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ORIGINAL RESEARCH

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^2 =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.¹ 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.² 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.³ Memantine blocks the effects of sustained, pathologically elevated levels of glutamate, which could otherwise lead to neuronal dysfunction.⁴⁻⁶ In addition, memantine may also upregulate NMDA receptor expression, causing activation in the presence of a strong stimulus.⁷

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).¹² 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 (http://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 ≥ 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 threearm (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 intentionto-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,^{14,17,20,21} n=1,500; combination therapy with memantine and cholinesterase inhibitors vs cholinesterase inhibitors: seven studies,^{15,18,22–26} 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),²² 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's¹⁷ 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^2 =47%; Figure 1), delusion (SMD =-0.12; 95% CIs =-0.18, -0.06; P=0.0002; I^2 =0%; Figure 2), disinhibition (SMD =-0.08; 95% CIs =-0.15, -0.00; P=0.04; I^2 =0%; Figure 3), and nighttime disturbance/diurnal rhythm disturbances (SMD =-0.10; 95% CIs =-0.18, -0.02; P=0.02; I^2 =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^2 =0%; Figure 5) and irritability/lability (SMD =-0.09; 95% CIs =-0.19, 0.01; P=0.07; I^2 =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
Monotherapy Kitamura et al, ¹⁷ Japan, industry	315	I. DB-RCT 2. 24 weeks 3. FAS	I. AD, DSM-IV, and NINCDS-ADRDA 2. Age ≥50 years, MMSE 5–14, FAST 6a–7a 3. Moderate to severe	73.3±9.4
			 NR Not allowed concomitant drug use: AE, AP, APD, DON, MR, NMDARI, S/H, TD; allowed concomitant use within 2 weeks: BRO, LOR, RIL, TIA 	
Nakamura et al, ¹⁴ Japan, industry	432	I. DB-RCT 2. 24 weeks 3. FAS	 AD, DSM-IV, and NINCDS-ADRDA Age ≥50 years, MMSE 5–14, FAST 6a–7a Moderate to severe Exclusion: severe psychiatric disorder other than probable AD Not allowed concomitant drug use: AE, AP, APD, DON, MR, NMDARI, S/H, TD; allowed concomitant use: BRO, LOR, RIL, 	74.6±8.4
Peskind et al, ²⁰ USA, industry	403	I. DB-RCT 2. 24 weeks 3. ITT	 TIA ≤ 150 mg/day I. AD, NINCDS-ADRDA 2. Age ≥50 years, MMSE 10-22 3. Mild to moderate 4. Exclusion: psychiatric disorder other than probable AD 5. Allowed concomitant drug use: ADD, AH, AI, GB, GIN, OLA, RIS, TD, TOC 	77.5
van Dyck et al, ²¹ USA, industry	350	I. DB-RCT 2. 24 weeks 3. ITT	 AD, NINCDS-ADRDA Age ≥50 years, MMSE 5–14 Moderate to severe Exclusion: psychiatric disorder other than probable AD Allowed concomitant drug use:AAPD,ADD,AH,AI, LAX,TD,TOC 	78.2
Combination thera	рy			
Araki et al, ²² Japan, nonindustry	37	I. O-RCT 2. 24 weeks 3. FAS	I. AD, DSM-IV, and ICD-10 2. HDS-R 3–16 3. Moderate to severe 4. NR 5. NR	78.8±7.7
Grossberg et al, ²³ international, industry	677	I. DB-RCT 2. 24 weeks 3. ITT	 AD, DSM-IV-TR, and NINCDS-ADRDA Age ≥50 years, MMSE 3–14 Moderate to severe Exclusion: DSM-IV Axis I disorder other than AD NR 	76.5
Herrmann et al, ²⁴ Canada, industry	369	I. DB-RCT 2. 24 weeks 3. FAS	 AD, NINCDS-ADRDA Age ≥50 years, MMSE 5–15, NPI ≥13, NPI agitation/aggression score ≥1 Moderate to severe Exclusion: psychiatric disorder other than probable AD Concomitant drug use: ADD 23.6%, ANX 3.3%, APD 22.2% 	74.9

Male (%)	Race (%)	Baseline cognitive function scales (mean ± SD)	Intervention, dose (mg/day)	n	Efficacy outcomes ^a
29.3	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)
35.7	Japanese: 100	MMSE: 9.9±3.0; SIB: 71.0±17.9	MEM 20 mg (Fi) PLA	221 211	MEM > PLA: Behave-AD, SIB ; MEM = PLA: CIBIC-Plus , FAST, MENFIS
41.2	Caucasian: 91.3, others: 8.7	ADAS-cog: 27.3; MMSE: 17.3	MEM 20 mg (Fi) PLA	201 202	MEM > PLA: ADAS-cog , CIBIC-Plus, NPI12; MEM = PLA: ADCS-ADL23
28.6	Caucasian: 80.9; others: 19.1	MMSE: 10.1; SIB: 76.4	MEM 20 mg (Fi)	178	MEM = PLA: ADCS-ADL19 , BGP, CIBIC-Plus, FAST, NPI12, SIB
48.6	Japanese: 100	MMSE: 16.1	MEM 20 mg (Fi) + DON (100%, NR) DON (100%, NR)	19 18	MEM + DON > DON: CDT, CGI-I, MMSE, NPII0, ZBI ; MEM + DON = DON: NIRS (mean of all channels)
28.0	Caucasian: 94.1; others: 5.9	MMSE: 10.8; SIB: 76.0	MEM-ER 28 mg (Fi) + ChEIs (DON [69%, 8.0 mg], GAL [21%, 13.5 mg], RIV [9%, 6.8 mg]) PLA + ChEIs (DON [63%, 7.8 mg], GAL [20%,	342 335	MEM (ER) + ChEIs > PLA + ChEIs: CIBIC-Plus , NPI12, SIB , VFT; MEM (ER) + ChEIs = PLA + ChEIs: ADCS-ADL19
41.7	NR	MMSE: 11.8; SIB: 82.1	I 3.5 mg], RIV [12%, 6.8 mg]) MEM 20 mg (Fi) + ChEls (combination therapy 95%) PLA + ChEls (combination therapy 97%)	182 187	MEM + ChEls = PLA + ChEls: ADCS-ADL19, CIBIC-Plus, CMAI, NPI12, SIB

(Continued)

Table I (Continued)

Study, country, sponsorship	Total (n)	Methods: 1. Study design 2. Duration	Patients I. Diagnosis 2. Inclusion criteria	Age mean ± SD, years
		3. Analyzed	3. Study-defined disease severity	years
		, population	4. Mental disorder comorbidities	
			5. Concomitant drug	
Howard et al, ¹⁸	295	I. DB-RCT	I. AD, NINCDS-ADRDA	77.1±8.4
UK, nonindustry		2. 52 weeks	2. Age \geq 50 years, MMSE 5–13	
		3. OC	3. Moderate to severe	
			4. NR	
			5. NR	
Nakamura et al, ¹⁵	546	I. DB-RCT	I. AD, DSM-IV-TR, and NINCDS-ADRDA	78.5
Japan, industry		2. 24 weeks	2. Age \geq 50 years, MMSE 1–14, SIB 30–85	
		3. FAS	3. Moderate to severe	
			4. Exclusion: severe psychiatric disorder other than probable AD	
			5. 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	
Porsteinsson et al, ²⁵	433	I. DB-RCT	I. AD, NINCDS-ADRDA	75.4
USA, industry		2. 24 weeks	2. Age \geq 50 years, MMSE 10–22	
		3. ITT	3. Mild to moderate	
			4. Exclusion: psychiatric disorder other than probable AD	
			5. NR	
Tariot et al, ²⁶ USA,	404	I. DB-RCT	I. AD, NINCDS-ADRDA	75.5
industry		2. 24 weeks	2. Age \geq 50 years, MMSE 5–14	
/		3. ITT	3. Moderate to severe	
			4. Exclusion: psychiatric disorder other than probable AD	
			5. Concomitant drug use: ACE 37.0%, ASC 19.4%, CAL 11.4%, GB	
			13.6%, MV 39.2%, PAR 14.1%, TOC 62.3%	

Note: ^aPrimary 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-12, General Health Questionnaire 12; GIN, ginseng; HDS-R, Hasegawa's Dementia Scale-Revision; ICD-10, 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,

(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 ^a
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, SIB
			PLA + DON (100%, 6.9 mg)	273	
47.8	NR	ADAS-cog: 27.4;	MEM 20 mg (Fi) + ChEls	217	MEM + ChEls = PLA + ChEls:
47.0	INK	MMSE: 16.8	(DON [71%, 9.5 mg], GAL [14%, 19.7 mg], RIV [15%, 9.2 mg])	217	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	MEM + DON > PLA + DON: ADCS-ADL , BGP, CIBIC-Plus
			PLA + DON (100%, 9.5 mg)	201	NPI12, SIB

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	0.003	2.06	207	-0.33	2.13	107	8.5	0.16 (-0.07, 0.39)	+	
Nakamura et al (2011)14	-0.05	1.19	217	0.26	1.55	208	10.5	-0.22 (-0.42, -0.03)		
Peskind et al (2006)20	0	1.3	191	0.1	1.63	190	10.0	-0.07 (-0.27, 0.13)		
van Dyck et al (2007)21	-0.1	2.9	161	0.3	2.8	154	9.0	-0.14 (-0.36, 0.08)		
Subtotal (95% CI)			776			659	37.9	-0.08 (-0.23, 0.08)	◆	
Heterogeneity: $\tau^2=0.01$; $\chi^2=0$	6.52, df=3 (P=0	0.09); <i>I</i> ² =54%							-	
Test for overall effect: Z=0.9	6 (P=0.34)									
Combination therapy										
Araki et al (2014)22	0.42	1.16	12	3.08	3.15	13	1.0	-1.07 (-1.91, -0.22)		
Grossberg et al (2013) ²³	-0.4	2.44	318	0	2.5	321	12.5	-0.16 (-0.32, -0.01)		
Herrmann et al (2013) ²⁴	-1.5	3.16	159	-1.71	2.91	165	9.2	0.07 (-0.15, 0.29)	_ 	
Howard et al (2012)18	0.36697248	3.1140677	109	1.1743119	2.9933384	109	7.2	-0.26 (-0.53, 0.00)		
Nakamura et al (2016)15	-0.1	1.31	267	0.1	1.43	267	11.7	-0.15 (-0.32, 0.02)		
Porsteinsson et al (2008)25	0	1.97	212	0	1.97	209	10.5	0.00 (-0.19, 0.19)		
Tariot et al (2004) ²⁶	-0.1	2.15	193	0.5	2.83	189	10.0	-0.24 (-0.44, -0.04)		
Subtotal (95% CI)			1,270			1,273	62.1	-0.14 (-0.25, -0.02)	•	
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	11.94, df=6 (P=	0.06); /2=50%								
Test for overall effect: Z=2.3	1 (<i>P</i> =0.02)									
Fotal (95% CI)			2,046			1,932	100	-0.11 (-0.20, -0.03)	•	
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	18.90, <i>df</i> =10 (F	e=0.04); /2=47	%					+	· · · · · ·	-1
Test for overall effect: Z=2.5	2 (P=0.01)							-3	2 –1 0	1
Test for subgroup difference	s: $\gamma^2 = 0.38$ df=	1 (P=0 54): 12	=0%						Favors (memantine) Favo	ors (control)

Figure I (Continued)

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% Cl	SMD IV, random, 95% CI
Mild-to-moderate									
Peskind et al (2006)20	0	1.3	191	0.1	1.63	190	10.0	-0.07 (-0.27, 0.13)	
Porsteinsson et al (2008)25	0	1.97	212	0	1.97	209	10.5	0.00 (-0.19, 0.19)	_ _
Subtotal (95% CI)			403			399	20.5	-0.03 (-0.17, 0.11)	
leterogeneity: $\tau^2=0.00$; $\chi^2=0$	0.23, df=1 (P=0	0.63); / ² =0%							
est for overall effect: Z=0.4	6 (P=0.65)								
Moderate-to-severe									
Araki et al (2014) ²²	0.42	1.16	12	3.08	3.15	13	1.0	-1.07 (-1.91, -0.22)	
Grossberg et al (2013)23	-0.4	2.44	318	0	2.5	321	12.5	-0.16 (-0.32, -0.01)	
Herrmann et al (2013)24	-1.5	3.16	159	-1.71	2.91	165	9.2	0.07 (-0.15, 0.29)	
Howard et al (2012)18	0.36697248	3.1140677	109	1.1743119	2.9933384	109	7.2	-0.26 (-0.53, 0.00)	
Kitamura et al (2011)17	0.003	2.06	207	-0.33	2.13	107	8.5	0.16 (-0.07, 0.39)	
Nakamura et al (2011)14	-0.05	1.19	217	0.26	1.55	208	10.5	-0.22 (-0.42, -0.03)	
Nakamura et al (2016)15	-0.1	1.13	267	0.1	1.43	267	11.7	-0.15 (-0.32, 0.02)	
Fariot et al (2004)26	-0.1	2.15	193	0.5	2.83	189	10.0	-0.24 (-0.44, -0.04)	_ _
an Dyck et al (2007)21	-0.1	2.9	161	0.3	2.8	154	9.0	-0.14 (-0.36, 0.08)	
Subtotal (95% CI)			1,643			1,533	79.5	-0.14 (-0.24, -0.03)	•
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	16.98, df=8 (P=	=0.03); /2=53%	5						
Test for overall effect: Z=2.4	9 (<i>P</i> =0.01)								
otal (95% CI)			2,046			1,932	100	-0.11 (-0.20, -0.03)	•
leterogeneity: r ² =0.01; χ^{2} =	18.90, <i>df</i> =10 (F	P=0.04); /2=47	%					+	
est for overall effect: Z=2.5	2 (P=0.01)							-2	-1 0 1

Figure I Forest plot of agitation/aggression scores.

