 0 Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>18</sup> -0.27522936 2.956072 <sup>-1</sup> Kitamura et al (2011) <sup>17</sup> -0.246 1.679	5							
Grossberg et al (2013) <sup>23</sup> -0.4 2.47 Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>16</sup> -0.27522936 2.956072 <sup>2</sup> Kitamura et al (2011) <sup>17</sup> -0.246 1.679								
Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>18</sup> -0.27522936 2.956072 <sup>-1</sup> Kitamura et al (2011) <sup>17</sup> -0.246 1.679	12	2.69	2.14	13		Not estimable		
Herrmann et al (2013) <sup>24</sup> -0.65 2.85 Howard et al (2012) <sup>18</sup> -0.27522936 2.956072 <sup>2</sup> Kitamura et al (2011) <sup>17</sup> -0.246 1.679	318	-0.1	2.4	321	16.3	-0.12 (-0.28, 0.03)		
Kitamura et al (2011) <sup>17</sup> –0.246 1.679	159	-0.5	2.67	165	8.3	-0.05 (-0.27, 0.16)		
Kitamura et al (2011) <sup>17</sup> -0.246 1.679	109	-0.11009174	2.9006367	109	5.6	-0.06 (-0.32, 0.21)	<del></del>	
	207	0.07	1.9	107	7.2	-0.18 (-0.41, 0.05)		
Nakamura et al (2011) <sup>14</sup> -0.15 1.68	217	0.13	1.9	208	10.8	-0.16 (-0.35, 0.03)		
Nakamura et al (2016) <sup>15</sup> –0.1 1.16	267	0.1	1.5	267	13.6	-0.15 (-0.32, 0.02)		
Tariot et al (2004) <sup>26</sup> 0.2 2.02	193	0.4	2.55	189	9.8	-0.09 (-0.29, 0.11)		
van Dyck et al (2007) <sup>21</sup> –0.2 3.4	161	0.2	3	154	8.0	-0.12 (-0.35, 0.10)		
Subtotal (95% CI)	1,643			1,533	79.6	-0.12 (-0.19, -0.05)	•	
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =1.18, $df$ =7 ( $P$ =0.99); $I^2$ =0%	,			,		(,)	•	
Test for overall effect: $Z=3.37$ ( $P=0.0007$ )								
Total (95% CI)				1,932	100	-0.12 (-0.18, -0.06)		
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =3.78, $df$ =9 ( $P$ =0.93); $I^2$ =0% [Fest for overall effect: $Z$ =3.70 ( $P$ =0.0002)	2,046						•	

Figure 2 Forest plot of delusion scores.

Favors (memantine)

Favors (control)



### Severity of disease SMD IV, SMD IV, Study or Memantine Control Weight random. 95% CI random. 95% CI subgroup Mean SD Total Mean SD Total (%) Mild-to-moderate Peskind et al (2006)2 1.01 191 -0.1 1.02 190 12.8 0.10 (-0.10, 0.30) 1.49 212 0.1 209 -0.06 (-0.26, 0.13) Porsteinsson et al (2008)25 1.6 **Subtotal (95% CI)** Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =1.33, df=1 (P=0.25); $I^2$ =25% 403 399 26.9 0.01 (-0.15, 0.17) Test for overall effect: Z=0.17 (P=0.87) Moderate-to-severe Araki et al (2014)22 -0.81 (-1.63, 0.01) 12 2.67 13 -0.080.29 1.54 0.8 Grossberg et al (2013)23 1.85 318 21.4 -0.11 (-0.27, 0.04) -0.39 -0.1 165 Herrmann et al (2013)24 2.28 159 2.12 10.8 -0.13 (-0.35, 0.09) Howard et al (2012)18 0.05504587 2.5813966 109 0.12844037 2.2073149 109 7.3 -0.03 (-0.30, 0.24) 207 193 Kitamura et al (2011)11 0.0207 1.881 0.36 1.77 107 9.4 -0.18 (-0.42, 0.05) Tariot et al (2004)<sup>26</sup> 12.8 2.01 189 -0.05 (-0.25, 0.15) 0 0.1 1.81 van Dyck et al (2007)<sup>21</sup> Subtotal (95% CI) 161 **1,159** -0.09 (-0.31, 0.13) -0.11 (-0.19, -0.03) 2.3 0.2 2.2 154 10.6 Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =3.89, df=6 (P=0.69); $I^2$ =0% Test for overall effect: Z=2.55 (P=0.01) Total (95% CI) 1.457 100 -0.08 (-0.15, -0.00) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =7.40, df=8 (P=0.49); $I^2$ =0% 0.5 Test for overall effect: Z=2.09 (P=0.04) -0.5

Figure 3 Forest plot of disinhibition scores.

Test for subgroup differences:  $\chi^2$ =1.79, df=1 (P=0.18);  $I^2$ =44.3%

Therapeutic strate	gy												
Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI			ID IV, ndom, 98	5% CI	
Monotherapy													
Nakamura et al (2011)14	0	0.53	217	0.06	0.61	208	11.7	-0.10 (-0.30, 0.09)			-	_	
Peskind et al (2006)20	0.1	1.05	191	0.2	1.25	190	10.9	-0.09 (-0.29, 0.11)			•	_	
van Dyck et al (2007)21	-0.2	3.1	161	-0.1	2.9	154	9.6	-0.03 (-0.25, 0.19)					
Subtotal (95% CI)			569			552	32.2	-0.08 (-0.20, 0.04)		-			
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =	0.24, df=2 (P=	0.89); /2=0%											
Test for overall effect: Z=1.3	31 (P=0.19)												
Combination therapy													
Grossberg et al (2013)23	-0.5	2.67	317	0.1	2.83	321	14.8	-0.22 (-0.37, -0.06)			_		
Herrmann et al (2013)24	-0.36	3.19	159	-0.12	3.11	165	9.8	-0.08 (-0.29, 0.14)			•		
Howard et al (2012)18	0.09174312	3.5159459	109	0.83486239	3.9639901	109	7.3	-0.20 (-0.46, 0.07)	_	•	_	-	
Nakamura et al (2016) <sup>15</sup>	-0.1	0.57	267	0	0.6	267	13.4	-0.17 (-0.34, -0.00)					
Porsteinsson et al (2008)25	0.4	2.32	212	0	2.05	209	11.6	0.18 (-0.01, 0.37)			+		
Tariot et al (2004)26	0.2	2.57	193	0.6	2.48	189	10.9	-0.16 (-0.36, 0.04)			-+		
Subtotal (95% CI)			1,257			1,260	67.8	-0.11 (-0.23, 0.02)					
Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =	12.01, df=5 (P	=0.03); I <sup>2</sup> =589	%										
Test for overall effect: Z=1.6	88 (P=0.09)												
Total (95% CI)			1,826			1,812	100	-0.10 (-0.18, -0.02)		<	<b>►</b>		
Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =	12.47, df=8 (P	=0.13); I <sup>2</sup> =369	%						+		_		
Test for overall effect: Z=2.3	33 (P=0.02)								-0.5	-0.25	0	0.25	0.
Test for subgroup difference	es: $\chi^2$ =0.10, df=	=1 (P=0.75); I <sup>2</sup>	2=0%						Favo	rs (memantin	ie)	Favors (contr	ol)

Figure 4 (Continued)

