# Cholinesterase inhibitors and memantine for Parkinson's disease dementia and Lewy body dementia: A meta-analysis

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Abstract. Recently, several randomized controlled trials on the use of cholinesterase inhibitors or memantine as treatments for cognitive impairment in Parkinson's disease (CIND-PD), Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) were completed. The present study provided a meta-analysis of these studies to evaluate the efficacy of cholinesterase inhibitors and memantine on CIND-PD, PDD and DLB. The Cochrane Library, Pubmed, Embase and Web of Science databases were searched to retrieve eligible studies. As primary efficacy outcomes, cognitive function, global impression, behavioral symptoms and motor function were selected, while falling and adverse events were regarded as safety outcomes. Of note, domain-specific cognitive function was assessed as a primary efficacy outcome and falling as a safety outcome, which, to the best of our knowledge, has not been studied previously in CIND-PD, PDD and DLB. A total of 15 trials were included in the present meta-analysis. The results revealed that treatment with cholinesterase inhibitors resulted in improvements in cognitive function, the clinician's global impression, behavioral symptoms and motor function, in accordance with the results of previous studies. Furthermore, it was revealed that cholinesterase inhibitors had a significant effect on attention, processing speed, executive functions, memory and language; however, they did not improve visuospatial cognition compared with placebos. Memantine had a significant effect on attention, processing speed and executive functions. In addition, cholinesterase inhibitors and memantine did not significantly reduce falling. It was demonstrated that an increased number of adverse events occurred in the pooled cholinesterase inhibitors and memantine group, compared with that in the placebo group (risk ratio (RR)=1.09; 95% confidence interval (CI): 1.04-1.16; P=0.001); however, in the subgroup analysis, only the rivastigmine group experienced significantly more adverse events than the placebo group (85 vs. 73%; RR=1.18; 95% CI: 1.08-1.29; P=0.0001), but donepezil and memantine did not produce any significant adverse events. In conclusion, cholinesterase inhibitors and memantine have an effect not only on global cognitive function and motor function, but also on attention, processing speed, executive functions, memory and language. However, careful monitoring of the side effects of rivastigmine may be required. Further clinical trials are required to verify these conclusions.

### Introduction

The most common types of dementia are Alzheimer's dementia (AD) and Parkinson's disease dementia (PDD), while dementia with Lewy bodies (DLB) is the second most common type of dementia, accounting for 15-20% of the global incidence of dementia (1-3). PDD and DLB are characterized by accumulation of Lewy bodies in brain cells (4). From a clinical and neuropathological perspective, DLB and PDD are similar conditions with the same features, namely dementia, parkinsonism, hallucinations and fluctuations of attention or arousal (5). They may be distinguished on the basis of the relative timing of dementia and Parkinsonism. Several meta-analyses have been performed to examine the efficacy and safety of cholinesterase inhibitors and memantine, or each drug separately, on CIND-PD, PDD and DLB (6-9). The studies reported that cholinesterase inhibitors and memantine improve the global impression, cognitive function, psychiatric symptoms or motor function. They evaluated cognitive function via the use of certain screening tests, including the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). To the best of our knowledge, no previous meta-analysis has focused on cognitive domains, including attention, processing speed, executive functions, memory and language. The present study hypothesized that cholinesterase inhibitors and memantine may also improve the patients' cognitive domains in addition to global cognitive function, which may further prove their efficacy. In addition, falls are a common and severe complication of PD patients and seriously affect their daily safety, prognosis and quality

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*Key words:* cholinesterase inhibitors, memantine, Parkinson's disease, dementia, Lewy body dementia, meta-analysis

of life (10), and thus, the effect of cholinesterase inhibitors and memantine on falls was also investigated.

#### Materials and methods

Search strategy. The Cochrane Library, as well as the Pubmed, Embase and Web of Science databases, were searched for relevant studies on clinical trials on cognitive impairment in Parkinson's disease (CIND-PD), PDD or DLB published before July 2018. The search terms were as follows: ('Lewy Body Disease' OR 'DLB' OR 'LBD' OR 'dementia with Lewy bod\*' OR 'Lewy bodies dementia' OR 'Lewy Bodies' OR 'lewy\* bod\*') and {'Parkinson Disease' OR 'parkinson\* disease dement\*' OR 'PDD' OR ['cognit\*' and ('PD' or 'parkinson\*')] OR 'PD-CIND' OR ('CIND' and 'parkinson\*')} and ['Cholinesterase Inhibitors' OR 'cholinesterase inhibitor\*' OR 'Galantamine' OR 'galantamine' OR 'galanthamine' OR ('reminyl\*' or 'Nivalin\*' or 'Razadyne\*') OR 'donepezil' OR ('Aricept\*' or 'E2020') OR 'rivastigmine' OR ('Exelon\*' or 'SDZ ENA 713') OR ('Memantine' OR 'Namenda' OR 'Ebixa' OR 'Mntine')].