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

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	SMD IV, random, 95% Cl
alarmurs at al (201) ¹⁴ - 0.15 1.88 217 0.13 1.9 208 10.8 - 0.16 (-0.35, 0.03) an Oyck et al (2007) ¹⁶ - 0.2 3.4 161 0.2 3 154 50 - 0.7 (-0.23, 0.43, -0.03) an Oyck et al (2007) ¹⁶ - 0.2 3.4 161 0.2 3 154 50 - 0.12 (-0.35, 0.10) betto (196, C) 0 - 776 535, 0 - 0.17 (-0.23, 0.10) cetterogenety, "=0.05, $y=0.50$, $y=5.50$, $y=5.5$, $y=5.5$ stor overall etc. 2-3.23 ($P=0.001$) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 2.289 2.14 13 0.4 0.4 0.5 (-0.25, 0.016) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 2.48 2.47 135 - 0.17 (-0.23, 0.017) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 1.5 2.47 136 - 0.05 (-0.32, 0.016) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 1.5 2.47 136 - 0.05 (-0.32, 0.016) contensions et al (2008) ¹⁶ - 0.1 1.4 212 - 0.1 1.64 209 10.3 0.00 (-0.16, 0.016) contensions et al (2008) ¹⁷ - 0.1 1.4 212 - 0.1 1.64 209 10.3 0.00 (-0.16, 0.016) tetrogenety, "-0.00, $y=1.65$, $dr=6$ (P=0.93); P=0% est for overall effect: 2=2.20 (P=0.03) contensions et al (2008) ¹⁷ - 0.1 1.47 212 - 0.1 1.64 209 10.3 0.00 (-0.16, 0.016) contensions et al (2008) ¹⁷ - 0.1 1.47 191 0.2 1.36 190 0.7 - 0.23 (-0.43, -0.03) rand on, 95% C1 tetrogenety, "-0.00, $y=2.3.78$, $dr=0$ (P=0.93); P=0\% est for overall effect: 2=0.30 (P=0.03) tet (95%, C1) tetro overall effect: 2=0.30 (P=0.33); P=0\% est for overall effect: 2=0.30 (P=	Monotherapy									
alarmurs at al (201) ¹⁴ - 0.15 1.88 217 0.13 1.9 208 10.8 - 0.16 (-0.35, 0.03) an Oyck et al (2007) ¹⁶ - 0.2 3.4 161 0.2 3 154 50 - 0.7 (-0.23, 0.43, -0.03) an Oyck et al (2007) ¹⁶ - 0.2 3.4 161 0.2 3 154 50 - 0.12 (-0.35, 0.10) betto (196, C) 0 - 776 535, 0 - 0.17 (-0.23, 0.10) cetterogenety, "=0.05, $y=0.50$, $y=5.50$, $y=5.5$, $y=5.5$ stor overall etc. 2-3.23 ($P=0.001$) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 2.289 2.14 13 0.4 0.4 0.5 (-0.25, 0.016) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 2.48 2.47 135 - 0.17 (-0.23, 0.017) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 1.5 2.47 136 - 0.05 (-0.32, 0.016) combination therapy rank et al (2017) ¹⁶ - 0.4 2.47 178 - 0.1 1.5 2.47 136 - 0.05 (-0.32, 0.016) contensions et al (2008) ¹⁶ - 0.1 1.4 212 - 0.1 1.64 209 10.3 0.00 (-0.16, 0.016) contensions et al (2008) ¹⁷ - 0.1 1.4 212 - 0.1 1.64 209 10.3 0.00 (-0.16, 0.016) tetrogenety, "-0.00, $y=1.65$, $dr=6$ (P=0.93); P=0% est for overall effect: 2=2.20 (P=0.03) contensions et al (2008) ¹⁷ - 0.1 1.47 212 - 0.1 1.64 209 10.3 0.00 (-0.16, 0.016) contensions et al (2008) ¹⁷ - 0.1 1.47 191 0.2 1.36 190 0.7 - 0.23 (-0.43, -0.03) rand on, 95% C1 tetrogenety, "-0.00, $y=2.3.78$, $dr=0$ (P=0.93); P=0\% est for overall effect: 2=0.30 (P=0.03) tet (95%, C1) tetro overall effect: 2=0.30 (P=0.33); P=0\% est for overall effect: 2=0.30 (P=	Kitamura et al (2011)17	-0.246	1.679	207	0.07	1.9	107	7.2	-0.18 (-0.41, 0.05)	
an Dyck stal (2007) ¹¹ - 0.2 3.4 (fe) 0.2 3 (for $3, 2, 2, 3, 3, 4$ (fe) 0.2 3 (for $3, 2, 2, 3, 3, 10^{-1}$ deterogeneity: $f = 0.00$, $2^{-0.20}$, $d = 3$, $d = 0.2$; $P = 0.25$; $P = 0.05$; and $E = 0.00$, $2^{-0.20}$, $d = 3$, $d = 0.2$; $P = 0.05$; and $E = 0.00$; $2^{-0.20}$, $d = 3$, $d = 0.00$; $P = 0.25$; $P = 0.05$; and $E = 0.00$; $2^{-0.20}$, $d = 3$, $d = 0.00$; $P = 0.25$; $P = 0.05$; and $E = 0.00$; $2^{-0.20}$, $d = 3$, $d = 0.00$; $P = 0.00$; and $E = 0.00$; $P = 0.00$; $P = 0.00$; $P = 0.00$; P = 0.05; $P = 0.00$; $P = 0.00$; $P = 0.05$; $P = 0.05$; P = 0.05; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; P = 0.05; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; P = 0.05; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; P = 0.05; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; $P = 0.05$; P = 0.05; $P = 0.05$; $P =$	()									
$ \frac{1}{164} \frac{1}{162} \frac{1}{162} \frac{1}{163} \frac{1}{162} \frac{1}{164} \frac{1}{1663} \frac{1}{162} \frac{1}{164} \frac{1}{1663} \frac{1}{164} \frac$							154			
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Subtotal (95% CI)			776			659			◆
rais et al (2014) ²¹ 0 0 0 12 2.66 2.14 13 Not estimable construct al (2013) ²¹ -0.4 2.47 316 -0.1 2.4 321 16.3 -0.12 (-0.28.0.03) -0.12 (-0.28.0.03) -0.12 (-0.28.0.03) -0.12 (-0.28.0.27.0.16) -0.12 (-0.28.0.27.0.16) -0.12 (-0.28.0.27.0.16) -0.11 1.5 2.67 13.6 -0.16 (-0.28.0.22.0.2) -0.11 1.5 2.67 13.6 -0.16 (-0.28.0.22.0.2) -0.11 1.5 2.67 13.6 -0.16 (-0.28.0.22.0.2) -0.11 1.5 2.67 13.6 -0.16 (-0.28.0.2.0.2) -0.11 1.5 2.67 13.6 -0.16 (-0.28.0.2.0.2) -0.11 1.5 2.67 13.6 -0.16 (-0.28.0.2.0.2) -0.11 -0.12 (-0.18, -0.06) -0.25 0.02 (-0.29.0.1) -0.12 (-0.18, -0.06) -0.25 0.02 (-0.29.0.1) -0.12 (-0.18, -0.06) -0.12 (-0.18, -0.06) -0.25 0.02 (-0.29.0.1) -0.5 -0.25 0 0 0.25 0.3 -0.25 0.0 -0.2			0.92); /²=0%							
$ \begin{array}{c} \mbodel{transmin} criate(2013)^{12} & -0.4 & 2.47 & 318 & -0.1 & 2.4 & 321 & 16.3 & -0.12 (-2.02, 0.03) \\ \mbodel{transmin} criate(3013)^{12} & -0.65 & 2.85 & 159 & -0.5 & 2.67 & 155 & 8.3 & -0.05 (-0.27, 0.16) \\ \mbodel{transmin} criate(3008)^{12} & -0.1 & 1.16 & 270 & 100 & 5.6 & -0.06 (-0.32, 0.21) \\ \mbodel{transmin} criate(3008)^{12} & -0.1 & 1.16 & 270 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(3008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 200 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(3008)^{12} & -0.1 & 1.64 & 210 & 1.270 & 64.3 & -0.09 (-0.20, 0.11) \\ \mbodel{transmin} criate(3008)^{12} & 0.2 & 2.02 & 103 & 0.4 & 2.55 & 189 & 9.8 & -0.09 (-0.20, 0.10) \\ \mbodel{transmin} criate(3008)^{12} & -0.1 & 1.64 & 210 & -0.12 (-0.18, -0.06) \\ \mbodel{transmin} criate(35\% Cl) & 2.04 & 1.370 & 100 & -0.12 (-0.18, -0.06) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.27 & 191 & 0.2 & 1.36 & 190 & 9.7 & -0.23 (-0.43, -0.03) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.27 & 191 & 0.2 & 1.36 & 190 & 9.7 & -0.23 (-0.43, -0.03) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & 0.00 (-0.19, 0.19) \\ \mbodel{transmin} criate(32008)^{12} & -0.1 & 1.4 & 212 & -0.1 & 1.64 & 209 & 10.8 & -0.61 (-0.32, 0.01) \\ \mbodel{transmin} criate(32008)^{12} & -0.4 & 2.47 & 318 & -0.1 & 2.4 & 321 & 16.3 & -0.12 (-0.28, 0.03) \\ trans$	Combination therapy									
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Araki et al (2014)22	0	0	12	2.69	2.14	13		Not estimable	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Grossberg et al (2013)23	-0.4	2.47	318	-0.1	2.4	321	16.3	-0.12 (-0.28, 0.03)	_ _
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akamura et al (2016) ¹⁶ -0.1 1.16 267 0.1 1.5 267 13.6 -0.15 (2.0.2.0.2) orderlessone et al (2008) ²⁶ -0.1 1.4 212 -0.1 1.64 209 10.8 -0.06 (-0.19.0.19) ariot et al (2004) ²⁶ 0.2 2.02 193 0.4 2.55 189 9.8 -0.09 (-0.2.9.0.1) ubtolal (95% C) 1.270 1.270 1.270 1.273 6.4.3 -0.09 (-0.2.9.0.1) based terrogenetic: $z^{2}=2.02$ ($z^{2}=0.03$) otal (95% C) 2.20 ($z^{2}=0.03$) based for subgroup differences: $z^{2}=1.63$. $dr=1$ ($P=0.29$); $P=38.6\%$ Favors (memantine) Favors (control Weight SMD V, random, 95% Cl SM	. ,									
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ariot et al (2004) ²¹ 0.2 2.02 193 0.4 2.55 188 9.8 -0.06 (-0.29, 0.11) utotal (95% CI) 1.273 64.3 -0.09 (-0.17, -0.01) teterogenetiy: t^2 =0.00; t^2 =1.65, dr =5 (P =0.89); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=2.0 (P =0.08); P =0% est for overall effect: Z=0.02; t^2 =2.58, df =1 (P =0.11); P =61% est for overall effect: Z=0.09 (P =0.33) ideterogenetiy: t^2 =0.02; t^2 =2.58, df =1 (P =0.11); P =61% est for overall effect: Z=0.09 (P =0.33) ideterogenetiy: t^2 =0.02; t^2 =2.58, df =1 (P =0.11); P =61% est for overall effect: Z=0.09 (P =0.33) ideterogenetig: t^2 =0.02 (D =0.1 1.12; P =0.1 2.2 6.9 2.14 13 Not estimable rootsetler gat (2013) ²¹ - 0.4 2.47 318 -0.1 2.44 321 16.3 -0.12 (C -28, 0.03) est for overall effect: Z=0.09 (P =0.33) idetart-10.6 2.26 5 159 -0.2 5 159 -0.2 5 158 -0.2 (C -0.04 (O -0.51 0.69 (P =0.32) idetart-10.6 2.26 2.9560721 109 -0.11009174 2.9006367 109 5.6 -0.06 (C -32, 0.02) est for overall effect: Z=0.37 (P =0.0007) idetart-10.6 2.20 13 0.4 2.55 189 9.8 -0.09 (C -0.25 0.00 0.4 1005 100 -0.12 (C -0.18, -0.06 (C -23, 0.01) est for overall effect: Z=3.37 (P =0.0007) est for ove										-
ububble (95% C) 1,270 1,273 64.3 $-0.09(-0.17, -0.01)$ eterogeneity: $t^2=0.00$, $t^2=1.65$, $df=5$ ($P=0.89$); $P=0\%$ 1,273 64.3 $-0.09(-0.17, -0.01)$ otal (95% C) 2,046 1,932 100 $-0.12(-0.18, -0.06)$ otal (95% C) 2,046 1,932 100 $-0.12(-0.18, -0.06)$ set for overall effect: Z=370 ($P=0.0002$): $P=38.6\%$ Favors (memantine) Favors (control Vice) set for subgroup differences: $t^{2}=1.63$, $df=1$ ($P=0.20$): $P=38.6\%$ $P=38.6\%$ SMD IV, random, 95% CI SMD IV, random, 95% CI ibido-modente eskind et al (2006) ²⁶ -0.1 1.27 101 0.2 1.38 190 9.7 -0.23 ($-0.43, -0.03$) orstemsson et al (2006) ²⁶ -0.1 1.27 101 0.2 1.38 190 9.7 -0.23 ($-0.43, -0.03$) orstemsson et al (2006) ²⁶ -0.1 1.4 212 -0.1 1.64 209 108 $0.00 (-0.19, 0.19)$ $0.00 (-0.19, 0.19)$ otartate-osevere rad (2013) ²⁶ -0.4 2.77 18.6 0.3 $-0.06 (-0.27, 0.16)$ $-0.16 (-0.32, 0.21)$,	
$\frac{1}{195\%} (1) = \frac{1}{1000} (1) = \frac{1}{100} $		0.2	2.02		0.4	2.00				•
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Heterogeneity: $\tau^2=0.00$; $\chi^2=$		0.89); /²=0%	.,			.,	••	,,	•
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Total (95% CI)	- (,		2,046			1,932	100	-0.12 (-0.18, -0.06)	•
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $			0.93); /²=0%							
Severity of disease tudy or Mean SD Total Control Mean SD Total (%) SMD IV, random, 95% Cl SMD IV, random, 95% C		. ,	(D=0.00) /2	-20.00/						
tudy or ubgroup Memantine Mean SD Total Control Mean SD Total Weight (%) SMD IV, random, 95% CI SMD IV, random, 95% CI lidd-to-moderate eskind et al (2008) ³⁰ -0.1 1.27 191 0.2 1.36 190 9.7 -0.23 (-0.43, -0.03) orsteinsson et al (2008) ³⁰ -0.1 1.4 212 -0.1 1.64 209 1.08 0.00 (-0.19, 0.19) ubtotal (95% CI) 403 399 20.4 -0.11 (-0.33, 0.11) -0.11 (-0.33, 0.11) leterogeneity: r ² =0.02; r ² =2.58, df=1 (P=0.11); P=61% 403 399 20.4 -0.11 (-0.28, 0.03) orderate-to-severe trak et al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 165 8.3 -0.06 (-0.22, 0.21) ermann et al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 165 8.3 -0.06 (-0.22, 0.21) akamure et al (2011) ¹⁴ -0.15 1.68 217 0.13 1.9 208 10.8 -0.16 (-0.43, 0.05) akamure et al (2011) ¹⁴ -0.15 1	rest for subgroup difference	s. χ1.03, u1-	1 (F=0.20), F	-30.0%						Favors (memantine) Favors (control)
ubgroup Mean SD Total Mean SD Total (%) random, 95% Cl random, 95% Cl Hild-to-moderate eskind tal (2006) ²⁰ -0.1 1.27 191 0.2 1.36 190 9.7 -0.23 (-0.43, -0.03) orsteinsson et al (2008) ²⁰ -0.1 1.4 212 -0.1 1.64 209 10.8 0.00 (-0.19, 0.19) ubtotal (95% Cl) 403 399 20.4 -0.11 (-0.33, 0.11) -0.11 (-0.33, 0.11) uetrogeneity: r ² =0.02; r ² =2.58, df=1 (P=0.11); l ² =61% 403 399 20.4 -0.11 (-0.33, 0.11) orsteinsson et al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 165 8.3 -0.05 (-0.27, 0.16) worard et al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 156 8.3 -0.05 (-0.27, 0.16) worard et al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 158 8.3 -0.06 (-0.32, 0.21) -0.11 itamura et al (2011) ¹⁴ -0.15 1.68 <td< th=""><th>Severity of disease</th><th>•</th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></td<>	Severity of disease	•								
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or subgroup	Memantine			Control					
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Mean	SD	Total		SD	Total			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mild-to-moderate	Mean	SD	Total		SD	Total			
ubtotal (95% Cl) 403 399 20.4 -0.11 (-0.33, 0.11) teterogeneity: r ² =0.02; y ² =2.58, df=1 (P=0.11); l ² =61% 98 P=0.11); l ² =61% test or overall effect: Z=0.98 (P=0.33) 12 2.69 2.14 13 Not estimable trask tet al (2014) ²² 0 0 12 2.69 2.14 13 Not estimable trask tet al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 165 8.3 -0.05 (-0.27, 0.16) oward et al (2012) ¹⁶ -0.27522936 2.9560721 09 0.11009174 2.9006367 109 5.6 -0.06 (-0.32, 0.21) itamura et al (2011) ¹⁴ -0.15 1.68 217 0.13 1.9 208 10.8 -0.16 (-0.35, 0.03) akamura et al (2011) ¹⁴ -0.15 1.68 217 0.13 1.9 208 10.8 -0.06 (-0.23, 0.02) atiat (2007) ¹¹ -0.2 3.4 161 0.2 3 154 -0.12 (-0.29, 0.11) -0.12 (-0.19, -0.05) atiot et al (2007) ¹¹ -0.2 3.4 161 0.2 3 153 79.6 <	Mild-to-moderate				Mean			(%)	random, 95% CI	
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est for overall effect: $Z=0.98$ ($P=0.33$) loderate-to-severe raki et al (2014) ²² 0 0 12 2.69 2.14 13 Not estimable irossberg et al (2014) ²² 0 0 12 2.69 2.14 13 Not estimable irossberg et al (2013) ²⁴ -0.4 2.47 318 -0.1 2.4 321 16.3 -0.12 (-0.28, 0.03) oward et al (2013) ²⁴ -0.65 2.85 159 -0.5 2.67 165 8.3 -0.05 (-0.27, 0.16) oward et al (2011) ¹⁷ -0.246 1.679 207 0.07 1.9 107 7.2 -0.18 (-0.41, 0.05) akamura et al (2011) ¹⁷ -0.15 1.68 217 0.13 1.9 208 10.6 -0.5 (-0.32, 0.02) ariot et al (2007) ¹⁶ 0.2 2.02 193 0.4 2.55 189 9.8 -0.09 (-0.29, 0.11) ariot et al (2007) ¹⁶ 0.2 3.4 161 0.2 3 154 8.0 -0.12 (-0.18, -0.06) eterogeneity: $r^2=0.00; r^2=1.18, df=7$ (P=0.93); P=0% est f	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵	-0.1	1.27	191 212	Mean 0.2	1.36	190 209	(%) 9.7 10.8	random, 95% CI -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19)	