### Severity of disease Study or subgroup SMD IV, random, 95% CI SMD IV, random, 95% CI Control Mean Total SD Total (%) Mild-to-moderate Peskind et al (2006)20 1.05 2.32 191 0.2 1.25 2.05 190 10.9 -0.09 (-0.29, 0.11) 0.18 (-0.01, 0.37) Porsteinsson et al (2008)<sup>25</sup> 209 11.6 212 0.4 0 Subtotal (95% CI) Heterogeneity: $\tau^2$ =0.03; $\chi^2$ =3.60, df=1 (P=0.06); $I^2$ =72% 403 399 22.5 0.05 (-0.21, 0.31) Test for overall effect: Z=0.37 (P=0.71) Moderate-to-severe Grossberg et al (2013)<sup>23</sup> Herrmann et al (2013)<sup>24</sup> 0.1 -0.12 321 165 -0.52.67 317 2.83 14.8 -0.22 (-0.37, -0.06) -0.36 3.19 159 -0.08 (-0.29, 0.14) 3.11 9.8 Howard et al (2012)<sup>18</sup> Nakamura et al (2011)<sup>14</sup> 0.09174312 3.5159459 0.53 109 217 0.83486239 3.9639901 109 208 7.3 11.7 -0.20 (-0.46, 0.07) -0.10 (-0.30, 0.09) 0 0.06 0.61 Nakamura et al (2016)<sup>15</sup> Tariot et al (2004)<sup>26</sup> -0.1 0.2 0.57 2.57 267 193 0 0.6 0.6 2.48 267 189 13.4 10.9 -0.17 (-0.34, -0.00) -0.16 (-0.36, 0.04) van Dyck et al (2007)<sup>21</sup> Subtotal (95% CI) -0.2 3.1 161 -0.1 2.9 154 9.6 -0.03 (-0.25, 0.19) -0.15 (-0.22, -0.07) 1.423 1.413 77.5 Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =2.63, df=6 (P=0.85); $I^2$ =0% Test for overall effect: Z=3.87 (P=0.0001) Total (95% CI) 1,826 1,812 100 -0.10 (-0.18, -0.02) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =12.47, df=8 (P=0.13); $I^2$ =36% Test for overall effect: Z=2.33 (P=0.02) -0.5 -0.250 0.25 0.5 Test for subgroup differences: $\chi^2$ =1.96, df=1 (P=0.16); $I^2$ =49.0% Favors (memantine) Favors (control)

Figure 4 Forest plot of nighttime disturbance/diurnal rhythm disturbance scores.

Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

Study or	Memantine			Control			Weight	SMD IV,	SMD IV,	
subgroup	Mean	SD	Total	Mean	SD	Total	(%)	random, 95% CI	random,	95% CI
Monotherapy										
Kitamura et al (2011)17	-0.109	1.489	207	0.15	1.36	107	7.1	-0.18 (-0.41, 0.06)	-	
Nakamura et al (2011)14	0	0.93	217	0.05	1.19	208	10.8	-0.05 (-0.24, 0.14)		_
Peskind et al (2006)20	0	1.02	191	0.2	1.07	190	9.6	-0.19 (-0.39, 0.01)	-	
an Dyck et al (2007)21	0	2.1	161	0	2	154	8.0	0.00 (-0.22, 0.22)	-	_
Subtotal (95% CI)			776			659	35.5	-0.10 (-0.21, 0.00)	<b>•</b>	
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =2 Test for overall effect: Z=1.9		).51); <i>I</i> <sup>2</sup> =0%								
	0 (7 =0.00)									
Combination therapy										
Araki et al (2014)22	0.17	0.39	12	1.85	2.48	13	0.6	-0.90 (-1.73, -0.07)		
Grossberg et al (2013) <sup>23</sup>	0	1.83	318	-0.1	1.89	321	16.2	0.05 (-0.10, 0.21)	+	-
Herrmann et al (2013)24	0.03	2.43	159	0.08	2.12	165	8.2	-0.02 (-0.24, 0.20)	-	_
Howard et al (2012)18	0.17431193	1.8799332	109	0.53211009	2.692819	109	5.5	-0.15 (-0.42, 0.11)		-
Nakamura et al (2016)15	0.1	0.73	267	0.1	0.81	267	3.6	0.00 (-0.17, 0.17)	-	_
Porsteinsson et al (2008)25	0.1	1.47	212	0.2	1.16	209	10.7	-0.08 (-0.27, 0.12)		-
ariot et al (2004)26	0.1	1.59	193	0.2	1.49	189	9.7	-0.06 (-0.27, 0.14)		_
Subtotal (95% CI)			1,270			1,273	64.5	-0.04 (-0.12, 0.05)	•	•
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =6	6.59, df=6 (P=0	).36); <i>I</i> <sup>2</sup> =9%								
est for overall effect: Z=0.8	4 (P=0.40)									
			2,046			1,932	100	-0.06 (-0.12, 0.01)	•	
Total (95% CI)			2,040							
<b>Fotal (95% CI)</b> Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =9	9.98, df=10 (P=	=0.44); <i>I</i> <sup>2</sup> =0%	2,046			,		-	1	
, ,		=0.44); <i>I</i> <sup>2</sup> =0%	2,046			,			2 -1 0	1
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =9	9 (P=0.07)		·			,				
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =9 Test for overall effect: Z=1.7	9 (P=0.07)		·			,			2 –1 0 Favors (memantine)	1 Favors (control)
Heterogeneity: $v^2$ =0.00; $\chi^2$ =(rest for overall effect: Z=1.7 rest for subgroup difference	9 (P=0.07) s: χ²=0.95, df=		·			,				
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =9 Test for overall effect: Z=1.7	9 (P=0.07) s: χ²=0.95, df=		·	Control			Weight			
Heterogeneity: $v^2$ =0.00; $\chi^2$ =5 [est for overall effect: Z=1.7 Fest for subgroup difference	9 (P=0.07) s: χ²=0.95, df=		·	Control Mean	SD	Total	Weight (%)	=	Favors (memantine)	Favors (control)
Heterogeneity: r²=0.00; χ²=st Fest for overall effect: Z=1.7 Fest for subgroup difference Severity of disease Study or subgroup	9 ( $P$ =0.07) s: $\chi^2$ =0.95, $df$ =	1 ( <i>P</i> =0.33); <i>I</i> <sup>2</sup> =	=0%		SD			SMD IV,	Favors (memantine)	Favors (control)
Heterogeneity: r=0.00; r=st est for overall effect: Z=1.7 fest for subgroup difference Severity of disease study or subgroup	9 ( $P$ =0.07) s: $\chi^2$ =0.95, $df$ =	1 ( <i>P</i> =0.33); <i>I</i> <sup>2</sup> =	=0%		SD 1.07			SMD IV,	Favors (memantine)	Favors (control)
Heterogeneity: $v^2$ =0.00; $\chi^2$ =4; est for overall effect: Z=1.7 fest for subgroup difference  Severity of disease Study or subgroup  Mild-to-moderate Peskind et al (2006) <sup>20</sup>	9 ( <i>P</i> =0.07) s: χ <sup>2</sup> =0.95, <i>df</i> = Memantine Mean	1 (P=0.33); I <sup>2</sup> =	=0% Total	Mean		Total	(%)	SMD IV, random, 95% CI	Favors (memantine)	Favors (control)
eleterogeneity: r=0.00; r=elect for overall effect: Z=1.7 elect for overall effect: Z=1.7 elect for subgroup difference  Severity of disease study or subgroup  dild-to-moderate Peakind et al (2006) <sup>20</sup> Porsteinsson et al (2008) <sup>20</sup>	9 ( <i>P</i> =0.07) s: χ <sup>2</sup> =0.95, <i>df</i> = <b>Memantine</b> <b>Mean</b>	1 (P=0.33); I <sup>2</sup> = SD 1.02	=0%  Total  191	Mean 0.2	1.07	Total	9.6	SMD IV, random, 95% CI	Favors (memantine)	Favors (control)
Heterogeneity: r*=0.00; r*=4 est for overall effect: Z=1.7 est for subgroup difference  Severity of disease  Budy or  Budgroup  Mild-to-moderate  Peskind et al (2006)*3  Porsteinsson et al (2008)*5  Bubtotal (95% CI)	9 (P=0.07) s: χ²=0.95, df= Memantine Mean 0 0.1	1 (P=0.33); I <sup>2</sup> =  SD  1.02 1.47	Total  191 212	Mean 0.2	1.07	Total 190 209	9.6 10.7	SMD IV, random, 95% CI -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	Favors (memantine)	Favors (control)
Heterogeneity: $r^2$ =0.00; $\chi^2$ =4 fest for overall effect: Z=1.7 fest for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) <sup>20</sup> Porsteinsson et al (2008) <sup>25</sup> Subtotal (95%, CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =4	9 ( <i>P</i> =0.07) s: χ <sup>2</sup> =0.95, <i>df</i> = s Memantine Mean 0 0.1 0.67, <i>df</i> =1 ( <i>P</i> =0	1 (P=0.33); I <sup>2</sup> =  SD  1.02 1.47	Total  191 212	Mean 0.2	1.07	Total 190 209	9.6 10.7	SMD IV, random, 95% CI -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	Favors (memantine)	Favors (control)
Heterogeneity: r*=0.00; x*=4 Fest for overall effect: Z=1.7 Fest for subgroup difference  Severity of disease Study or subgroup  Mild-to-moderate  Peskind et al (2006)**  Orstelinson et al (2008)**  Subtotal (95% CI)  Heterogeneity: r*=0.00; x*=4 Fest for overall effect: Z=1.8	9 ( <i>P</i> =0.07) s: χ <sup>2</sup> =0.95, <i>df</i> = s Memantine Mean 0 0.1 0.67, <i>df</i> =1 ( <i>P</i> =0	1 (P=0.33); I <sup>2</sup> =  SD  1.02 1.47	Total  191 212	Mean 0.2	1.07	Total 190 209	9.6 10.7	SMD IV, random, 95% CI -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	Favors (memantine)	Favors (control)
Heterogeneity: $v^2$ =0.00; $\chi^2$ =5 [est for overall effect: $Z$ =1.7 [est for subgroup difference]  Severity of disease [study or]	9 ( <i>P</i> =0.07) s: χ <sup>2</sup> =0.95, <i>df</i> = s Memantine Mean 0 0.1 0.67, <i>df</i> =1 ( <i>P</i> =0	1 (P=0.33); I <sup>2</sup> =  SD  1.02 1.47	Total  191 212	Mean 0.2	1.07	Total 190 209	9.6 10.7	SMD IV, random, 95% CI -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	Favors (memantine)	Favors (control)
Heterogeneity: $r^2$ =0.00; $\chi^2$ =4 feet for overall effect: $Z$ =1.7 feet for subgroup difference  Severity of disease Study or subgroup  Mild-to-moderate Peskind et al (2006) <sup>26</sup> Subtotal (98% CI) Heterogeneity: $r^2$ =0.00; $\chi^2$ =4 feet for overall effect: $Z$ =1.8  Moderate-to-severe	9 (P=0.07) s: x <sup>2</sup> =0.95, df= e Memantine Mean 0 0.1 0.67, df=1 (P=0.07)	SD  1.02 1.47 0.41); I <sup>2</sup> =0%	Total  191 212 403	0.2 0.2	1.07 1.16	Total 190 209 399	9.6 10.7 <b>20.3</b>	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)	Favors (memantine)	Favors (control)
eleterogeneity: r=0.00; r=elest for overall effect: Z=1.7 feest for subgroup difference  Severity of disease study or subgroup  Mild-to-moderate  Peskind et al (2006) <sup>20</sup> Porsteinsson et al (2008) <sup>25</sup> Subtotal (95% CI)  eleterogeneity: r=0.00; r=1.8  Moderate-to-severe  kraki et al (2014) <sup>22</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07) 0.17	SD  1.02 1.47 0.41); I <sup>2</sup> =0%	Total 191 212 403	0.2 0.2	1.07 1.16	Total 190 209 399	9.6 10.7 <b>20.3</b>	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.01) -0.13 (-0.27, 0.01)	Favors (memantine)	Favors (control)
Heterogeneity: r²=0.00; r²=t Fest for overall effect: Z=1.7 Fest for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) <sup>20</sup> Porsteinsson et al (2008) <sup>25</sup> Subtrato (95% CI) Heterogeneity: r²=0.00; r²=t Fest for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) <sup>22</sup> Forossberg et al (2013) <sup>23</sup> Hermann et al (2013) <sup>23</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07)  0.17	SD 1.02 1.47 0.41); I <sup>2</sup> =0%	Total  191 212 403	0.2 0.2 0.2	1.07 1.16 2.48 1.89	Total 190 209 399	9.6 10.7 <b>20.3</b> 0.6 16.2	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) -0.05 (-0.10, 0.21) -0.02 (-0.24, 0.20)	Favors (memantine)	Favors (control)