Selection criteria. Randomized, placebo-controlled trials that assessed the efficacy of cholinesterase inhibitors in patients with CIND-PD, DLB and PDD were selected for the present meta-analysis. The inclusion criteria were as follows: Patients with PD were included if they fulfilled the UK PD Society Brain Bank clinical diagnostic criteria for PD or clinically definite and probable PD diagnosis (11-14), and if they subsequently developed dementia, met the Diagnostic and Statistical Manual of Mental Disorders fourth edition/revised fourth edition or the Movement Disorders Society criteria at least 1 year after the onset of PD symptoms (15); DLB patients were included if they met the consensus guidelines for the clinical and pathological diagnosis of DLB or revised consensus criteria (16).

Data extraction and quality assessment. Two authors independently selected trials for inclusion in the meta-analysis and extracted information on the study design, patient selection criteria, drug doses, trial durations, primary and secondary outcomes, discontinuations and adverse events in each trial. Disagreements were resolved by discussion with other team members or by contacting the original investigators, who were all sent emails with requests to provide the exact data. For any missing standard deviation data, which were not obtainable from the primary investigators, estimated values calculated using the formula no. 8.5.2.3 in the Cochrane handbook were used in the analysis (17). The Cochrane criteria were used to assess risk of bias (18), and Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Profiler software (version 3.6; Cochrane, London, UK) was used to evaluate the quality of the studies according to the GRADE methods (19).

Statistical analysis. The meta-analysis was performed using RevMan software (version 5.3; Cochrane), employing the inverse variance method. Heterogeneity was assessed using the Chi-squared and I<sup>2</sup> statistical tests, and considered significant if P<0.05 and I<sup>2</sup>>50% was obtained by the former and the latter test, respectively. If I<sup>2</sup>>50%, a sensitivity analysis was performed to determine the reasons for heterogeneity. In

this commonly used sensitivity analysis method, each study included is eliminated one by one, followed by effect-size calculation, or the inclusion criteria are changed or certain types of literature are removed prior to effect volume combination. For continuous data, mean differences (MD) or standardized mean differences (SMD) were used in combination with the effect-size (Hedges'g) data. For dichotomous data, the risk ratio (RR) was estimated along with associated 95% confidence interval (CI). Overall, SMD and RR with 95% CI were estimated with Mantel-Haenszel fixed-effects (20) or DerSimonian-Laird random-effects models (21). When it was confirmed that there was no heterogeneity, pooled SMD and RR were calculated according to the Mantel-Haenszel fixed-effects model (P>0.05 or  $I^2 < 50\%$ ). If there was evidence of heterogeneity, pooled SMD and RR were calculated according to the DerSimonian-Laird random-effects model  $(P<0.05 \text{ or } I^2>50\%)$ . Begg's funnel plots were drawn to evaluate publication bias.

## Results

Study selection and characteristics. A total of 2,135 records of trials for the treatment of PD-CIND, PDD or DLB were retrieved from the Cochrane Library, Pubmed, Embase and Web of Science. Of these studies, a large quantity was not relevant, including studies regarding other diseases or interventions, or duplications. A total of 237 records were considered suitable after screening the titles and abstracts. Finally, of the 237 full-text articles, only 15 trials [six donepezil (22-27), five rivastigmine (10,28-31) and four memantine trials (32-35)] were included in the present meta-analysis. The flow chart for the selection of studies is presented in Fig. 1 and the details of each included article are presented in Table I. The methodological quality of all studies evaluated using the Cochrane risk of bias criteria is provided in Fig. 2.