raki et al $(2014)^{32}$ 0 0 12 2.69 2.14 13 Not estimable rorossberg et al $(2013)^{32}$ -0.4 2.47 318 -0.1 2.4 321 16.3 -0.12 (-0.28, 0.03) errmann et al $(2013)^{34}$ -0.65 2.85 159 -0.5 2.67 165 8.3 -0.05 (-0.27, 0.16) loward et al $(2012)^{16}$ -0.27522936 2.9560721 109 -0.11009174 2.9006367 109 5.6 -0.06 (-0.32, 0.21) ritamura et al $(2011)^{17}$ -0.246 1.679 207 0.07 1.9 107 7.2 -0.18 (-0.41, 0.05) akamura et al $(2011)^{16}$ -0.1 1.68 217 0.13 1.9 208 10.8 -0.16 (-0.35, 0.03) akamura et al $(2011)^{16}$ -0.1 1.16 267 0.1 1.5 267 13.6 -0.15 (-0.32, 0.02) ariot et al $(2007)^{21}$ -0.2 3.4 161 0.2 3 154 8.0 -0.12 (-0.28, 0.10) ubtotal $(95\% CI)$ 1,64 1,00 eterogeneity: r^2 -0.00; r^2 =1.18, df=7 (P=0.99); P=0\% est for overall effect: Z=3.70 (P=0.093); P=0\% est for overall effect: Z=3.70 (P=0.093); P=0\%	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI)	-0.1 -0.1	1.27 1.4	191 212	Mean 0.2	1.36	190 209	(%) 9.7 10.8	random, 95% CI -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: <i>τ</i> ² =0.02; <i>χ</i> ² =2	-0.1 -0.1 2.58, <i>df</i> =1 (<i>P</i> =0	1.27 1.4	191 212	Mean 0.2	1.36	190 209	(%) 9.7 10.8	random, 95% CI -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19)	
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oward et al (2012) ¹⁶ -0.27522936 2.9560721 109 -0.11009174 2.9006367 109 5.6 -0.06 -0.32 0.21) itamura et al (2011) ¹⁷ -0.246 1.679 207 0.07 1.9 007 7.2 -0.18 $(-0.41, 0.05)$ akamura et al (2011) ¹⁶ -0.15 1.68 217 0.13 1.9 208 10.8 -0.16 $(-0.32, 0.02)$ akamura et al (2016) ¹⁵ -0.1 1.16 267 0.1 1.5 267 13.6 -0.15 $(-0.32, 0.02)$ ariot et al (2007) ²¹ 0.2 2.02 193 0.4 2.55 189 9.8 $-0.09 (-0.29, 0.11)$ an Dyck et al (2007) ²¹ -0.2 3.4 161 0.2 3 154 8.0 $-0.12 (-0.35, 0.10)$ ubtotal (95% Cl) 1.643 1.533 79.6 $-0.12 (-0.18, -0.06)$ $-0.12 (-0.18, -0.06)$ eterogeneity: $r^2=0.00; r^2=3.78$, $dr=9 (P=0.93); l^2=0\%$ $eterogeneity: r^2=3.70 (P=0.0002)$ $-0.5 - 0.25$ 0 0.25 0	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: τ^2 =0.02; χ^2 =2	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33)	1.27 1.4 9.11); J ² =61%	191 212 403	0.2 -0.1	1.36 1.64	190 209 399	(%) 9.7 10.8	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11)	
itamura et al $(2011)^{17}$ -0.246 1.679 207 0.07 1.9 107 7.2 -0.18 (-0.41, 0.05) akamura et al $(2011)^{14}$ -0.15 1.68 217 0.13 1.9 208 10.8 -0.16 (-0.35, 0.03) akamura et al $(2016)^{15}$ -0.1 1.16 267 0.1 1.5 267 13.6 -0.15 (-0.32, 0.02) an Dyck et al $(2007)^{21}$ -0.2 3.4 161 0.2 3 154 8.0 -0.12 (-0.35, 0.10) an Dyck et al $(2007)^{21}$ -0.2 3.4 161 0.2 3 154 8.0 -0.12 (-0.35, 0.10) abetrogeneity: r^2 -0.00; χ^2 =1.18, df=7 (P=0.99); l ² =0% est for overall effect: Z=3.37 (P=0.0917) otal (95% CI) 2,046 1,932 100 -0.12 (-0.18, -0.06) eterogeneity: r^2 -0.00; χ^2 =3.78, df=9 (P=0.93); l ² =0% est for overall effect: Z=3.70 (P=0.0902) -0.25 0 0.25 0	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =: Test for overall effect: Z=0.9 Moderate-to-severe	-0.1 -0.1 2.58, <i>df</i> =1 (<i>P</i> =0 8 (<i>P</i> =0.33) 0	1.27 1.4 0.11); I ² =61% 0	191 212 403 12 318	Mean 0.2 -0.1 2.69 -0.1	1.36 1.64 2.14 2.4	190 209 399 13 321	(%) 9.7 10.8 20.4 16.3	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Peskind et al $(2006)^{20}$ Porsteinsson et al $(2008)^{25}$ Subtotal (95% CI) Heterogeneity: $r^2=0.02$; $\chi^2=$: Test for overall effect: Z=0.9 Moderate-to-severe Araki et al $(2014)^{22}$	-0.1 -0.1 2.58, <i>df</i> =1 (<i>P</i> =0 8 (<i>P</i> =0.33) 0 -0.4	1.27 1.4 0.11); /²=61% 0 2.47	191 212 403 12 318	Mean 0.2 -0.1 2.69 -0.1	1.36 1.64 2.14 2.4	190 209 399 13 321	(%) 9.7 10.8 20.4 16.3	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =7 Test for overall effect. Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65	1.27 1.4 0.11); I ² =61% 0 2.47 2.85	191 212 403 12 318 159	0.2 -0.1 2.69 -0.1 -0.5	1.36 1.64 2.14 2.4 2.67	190 209 399 13 321 165	(%) 9.7 10.8 20.4 16.3 8.3	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.02; r^{2=1}$ Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Herrmann et al (2013) ²⁴ Howard et al (2012) ¹⁶	-0.1 -0.1 2.58, <i>df</i> =1 (<i>P</i> =0 8 (<i>P</i> =0.33) 0 -0.4 -0.65 -0.27522936	1.27 1.4 0.11); / ² =61% 0 2.47 2.85 2.9560721	191 212 403 12 318 159 109	0.2 -0.1 2.69 -0.1 -0.5 -0.11009174	1.36 1.64 2.14 2.4 2.67 2.9006367	190 209 399 13 321 165 109	(%) 9.7 10.8 20.4 16.3 8.3 5.6	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21)	
ariot et al $(2004)^{36}$ 0.2 2.02 193 0.4 2.55 189 9.8 $-0.09(-0.29, 0.11)$ an Dyck et al $(2007)^{21}$ -0.2 3.4 161 0.2 3 154 8.0 $-0.12(-0.35, 0.10)$ ubtotal (95% CI) 1,643 1,533 79.6 $-0.12(-0.19, -0.05)$ eterogeneity: $r^2=0.00; r^2=1.18, df=7$ (P=0.99); $l^2=0\%$ est for overall effect: Z=3.37 (P=0.0007) otal (95% CI) 2,046 1,932 100 $-0.12(-0.18, -0.06)$ eterogeneity: $r^2=0.00; r^2=3.78, df=9$ (P=0.93); $l^2=0\%$ est for overall effect: Z=3.70 (P=0.0002) $-0.5 -0.25 0 0.25 0$	Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.02$; $\chi^2=:$ Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ³⁴	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246	1.27 1.4 0.11); l ² =61% 0 2.47 2.85 2.9560721 1.679	191 212 403 12 318 159 109 207	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07	1.36 1.64 2.14 2.4 2.67 2.9006367 1.9	190 209 399 13 321 165 109 107	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05)	
an Dyck et al $(2007)^{21}$ -0.2 3.4 161 0.2 3 154 8.0 -0.12 (-0.35, 0.10) ubtotal (95% Cl) 1,643 1,533 79.6 -0.12 (-0.19, -0.05) leterogeneity: $t^2=0.00; \chi^2=1.18, df=7$ (P=0.99); $l^2=0\%$ est for overall effect: Z=3.37 (P=0.0007) otal (95% Cl) 2,046 1,932 100 -0.12 (-0.18, -0.06) eterogeneity: $t^2=0.00; \chi^2=3.78, df=9$ (P=0.93); $l^2=0\%$ est for overall effect: Z=3.70 (P=0.0002) -0.52 0 0.25 0	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁶ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =; Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Herrman et al (2013) ²⁴ Howard et al (2012) ¹⁶ Kitamura et al (2011) ¹⁷	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.25	1.27 1.4 0.11); l ² =61% 0 2.47 2.85 2.9560721 1.679 1.68	191 212 403 12 318 159 109 207 217	0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13	1.36 1.64 2.14 2.4 2.67 2.9006367 1.9 1.9	190 209 399 13 321 165 109 107 208	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.08 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.45, 0.03)	
ubtotal (95% Cl) 1,643 1,533 79.6 -0.12 (-0.19, -0.05) teterogeneity: x²=0.00; x²=1.18, df=7 (P=0.99); l²=0% est for overall effect: Z=3.77 (P=0.007) otal (95% Cl) 2,046 1,932 100 -0.12 (-0.18, -0.06) teterogeneity: x²=0.00; x²=3.78, df=9 (P=0.93); l²=0% est for overall effect: Z=3.70 (P=0.0002) -0.55 0 0.25 0	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =; Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2013) ²⁴ Howard et al (2013) ⁴⁶ Kitamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁵	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1	1.27 1.4 0.11); /2=61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16	191 212 403 12 318 159 109 207 217 267	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.1 -0.1 0.07 0.13 0.1	1.36 1.64 2.14 2.4 2.67 2.9006367 1.9 1.5	190 209 399 13 321 165 109 107 208 267	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.32, 0.02)	
leterogeneity: t ² =0.00; χ^2 =1.18, df=7 (P=0.99); l ² =0% est for overall effect: Z=3.37 (P=0.0007) otal (95% Cl) 2,046 1,932 100 -0.12 (-0.18, -0.06) leterogeneity: t ² =0.00; χ^2 =3.78, df=9 (P=0.93); l ² =0% est for overall effect: Z=3.70 (P=0.0002) -0.5 -0.25 0 0.25 0	Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =; Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014)³² Aramman et al (2013) ³⁴ Howard et al (2012) ⁴⁸ (Xiamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁶ Tariot et al (2004) ³⁸	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2	1.27 1.4 0.11); l ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02	191 212 403 12 318 159 109 207 217 267 193	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.05 (-0.29, 0.11)	
est for overall effect: Z=3.37 (P=0.0007) otal (95% CI) 2,046 1,932 100 -0.12 (-0.18, -0.06) teterogeneity: r ² =0.00; z ² =3.78, df=9 (P=0.93); l ² =0% est for overall effect: Z=3.70 (P=0.0002) -0.5 0 0.25 0	Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =: Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ³³ Herrmann et al (2013) ³³ Howard et al (2013) ³⁴ Howard et al (2013) ³⁴ Howard et al (2013) ³⁵ Kitamura et al (2011) ¹⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ³⁵ Tariot et al (2004) ³⁶ van Dyck et al (2007) ²⁷	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2	1.27 1.4 0.11); l ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02	191 212 403 12 318 159 207 217 267 193 161	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189 154	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8 8.0	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.15 (-0.32, 0.02) -0.09 (-0.29, 0.11) -0.12 (-0.35, 0.10)	
leterogeneity: r²=0.00; r²=3.78, df=9 (P=0.93); l²=0% est for overall effect: Z=3.70 (P=0.0002)	Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.02; \chi^2=:$ Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ³³ Hermrann et al (2013) ³³ Howard et al (2013) ³⁴ Howard et al (2013) ³⁶ Howard et al (2013) ³⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2016) ¹⁵ Tariot et al (2004) ³⁶ van Dyck et al (2007) ²¹ Subtotal (95% CI)	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2 -0.1 0.2 -0.2	1.27 1.4 .11); <i>I</i> ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02 3.4	191 212 403 12 318 159 207 217 267 193 161	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189 154	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8 8.0	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.15 (-0.32, 0.02) -0.09 (-0.29, 0.11) -0.12 (-0.35, 0.10)	
est for overall effect: Z=3.70 (P=0.0002) -0.5 -0.25 0 0.25 0	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁶ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =; Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Torsosberg et al (2014) ²³ Horward et al (2012) ¹⁸ (diamura et al (2012) ¹⁹ (diamura et al (2011) ¹⁷ Vakamura et al (2011) ¹⁷ Vakamura et al (2016) ¹⁵ Tariot et al (2004) ²⁸ Araiot et al (2004) ²⁷ Subtotal (95% CI) Heterogeneity: r^2 =0.00; χ^2 =	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2 -0.2 118, df=7 (P=0	1.27 1.4 .11); <i>I</i> ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02 3.4	191 212 403 12 318 159 207 217 267 193 161	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189 154	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8 8.0	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.15 (-0.32, 0.02) -0.09 (-0.29, 0.11) -0.12 (-0.35, 0.10)	
	Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: r^2 =0.02; χ^2 =: Fest for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ³³ Hermrann et al (2013) ³³ Howard et al (2013) ³⁴ Howard et al (2013) ³⁵ Howard et al (2013) ³⁶ Howard et al (2013) ³⁶ Howard et al (2013) ³⁶ Fariot et al (2007) ²⁷ Subtotal (95% CI) Heterogeneity: r^2 =0.00; χ^2 = Fest for overall effect: Z=3.3	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2 -0.2 118, df=7 (P=0	1.27 1.4 .11); <i>I</i> ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02 3.4	191 212 403 12 318 159 109 207 217 267 193 161 1,643	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8 8.0 79.6	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.15 (-0.32, 0.02) -0.09 (-0.29, 0.11) -0.12 (-0.19, -0.05)	
est for subgroup differences: $\chi^2=0.01$, df=1 (P=0.94); l ² =0% Favors (memantine) Favors (contro	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁶ Subtotal (95% CI) Heterogeneity: r^2 =0.02; $\chi^{2=;}$ Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²⁴ Hermann et al (2013) ²⁴ Howard et al (2013) ²⁴ Howard et al (2011) ¹⁷ Vakamura et al (2011) ¹⁷ Vakamura et al (2011) ¹⁹ Tariot et al (2004) ²⁶ ran Dyck et al (2004) ²⁶ ran Dyck et al (2007) ²⁷ Subtotal (95% CI) Heterogeneity: r^2 =0.00; χ^2 =; Test for overall effect: Z=3.3	-0.1 -0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2 -0.1 0.2 -0.2 1.18, df=7 (P=0 7 (P=0.0007) 3.78, df=9 (P=0	1.27 1.4 1.11); <i>I</i> ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02 3.4 9.99); <i>I</i> ² =0%	191 212 403 12 318 159 109 207 217 267 193 161 1,643	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8 8.0 79.6	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.15 (-0.32, 0.02) -0.09 (-0.29, 0.11) -0.12 (-0.19, -0.05)	random, 95% Cl
	Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁶ Subtotal (95% CI) Heterogeneity: $r^2=0.02$, $\chi^2=$: Test for overall effect: Z=0.9 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Hermann et al (2013) ²⁴ Howard et al (2013) ²⁶ Howard et al (2011) ¹⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2007) ²¹ Subtotal (95% CI) Heterogeneity: $r^2=0.00$; $\chi^2=$ Test for overall effect: Z=3.3 Total (95% CI)	-0.1 -0.1 2.58, df=1 (P=0 8 (P=0.33) 0 -0.4 -0.65 -0.27522936 -0.246 -0.15 -0.1 0.2 -0.2 1.18, df=7 (P=0 7 (P=0.0007) 3.78, df=9 (P=0 0 (P=0.0002)	1.27 1.4 .11); <i>l</i> ² =61% 0 2.47 2.85 2.9560721 1.679 1.68 1.16 2.02 3.4 3.4 3.99); <i>l</i> ² =0%	191 212 403 12 318 159 109 207 217 267 193 161 1,643 2,046	Mean 0.2 -0.1 2.69 -0.1 -0.5 -0.11009174 0.07 0.13 0.1 0.4	1.36 1.64 2.14 2.4 2.9006367 1.9 1.9 1.5 2.55	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 9.7 10.8 20.4 16.3 8.3 5.6 7.2 10.8 13.6 9.8 8.0 79.6	random, 95% Cl -0.23 (-0.43, -0.03) 0.00 (-0.19, 0.19) -0.11 (-0.33, 0.11) Not estimable -0.12 (-0.28, 0.03) -0.05 (-0.27, 0.16) -0.06 (-0.32, 0.21) -0.18 (-0.41, 0.05) -0.16 (-0.35, 0.03) -0.15 (-0.32, 0.02) -0.09 (-0.29, 0.11) -0.12 (-0.19, -0.05)	random, 95% Cl