eleterogeneity: r=0.00; r=elest for overall effect. Z=1.7 est for subgroup difference.  Severity of disease study or subgroup.  Mild-to-moderate Peekind et al (2008) <sup>20</sup> Porsteinsson et al (2008) <sup>20</sup> Subtotal (95% CI) eleterogeneity: r=0.00; r²=1 est for overall effect. Z=1.8 Moderate-to-severe vaki et al (2014) <sup>22</sup> Grossberg et al (2013) <sup>23</sup> Horman et al (2013) <sup>24</sup> Howard et al (2013) <sup>24</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07)  0.17 0 0.03	SD 1.02 1.47 2.41); $i^2$ =0%	Total  191 212 403	0.2 0.2 0.2	1.07 1.16 2.48 1.89 2.12	Total  190 209 399	9.6 10.7 <b>20.3</b> 0.6 16.2 8.2	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) 0.05 (-0.10, 0.21)	Favors (memantine)	Favors (control)
Heterogeneity: $r^2$ =0.00; $\chi^2$ =1 fest for overall effect: $Z$ =1.7 fest for subgroup difference  Severity of disease  Study or subgroup  Mild-to-moderate  Peskind et al (2008) <sup>20</sup> Porsteinsson et al (2008) <sup>20</sup> Porsteinsson et al (2008) <sup>20</sup> Heterogeneity: $r^2$ =0.00; $\chi^2$ =1 fest for overall effect: $Z$ =1.8  Moderate-to-severe  Araki et al (2014) <sup>22</sup> Grossberg et al (2013) <sup>23</sup> Herrmann et al (2013) <sup>24</sup> Herrmann et al (2013) <sup>26</sup> Herrmann et al (2013) <sup>27</sup> Herrmann et al (2011) <sup>27</sup> Kitamura et al (2011) <sup>27</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07)  0.17 0 0.03 0.17431193	1 (P=0.33); P= SD  1.02 1.47 1.47 0.39 1.83 2.43 1.8799332 1.489	Total  191 212 403  12 318 159 109	0.2 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15	1.07 1.16 2.48 1.89 2.12 2.692819	Total  190 209 399  13 321 165 109	9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) 0.05 (-0.10, 0.21) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.16 (-0.41, 0.06)	Favors (memantine)	Favors (control)
eleterogeneity: $r^2$ =0.00; $\chi^2$ =1 est for overall effect: Z=1.7 est for overall effect: Z=1.7 est for subgroup difference study or subgroup.  Allid-to-moderate eskind et al (2006) <sup>20</sup> eorsteinsson et al (2008) <sup>25</sup> subtotal (95% CI) effectogeneity: $r^2$ =0.00; $\chi^2$ =1 est for overall effect: Z=1.8 Aoderate-to-severe vasit et al (2014) <sup>22</sup> efforssberg et al (2013) <sup>23</sup> efformann et al (2013) <sup>24</sup> followard et al (2012) <sup>18</sup> Gitamura et al (2011) <sup>17</sup> valkamura et al (2011) <sup>18</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.47)  0.17 0 0.03 0.17431193 -0.109	SD 1.02 1.47 1.41); $i^2$ =0% 0.39 1.83 2.43 1.8799332 1.489 0.93	Total  191 212 403  12 318 159 109 207 217	0.2 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19	Total  190 209 399  13 321 165 109 107 208	9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) 0.05 (-0.10, 0.21) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14)	Favors (memantine)	Favors (control)
eleterogeneity: $r^2$ =0.00; $\chi^2$ =1 fest for overall effect. Z=1.7 fest for subgroup difference  Severity of disease study or subgroup  Mild-to-moderate  Peskind et al (2006) <sup>20</sup> Porsteinsson et al (2008) <sup>25</sup> Subtotal (95% CI)  Heterogeneity: $r^2$ =0.00; $\chi^2$ =1 fest for overall effect. Z=1.8  Moderate-to-severe  Araki et al (2014) <sup>23</sup> Grossberg et al (2013) <sup>24</sup> Howard et al (2011) <sup>14</sup> Valkamura et al (2011) <sup>17</sup> Valkakamura et al (2011) <sup>18</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07)  0.17 0 0.03 0.07431193 -0.109 0 0.1	SD  1.02 1.47 0.41); $i^2$ =0%  0.39 1.83 2.43 1.8799332 1.489 0.93 0.73	Total  191 212 403  12 318 159 109 207 217 267	0.2 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81	Total  190 209 399  13 321 165 109 107 208 267	9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) 0.05 (-0.10, 0.21) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14) 0.00 (-0.17, 0.17)	Favors (memantine)	Favors (control)
eleterogeneity: $r^*$ =0.00; $\chi^*$ =1 est for overall effect: $Z$ =1.7 est for subgroup difference  Severity of disease  Study or subgroup  Mild-to-moderate  Peskind et al (2008) <sup>20</sup> Porsteinsson et al (2008) <sup>20</sup> Subtotal (95% CI)  Heterogeneity: $r^*$ =0.00; $\chi^*$ =1 est for overall effect: $Z$ =1.8  Moderate-to-severe  varaki et al (2014) <sup>22</sup> Grossberg et al (2013) <sup>23</sup> Herrmann et al (2013) <sup>24</sup> Herrmann et al (2013) <sup>24</sup> Herrmann et al (2011) <sup>17</sup> Hakamura et al (2011) <sup>17</sup> Hakamura et al (2016) <sup>15</sup> Fariot et al (2004) <sup>26</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07)  0.17 0 0.03 0.17431193 -0.109 0 0.1	1 (P=0.33); P= SD  1.02 1.47 1.47 1.41); P=0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59	Total  191 212 403  12 318 159 109 207 217 267 193	0.2 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	Total  190 209 399  13 321 165 109 107 208 267 189	9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) 0.05 (-0.10, 0.21) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.16 (-0.41, 0.06) -0.05 (-0.24, 0.14) -0.06 (-0.27, 0.14)	Favors (memantine)	Favors (control)
eleterogeneity: $r^2$ =0.00; $\chi^2$ =1 est for overall effect: Z=1.7 est for subgroup difference  Severity of disease study or subgroup  Alid-to-moderate  Peskind et al (2006) <sup>20</sup> Porsteinsson et al (2008) <sup>25</sup> Subtotal (95% CI)  feterogeneity: $r^2$ =0.00; $\chi^2$ =1 est for overall effect: Z=1.8  Anderate-to-severe  Araki et al (2014) <sup>22</sup> Forssberg et al (2013) <sup>23</sup> Forsberg et al (2013) <sup>23</sup> Forsberg et al (2013) <sup>24</sup> Forsberg et al (2011) <sup>17</sup> Jakamura et al (2011) <sup>18</sup> Jakamura et al (2011) <sup>19</sup> Jakamura et al (2010) <sup>26</sup> Jariot et al (2007) <sup>21</sup> Jan Dyck et al (2007) <sup>21</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine Mean  0 0.1 0.67, $df$ =1 (P=0.07)  0.17 0 0.03 0.07431193 -0.109 0 0.1	SD  1.02 1.47 0.41); $i^2$ =0%  0.39 1.83 2.43 1.8799332 1.489 0.93 0.73	Total  191 212 403  12 318 159 109 207 217 267 193 161	0.2 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81	190 209 399 13 321 165 109 208 267 189 154	9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14) -0.00 (-0.24, 0.14) -0.00 (-0.27, 0.14) -0.00 (-0.22, 0.22)	Favors (memantine)	Favors (control)
eleterogeneity: $r^*$ =0.00; $\chi^*$ =1 est for overall effect: $Z$ =1.7 est for subgroup difference  Severity of disease  Study or subgroup  Mild-to-moderate  Peskind et al (2008) <sup>20</sup> Porsteinsson et al (2008) <sup>20</sup> Subtotal (95% CI)  Heterogeneity: $r^*$ =0.00; $\chi^*$ =1 est for overall effect: $Z$ =1.8  Moderate-to-severe  varaki et al (2014) <sup>22</sup> Grossberg et al (2013) <sup>23</sup> Herrmann et al (2013) <sup>24</sup> Herrmann et al (2013) <sup>24</sup> Herrmann et al (2011) <sup>17</sup> Hakamura et al (2011) <sup>17</sup> Hakamura et al (2016) <sup>15</sup> Fariot et al (2004) <sup>26</sup>	9 (P=0.07) s: $\chi^2$ =0.95, $df$ =  Memantine  0 0.1 0.67, $df$ =1 (P=0.07)  0.17 0 0.03 -0.17431193 -0.109 0 0.1 0.1	SD  1.02 1.47 0.41); I*=0%  0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59 2.1	Total  191 212 403  12 318 159 109 207 217 267 193	0.2 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	Total  190 209 399  13 321 165 109 107 208 267 189	9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7	SMD IV, random, 95% CI  -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)  -0.90 (-1.73, -0.07) 0.05 (-0.10, 0.21) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.16 (-0.41, 0.06) -0.05 (-0.24, 0.14) -0.06 (-0.27, 0.14)	Favors (memantine)	Favors (control)