#### Efficacy outcomes

*Global cognitive function*. Of the trials included, 12 (10,22-30,32,33) evaluated cognitive function using the MMSE and MoCA (Fig. 3). The standard mean difference in participants who received cholinesterase inhibitors or memantine vs. placebo was 0.46 (95% CI: 0.36-0.55; P<0.00001), suggesting significant benefits. Regarding different subgroups, benefits were determined for donepezil in DLB (SMD=0.63; 95% CI: 0.42-0.84; P<0.00001) and in PDD (SMD=0.51; 95% CI: 0.36-0.66; P<0.00001), and for rivastigmine in PDD (SMD=0.45; 95% CI: 0.28-0.62; P<0.00001), but not for rivastigmine in DLB or memantine in either DLB or PDD.

*Cognitive domains*. A total of seven trials (23,25-27,29,31,33) examined the cognitive domains of attention, processing speed and executive functions (Fig.4A). The results of the meta-analysis indicated that cholinesterase inhibitors and memantine provided significant benefits compared with placebo (MD=1.19; 95% CI: 0.65-1.73; P<0.0001). Furthermore, three trials (23,26,33) examined the cognitive domain of memory (Fig. 4B). The meta-analysis revealed that treatment with cholinesterase inhibitors achieved a significant improvement in patients compared with placebo (MD=0.24; 95% CI: 0.11-0.37; P=0.0003). In addition, three trials (26,29,33) examined visuospatial cognition

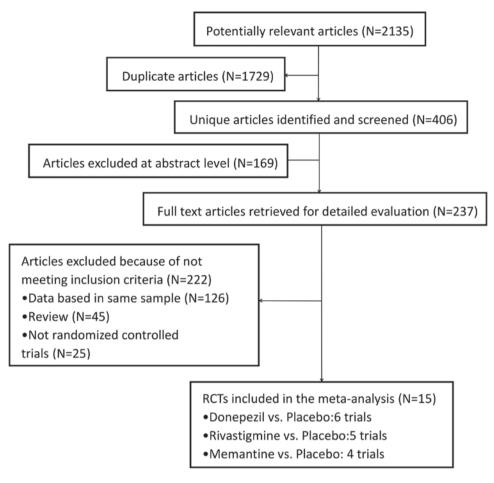


Figure 1. Flow diagram of study selection for the meta-analysis. RCT, randomized controlled trial.

(Fig. 4C). The results indicated that cholinesterase inhibitors did not improve visuospatial function when compared with the placebo (MD=0.13; 95% CI: -0.45-0.71; P=0.65). Finally, four trials (23,25,29,33) examined the cognitive domain of language (Fig. 4D). The meta-analysis revealed that cholinesterase inhibitors had a significant effect in patients compared with placebo (MD=1.44; 95% CI: 0.34-2.53; P=0.01).

*Global impression*. A total of seven trials (23-25,29,32,34,35) examined the subjects on the Clinician's Global Impression of Change (CGIC) scale. As indicated in the forest plot in Fig. 5, significant improvements in participants treated with the drugs compared with the placebo were revealed (RR=1.29; 95% CI: 1.15-1.45; P<0.0001). Furthermore, in the following subgroups, significant benefits compared with the placebo group were identified: DLB treated with donepezil 3 mg (RR=2.06; 95% CI: 1.18-3.60), donepezil 5 mg (RR=2.13; 95% CI: 1.22-3.70) and donepezil 10 mg (RR=1.93; 95% CI: 1.08-3.43); and PDD treated with rivastigmine (RR=1.37; 95% CI: 1.05-1.79). However, no significant benefits were determined for donepezil in PDD, memantine in PDD and DLB.

*Behavioral symptoms*. Altered Neuropsychiatric Inventory (NPI) scores were determined by nine trials (22,23,25,26,28, 29,31,32,34). As presented in Fig. 6, meta-analysis revealed a significant effect on NPI-10 among all studies [MD=-1.73; 95% CI: -(2.84-0.62); P=0.002].

*Motor function*. A total of 10 trials assessed motor function (10,22-24,26,27,30-32,34). Compared with the placebo, patients treated with cholinesterase inhibitors and memantine exhibited improvements in motor function (Fig. 7). The results of the meta-analysis suggested a significant effect on patients treated with drugs compared with placebo [MD=-1.38; 95% CI: -(1.96-0.79); P<0.00001]. However, only rivastigmine in PDD provided a significant benefit [MD=-2.32; 95% CI: -(3.09-1.55); P<0.00001], while donepezil in PDD or DLB, rivastigmine in DLB, and memantine in PDD and/or DLB did not. Furthermore, a subgroup analysis revealed that the dose of donepezil had no significant effect in improving DLB.