Figure 2 Forest plot of delusion scores.

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

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% Cl	SMD IV, random, 95% CI
• •	Mean	08	Total	Mean	08	Total	(70)		
Monotherapy Kitamura et al (2011) ¹⁷	0.0207	1.881	207	0.36	1.77	107	9.4	-0.18 (-0.42, 0.05)	
Peskind et al (2006)20	0	1.01	191	-0.1	1.02	190	12.8	0.10 (-0.10, 0.30)	-
()	0	2.3	161	-0.1	2.2	154	12.6		
an Dyck et al (2007) ²¹	0	2.5	559	0.2	2.2	451	32.7	-0.09 (-0.31, 0.13)	
Subtotal (95% CI)	0 45	0 40) 12-400/	559			451	32.1	-0.05 (-0.21, 0.12)	
leterogeneity: $\tau^2=0.01$; $\chi^2=3$ est for overall effect: Z=0.5		0.16), /-=42%							
ombination therapy									
vraki et al (2014)22	-0.08	0.29	12	1.54	2.67	13	0.8	-0.81 (-1.63, 0.01)	
Grossberg et al (2013) ²³	-0.2	1.85	318	0	1.71	321	21.4	-0.11 (-0.27, 0.04)	
Herrmann et al (2013) ²⁴	-0.39	2.28	159	-0.1	2.12	165	10.8	-0.13 (-0.35, 0.09)	
loward et al (2012)18	0.05504587	2.5813966	109	0.12844037	2.2073149	109	7.3	-0.03 (-0.30, 0.24)	
Porsteinsson et al (2008)25	0	1.49	212	0.1	1.6	209	14.1	-0.06 (-0.26, 0.13)	
ariot et al (2004) ²⁶	0	2.01	193	0.1	1.81	189	12.8	-0.05 (-0.25, 0.15)	
Subtotal (95% CI)	~	2.01	1,003	0.1		1,006	67.3	-0.09 (-0.18, -0.01)	▲
leterogeneity: $\tau^2=0.00$; $\chi^2=3$	3 54 df=5 (P-	0.62): /2=0%	1,003			1,000	57.5	-0.03 (-0.10, -0.01)	•
est for overall effect: Z=2.0		0.02), 7 -078							
otal (95% CI)			1.562			1.457	100	-0.08 (-0.15, -0.00)	•
Heterogeneity: $\tau^2=0.00$; $\chi^2=7$	7.40, df=8 (P=	0.49); /²=0%	.,			.,			
		.,,							-1 -0.5 0 0.5 1
est for subgroup differences	s: χ ² =0.21, df=	:1 (<i>P</i> =0.65); I ²	=0%						Favors (memantine) Favors (control
est for subgroup difference: Severity of disease	s: χ ² =0.21, df=	:1 (P=0.65); I ²	=0%	Control			Weight	SMD IV,	
est for subgroup difference Severity of disease tudy or	s: χ ² =0.21, df=	1 (<i>P</i> =0.65); / ² SD	=0% Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% Cl	Favors (memantine) Favors (control
est for subgroup difference Severity of disease Study or Jubgroup	s: χ²=0.21, <i>df</i> = Memantine				SD	Total			Favors (memantine) Favors (control
est for subgroup difference Severity of disease study or ubgroup fild-to-moderate	s: χ²=0.21, <i>df</i> = Memantine				SD	Total			Favors (memantine) Favors (control
est for subgroup difference: Severity of disease tudy or ubgroup Nild-to-moderate teskind et al (2006) ²⁰	s: χ^2 =0.21, df= Memantine Mean	SD	Total	Mean	-		(%)	random, 95% CI	Favors (memantine) Favors (control
est for subgroup difference Severity of disease tudy or ubgroup tild-to-moderate eskind et al (2006) ²⁰ orsteinsson et al (2008) ²⁵	s: χ^2 =0.21, df= Memantine Mean	SD	Total	Mean -0.1	1.02	190	(%)	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13)	Favors (memantine) Favors (control
est for subgroup difference: Severity of disease tudy or ubgroup lild-to-moderate eskind et al (2006) ²⁰ forsteinsson et al (2008) ²⁵ ubtotal (85% CI)	s: χ ² =0.21, <i>df</i> = Memantine Mean 0 0	SD 1.01 1.49	Total 191 212	Mean -0.1	1.02	190 209	(%) 12.8 14.1	random, 95% Cl 0.10 (-0.10, 0.30)	Favors (memantine) Favors (control
est for subgroup difference: ieverity of disease tudy or ubgroup iiid-to-moderate eskind et al (2006) ²⁰ orsteinsson et al (2008) ²¹ ubtotal (95% CI) eterogeneity: $r^2=0.00; x^2=r$	s: χ ² =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1	SD 1.01 1.49	Total 191 212	Mean -0.1	1.02	190 209	(%) 12.8 14.1	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13)	Favors (memantine) Favors (control
Severity of disease tudy or ubgroup tild-to-moderate eskind et al (2006) ²⁰ orsteinsson et al (2008) ³¹ ubtotal (95% CI) leterogeneity: $t^2=0.00; \chi^2=1$	s: χ ² =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1	SD 1.01 1.49	Total 191 212	Mean -0.1	1.02	190 209	(%) 12.8 14.1	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13)	Favors (memantine) Favors (control
est for subgroup difference: Severity of disease tudy or ubgroup Mid-to-moderate teskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ subtotal (95% CI) leterogeneily: $r^2=0.00; \chi^2=r$ est for overall effect: Z=0.1 Moderate-to-severe	s: χ^2 =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.08	SD 1.01 1.49	Total 191 212	Mean -0.1 0.1	1.02	190 209 399 13	(%) 12.8 14.1 26.9 0.8	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13)	Favors (memantine) Favors (control
est for overall effect: Z=2.0 rest for subgroup difference: Severity of disease study or ubgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Jubtotal (8% CI) leterogeneity: r^2 =0.00; χ^2 = rest for overall effect: Z=0.1 Moderate-to-severe vraki et al (2014) ²² Torosberg et al (2013) ²³	s: x ² =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=0 7 (P=0.87)	SD 1.01 1.49 0.25); <i>I</i> ² =25%	Total 191 212 403	Mean -0.1 0.1	1.02 1.6	190 209 399	(%) 12.8 14.1 26.9	random, 95% Cl 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17)	Favors (memantine) Favors (control
The state of the	s: χ^2 =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.08	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29	Total 191 212 403 12	Mean -0.1 0.1	1.02 1.6 2.67	190 209 399 13	(%) 12.8 14.1 26.9 0.8	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.81 (-1.63, 0.01)	Favors (memantine) Favors (control
est for subgroup difference: Severity of disease itudy or ubgroup Mild-to-moderate reskind et al (2006) ²⁵ ubtotal (95% CI) leterogeneity: $r^2=0.00; \chi^2=r^2$ lest for overall effect: Z=0.11 Moderate-to-severe uraki et al (2014) ²² foroskerg et al (2013) ²³	s: χ^2 =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.08 -0.2	SD 1.01 1.49 0.25); /²=25% 0.29 1.85	Total 191 212 403 12 318	Mean -0.1 0.1 1.54 0	1.02 1.6 2.67 1.71	190 209 399 13 321	(%) 12.8 14.1 26.9 0.8 21.4	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.81 (-1.63, 0.01) -0.11 (-0.27, 0.04)	Favors (memantine) Favors (control SMD IV,
est for subgroup difference: Severity of disease tudy or ubgroup Mid-to-moderate reskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ tubtotal (95% CI) letterogeneity: $t^2=0.00; \chi^2=1$ est for overall effect: Z=0.1 Moderate-to-severe traki et al (2014) ²² Prossberg et al (2013) ²³ lermmann et al (2013) ²⁴ loward et al (2021) ¹⁶	s: <i>x</i> ² =0.21, <i>df</i> = Memantine Mean 0 0 1.33, <i>df</i> =1 (<i>P</i> =1 7 (<i>P</i> =0.87) −0.08 −0.2 −0.39	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29 1.85 2.28	Total 191 212 403 12 318 159	Mean -0.1 0.1 1.54 0 -0.1	1.02 1.6 2.67 1.71 2.12	190 209 399 13 321 165	(%) 12.8 14.1 26.9 0.8 21.4 10.8	random, 95% Cl 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.81 (-1.63, 0.01) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09)	Favors (memantine) Favors (control SMD IV,
Severity of disease tudy or ubgroup lilid-to-moderate teskind et al (2006) ²⁰ orsteinsson et al (2008) ²⁵ ubtotal (95% CI) leterogeneity: $r^2=0.00; \chi^2=r$ est for overall effect: Z=0.1 loderate-to-severe raki et al (2014) ²² irossberg et al (2013) ²³ lerrman et al (2013) ²¹ loward et al (2011) ⁷¹ itamure et al (2011) ⁷²	s: χ^2 =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.08 -0.2 -0.39 0.05504587	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29 1.85 2.28 2.5813966	Total 191 212 403 12 318 159 109	Mean -0.1 0.1 1.54 0 -0.1 0.12844037	1.02 1.6 2.67 1.71 2.12 2.2073149	190 209 399 13 321 165 109	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24)	Favors (memantine) Favors (control SMD IV,
Severity of disease tudy or ubgroup lild-to-moderate eskind et al (2006) ²⁰ orsteinsson et al (2008) ²⁵ ubtotal (95% CI) leterogeneiity: $r^2=0.00; \chi^2=r$ est for overall effect: Z=0.11 loderate-to-severe raki et al (2014) ²² irrossberg et al (2013) ²³ lermrann et al (2013) ²³ lermran et al (2013) ²¹ litamura et al (2011) ¹⁷ ariot et al (2004) ³⁰	s: χ^2 =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.08 -0.2 -0.39 0.05504587 0.0207	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29 1.85 2.28 2.5813966 1.881	Total 191 212 403 12 318 159 109 207	Mean -0.1 0.1 1.54 0 -0.1 0.12844037 0.36	1.02 1.6 2.67 1.71 2.12 2.2073149 1.77	190 209 399 13 321 165 109 107	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3 9.4	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.81 (-1.63, 0.01) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24) -0.18 (-0.42, 0.05)	Favors (memantine) Favors (control SMD IV,
est for subgroup difference: Severity of disease tudy or ubgroup Nild-to-moderate eskind et al (2006) ²⁰ forsteinsson et al (2008) ²⁵ ubtotal (95% CI) letterogeneity: $r^2=0.00; \chi^2=$: est for overall effect: Z=0.1 Noderate-to-severe raki et al (2014) ²² loward et al (2013) ²³ lermmann et al (2013) ²³ loward et al (2012) ¹⁸ litamura et al (2011) ¹⁷ ariot et al (2007) ²¹	 S: x²=0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.29 -0.39 0.05504587 0.0207 0 	SD 1.01 1.49 0.25); /²=25% 0.29 1.85 2.28 2.5813966 1.881 2.01	Total 191 212 403 12 318 159 109 207 193	Mean -0.1 0.1	1.02 1.6 2.67 1.71 2.12 2.2073149 1.77 1.81	190 209 399 13 321 165 109 107 189	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3 9.4 12.8	random, 95% Cl 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24) -0.18 (-0.42, 0.05) -0.05 (-0.25, 0.15) -0.09 (-0.31, 0.13)	Favors (memantine) Favors (control SMD IV,
est for subgroup difference: Severity of disease tudy or ubgroup tild-to-moderate leskind et al (2006) ²⁰ orsteinsson et al (2008) ²⁵ ubtotal (96% CI) leterogeneity: $r^2=0.00; \chi^2=r$ est for overall effect: $Z=0.1$ toderate-to-severe raki et al (2014) ²² rossberg et al (2013) ²³ lemman et al (2013) ²⁴ loward et al (2011) ¹⁶ itamure et al (2011) ¹⁷ ariot et al (2004) ²⁸ an Dyck et al (2007) ²¹ ubtotal (95% CI)	s: χ^2 =0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.08 -0.2 -0.39 0.05504587 0.0207 0 0	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29 1.85 2.28 2.5813966 1.881 2.01 2.3	Total 191 212 403 12 318 159 109 207 193 161	Mean -0.1 0.1	1.02 1.6 2.67 1.71 2.12 2.2073149 1.77 1.81	190 209 399 13 321 165 109 107 189 154	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3 9.4 12.8 10.6	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24) -0.18 (-0.42, 0.05) -0.05 (-0.25, 0.15)	Favors (memantine) Favors (control SMD IV,
est for subgroup difference: Severity of disease tudy or ubgroup lild-to-moderate eskind et al (2006) ³⁵ orsteinsson et al (2008) ³⁵ ubtotal (95% CI) eterogeneity: $r^2=0.00; \chi^2=r$ est for overall effect: Z=0.11 loderate-to-severe raki et al (2014) ²² irrossberg et al (2013) ³³ errmann et al (2013) ³² oward et al (2013) ³¹ and byte et al (2001) ¹⁷ and tet al (2004) ²⁸ an Dyck et al (2007) ²⁷¹ ubtotal (95% CI) eterogeneity: $r^2=0.00; \chi^2=\zeta$	 s: x²=0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.2 -0.39 0.05504587 0.0207 0 0.389, df=6 (P=1 	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29 1.85 2.28 2.5813966 1.881 2.01 2.3	Total 191 212 403 12 318 159 109 207 193 161	Mean -0.1 0.1	1.02 1.6 2.67 1.71 2.12 2.2073149 1.77 1.81	190 209 399 13 321 165 109 107 189 154	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3 9.4 12.8 10.6	random, 95% Cl 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24) -0.18 (-0.42, 0.05) -0.05 (-0.25, 0.15) -0.09 (-0.31, 0.13)	Favors (memantine) Favors (control SMD IV,
est for subgroup difference: Severity of disease tudy or ubgroup fild-to-moderate teskind et al (2006) ²⁰ forsteinsson et al (2008) ²⁵ ubtotal (96% CI) leterogeneity: $r^2=0.00; \chi^2=r$ est for overall effect: $Z=0.1$ loderate-to-severe traki et al (2014) ²² forssberg et al (2013) ²³ lerrmann et al (2013) ²⁴ loward et al (2012) ¹⁸ itamura et al (2017) ¹⁷ anto et al (2004) ²⁸ an Dyck et al (2007) ²¹ ubtotal (96% CI) leterogeneity: $r^2=0.00; \chi^2=r$ est for overall effect: $Z=2.5$	 s: x²=0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.2 -0.39 0.05504587 0.0207 0 0.389, df=6 (P=1 	SD 1.01 1.49 0.25); <i>I</i> ² =25% 0.29 1.85 2.28 2.5813966 1.881 2.01 2.3	Total 191 212 403 12 318 159 109 207 193 161	Mean -0.1 0.1	1.02 1.6 2.67 1.71 2.12 2.2073149 1.77 1.81	190 209 399 13 321 165 109 107 189 154	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3 9.4 12.8 10.6	random, 95% Cl 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24) -0.18 (-0.42, 0.05) -0.05 (-0.25, 0.15) -0.09 (-0.31, 0.13)	Favors (memantine) Favors (control SMD IV,
est for subgroup difference: Severity of disease tudy or ubgroup dild-to-moderate reskind et al (2006) ²⁰ forsteinsson et al (2008) ²⁵ tubtotal (95% CI) leterogeneiity: $\tau^2=0.00; \chi^2=\tau^2$ est for overall effect: Z=0.1 Moderate-to-severe rarkit et al (2014) ²² forossberg et al (2013) ²³ lermann et al (2013) ²⁴	 s: x²=0.21, df= Memantine Mean 0 0 1.33, df=1 (P=1 7 (P=0.87) -0.2 -0.39 0.05504587 0.0207 0 0 3.89, df=6 (P=1 5 (P=0.01) 	SD 1.01 1.49 0.25); l ² =25% 0.29 1.85 2.28 2.5813966 1.881 2.01 2.3 0.69); l ² =0%	Total 191 212 403 12 318 159 109 207 193 161 1,159	Mean -0.1 0.1	1.02 1.6 2.67 1.71 2.12 2.2073149 1.77 1.81	190 209 399 13 321 165 109 107 189 154 1,058	(%) 12.8 14.1 26.9 0.8 21.4 10.8 7.3 9.4 12.8 10.6 73.1	random, 95% CI 0.10 (-0.10, 0.30) -0.06 (-0.26, 0.13) 0.01 (-0.15, 0.17) -0.11 (-0.27, 0.04) -0.13 (-0.35, 0.09) -0.03 (-0.30, 0.24) -0.18 (-0.42, 0.05) -0.05 (-0.25, 0.15) -0.09 (-0.31, 0.13) -0.11 (-0.19, -0.03)	Favors (memantine) Favors (control SMD IV,