1,932 100

-0.06 (-0.12, 0.01)

Figure 5 Forest plot of hallucination scores.

Test for overall effect: Z=1.79 (P=0.07)

Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

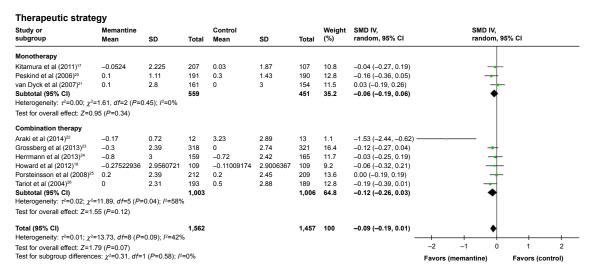
Favors (control)

Favors (memantine)

Heterogeneity:  $\tau^2$ =0.00;  $\chi^2$ =9.98, df=10 (P=0.44);  $I^2$ =0%

Test for subgroup differences:  $\chi^2$ =1.34, df=1 (P=0.25);  $I^2$ =25.2%

Total (95% CI)



### Severity of disease

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	SMD IV, random, 95% CI	
Mild-to-moderate										
Peskind et al (2006)20	0.1	1.11	191	0.3	1.43	190	12.8	-0.16 (-0.36, 0.05)		
Porsteinsson et al (2008)25	0.2	2.39	212	0.2	2.45	209	13.6	0.00 (-0.19, 0.19)	+	
Subtotal (95% CI)			403			399	26.4	-0.07 (-0.23, 0.08)	<b>◆</b>	
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =	1.21, df=1 (P=0	0.27); I <sup>2</sup> =18%								
Test for overall effect: Z=0.9	96 (P=0.34)									
Moderate-to-severe										
Araki et al (2014)22	-0.17	0.72	12	3.23	2.89	13	1.1	-1.53 (-2.44, -0.62)		
Grossberg et al (2013)23	-0.3	2.39	318	0	2.74	321	16.4	-0.12 (-0.27, 0.04)		
Herrmann et al (2013)24	-0.8	3	159	-0.72	2.42	165	11.7	-0.03 (-0.25, 0.19)	<del>-</del>	
Howard et al (2012)18	-0.27522936	2.9560721	109	-0.11009174	2.9006367	109	9.2	-0.06 (-0.32, 0.21)	<del></del>	
Kitamura et al (2011) <sup>17</sup>	-0.0524	2.225	207	0.03	1.87	107	10.8	-0.04 (-0.27, 0.19)	<del>-</del>	
Tariot et al (2004)26	0	2.31	193	0.5	2.88	189	12.8	-0.19 (-0.39, 0.01)		
van Dyck et al (2007)21	0.1	2.8	161	0	3	154	11.5	0.03 (-0.19, 0.26)	+	
Subtotal (95% CI)			1,159			1,058	73.6	-0.10 (-0.23, 0.03)	•	
Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =	12.48, df=6 (P=	0.05); I <sup>2</sup> =52%	6							
Test for overall effect: Z=1.5	50 (P=0.13)									
Total (95% CI)			1,562			1,457	100	-0.09 (-0.19, 0.01)	•	
Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =	13.73, df=8 (P=	0.09); I <sup>2</sup> =42%	6					-		-+
Test for overall effect: Z=1.7	'9 (P=0.07)								-2 -1 0 1	2
Test for subgroup difference	es: $\chi^2$ =0.05, $df$ =	1 (P=0.82); I <sup>2</sup>	=0%						Favors (memantine) Favors (co	ontrol)

Figure 6 Forest plot of irritability/lability scores.

Therapeutic strategy

Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

2.046

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	SMD IV, random, 95% CI
Monotherapy									
Kitamura et al (2011)17	-0.0768	3.473	207	0.06	3.49	107	7.8	-0.04 (-0.27, 0.19)	<del>-</del>
Nakamura et al (2011)14	-0.03	1.25	217	0.31	1.34	208	10.7	-0.00 (-0.19, 0.19)	+
Peskind et al (2006) <sup>20</sup>	0.1	1.09	191	0.2	1.21	190	9.9	-0.09 (-0.29, 0.11)	<del></del>
van Dyck et al (2007)21	-0.1	2.8	161	-0.1	3.6	154	8.5	0.00 (-0.22, 0.22)	<del></del>
Subtotal (95% CI)			776			659	37.0	-0.03 (-0.14, 0.07)	<b>*</b>
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =0	0.45, df=3 (P=0	0.93); I <sup>2</sup> =0%							
Test for overall effect: Z=0.6	1 (P=0.54)								
Combination therapy									
Araki et al (2014)22	0.25	1.42	12	3	2.71	13	0.7	-1.21 (-2.08, -0.35)	
Grossberg et al (2013)23	-0.6	3.07	318	-0.2	2.82	321	14.2	-0.14 (-0.29, 0.02)	
Herrmann et al (2013)24	-0.31	3.9	159	-0.65	3.53	165	8.7	0.09 (-0.13, 0.31)	+-
Howard et al (2012)18	0.23853211	3.9179054	109	1.0550459	3.8461979	109	6.3	-0.21 (-0.48, 0.06)	<del></del>
Nakamura et al (2016) <sup>15</sup>	0	1.23	267	0.1	1.33	267	12.6	-0.08 (-0.25, 0.09)	<del></del>
Porsteinsson et al (2008) <sup>25</sup>	0.2	2.83	212	0.3	2.66	209	10.6	-0.04 (-0.23, 0.15)	<del>-</del>
Tariot et al (2004)28	0.4	2.82	193	0.2	3.43	189	9.9	0.06 (-0.14, 0.26)	<del> -</del>
Subtotal (95% CI)			1,270			1,273	63.0	-0.07 (-0.19, 0.05)	•
Heterogeneity: $\tau^2=0.01$ ; $\chi^2=1$	12.35, df=6 (P=	=0.05); I <sup>2</sup> =51%	6					,	1
Test for overall effect: Z=1.1	6 (P=0.25)	•							

1.932 100

-0.05 (-0.13, 0.02)

Figure 7 (Continued)

Total (95% CI)

Heterogeneity:  $\tau^2$ =0.00;  $\chi^2$ =13.02, df=10 (P=0.22);  $I^2$ =23% Test for overall effect: Z=1.41 (P=0.16) Test for subgroup differences:  $\chi^2$ =0.22, df=1 (P=0.64);  $I^2$ =0%

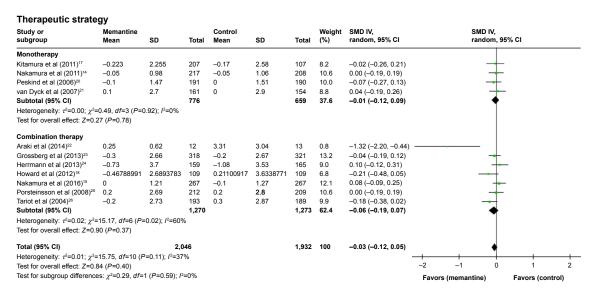
Favors (memantine)

Favors (control)