*Falling*. A considerable number of patients experience falls as a complication of PDD and five of the trials included (10,25,29,32,35) reported on the quantity of falling. As presented in Fig. 8, the meta-analysis revealed that cholinesterase inhibitors and memantine did not significantly reduce falling compared with the placebo (RR=0.74; 95% CI: 0.51-1.08; P=0.12), thereby demonstrating that treatment with the drugs did not significantly prevent falls.

Adverse events. Adverse events were inconsistently mentioned and reported by 13 trials (10,22-28,30-32,34,35). The common adverse events were cholinergic in nature (nausea, vomiting), aggravation of Parkinson and psychiatric symptoms (tremor,

							n of each			
First author (year)	Total (n)	Condition	Duration/design	Drug	Age (mean $\pm$ SD)	Males (%)	group	Dose (mg/day)	Outcomes	(Refs.)
Aarsland (2002)	14	CIND-PD	10 weeks	DON	71±3.9	92	12	10 (flexible dose)	MMSE, CIBIC-plus,	(24)
Ravina (2005)	22	PDD	10 weeks	DON	DON/PLA: 75.0±9.8	DON/PLA: 100	19	10 (flexible dose)	UFDR3-III001, NF1 MMSE, CGI-CADAS-cog,	(27)
			(crossover design)	PLA	PLA/DON: 72.1±8.1	PLA/DON: 60	19		MDRS, BPRS, UPDRS-motor	
Mori (2012)	140	DLB	12 weeks	DON 10 mg	DON 10 mg: 78.6±6.1	DON 10 mg: 11.1	37	10 (flexible dose)	MMSE, WMS-R, WAIS-III,	(23)
				DON 5 mg	DON 5 mg: 77.9±6.8	DON 5 mg: 50.0	33	5 (flexible dose)	NPI, VF, VPTA, UPDRS-motor	
				DON 3 mg	DON 3 mg: 79.6±4.5	DON 3 mg: 48.6	35	3 (flexible dose)		
				PLA	PLA: /8.0±4./	PLA: 28.1	ŝ	PLA		
Ikeda (2015)	142	DLB	12 weeks	DON 10 mg	DON 10 mg: 77.7±6.8	DON 10 mg: 42.9	49	10 (fixed dose)	MMSE, NPI, UPDRS-motor	(22)
				DON 5 mg	DON 5 mg: 78.8±5.1	DON 5 mg: 44.4	47	5 (fixed dose)		
				PLA	PLA: 77.2±6.1	PLA: 38.6	46			
Dubois (2012)	550	PDD	24 weeks	DON 10 mg	DON 10 mg: 70.8±7.46	DON 10 mg: 75	182	10 (fixed dose)	CIBIC-plus, MMSE, VF, BTA,	(25)
				DON 5 mg	DON 5 mg: 72.0±6.83	DON 5 mg: 65	195	5 (fixed dose)	ADAS-cog, NPI	
				PLA	PLA: 72.9±6.48	PLA: 65	173	PLA		
McKeith (2000)	120	DLB	20 weeks	RIV	RIV: 73.9±6.5	RIV: 52.5	59	12 (flexible dose)	NPI, CGC-plus, MMSE	(28)
				PLA	PLA: 73.9±6.4	PLA: 60.7	61			
Emre (2010)	199	DLB and PDD	24 weeks	MEM	MEM: 74.4±5.8	MEM: 53.1	96	MEM: 20 (fixed dose)	MEM: 20 (fixed dose) ADCS-CGIC, NPI, UPDRS	(34)
				PLA	PLA: 72.5±7.0	PLA: 57.6	66			
Leroi (2009)	25	PDD	16 weeks (from	MEM	MEM: 76.7±7.8	MEM: 36.4	11	MEM: 20 (fixed)	MMSE, NPI, UPDRS-3, CIBIC-Plus	(32)
			17 weeks to 22	PLA	PLA: 74.7±7.9	PLA: 4.3	14			
			weeks: Off drug)							
Leroi (2004)	16	PDD or	18 weeks	DON	DON: 66.2±9.3	DON: 85.7	L	10 mg (flexible dose)	Cognitive domains, VMI, NPI,	(26)
		CIND-PD		PLA	PLA: 70.8±11.8	PLA: 44.4	6		UPDRS-ADL, Motor function,	
									Complication of treatment	
Emre (2004)	541	PDD	24 weeks	RIV	RIV: 72.8±6.7	RIV: 64.6	362	12 mg (flexible dose)	ADAS-cog, ADCS-CGIC, NPI-10,	(29)
				PLA	PLA: 72.4±6.4	PLA: 65.4	179		MMSE, VF, CDT, UPDRS-motor	
Mamikonyan (2015)	28	CIND-PD	10 weeks	RIV patch	64.3±8.2	78.6	27	9.5 mg (flexible dose)	ADCS-CGIC, MoCA, PDRS-motor	(30)
			(crossover design)	PLA			27			
Wesnes (2002)	92	DLB	20 weeks	RIV	RIV: 73.9±6.5	RIV: 52.5	41	12 mg (flexible dose)	DSST, attention, processing speed,	(31)
			(crossover design)	PLA	PLA: 73.9±6.4	PLA: 60.7	51		Stroop Congruent Test, Trails A/B, Word Association Test	
Li (2015)	81	PD-MCI, PDD 12 months	12 months	RIV	RIV: 67.5±not clear	RIV: 73.2	41	3 mg (flexible dose)	MoCA, falls	(10)
				PLA	PLA: 66.9±not	PLA: 52.5	40			
				clear						
Aarsland (2009)	72	PDD, DLB	24 weeks (from	MEM	MEM: 76.9±6.1	MEM: 79.4	34	20 mg (flexible dose)	CGIC, MMSE, NPI, UPDRS	(33)
			17 weeks to 22	PLA	PLA: 76.2±5.8	PLA: 71.1	38			
			(Snin IIO (Sumo)							