Figure 3 Forest plot of disinhibition scores.

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

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI		SME) IV, om, 95%	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	81 (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)			<u> </u>		
Nakamura et al (2016) ¹⁵	-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)		\sim			
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	12.01, df=5 (P	=0.03); /²=58%	6										
Test for overall effect: Z=1.6	68 (P=0.09)												
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); / ² =36%	6					-	+		_		
Test for overall effect: Z=2.3	3 (P=0.02)							-	-0.5	-0.25	0	0.25	C

Figure 4 (Continued)

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	SMI	0 IV, Iom, 95% Cl	
Mild-to-moderate											
Peskind et al (2006)20	0.1	1.05	191	0.2	1.25	190	10.9	-0.09 (-0.29, 0.11)			
Porsteinsson et al (2008)25	0.4	2.32	212	0	2.05	209	11.6	0.18 (-0.01, 0.37)			-
Subtotal (95% CI)			403			399	22.5	0.05 (-0.21, 0.31)			
Heterogeneity: r ² =0.03; \chi ² =	3.60, df=1 (P=	0.06); I ² =72%									
Test for overall effect: Z=0.3	7 (P=0.71)										
Moderate-to-severe											
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 (2011)14	0	0.53	217	0.06	0.61	208	11.7	-0.10 (-0.30, 0.09)			
Nakamura et al (2016) ¹⁵	-0.1	0.57	267	0	0.6	267	13.4	-0.17 (-0.34, -0.00)			
Tariot et al (2004) ²⁶	0.2	2.57	193	0.6	2.48	189	10.9	-0.16 (-0.36, 0.04)			
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)			1,423			1,413	77.5	-0.15 (-0.22, -0.07)			
Heterogeneity: $\tau^2=0.00$; $\chi^2=$	2.63, df=6 (P=	0.85); /²=0%									
Test for overall effect: Z=3.8	7 (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); /2=36%	6						+ +		+
Test for overall effect: Z=2.3	3 (P=0.02)							-	-0.5 -0.25	0 0.25	0.5
Test for subgroup difference		1 (P=0 16) /2	=49.0%						Favors (memantine) Favors (con	trol

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% Cl	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)	
van 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)	◆
Heterogeneity: $\tau^2=0.00$; $\chi^2=2$ Test for overall effect: Z=1.9		0.51); /²=0%							
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)23	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		109	5.5	-0.15 (-0.42, 0.11)	
Nakamura et al (2012)	0.17431133	0.73	267	0.33211003	0.81	267	3.6	0.00 (-0.17, 0.17)	
Porsteinsson et al (2008)25	0.1		207	0.1	1.16	209	10.7		
· · · ·		1.47						-0.08 (-0.27, 0.12)	-
Tariot 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)		2011 12-00/	1,270			1,273	64.5	-0.04 (-0.12, 0.05)	•
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.00$ Test for overall effect: Z=0.8).36); /2=9%							
	. (
Total (95% CI) Heterogeneity: τ ² =0.00; χ ² =9	9 98 df=10 (P=	=0 44)· /2=0%	2,046			1,932	100	-0.06 (-0.12, 0.01)	•
Test for overall effect: Z=1.7		0.11), 7 070							2 -1 0 1
	9 (P=0.07)								-2 -1 0 1
Test for subgroup difference	s: χ²=0.95, df=	1 (<i>P</i> =0.33); <i>I</i> ² =	=0%						Favors (memantine) Favors (control
Test for subgroup difference		1 (<i>P</i> =0.33); <i>I</i> ² =	=0%						Favors (memantine) Favors (control
Test for subgroup difference Severity of disease	•	1 (<i>P</i> =0.33); <i>I</i> ² =	=0%						
Test for subgroup difference		1 (<i>P</i> =0.33); <i>I</i> ² =	=0% Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	Favors (memantine) Favors (control SMD IV, random, 95% Cl
Test for subgroup difference Severity of disease Study or	Memantine				SD	Total			SMD IV,
Test for subgroup difference Severity of disease Study or subgroup	Memantine				SD	Total		random, 95% Cl	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰	Memantine Mean	SD	Total	Mean			(%)	-0.19 (-0.39, 0.01)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵	Memantine Mean	SD	Total 191 212	Mean 0.2	1.07	190 209	9.6 10.7	-0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2008) ²⁶ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI)	Memantine Mean 0 0.1	SD 1.02 1.47	Total	Mean 0.2	1.07	190	(%) 9.6	-0.19 (-0.39, 0.01)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵	Memantine Mean 0 0.1 0.67, <i>df</i> =1 (<i>P</i> =0	SD 1.02 1.47	Total 191 212	Mean 0.2	1.07	190 209	9.6 10.7	-0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: r ² =0.00; χ ² =1 Test for overall effect: Z=1.8	Memantine Mean 0 0.1 0.67, <i>df</i> =1 (<i>P</i> =0	SD 1.02 1.47	Total 191 212	Mean 0.2	1.07	190 209	9.6 10.7	-0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2008) ²⁶ Porsteinsson et al (2008) ²⁶ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=t$ Test for overall effect: Z=1.8 Moderate-to-severe	Memantine Mean 0 0.1 0.67, df=1 (P=(4 (P=0.07)	SD 1.02 1.47 0.41); <i>l</i> ² =0%	Total 191 212 403	Mean 0.2 0.2	1.07 1.16	190 209 399	9.6 10.7 20.3	-0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01)	SMD IV,
Test for subgroup difference Severity of disease Study or Subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1.8$ Moderate-to-severe Araki et al (2014) ²²	Memantine Mean 0 0.1 0.67, df=1 (P=(4 (P=0.07) 0.17	SD 1.02 1.47 0.41); <i>I</i> ² =0%	Total 191 212 403 12	Mean 0.2 0.2 1.85	1.07 1.16 2.48	190 209 399 13	(%) 9.6 10.7 20.3 0.6	random, 95% Cl -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01) -0.90 (-1.73, -0.07)	SMD IV,
Test for subgroup difference Study or subgroup Mild-to-moderate Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00$, $\chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³	Memantine Mean 0 0.1 0.67, df=1 (P=(4 (P=0.07) 0.17 0	SD 1.02 1.47 0.41); /²=0% 0.39 1.83	Total 191 212 403 12 318	Mean 0.2 0.2 1.85 -0.1	1.07 1.16 2.48 1.89	190 209 399 13 321	(%) 9.6 10.7 20.3 0.6 16.2	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)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=t$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³	Memantine Mean 0 0.1 0.67, <i>df</i> =1 (<i>P</i> =(4 (<i>P</i> =0.07) 0.17 0 0.03	SD 1.02 1.47 0.41); <i>I</i> ² =0% 0.39 1.83 2.43	Total 191 212 403 12 318 159	Mean 0.2 0.2 1.85 -0.1 0.08	1.07 1.16 2.48 1.89 2.12	190 209 399 13 321 165	(%) 9.6 10.7 20.3 0.6 16.2 8.2	random, 95% Cl -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)	SMD IV,
Test for subgroup difference Severity of disease Study or Subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00$, $\chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Hermann et al (2013) ²⁴ Howard et al (2012) ¹⁸	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193	SD 1.02 1.47 0.41); f ² =0% 0.39 1.83 2.43 1.8799332	Total 191 212 403 12 318 159 109	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009	1.07 1.16 2.48 1.89 2.12 2.692819	190 209 399 13 321 165 109	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5	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)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2008) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; r^2=0.00; r^2=$	Memantine Mean 0 0.1 0.67, df=1 (P=(4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109	SD 1.02 1.47 0.41); <i>I</i> ² =0% 0.39 1.83 2.43 1.8799332 1.489	Total 191 212 403 12 318 159 109 207	Mean 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 1.36	190 209 399 13 321 165 109 107	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1	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) -0.05 (-0.42, 0.20) -0.15 (-0.42, 0.11) -0.18 (-0.41, 0.06)	SMD IV,
Test for subgroup difference Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=t$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Forssberg et al (2013) ²⁴ Howard et al (2012) ¹⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0	SD 1.02 1.47 0.41); <i>P</i> =0% 0.39 1.83 2.43 1.8799332 1.489 0.93	Total 191 212 403 12 318 159 109 207 217	Mean 0.2 0.2 1.85 -0.1 0.08 0.08 0.5321009 0.15 0.05	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19	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	random, 95% Cl -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) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14)	SMD IV,
Test for subgroup difference Severity of disease Study or Subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2014) ²³ Howard et al (2011) ¹⁴ Nakamura et al (2011) ¹⁵	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1	SD 1.02 1.47 0.41); l 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	Mean 0.2 0.2 0.2 0.3 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 13 321 165 109 107 208 267	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6	random, 95% CI -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01) -0.13 (-0.27, 0.01) -0.02 (-0.24, 0.02) -0.02 (-0.42, 0.11) -0.18 (-0.41, 0.06) -0.05 (-0.42, 0.14) 0.00 (-0.17, 0.17)	SMD IV,
Test for subgroup difference Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=t$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Forssberg et al (2013) ²⁴ Howard et al (2012) ¹⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0	SD 1.02 1.47 0.41); <i>P</i> =0% 0.39 1.83 2.43 1.8799332 1.489 0.93	Total 191 212 403 12 318 159 109 207 217	Mean 0.2 0.2 1.85 -0.1 0.08 0.08 0.5321009 0.15 0.05	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19	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	random, 95% Cl -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) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14)	SMD IV,
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% C1) Heterogeneity: $r^2=0.00; \chi^2=t$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2013) ²⁴ Howard et al (2013) ²⁴ Howard et al (2011) ¹⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁶ Nakamura et al (2014) ²⁵ Tariot et al (2007) ²⁷	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1	SD 1.02 1.47 0.41); l ² =0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73	Total 191 212 403 12 318 159 207 217 267 217 261	Mean 0.2 0.2 0.2 0.3 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 13 321 165 109 107 208 267 189 154	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0	random, 95% Cl -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) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.22, 0.22)	SMD IV,
Test for subgroup difference Severity of disease Study or Subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2014) ²³ Howard et al (2014) ²³ Howard et al (2013) ²³ Howard et al (2013) ²³ Howard et al (2011) ¹⁴ Nakamura et al (2016) ¹⁵ Tariot et al (2004) ²⁶ van Dyck et al (2007) ²¹ Subtotal (95% CI)	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1 0.1 0.1 0.1 0	SD 1.02 1.47 0.41); f=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	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1 0.2	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	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	random, 95% CI -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01) -0.5 (-0.10, 0.21) -0.05 (-0.10, 0.21) -0.15 (-0.42, 0.14) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14) -0.06 (-0.27, 0.14)	SMD IV,
Test for subgroup difference Subgroup difference Subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²⁴ Herman et al (2013) ²⁴ Howard et al (2012) ¹⁹ Kitamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷ Nakamura et al (2016) ¹⁶ Tariot et al (2004) ²⁶ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1 0.1 0.1 0.1 0.7 9 7.97, df=8 (P=0	SD 1.02 1.47 0.41); f=0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59 2.1	Total 191 212 403 12 318 159 207 217 267 217 261	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1 0.2	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	190 209 399 13 321 165 109 107 208 267 189 154	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0	random, 95% Cl -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) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.22, 0.22)	SMD IV,
Test for subgroup difference Severity of disease Study or Subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2013) ²³ Howard et al (2013) ²³ Howard et al (2013) ²⁴ Howard et al (2013) ²⁶ Hokamura et al (2016) ¹⁵ Tariot et al (2007) ²⁷ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1 0.1 0.1 0.1 0.7 9 7.97, df=8 (P=0	SD 1.02 1.47 0.41); f=0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59 2.1	Total 191 212 403 12 318 159 109 207 207 207 207 207 193 161 1,643	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1 0.2	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0 79.7	random, 95% Cl -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01) -0.13 (-0.27, 0.01) -0.02 (-0.24, 0.02) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.18 (-0.41, 0.06) -0.05 (-0.27, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.21, 0.03)	SMD IV,
Test for subgroup difference Subgroup difference Subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Herrmann et al (2013) ²⁴ Howard et al (2011) ¹⁴ Nakamura et al (2011) ¹⁵ Nakamura et al (2011) ¹⁵ Nakamura et al (2011) ¹⁶ Nakamura et al (2011) ¹⁶ Subtotal (95% CI) Total (95% CI)	Memantine Mean 0 0.1 0.67, df=1 (P=(4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 8 (P=0.28)	SD 1.02 1.47 0.41); <i>P</i> =0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59 2.1 0.44); <i>P</i> =0%	Total 191 212 403 12 318 159 207 217 267 217 261	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1 0.2	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	190 209 399 13 321 165 109 107 208 267 189 154	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0	random, 95% Cl -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) -0.18 (-0.41, 0.06) -0.05 (-0.24, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.22, 0.22)	SMD IV,
Test for subgroup difference Subgroup difference Subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=1$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Herrmann et al (2013) ²⁴ Howard et al (2011) ¹⁴ Nakamura et al (2011) ¹⁵ Nakamura et al (2011) ¹⁵ Nakamura et al (2011) ¹⁶ Nakamura et al (2011) ¹⁶ Subtotal (95% CI) Total (95% CI)	Memantine Mean 0 0.1 0.67, df=1 (P=(4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 8 (P=0.28)	SD 1.02 1.47 0.41); <i>P</i> =0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59 2.1 0.44); <i>P</i> =0%	Total 191 212 403 12 318 159 109 207 207 207 207 207 193 161 1,643	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1 0.2	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0 79.7	random, 95% Cl -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01) -0.13 (-0.27, 0.01) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.16 (-0.42, 0.11) -0.05 (-0.24, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.27, 0.14) -0.06 (-0.22, 0.22) -0.04 (-0.11, 0.03) -0.06 (-0.12, 0.01)	SMD IV, random, 95% Cl
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% C1) Heterogeneity: $r^2=0.00; \chi^2=t$ Test for overall effect: Z=1.8 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2013) ²⁴ Howard et al (2013) ²⁴ Howard et al (2011) ¹⁶ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁷ Nakamura et al (2011) ¹⁶ Nakamura et al (2014) ²⁵ Tariot et al (2007) ²⁷	Memantine Mean 0 0.1 0.67, df=1 (P=0 4 (P=0.07) 0.17 0 0.03 0.17431193 -0.109 0 0.1 0.1 0 7.97, df=8 (P=0 8 (P=0.28) 9.98, df=10 (P= 9 (P=0.07)	SD 1.02 1.47 0.41); <i>I</i> ² =0% 0.39 1.83 2.43 1.8799332 1.489 0.93 0.73 1.59 2.1 0.44); <i>I</i> ² =0%	Total 191 212 403 118 159 109 207 217 267 193 161 1,643 2,046	Mean 0.2 0.2 1.85 -0.1 0.08 0.5321009 0.15 0.05 0.1 0.2	1.07 1.16 2.48 1.89 2.12 2.692819 1.36 1.19 0.81 1.49	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 9.6 10.7 20.3 0.6 16.2 8.2 5.5 7.1 10.8 13.6 9.7 8.0 79.7	random, 95% Cl -0.19 (-0.39, 0.01) -0.08 (-0.27, 0.12) -0.13 (-0.27, 0.01) -0.13 (-0.27, 0.01) -0.02 (-0.24, 0.20) -0.15 (-0.42, 0.11) -0.16 (-0.42, 0.11) -0.05 (-0.24, 0.14) 0.00 (-0.27, 0.14) 0.00 (-0.27, 0.14) -0.06 (-0.22, 0.22) -0.04 (-0.11, 0.03) -0.06 (-0.12, 0.01)	SMD IV,