### Severity of disease Study or subgroup Control Mean SMD IV, random, 95% CI SMD IV, random, 95% CI Memantine Total (%) Total Mild-to-moderate Peskind et al (2006)20 191 -0.09 (-0.29, 0.11) 1.09 0.2 1.21 190 9.9 Porsteinsson et al (2008)25 2.83 212 0.3 2.66 209 10.6 -0.04 (-0.23, 0.15) Subtotal (95% CI) 403 399 20.5 -0.06 (-0.20, 0.08) Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 0.13$ , df = 1 (P = 0.72); $I^2 = 0\%$ Test for overall effect: Z=0.85 (P=0.39) Moderate-to-severe -1.21 (-2.08, -0.35) -0.14 (-0.29, 0.02) Araki et al (2014)22 12 318 3 -0.2 0.7 14.2 Grossberg et al (2013)<sup>23</sup> 3.07 -0.6 Herrmann et al (2013)<sup>24</sup> Howard et al (2012)<sup>18</sup> 165 109 8.7 6.3 0.09 (-0.13, 0.31) -0.21 (-0.48, 0.06) -0.31 39 159 -0.65 3.53 0.23853211 3.9179054 109 1.0550459 3.8461979 Kitamura et al (2011)17 -0.0768 3.473 207 0.06 3.49 107 7.8 10.7 -0.04 (-0.27, 0.19) -0.00 (-0.19, 0.19) Nakamura et al (2011)14 -0.03 1.25 217 0.31 134 208 Nakamura et al (2016)<sup>15</sup> 1 23 267 0.1 1.33 267 12.6 -0.08 (-0.25, 0.09) Tariot et al (2004)26 0.4 2.82 193 0.2 3.43 189 9.9 0.06 (-0.14, 0.26) van Dyck et al (2007)21 -0.1 2.8 161 -0.1 3.6 154 8.5 0.00 (-0.22, 0.22) Subtotal (95% CI) 1,643 1,533 -0.05 (-0.14, 0.04) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =12.87, df=8 (P=0.12); $I^2$ =38% Test for overall effect: Z=1.10 (P=0.27) Total (95% CI) -0.05 (-0.13, 0.02) 1,932 100 Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =13.02, df=10 (P=0.22); $I^2$ =23% Test for overall effect: Z=1.41 (P=0.16) Test for subgroup differences: $\chi^2$ =0.01, df=1 (P=0.92); $I^2$ =0% Favors (memantine) Favors (control)

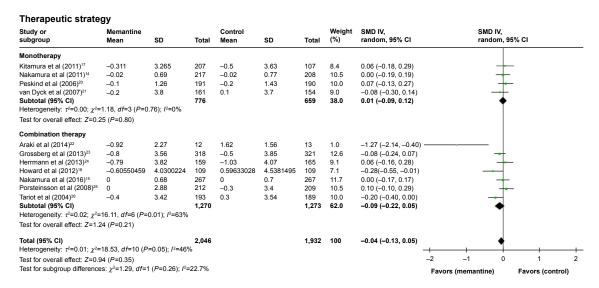
Figure 7 Forest plot of aberrant motor activity/activity disturbance scores.

Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.



### Severity of disease Study or SMD IV, SMD IV, random, 95% CI Contro Weight SD SD random, 95% CI subgroup Mean Total Mean Total (%) Mild-to-moderate Peskind et al (2006)20 1.51 190 -0.07 (-0.27, 0.13) Porsteinsson et al (2008)25 0.2 2.69 212 0.2 2.8 209 10.6 0.00 (-0.19, 0.19) Subtotal (95% CI) 403 20.5 399 -0.03 (-0.17, 0.11) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =0.22, df=1 (P=0.64); $I^2$ =0% Test for overall effect Z=0.45 (P=0.65) Moderate-to-severe Araki et al (2014)22 0.62 12 3.31 3.04 13 0.8 -1.32 (-2.20, -0.44) 0.25 Grossberg et al (2013)23 -0.3 2.66 318 -0.2 321 13.2 -0.04 (-0.19, 0.12) 2.67 Herrmann et al (2013)24 -0.733.7 159 -1.083.53 165 9.0 0.10 (-0.12, 0.31) 109 -0.21 (-0.48, 0.05) Howard et al (2012)18 2.6893783 6.8 Kitamura et al (2011)17 -0.223 2.255 207 -0.17 2.58 107 8.2 -0.02 (-0.26, 0.21) 10.6 0.00 (-0.19, 0.19) Nakamura et al (2011)14 217 -0.05 0.98 -0.051.06 208 Nakamura et al (2016)15 1.21 267 -0.1 1.27 267 12.1 0.08 (-0.09, 0.25) -0.2 Tariot et al (2004)26 2.73 193 0.3 2.87 189 9.9 -0.18 (-0.38, 0.02) Van Dyck et al (2007)21 2.7 161 154 8.8 Subtotal (95% CI) 1,643 1,533 79.5 -0.04 (-0.14, 0.06) Heterogeneity: $\tau^2$ =0.01: $\tau^2$ =15.52. df=8 (P=0.05): $I^2$ =48% Test for overall effect: Z=0.77 (P=0.44) 1,932 100 -0.03 (-0.12, 0.05) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =15.75, df=10 (P=0.11); $I^2$ =37% Test for overall effect: Z=0.84 (P=0.40) -1 Test for subgroup differences: $\chi^2$ =0.01, df=1 (P=0.93); $I^2$ =0% Favors (control)

Figure 8 Forest plot of anxiety/phobia scores.



### Severity of disease Study or subgroup SMD IV, random, 95% CI SMD IV, random, 95% CI Memantine Mean SD Total SD Total (%) Mild-to-moderate Peskind et al (2006)20 1.26 191 -0.2 1.43 190 10.0 0.07 (-0.13, 0.27) Porsteinsson et al (2008)<sup>25</sup> 212 -0.3 3.4 209 10.5 0.10 (-0.10, 0.29) Subtotal (95% CI) 403 399 20.5 0.09 (-0.05, 0.22) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =0.00, df=1 (P=0.88); $I^2$ =0% Test for overall effect: Z=1.20 (P=0.23) -1.27 (-2.14, -0.40) -0.08 (-0.24, 0.07) Araki et al (2014)22 12 318 1.62 -0.5 1.0 12.6 Grossberg et al (2013)23 3.85 321 -0.8 3.56 Herrmann et al (2013)<sup>24</sup> -0.79 -1.03 4.07 0.06 (-0.16, 0.28) Howard et al (2012)18 -0.60550459 4.0300224 109 0.59633028 4.5381495 109 7.1 -0.28 (-0.55, -0.01) 207 217 -0.5 -0.02 107 208 0.06 (-0.18, 0.29) 0.00 (-0.19, 0.19) Kitamura et al (2011)<sup>17</sup> 3.265 8.4 10.5 Nakamura et al (2011)1 -0.02 0.77 0.69 Nakamura et al (2016)<sup>15</sup> 0 0.68 267 11.7 0.00 (-0.17, 0.17) -0.4 0.3 Tariot et al (2004)26 3.42 193 3.54 189 10.0 -0.20 (-0.40, 0.00) van Dyck et al (2007)<sup>21</sup> Subtotal (95% CI) 9.0 **79.5** -0.08 (-0.30, 0.14) -0.08 (-0.18, 0.02) -0.2 1.643 1.533 Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =14.92, df=8 (P=0.06); $I^2$ =46% Test for overall effect: Z=1.47 (P=0.14) Total (95% CI) 1,932 100 -0.04 (-0.13, 0.05) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =18.53, df=10 (P=0.05); $I^2$ =46% Test for overall effect: Z=0.94 (P=0.35) Test for subgroup differences: $\chi^2$ =3.38, df=1 (P=0.07); $I^2$ =70.4% Favors (memantine)

Figure 9 Forest plot of apathy scores.