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Table I. Summary of studies included in the present meta-analysis.

n of each se (mean ± SD) Males (%) group Dose (mg/day) Outcomes (Refs.)	$ 73.8\pm 5^{a}, 75.2\pm 5.6^{b} MEM: 75^{a}, 100^{b} 18 (12/6) 20 mg (flexible dose) Survival (35) 76.5\pm 4.7^{a}, 75.6\pm 4.6^{b} PLA: 66.7^{a}, 60^{b} 14 (9/5) $	<sup>4</sup> Subgroup 1, <sup>b</sup> aubgroup 2. PDD, Parkinson's disease with dementia with Lewy bodies; MCI, mild cognitive impairment; PLA, placebo; MEM, memantine; RIY, rivastigmine; CIND-PD, cognitive impairment in Parkinson's disease with dementia; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; PLA, placebo; MEM, memantine; RIY, rivastigmine; CIND-PD, cognitive impairment in Parkinson's disease; DON, donepezil; MMSE, Mini Mental State Examination; MoCa, Montreal Cognitive Assessment; CIBIC, Clinician's Interview-Based Impression of Change; UPDRS, Unified Parkinson's Disease Rating Scale; NPI, Neuropsychiatric Inventory; CGI-CORCAS, Clinical Global Impression-Cognitive Drug Research Computerized Assessment; BPRS, Brief Psychosis Rating Scale; MDRS, Mattis Dementia Rating Scale; VF, Verbal Fluency; VMI, develop-mental test of Scale-Montreal Procession in Cardio and Scale; MDRS, Mattis Dementia Rating Scale; VF, Verbal Fluency; VMI, develop-mental test of Visuel-Montreal Procession in Cardio and Scale; MDRS, Mattis Dementia Rating Scale; VF, Verbal Fluency; VMI, develop-mental test of Schenker Memory Scale-Revised, CDT, Otherword, Scale, Scale-Revised, CDT, Otherword, Scale, Scale-Revised, CDT, Otherword, Schenker Memory Scale, MDRS, Mattis Dementia Rating Scale; VDT, Visual Breegton Control University Scales Investor Discon Assessment Scale Accession Assessment Scale Activities Scale Activities Scale Accession Assessment Scale Accession Assessment Assessment Apple Scale Accession Assessment Apple Scale Accession Assessment Apple Scale Accession Accession Accession Scale Accession Assessment Apple Scale Accession Access
	() 20 mg (f)	memantine; RI <sup>-</sup> ange; UPDRS, t Mattis Dementii )T, clock drawin
n of eac group		acebo; MEM, pression of Ch Scale; MDRS, e-Revised; CT ssessment Scr
Males (%)	MEM: 75 <sup>a</sup> , 100 <sup>b</sup> PLA: 66.7 <sup>a</sup> , 60 <sup>b</sup>	impairment; PLA, pl: s Interview-Based Imp ief Psychosis Rating S (echsler Memory Scali Alzheimer's Disease A
Age (mean ± SD)	MEM MEM: 73.8±5.5 <sup>a</sup> , 75.2±5.6 <sup>b</sup> PLA PLA: 76.5±4.7 <sup>a</sup> , 75.6±4.6 <sup>b</sup>	ewy bodies; MCI, mild cognitive ive Assessment; CIBIC, Clinician's zed Assessment System: BPRS, Br dult IntelligenceScale; WMS-R, W mrression of Change: ADAS, cop. 1
Drug	MEM PLA	nentia with ] ntreal Cognii A Computeri I Wechsler A In's Global I
Duration/design	24 weeks	ith dementia; DLB, der kamination; MoCa, Mo Cognitive Drug Researc t for Agnosia; WAIS-II merative Study-Clinicia
Total (n) Condition	PDD; DLB 24 weeks	nson's disease w ui Mental State E; obal Impression-( al Perception Tes ner's Disease Coo
Total (n)	75	2. PDD, Parki il; MMSE, Min &S, Clinical Gk n; VPTA, Visuk CGIC. Alzheim
First author (year)	Stubendorff (2014)	<ul> <li>Subgroup 1, <sup>b</sup>subgroup disease; DON, donepezi Inventory; CGI-CDRCA Visual-Motor Integration of Daily Livine: ADCS4.</li> </ul>