Figure 5 Forest plot of hallucination scores.

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

Therapeutic strate	gy								
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	-0.0524	2.225	207	0.03	1.87	107	10.8	-0.04 (-0.27, 0.19)	
Peskind et al (2006)20	0.1	1.11	191	0.3	1.43	190	12.8	-0.16 (-0.36, 0.05)	
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)			559			451	35.2	-0.06 (-0.19, 0.06)	◆
Heterogeneity: $\tau^2=0.00$; $\chi^2=$	1.61, df=2 (P=0	.45); / ² =0%							
Test for overall effect: Z=0.9	95 (P=0.34)								
Combination therapy									
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)	-
Howard et al (2012)18	-0.27522936	2.9560721	109	-0.11009174	2.9006367	109	9.2	-0.06 (-0.32, 0.21)	
Porsteinsson et al (2008)25	0.2	2.39	212	0.2	2.45	209	13.6	0.00 (-0.19, 0.19)	+
Tariot et al (2004) ²⁶	0	2.31	193	0.5	2.88	189	12.8	-0.19 (-0.39, 0.01)	
Subtotal (95% CI)			1,003			1,006	64.8	-0.12 (-0.26, 0.03)	◆
Heterogeneity: r ² =0.02; χ^2 =	11.89, df=5 (P=	0.04); /2=58%							
Test for overall effect: Z=1.5	55 (P=0.12)								
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); /2=42%						-	
Test for overall effect: Z=1.7	79 (P=0.07)								-2 -1 0 1 2
Test for subgroup difference		1 (P=0.58); I2	=0%						Favors (memantine) Favors (control)

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI			ID IV, 1dom, 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)			•		
Heterogeneity: τ ² =0.00; χ ² =	1.21, df=1 (P=0	.27); / ² =18%											
Test for overall effect: Z=0.9	6 (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)			-		
Howard et al (2012)18	-0.27522936	2.9560721	109	-0.11009174	2.9006367	109	9.2	-0.06 (-0.32, 0.21)			-		
Kitamura et al (2011)17	-0.0524	2.225	207	0.03	1.87	107	10.8	-0.04 (-0.27, 0.19)			-		
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); /2=52%	6										
Test for overall effect: Z=1.5	i0 (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>I</i> ² =42%	6					-			-		+
Test for overall effect: Z=1.7	9 (P=0.07)								-2	-1	0	1	2

Figure 6 Forest plot of irritability/lability scores. Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

Therapeutic strategy

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% Cl	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)	_	•—
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) ²⁰	0.1	1.09	191	0.2	1.21	190	9.9	-0.09 (-0.29, 0.11)	-	+
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)			776			659	37.0	-0.03 (-0.14, 0.07)	•	•
Heterogeneity: $\tau^2=0.00$; $\chi^2=0$	0.45, df=3 (P=0	0.93); /²=0%								
Test for overall effect: Z=0.6	1 (<i>P</i> =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)		4
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)		+
Nakamura et al (2016) ¹⁵	0	1.23	267	0.1	1.33	267	12.6	-0.08 (-0.25, 0.09)	-	+
Porsteinsson et al (2008) ²⁵	0.2	2.83	212	0.3	2.66	209	10.6	-0.04 (-0.23, 0.15)	-	-
Tariot et al (2004) ²⁶	0.4	2.82	193	0.2	3.43	189	9.9	0.06 (-0.14, 0.26)	-	-
Subtotal (95% CI)			1,270			1,273	63.0	-0.07 (-0.19, 0.05)	•	
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	12.35, df=6 (P=	=0.05); / ² =51%								
Test for overall effect: Z=1.1	6 (P=0.25)									
Total (95% CI)			2,046			1,932	100	-0.05 (-0.13, 0.02)		•
Heterogeneity: r ² =0.00; χ^2 =	13.02, df=10 (F	P=0.22); /2=23	%					-	· · · ·	· · · · · · · · · · · · · · · · · · ·
Test for overall effect: Z=1.4	1 (P=0.16)							-	-2 -1	0 1
Test for subgroup difference		1 (P=0 64) · /2	=0%						Favors (memantine)	Favors (control)

Figure 7 (Continued)

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	1.09	191	0.2	1.21	190	9.9	-0.09 (-0.29, 0.11)			_		
Porsteinsson et al (2008)25	0.2	2.83	212	0.3	2.66	209	10.6	-0.04 (-0.23, 0.15)			_		
Subtotal (95% Cl) Heterogeneity: τ ² =0.00; χ ² =0	0.13, df=1 (P=0	0.72); /²=0%	403			399	20.5	-0.06 (-0.20, 0.08)		•	•		
Test for overall effect: Z=0.8	5 (P=0.39)												
Moderate-to-severe													
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)			-		
Kitamura et al (2011)17	-0.0768	3.473	207	0.06	3.49	107	7.8	-0.04 (-0.27, 0.19)		_	_		
Nakamura et al (2011)14	-0.03	1.25	217	0.31	134	208	10.7	-0.00 (-0.19, 0.19)		_			
Nakamura et al (2016)15	0	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	79.5	-0.05 (-0.14, 0.04)		•			
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	12.87, df=8 (P=	=0.12); /2=38%								-			
Test for overall effect: Z=1.1	0 (<i>P</i> =0.27)												
Total (95% CI)	12.02 df=10/E	-0.221-12-22	2,046			1,932	100	-0.05 (-0.13, 0.02)		•			
Heterogeneity: $\tau^2=0.00$; $\chi^2=$		=0.22); 12=23	70						+	-		-	-
Test for overall effect: Z=1.4 Test for subgroup difference									-2 -	-1 (J	1	

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.