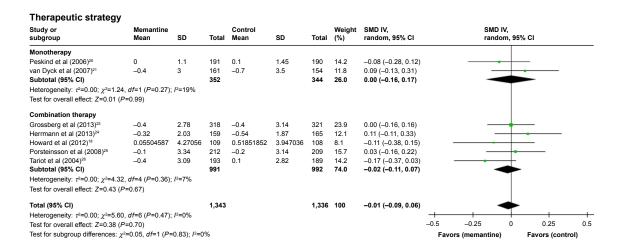
Therapeutic strateg	у									
Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	SMD IV randor	/, n, 95% CI
Monotherapy										
Kitamura et al (2011)17	-0.0297	1.861	207	-0.09	1.65	107	9.5	0.03 (-0.20, 0.27)		<del>-</del>
Peskind et al (2006)20	-0.1	1.45	191	0	1.57	190	12.8	-0.07 (-0.27, 0.13)	_	+
van Dyck et al (2007)21	0	2.4	161	-0.1	1.8	154	10.6	0.05 (-0.17, 0.27)		<del>-</del>
Subtotal (95% CI)			559			451	32.8	-0.00 (-0.13, 0.12)		<b>♦</b>
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =0.	67, df=2 (P=0.72	2); /2=0%								
Test for overall effect: Z=0.01	(P=0.99)									
Combination therapy										
Araki et al (2014)22	0	1.04	12	2.23	2.52	13	0.7	-1.10 (-1.95, -0.25)		
Grossberg et al (2013)23	-0.4	2.61	318	-0.4	2.37	321	21.4	0.00 (-0.16, 0.16)		+
Herrmann et al (2013)24	-0.39	2.35	159	-0.28	2.15	165	10.9	-0.05 (-0.27, 0.17)	_	+
Howard et al (2012)18	0.06422018	2.8063263	109	0.24770642	2.7526283	109	7.3	-0.07 (-0.33, 0.20)	_	+
Porsteinsson et al (2008)25	0.1	1.99	212	0.2	2.02	209	14.1	-0.05 (-0.24, 0.14)	-	+
Tariot et al (2004)26	0	1.97	193	0.2	2.26	189	12.8	-0.09 (-0.29, 0.11)	_	•+
Subtotal (95% CI)			1,003			1,006	67.2	-0.06 (-0.16, 0.04)		•
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =6.	44, df=5 (P=0.27	7); I <sup>2</sup> =22%								
Test for overall effect: Z=1.17	(P=0.24)									
Total (95% CI)			1,562			1,457	100	-0.04 (-0.11, 0.03)		•
Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =7.	59, df=8 (P=0.47	7); I <sup>2</sup> =0%							+ +	+
Test for overall effect: Z=1.02	(P=0.31)								-2 -1	0 1
Test for subgroup differences:		P=0.46); I <sup>2</sup> =0 <sup>6</sup>	%						Favors (memantine)	Favors (control)

Figure 10 (Continued)

### Severity of disease Study or subgroup Weight SMD IV, (%) random, 95% CI SMD IV, random, 95% CI Control Mean Total Total Mild-to-moderate Peskind et al (2006)20 -0.1 1.45 191 0 1.57 190 12.8 -0.07 (-0.27, 0.13) -0.05 (-0.24, 0.14) Porsteinsson et al (2008)<sup>25</sup> 0.2 0.1 212 2.02 209 **399** 1.99 14.1 26.9 Subtotal (95% CI) 403 -0.06 (-0.20, 0.08) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =0.01, df=1 (P=0.91); $I^2$ =0% Test for overall effect: Z=0.81 (P=0.42) Araki et al (2014)22 1.04 2.23 2.52 -1.10 (-1.95, -0.25) Grossberg et al (2013)<sup>23</sup> Herrmann et al (2013)<sup>24</sup> 2.37 2.15 0.00 (-0.16, 0.16) -0.05 (-0.27, 0.17) -0.4 2.61 318 -0.4 321 21.4 -0.28 165 10.9 -0.39 2.35 159 -0.07 (-0.33, 0.20) Howard et al (2012)18 0.06422018 2.8063263 109 0.24770642 2.7526283 109 7.3 9.5 Kitamura et al (2011)<sup>17</sup> -0.09 107 0.03 (-0.20, 0.27) -0.0297 1.861 207 1.65 Tariot et al (2004)26 0 1.97 193 0.2 2.26 189 12.8 -0.09 (-0.29, 0.11) 0.05 (-0.17, 0.27) van Dyck et al (2007)2 -0.1 154 10.6 2.4 161 1.8 Subtotal (95% CI) 1.159 1.058 73.1 -0.03 (-0.13, 0.06) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =7.46, df=6 (P=0.28); $I^2$ =20% Test for overall effect: Z=0.68 (P=0.49) 1.457 100 Total (95% CI) 1.562 -0.04 (-0.11, 0.03) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =7.59, df=8 (P=0.47); $I^2$ =0% Test for overall effect: Z=1.02 (P=0.31) -1 Test for subgroup differences: $\chi^2$ =0.08, df=1 (P=0.78); $I^2$ =0% Favors (memantine) Favors (control)

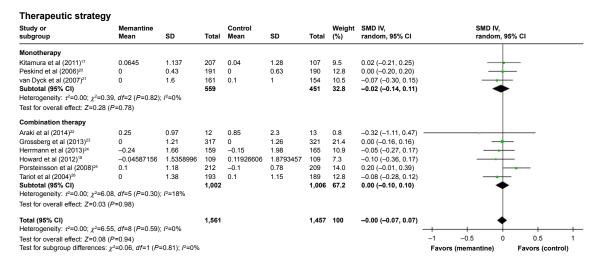
Figure 10 Forest plot of dysphoria scores.

Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.



### Severity of disease Study or subgroup SMD IV, random, 95% CI SMD IV, random, 95% CI Memantine Control SD SD Total Total Mild-to-moderate Peskind et al (2006)20 191 0.1 1.45 190 209 14.2 15.7 -0.08 (-0.28, 0.12) Porsteinsson et al (2008)25 -0.1 212 3.34 -0.2 3.14 0.03 (-0.16, 0.22) Subtotal (95% CI) 403 399 30.0 -0.02 (-0.16, 0.12) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =0.59, df=1 (P=0.44); $I^2$ =0% Test for overall effect: Z=0.29 (P=0.77) Moderate-to-severe Grossberg et al (2013)23 -0.4 2.78 318 -0.4 3.14 321 23.9 0.00 (-0.16, 0.16) -0.54 0.11 (-0.11, 0.33) Herrmann et al (2013)24 -0.32 2.03 159 1.87 165 12.1 8.1 14.2 Howard et al (2012)18 0.05504587 4.27056 109 0.51851852 3.947036 108 -0.11 (-0.38, 0.15) Tariot et al (2004)26 193 2.82 -0.17 (-0.37, 0.03) -0.43.09 0.1 189 van Dyck et al (2007)21 11.8 **70.0** 0.09 (-0.13, 0.31) -0.01 (-0.12, 0.09) -0.4 161 154 -0.7 Subtotal (95% CI) 940 937 Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =5.01, df=4 (P=0.29); $I^2$ =20% Test for overall effect: Z=0.24 (P=0.81) 1,343 Total (95% CI) 1,336 100 -0.01 (-0.09, 0.06) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =5.60, df=6 (P=0.47); $I^2$ =0% Test for overall effect: Z=0.38 (P=0.70) -0.5 -0.25 0.25 0.5 Test for subgroup differences: $\chi^2$ =0.01, df=1 (P=0.93); $I^2$ =0% Favors (memantine) Favors (control)

Figure 11 Forest plot of eating disturbance scores.