Study or Subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI	SMD IV, random	, 95% CI		
Ionotherapy												
Kitamura et al (2011)17	-0.223	2.255	207	-0.17	2.58	107	8.2	-0.02 (-0.26, 0.21)	_	L		
Vakamura et al (2011)14	-0.05	0.98	217	-0.05	1.06	208	10.6	0.00 (-0.19, 0.19)	_	L		
Peskind et al (2006) ²⁰	-0.1	1.47	191	0	1.51	190	10.0	-0.07 (-0.27, 0.13)		L		
an Dyck et al (2007)21	0.1	2.7	161	0	2.9	154	8.8	0.04 (-0.19, 0.26)				
Subtotal (95% CI)	0.1	2.1	776	0	2.5	659	37.6	-0.01 (-0.12, 0.09)				
Heterogeneity: $\tau^2=0.00$; $\chi^2=$	0.49, df=3 (P=0	.92); /²=0%						,,				
est for overall effect: Z=0.2	7 (P=0.78)											
Combination therapy												
Araki et al (2014)22	0.25	0.62	12	3.31	3.04	13	0.8	-1.32 (-2.20, -0.44)				
Grossberg et al (2013) ²³	-0.3	2.66	318	-0.2	2.67	321	13.2	-0.04 (-0.19, 0.12)	-	+		
Herrmann et al (2013) ²⁴	-0.73	3.7	159	-1.08	3.53	165	9.0	0.10 (-0.12, 0.31)	-	-		
Howard et al (2012)18	-0.46788991	2.6893783	109	0.21100917	3.6338771	109	6.8	-0.21 (-0.48, 0.05)		ł		
Nakamura et al (2016)15	0	1.21	267	-0.1	1.27	267	12.1	0.08 (-0.09, 0.25)	-	-		
Porsteinsson et al (2008)25	0.2	2.69	212	0.2	2.8	209	10.6	0.00 (-0.19, 0.19)	_	-		
Fariot et al (2004)26	-0.2	2.73	193	0.3	2.87	189	9.9	-0.18 (-0.38, 0.02)		ł		
Subtotal (95% CI)			1,270			1,273	62.4	-0.06 (-0.19, 0.07)	4	•		
Heterogeneity: τ^2 =0.02; χ^2 = Test for overall effect: Z=0.9		0.02); /²=60%										
Fotal (95% CI)		2,0	46			1,932	100	-0.03 (-0.12, 0.05)				
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	15.75, df=10 (P	=0.11); /2=37	%			-		-	· · · · ·			-+
		. ,, .							-2 -1	0	1	2
	. ,	1 (<i>P</i> =0.59); <i>I</i> ² :	=0%								s (control	n
Test for overall effect: Z=0.8 Test for subgroup difference	. ,	1 (<i>P</i> =0.59); <i>I</i> ²	=0%						Favors (memantine)		s (control	I)
Test for subgroup difference	s: χ²=0.29, df=1	1 (P=0.59); I ² :	=0%						Favors (memantine)	Favors	s (control	I)
Test for subgroup difference	s: χ²=0.29, df=1	1 (<i>P</i> =0.59); <i>I</i> ²	=0% Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% Cl	Favors (memantine) SMD IV,	Favors	s (control)	1)
Test for subgroup difference Severity of disease Study or	s: χ^2 =0.29, df =1 Memantine				SD	Total			Favors (memantine) SMD IV,	Favors	s (control)	1)
Fest for subgroup difference Severity of disease Study or subgroup Wild-to-moderate	s: χ²=0.29, df=1 P Memantine Mean	SD					(%)	random, 95% Cl	Favors (memantine) SMD IV,	Favors	s (control)	1)
Fest for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰	s: χ ² =0.29, <i>df</i> =1 Memantine Mean -0.1	SD	Total 191	Mean 0	1.51	190	(%)	random, 95% Cl -0.07 (-0.27, 0.13)	Favors (memantine) SMD IV,	Favors	s (control)	I)
Fest for subgroup difference Severity of disease Study or subgroup Wild-to-moderate	s: χ²=0.29, df=1 P Memantine Mean	SD	Total	Mean			(%)	random, 95% Cl	Favors (memantine) SMD IV,	Favors	s (control	1)
Fest for subgroup difference Severity of disease Study or subgroup Mild to-moderate Peskind et al (2006) ²⁰ Orsteinsson et al (2008) ²⁵ Subtotal (95% CI)	s: χ²=0.29, df=1 Memantine Mean -0.1 0.2	SD 1.47 2.69	Total 191 212	Mean 0	1.51	190 209	(%) 10.0 10.6	random, 95% CI -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19)	Favors (memantine) SMD IV,	Favors	s (control	
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: r ² =0.00; χ ² =	s: $\chi^2=0.29$, $df=1$ Memantine Mean -0.1 0.2 0.22, $df=1$ ($P=0$	SD 1.47 2.69	Total 191 212	Mean 0	1.51	190 209	(%) 10.0 10.6	random, 95% CI -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19)	Favors (memantine) SMD IV,	Favors	s (control)
Test for subgroup difference Severity of disease Study or subgroup Wild 40-moderate Peskind et al (2008) ⁵⁰ Porsteinsson et al (2008) ⁵⁵ Subtotal (95% CI) deterogeneity: $r^2=0.00; \chi^2=$ Test for overall effect Z=0.44 Moderate-to-severe	s: χ ² =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65)	SD 1.47 2.69 1.64); <i>I</i> ² =0%	Total 191 212	Mean 0 0.2	1.51 2.8	190 209 399	(%) 10.0 10.6	random, 95% CI -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19)	Favors (memantine) SMD IV,	Favors	s (control	
Fest for subgroup difference Severity of disease subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵	s: $\chi^2=0.29$, $df=1$ Memantine Mean -0.1 0.2 0.22, $df=1$ ($P=0$	SD 1.47 2.69	Total 191 212	Mean 0	1.51	190 209	(%) 10.0 10.6	random, 95% CI -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19)	Favors (memantine) SMD IV,	Favors	s (control)
Test for subgroup difference Severity of disease Study or subgroup Wild 40-moderate Peskind et al (2008) ⁵⁰ Porsteinsson et al (2008) ⁵⁵ Subtotal (95% CI) deterogeneity: $r^2=0.00; \chi^2=$ Test for overall effect Z=0.44 Moderate-to-severe	s: χ ² =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65)	SD 1.47 2.69 1.64); <i>I</i> ² =0%	Total 191 212 403	Mean 0 0.2	1.51 2.8	190 209 399	(%) 10.0 10.6 20.5	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11)	Favors (memantine) SMD IV,	Favors	s (control	
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2006) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) releterogeneity: r ² =0.0; χ ² = Fest for overall effect Z=0.4; Moderate-to-severe Araki et al (2014) ³²	s: $\chi^{2}=0.29$, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65) 0.25	SD 1.47 2.69 .64); <i>I</i> ² =0% 0.62	Total 191 212 403 12	Mean 0 0.2 3.31	1.51 2.8 3.04	190 209 399 13	(%) 10.0 10.6 20.5 0.8	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44)	Favors (memantine) SMD IV,	Favors	s (control	1)
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2008) ²⁶ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00$, $\chi^2=$ fest for overall effect Z=0.4! Moderate-to-severe Yarki et al (2014) ²² Grossberg et al (2013) ²³	s: χ^2 =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 6 (P=0.65) 0.25 -0.3	SD 1.47 2.69 .64); <i>I</i> ² =0% 0.62 2.66 3.7	Total 191 212 403 12 318	Mean 0 0.2 3.31 -0.2	1.51 2.8 3.04 2.67	190 209 399 13 321	(%) 10.0 10.6 20.5 0.8 13.2	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^{2=}$ Test for overall effect Z=0.41 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³	s: χ^2 =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65) 0.25 -0.3 -0.73	SD 1.47 2.69 .64); <i>I</i> ² =0% 0.62 2.66 3.7	Total 191 212 403 12 318 159	Mean 0 0.2 3.31 -0.2 -1.08	1.51 2.8 3.04 2.67 3.53	190 209 399 13 321 165	(%) 10.0 10.6 20.5 0.8 13.2 9.0	random, 95% CI -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) deterogeneity: $r^2=0.00; \chi^2=$ Fest for overall effect Z=0.4: Moderate-to-severe Vraki et al (2014) ²² Grossberg et al (2013) ²³ Herrmann et al (2013) ²⁴ Howard et al (2012) ¹⁶	s: $\chi^{2}=0.29$, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65) 0.25 -0.3 -0.73 -0.46788991	SD 1.47 2.69 .64); <i>I</i> ² =0% 0.62 2.66 3.7 2.6893783	Total 191 212 403 12 318 159 109	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917	1.51 2.8 3.04 2.67 3.53 3.6338771	190 209 399 13 321 165 109	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00; \chi^2=$ Test for overall effect Z=0.41 Moderate-to-severe Araki et al (2014) ²² Srossberg et al (2013) ²⁴ Howard et al (2013) ²⁴ Howard et al (2011) ¹⁶	s: χ^2 =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 6 (P=0.65) 0.25 -0.3 -0.46788991 -0.223	SD 1.47 2.69 	Total 191 212 403 12 318 159 109 207	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58	190 209 399 13 321 165 109 107	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05) -0.02 (-0.26, 0.21) 0.00 (-0.19, 0.19)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Wild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% CI) deterogeneity: $r^2=0.00, \chi^2=$ Test for overall effect Z=0.4: Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²³ Howard et al (2014) ²² Howard et al (2013) ²⁴ Howard et al (2011) ¹⁷ Vakamura et al (2011) ¹⁷	s: $\chi^{2}=0.29$, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65) 0.25 -0.3 -0.73 -0.46788991 -0.223 -0.05 0	SD 1.47 2.69 .64); P=0% 0.62 2.66 3.7 2.6893763 2.255 0.98 1.21	Total 191 212 403 12 318 159 109 207 217 267	Mean 0 0.2 -0.2 -1.08 0.21100917 -0.17 -0.05 -0.1	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06 1.27	190 209 399 13 321 165 109 107 208 267	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05) -0.02 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2008) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00$, $\chi^2=$ Test for overall effect Z=0.4! Moderate-to-severe Araki et al (2014) ²² Torssberg et al (2013) ²³ Hermann et al (2013) ²³ Hermann et al (2013) ²⁴ Howard et al (2011) ¹⁷ Vakamura et al (2011) ¹⁷ Vakamura et al (2011) ¹⁵ Fariot et al (2004) ²⁸	s: $\chi^{2}=0.29$, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65) 0.25 -0.3 -0.73 -0.46788991 -0.223 -0.5	SD 1.47 2.69 .64); <i>I</i> ² =0% 0.62 2.666 3.7 2.6893783 2.255 0.98	Total 191 212 403 12 318 159 109 207 217	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17 -0.05	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06	190 209 399 13 321 165 109 107 208	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1 9.9	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05) -0.02 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25) -0.18 (-0.38, 0.02)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2006) ²⁰ Porsteinsson et al (2008) ²⁵ Subtotal (95% C1) Heterogeneity: $r^2=0.00; \chi^2=$ Test for overall effect Z=0.41 Moderate-to-severe Araki et al (2014) ²² Grossberg et al (2013) ²⁴ Howard et al (2013) ²⁴ Howard et al (2011) ¹⁶ Vakamura et al (2011) ¹⁷ Vakamura et al (2011) ¹⁵ Iariot et al (2007) ²¹	s: χ^2 =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 6 (P=0.65) 0.25 -0.3 -0.73 -0.46788991 -0.223 -0.05 0 -0.2	SD 1.47 2.69 1.64); <i>I</i> ² =0% 0.62 2.66 3.7 2.6893783 2.255 0.98 1.21 2.73	Total 191 212 403 12 318 159 109 207 217 267 193	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17 -0.05 -0.1 0.3	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06 1.27 2.87	190 209 399 13 321 165 109 107 208 267 189 154	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25) -0.18 (-0.38, 0.02) 0.04 (-0.19, 0.26)	Favors (memantine) SMD IV,	Favors	s (control))
Test for subgroup difference Severity of disease Study or subgroup Mild-to-moderate Peskind et al (2008) ³⁰ Porsteinsson et al (2008) ³⁵ Subtotal (95% CI) Heterogeneity: $r^2=0.00$, $\chi^2=$ Test for overall effect Z=0.4! Moderate-to-severe Araki et al (2014) ²² Torssberg et al (2013) ²³ Hermann et al (2013) ²³ Hermann et al (2013) ²⁴ Howard et al (2011) ¹⁷ Vakamura et al (2011) ¹⁷ Vakamura et al (2011) ¹⁵ Fariot et al (2004) ²⁸	s: χ²=0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 6 (P=0.65) 0.25 -0.3 -0.46788991 -0.23 -0.46788991 -0.23 -0.5 0 -0.2 0.1 15.52, df=8 (P=	SD 1.47 2.69 .64); <i>P</i> =0% 0.62 2.66 3.7 2.6893783 2.255 0.98 1.21 2.73 2.7	Total 191 212 403 12 318 159 109 207 217 267 193 161 1,643	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17 -0.05 -0.1 0.3	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06 1.27 2.87	190 209 399 13 321 165 109 107 208 267 189	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1 9.9 8.8	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05) -0.02 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25) -0.18 (-0.38, 0.02)	Favors (memantine) SMD IV,	Favors	s (control))
The subgroup difference of the subgroup difference of the subgroup difference of the subgroup	s: χ²=0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 6 (P=0.65) 0.25 -0.3 -0.46788991 -0.23 -0.46788991 -0.23 -0.5 0 -0.2 0.1 15.52, df=8 (P=	SD 1.47 2.69 .64); <i>P</i> =0% 0.62 2.66 3.7 2.6893783 2.255 0.98 1.21 2.73 2.7	Total 191 212 403 12 318 159 207 217 267 217 267 193 161 1,643	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17 -0.05 -0.1 0.3	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06 1.27 2.87	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1 9.9 8.8 79.5	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05) -0.02 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25) -0.18 (-0.38, 0.02) 0.04 (-0.19, 0.26) -0.04 (-0.14, 0.06)	Favors (memantine) SMD IV,	Favors	s (control	
est for subgroup difference Severity of disease study or ubgroup Mild-to-moderate Peskind et al (2006) ³⁰ forsteinsson et al (2008) ³⁵ ububtal (95% CI) leterogeneity: $r^2=0.00$; $\chi^2=$ est for overall effect Z=0.41 Moderate-to-severe wraki et al (2014) ²² forssberg et al (2013) ²³ terrmann et al (2013) ²⁴ terrmann et al (2013) ²⁴ terrmann et al (2011) ¹¹ Lakamura et al (2011) ¹² Lakamura et al (2011) ¹² Lakamura et al (2004) ²⁸ fantot et al (2004) ²⁸ fantot et al (2004) ²⁹ fantot et al (2004) ²¹ Subtotal (95% CI)	s: χ ² =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 6 (P=0.65) 0.25 -0.3 -0.46788991 -0.223 -0.05 0 -0.2 0.1 15.52, df=8 (P= 7 (P=0.44)	SD 1.47 2.69 1.64); <i>P</i> =0% 0.62 2.66 3.7 2.6893783 2.255 0.98 1.21 2.73 2.7 0.05); <i>P</i> =48%	Total 191 212 403 159 109 207 217 267 193 161 1,643 2,046	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17 -0.05 -0.1 0.3	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06 1.27 2.87	190 209 399 13 321 165 109 107 208 267 189 154	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1 9.9 8.8 79.5	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25) -0.18 (-0.38, 0.02) 0.04 (-0.19, 0.26)	Favors (memantine) SMD IV,	Favors	s (control	
The subgroup difference control of the second stress of the subgroup difference control of the subgroup control of the second stress o	s: χ ² =0.29, df=1 Memantine Mean -0.1 0.2 0.22, df=1 (P=0 5 (P=0.65) 0.25 -0.3 -0.46788991 -0.23 -0.05 0 -0.2 -0.1 15.52, df=8 (P= 7 (P=0.44) 15.75, df=10 (P	SD 1.47 2.69 1.64); <i>P</i> =0% 0.62 2.66 3.7 2.6893783 2.255 0.98 1.21 2.73 2.7 0.05); <i>P</i> =48%	Total 191 212 403 159 109 207 217 267 193 161 1,643 2,046	Mean 0 0.2 3.31 -0.2 -1.08 0.21100917 -0.17 -0.05 -0.1 0.3	1.51 2.8 3.04 2.67 3.53 3.6338771 2.58 1.06 1.27 2.87	190 209 399 13 321 165 109 107 208 267 189 154 1,533	(%) 10.0 10.6 20.5 0.8 13.2 9.0 6.8 8.2 10.6 12.1 9.9 8.8 79.5	random, 95% Cl -0.07 (-0.27, 0.13) 0.00 (-0.19, 0.19) -0.03 (-0.17, 0.11) -1.32 (-2.20, -0.44) -0.04 (-0.19, 0.12) 0.10 (-0.12, 0.31) -0.21 (-0.48, 0.05) -0.02 (-0.26, 0.21) 0.00 (-0.19, 0.19) 0.08 (-0.09, 0.25) -0.18 (-0.38, 0.02) 0.04 (-0.19, 0.26) -0.04 (-0.14, 0.06)	Favors (memantine) SMD IV, random	Favors		")

Figure 8 Forest plot of anxiety/phobia scores.

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

Therapeutic strate	gy												
Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI			ID IV, Idom, 95%	6 CI	
Monotherapy													
Kitamura et al (2011)17	-0.311	3.265	207	-0.5	3.63	107	8.4	0.06 (-0.18, 0.29)			-		
Nakamura et al (2011)14	-0.02	0.69	217	-0.02	0.77	208	10.5	0.00 (-0.19, 0.19)			-		
Peskind et al (2006) ²⁰	-0.1	1.26	191	-0.2	1.43	190	10.0	0.07 (-0.13, 0.27)					
van Dyck et al (2007)21	-0.2	3.8	161	0.1	3.7	154	9.0	-0.08 (-0.30, 0.14)			-+-		
Subtotal (95% CI)			776			659	38.0	0.01 (-0.09, 0.12)			•		
Heterogeneity: $\tau^2=0.00$; $\chi^2=$	1.18, df=3 (P=0	.76); /2=0%											
Test for overall effect: Z=0.2	25 (<i>P</i> =0.80)												
Combination therapy													
Araki et al (2014)22	-0.92	2.27	12	1.62	1.56	13	1.0	-1.27 (-2.14, -0.40)			-		
Grossberg et al (2013)23	-0.8	3.56	318	-0.5	3.85	321	12.6	-0.08 (-0.24, 0.07)			-		
Herrmann et al (2013)24	-0.79	3.82	159	-1.03	4.07	165	9.1	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)		-	-		
Nakamura et al (2016)15	0	0.68	267	0	0.7	267	11.7	0.00 (-0.17, 0.17)			-		
Porsteinsson et al (2008)25	0	2.88	212	-0.3	3.4	209	10.5	0.10 (-0.10, 0.29)					
Tariot et al (2004) ²⁶	-0.4	3.42	193	0.3	3.54	189	10.0	-0.20 (-0.40, 0.00)					
Subtotal (95% CI)			1,270			1,273	62.0	-0.09 (-0.22, 0.05)			•		
Heterogeneity: $\tau^2=0.02$; $\chi^2=$	16.11, df=6 (P=	0.01); I2=63%											
Test for overall effect: Z=1.2	24 (P=0.21)												
Total (95% CI)			2,046			1,932	100	-0.04 (-0.13, 0.05)			•		
Heterogeneity: r2=0.01; x2=	18.53, df=10 (P	=0.05); /2=46%	6										
Test for overall effect: Z=0.9	94 (P=0.35)								-2	-1	0	1	2
Test for subgroup difference		I (P=0.26); I ² =	22.7%						Favors (memantir	ne)	Favors (cor	ntrol)

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	1.26	191	-0.2	1.43	190	10.0	0.07 (-0.13, 0.27)	
Porsteinsson et al (2008)25	0	2.88	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: r ² =0.01; x ² =	0.00, df=1 (P=0	.88); /²=0%							
Test for overall effect: Z=1.2	0 (P=0.23)								
Moderate-to-severe									
Araki et al (2014)22	-0.92	2.27	12	1.62	1.56	13	1.0	-1.27 (-2.14, -0.40)	
Grossberg et al (2013)23	-0.8	3.56	318	-0.5	3.85	321	12.6	-0.08 (-0.24, 0.07)	
Herrmann et al (2013)24	-0.79	3.82	159	-1.03	4.07	165	9.1	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)	
Kitamura et al (2011)17	-0.311	3.265	207	-0.5	3.63	107	8.4	0.06 (-0.18, 0.29)	
Nakamura et al (2011)14	-0.02	0.69	217	-0.02	0.77	208	10.5	0.00 (-0.19, 0.19)	- - -
Nakamura et al (2016)15	0	0.68	267	0	0.7	267	11.7	0.00 (-0.17, 0.17)	—
Tariot et al (2004)26	-0.4	3.42	193	0.3	3.54	189	10.0	-0.20 (-0.40, 0.00)	
van Dyck et al (2007)21	-0.2	3.8	161	0.1	3.7	154	9.0	-0.08 (-0.30, 0.14)	
Subtotal (95% CI)			1,643			1,533	79.5	-0.08 (-0.18, 0.02)	•
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	14.92, df=8 (P=	0.06); I2=46%							-
Test for overall effect: Z=1.4	7 (P=0.14)								
Total (95% CI)			2,046			1,932	100	-0.04 (-0.13, 0.05)	•
Heterogeneity: $\tau^2=0.01$; $\chi^2=$	18.53, df=10 (P	=0.05); /2=46%	6						
Test for overall effect: Z=0.9									-2 -1 0 1 2
Test for subgroup difference		(P=0.07); I ² =	70.4%						Favors (memantine) Favors (control)

Figure 9 Forest plot of apathy scores. Abbreviations: 95% CI, 95% confidence interval; IV, inverse variance; SD, standard deviation; SMD, standardized mean difference.

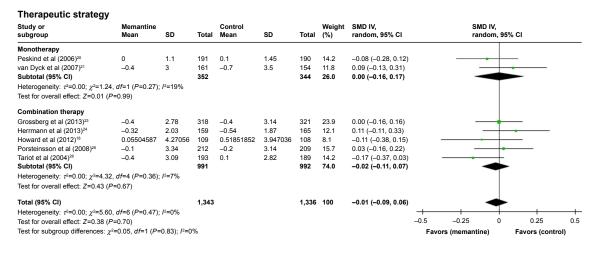
Therapeutic strategy Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI			D IV, dom, 95%	6 CI	
Monotherapy													-
Kitamura et al (2011)17	-0.0297	1.861	207	-0.09	1.65	107	9.5	0.03 (-0.20, 0.27)			-		
Peskind et al (2006)20	-0.1	1.45	191	0	1.57	190	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)			-		
Subtotal (95% CI)			559			451	32.8	-0.00 (-0.13, 0.12)			•		
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.00$	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: $\tau^2=0.00$; $\chi^2=6.00$	44, df=5 (P=0.27	7); /²=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: τ ² =0.00; χ ² =7.	59, df=8 (P=0.47	7); /2=0%							+		_		
Test for overall effect: Z=1.02	(P=0.31)								-2	-1	0	1	1
Test for subgroup differences:	$\gamma^2=0.54$, df=1 (l	P=0.46): /2=00	%						F	(memantin	-)	Favors (co	ntrol)

Figure 10 (Continued)

Severity of disease													
Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI			MD IV, andom, 959	% CI	
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)					
Porsteinsson et al (2008) ²⁵ Subtotal (95% CI)	0.1	1.99	212 403	0.2	2.02	209 399	14.1 26.9	-0.05 (-0.24, 0.14) -0.06 (-0.20, 0.08)			-		
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.00$	01, df=1 (P=0.91	1); /²=0%											
Test for overall effect: Z=0.81	(P=0.42)												
Moderate-to-severe													
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)			-+-		
Kitamura et al (2011)17	-0.0297	1.861	207	-0.09	1.65	107	9.5	0.03 (-0.20, 0.27)			-		
Tariot et al (2004)26	0	1.97	193	0.2	2.26	189	12.8	-0.09 (-0.29, 0.11)			-+-		
van Dyck et al (2007)21	0	2.4	161	-0.1	1.8	154	10.6	0.05 (-0.17, 0.27)			-		
Subtotal (95% CI)			1,159			1,058	73.1	-0.03 (-0.13, 0.06)			•		
Heterogeneity: $\tau^2=0.00$; $\chi^2=7.4$	46, df=6 (P=0.28	3); /²=20%									1		
Test for overall effect: Z=0.68	(P=0.49)												
Total (95% CI)			1,562			1,457	100	-0.04 (-0.11, 0.03)			•		
Heterogeneity: $\tau^2=0.00$; $\chi^2=7.5$	59, df=8 (P=0.47	7); /²=0%							+				
Test for overall effect: Z=1.02	(P=0.31)								-2	-1	0	1	2
Test for subgroup differences:	χ ² =0.08, df=1 (<i>I</i>	P=0.78); /2=00	%						Favo	rs (meman	tine)	Favors (co	ntrol)

Figure 10 Forest plot of dysphoria scores.

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



Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI			D IV, dom, 95% (CI	
Mild-to-moderate													
Peskind et al (2006)20	0	1.1	191	0.1	1.45	190	14.2	-0.08 (-0.28, 0.12)			•		
Porsteinsson et al (2008)25	-0.1	3.34	212	-0.2	3.14	209	15.7	0.03 (-0.16, 0.22)		_			
Subtotal (95% CI)			403			399	30.0	-0.02 (-0.16, 0.12)					
Heterogeneity: τ ² =0.00; χ ² =0.5	9, df=1 (P=0.44);	I2=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)		_		_	
Herrmann et al (2013)24	-0.32	2.03	159	-0.54	1.87	165	12.1	0.11 (-0.11, 0.33)					
Howard et al (2012)18	0.05504587	4.27056	109	0.51851852	3.947036	108	8.1	-0.11 (-0.38, 0.15)				_	
Tariot et al (2004)26	-0.4	3.09	193	0.1	2.82	189	14.2	-0.17 (-0.37, 0.03)					
van Dyck et al (2007)21	-0.4	3	161	-0.7	3.5	154	11.8	0.09 (-0.13, 0.31)		-			
Subtotal (95% CI)			940			937	70.0	-0.01 (-0.12, 0.09)					
Heterogeneity: τ ² =0.00; χ ² =5.0	1, df=4 (P=0.29);	I2=20%											
Test for overall effect: Z=0.24 (P=0.81)												
Total (95% CI)			1,343			1,336	100	-0.01 (-0.09, 0.06)			-		
Heterogeneity: $\tau^2=0.00$; $\chi^2=5.6$	0, df=6 (P=0.47);	/ ² =0%									-		
Test for overall effect: Z=0.38 (-0.5	-0.25	0	0.25	0.5
Test for subgroup differences:	,	0.93): /2=0	%						Favo	rs (memantin	e) F	avors (conti	rol)

Figure 11 Forest plot of eating disturbance scores.

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

Study or subgroup	Memantine Mean	SD	Total	Control Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI		SME) IV, lom, 95	% CI		
Monotherapy														
Kitamura et al (2011)17	0.0645	1.137	207	0.04	1.28	107	9.5	0.02 (-0.21, 0.25)		-				
Peskind et al (2006)20	0	0.43	191	0	0.63	190	12.8	0.00 (-0.20, 0.20)			-+-	_		
van Dyck et al (2007) ²¹	0	1.6	161	0.1	1	154	10.5	-0.07 (-0.30, 0.15)		_		-		
Subtotal (95% CI)			559			451	32.8	-0.02 (-0.14, 0.11)			•			
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.3$	9, df=2 (P=0.82)	; / ² =0%												
Test for overall effect: Z=0.28 (P=0.78)													
Combination therapy														
Araki et al (2014)22	0.25	0.97	12	0.85	2.3	13	0.8	-0.32 (-1.11, 0.47)			_			
Grossberg et al (2013)23	0	1.21	317	0	1.26	321	21.4	0.00 (-0.16, 0.16)			-	-		
Herrmann et al (2013)24	-0.24	1.66	159	-0.15	1.98	165	10.9	-0.05 (-0.27, 0.17)		_		-		
Howard et al (2012)18	-0.04587156	1.5358996	109	0.11926606	1.8793457	109	7.3	-0.10 (-0.36, 0.17)				-		
Porsteinsson et al (2008)25	0.1	1.18	212	-0.1	0.78	209	14.0	0.20 (-0.01, 0.39)			- H	-		
Tariot et al (2004) ²⁶	0	1.38	193	0.1	1.15	189	12.8	-0.08 (-0.28, 0.12)		_				
Subtotal (95% CI)			1,002			1,006	67.2	0.00 (-0.10, 0.10)			•			
Heterogeneity: τ ² =0.00; χ ² =6.0	8, df=5 (P=0.30)	; /²=18%												
Test for overall effect: Z=0.03 (P=0.98)													
Total (95% CI)			1,561			1,457	100	-0.00 (-0.07, 0.07)			•			
Heterogeneity: τ ² =0.00; χ ² =6.5	5, df=8 (P=0.59)	; /2=0%												-+-
Test for overall effect: Z=0.08 (P=0.94)								-1	-0.5	0	0	.5	1
Test for subgroup differences:	χ ² =0.06, df=1 (P=	=0.81); /²=0%							Favor	s (memantin	e)	Favor	s (contro	4)
Severity of disease														
Study or	Memantine			Control			Weight	SMD IV,		SMD	IV.			
subgroup	Mean	SD	Total	Mean	SD	Total	(%)	random, 95% CI			lom, 95	~ ~		

subgroup	wean	50	Total	wean	50	Total	(%)	random, 95% CI		ran	uom, 95	% CI	
Mild-to-moderate													
Peskind et al (2006)20	0	0.43	191	0	0.63	190	12.8	0.00 (-0.20, 0.20)			-+-	_	
Porsteinsson et al (2008)25	0.1	1.18	212	-0.1	0.78	209	14.0	0.20 (0.01, 0.39)			- H	•	
Subtotal (95% CI)			403			399	26.8	0.10 (-0.09, 0.30)					
Heterogeneity: $\tau^2=0.01$; $\chi^2=1.9$	98, df=1 (P=0.16)	; /2=50%											
Test for overall effect: Z=1.02	(P=0.31)												
Moderate-to-severe													
Araki et al (2014)22	0.25	0.97	12	0.85	2.3	13	0.8	-0.32 (-1.11, 0.47)					
Grossberg et al (2013)23	0	1.21	317	0	1.26	321	21.4	0.00 (-0.16, 0.16)			-	-	
Herrmann et al (2013)24	-0.24	1.66	159	-0.15	1.98	165	10.9	-0.05 (-0.27, 0.17)		-		-	
Howard et al (2012)18	-0.04587156	1.5358996	109	0.11926606	1.8793457	109	7.3	-0.10 (-0.36, 0.17)		_		-	
Kitamura et al (2011)17	0.0645	1.137	207	0.04	1.28	107	9.5	0.02 (-0.21, 0.25)					
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	0	1.6	161	0.1	1	154	10.5	-0.07 (-0.30, 0.15)		_	-+-	-	
Subtotal (95% CI)			1,158			1,058	73.2	-0.04 (-0.13, 0.04)			-		
Heterogeneity: $\tau^2=0.00$; $\chi^2=1.4$	42, df=6 (P=0.96)	; /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: $\tau^2=0.00$; $\chi^2=6.5$	55, df=8 (P=0.59)	; /2=0%											
Test for overall effect: Z=0.08	(P=0.94)								-1	-0.5	0	0.5	1
Test for subgroup differences:		=0.18); /2=43.	5%						Favo	rs (memantir	ie)	Favors (con	trol)

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 nighttime disturbance/diurnal rhythm disturbances were outcomes, where memantine was superior to control in the moderateto-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.¹⁰ 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,^{8,9} and anti-dementia drugs may prevent brain atrophy in patients with Alzheimer's disease.²⁷ 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

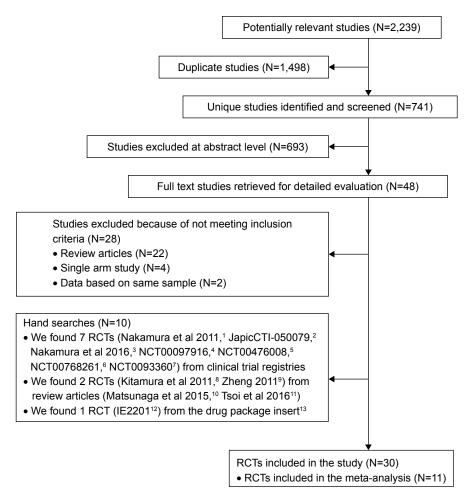


Figure SI PRISMA flow diagram.

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

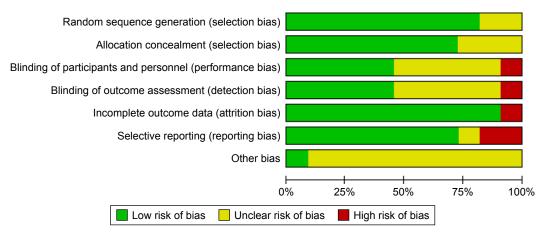
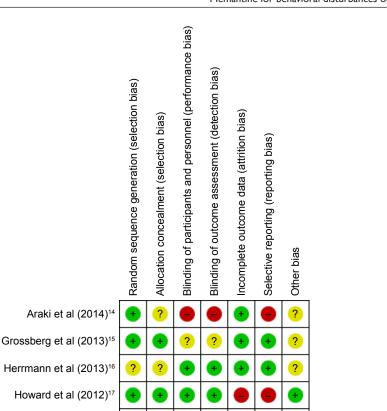


Figure S2 Risk of bias graph.



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Figure S3 Risk of bias summary.

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Nakamura et al (2011)1

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