### Severity of disease SMD IV. Study or Memantine Control SMD IV. Weiaht Mean SD Total Mean SD Total random 95% CI random 95% CI Mild-to-moderate Peskind et al (2006)2 0.43 191 0 0.63 190 12.8 0.00 (-0.20, 0.20) Porsteinsson et al (2008)25 212 -0.1 0.1 1.18 0.78 209 14.0 0.20 (0.01, 0.39) 399 Subtotal (95% CI) 403 26.8 0.10 (-0.09, 0.30) Heterogeneity: $\tau^2$ =0.01; $\chi^2$ =1.98, df=1 (P=0.16); $I^2$ =50% Test for overall effect: Z=1.02 (P=0.31) Moderate-to-severe Araki et al (2014)22 0.25 0.85 -0.32 (-1.11, 0.47) Grossberg et al (2013)<sup>23</sup> Herrmann et al (2013)<sup>24</sup> Ω 1 21 317 Λ 1 26 321 214 0.00 (-0.16, 0.16) -0.24 159 -0.15 165 10.9 -0.05 (-0.27, 0.17) 1.98 7.3 9.5 Howard et al (2012)18 -0.04587156 1.5358996 109 0.11926606 1.8793457 109 -0.10 (-0.36, 0.17) 0.0645 1.137 0.04 Tariot et al (2004)26 0 1.38 193 0.1 1.15 189 12.8 -0.08 (-0.28, 0.12) van Dyck et al (2007)21 10.5 73.2 Subtotal (95% CI) 1.158 1.058 -0.04 (-0.13, 0.04) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =1.42, df=6 (P=0.96); $I^2$ =0% Test for overall effect: Z=0.99 (P=0.32) Total (95% CI) 1.561 1.457 100 -0.00 (-0.07, 0.07) Heterogeneity: $\tau^2$ =0.00; $\chi^2$ =6.55, df=8 (P=0.59); $I^2$ =0% Test for overall effect: Z=0.08 (P=0.94) -0.5 0.5 Test for subgroup differences: $\chi^2=1.77$ , df=1 (P=0.18); $I^2=43.5\%$ Favo

Figure 12 Forest plot of euphoria scores.

Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

respect to apathy (P=0.07), this subgroup analysis showed that memantine was similar to control in moderate-to-severe Alzheimer's disease patients, as well as mild-to-moderate Alzheimer's disease patients (Figure 9).

Agitation/aggression, delusion, disinhibition, and night-time disturbance/diurnal rhythm disturbances were outcomes, where memantine was superior to control in the moderate-to-severe Alzheimer's disease patients' subgroup, but not in the mild-to-moderate Alzheimer's disease patients' subgroup (Figures 1–4).

# **Discussion**

This meta-analysis showed that memantine showed significant efficacy compared to controls in improving delusion, agitation/aggression, disinhibition, and nighttime disturbance/

diurnal rhythm disturbances in patients with Alzheimer's disease. Moreover, memantine seems to benefit the treatment of hallucination and irritability/lability. These symptoms are classified as positive symptoms. <sup>10</sup> Memantine was similar to controls for negative symptoms, such as dysphoria, anxiety/phobia, euphoria, apathy, aberrant motor activity/activity disturbances, and eating disturbances. Memantine improves cognitive functions, <sup>8,9</sup> and anti-dementia drugs may prevent brain atrophy in patients with Alzheimer's disease. <sup>27</sup> Therefore, we considered that the evidence that memantine did not deteriorate negative symptoms, such as behavioral disturbances in patients with Alzheimer's disease, was very important for the clinicians and the patients. If the patients receiving memantine have negative symptoms, the evidence suggests that the patients do not need to stop taking memantine.

Although we did not detect any considerable heterogeneity in all of the meta-analysis, we performed two subgroup analysis (severity of disease and therapeutic strategy) to detect confounding factors. We did not find significant subgroup differences. Subgroup analysis could provide the following evidence, although we did not address multiple comparisons: 1) memantine has benefits for the treatment of delusion in patients with not only combination therapy but also memantine monotherapy; 2) patients with combination therapy may have more benefits for the treatment of agitation/ aggression, and disinhibition than patients with memantine monotherapy; and 3) patients with moderate-severe Alzheimer's disease may have more benefit for the treatment of agitation/aggression, delusion, disinhibition and nighttime disturbance/diurnal rhythm disturbances than patients with mild-moderate Alzheimer's disease.

There were several limitations in this study which need to be addressed. First, patient characteristics differed between the studies examined including: symptom severity, inclusion criteria, race, ethnicity, and study duration. These differences could generate heterogeneity, when combining data for systematic review and meta-analysis. Second, most studies included in this study were industry-sponsored studies. Therefore, there remains a possibility for sponsorship bias in our results. Third, most of all studies included in the study did not report sufficient information about concomitant drugs such as psychotropic drugs (Table 1). Therefore, we did not examine whether concomitant drugs influence on the results of the meta-analysis. Fourth, because mean patients' age among the studies included in the meta-analysis were very similar (Table 1), we did not perform the metaregression analysis to examine whether the effect size of memantine was associated with patient age. Fifth, our study focused on memantine treatment for Alzheimer's disease. We considered that it needed to conduct a network metaanalysis of anti-dementia drugs for Alzheimer's disease on efficacy and safety because network meta-analysis can combine direct and indirect evidence to address the frequent absence of randomized trials that directly compare all the interventions of interest. This should offer suggestion on which pharmacological interventions for the Alzheimer's disease is best.

# **Conclusion**

The meta-analysis suggest that memantine has benefits for the treatment of most of the behavioral disturbances in patients with Alzheimer's disease. Memantine does not deteriorate negative symptoms as behavioral disturbances in patients with Alzheimer's disease.

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# Supplementary materials

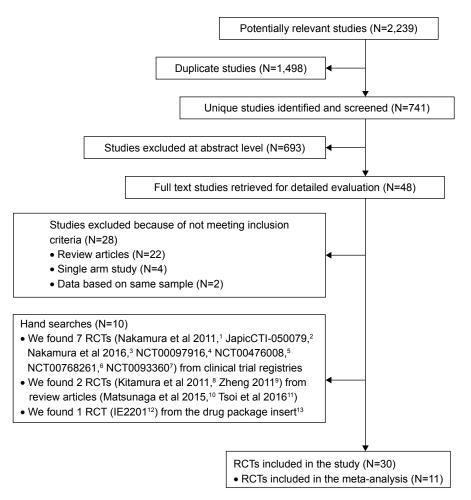


Figure SI PRISMA flow diagram.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial; N, number of randomized controlled trials.

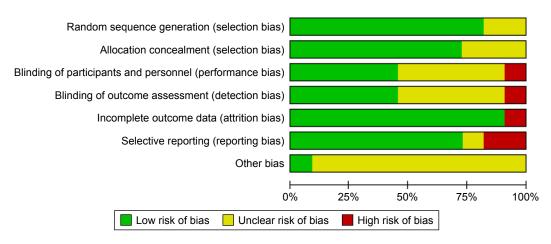


Figure S2 Risk of bias graph.

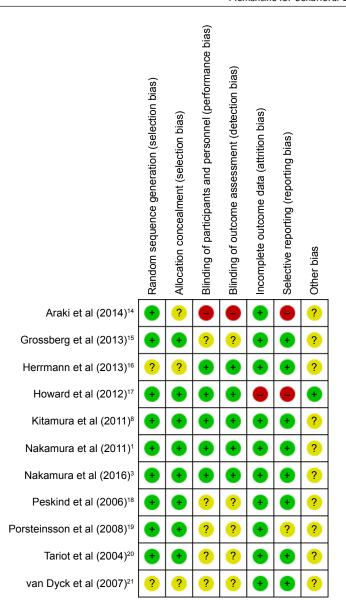


Figure S3 Risk of bias summary.

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