fall, somnolence, insomnia, hallucinations), urinary tract infection and respiratory tract infection; however, most adverse events were mild or moderate. As presented in Fig. 9, the results of the meta-analysis revealed more adverse events in the treatment groups compared with those in the placebo group (RR=1.09; 95% CI: 1.04-1.16; P=0.001). However, among the subgroups, only the rivastigmine group experienced significantly more adverse events compared the placebo group (RR=1.18; 95% CI: 1.08-1.29; P=0.0001; data not shown). Donepezil and memantine did not produce any significant adverse events compared with the placebo.

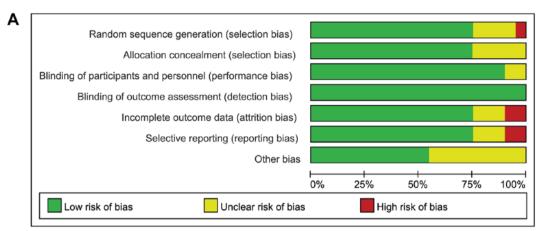
*Publication bias*. The publication bias regarding cognitive and motor function was determined by drawing Begg's funnel plots (Fig. 10A and B). The shape of the funnel plots exhibited no obvious asymmetry, which indicated the absence of significant heterogeneity between these selected studies, and the pooled results were not influenced by publication bias.

Sensitivity analysis. A sensitivity analysis was conducted to assess the stability of the results by sequential removal of individual studies. The heterogeneity (I<sup>2</sup>=75%) in global cognitive function is shown in Fig. 3, the study by Li *et al* (10) did not provide the mean differences with SDs, but rather electing to report the mean and SDs prior to and following treatment, which may have resulted in data conversion-associated errors. Following the exclusion of the study, the analysis results did not change. In Fig. 4A, numerous trials that examined cognitive domains were then assessed (I<sup>2</sup>=78%), it was found that the results did not change following the sequential removal of individual studies. The authors of the current study estimated that there was variability in measurement precision.

## Discussion

The present meta-analysis assessed the efficacy and safety of cholinesterase inhibitors and memantine in the treatment of CIND-PD, PDD and DLB, which contained four new more articles than a previous meta-analysis (9). To the best of our knowledge, the present study was the first meta-analysis to report on the effect of cholinesterase inhibitors and memantine in subjects with CIND-PD, PDD and DLB, including cognitive domains (attention, processing speed, executive functions, memory, visuospatial cognition and language). The results indicated that cholinesterase inhibitors had beneficial effects on attention, processing speed, executive functions, memory and language, but did not improve visuospatial cognition when compared with the placebo. Furthermore, memantine was revealed to improve attention, processing speed and executive functions. However, cholinesterase inhibitors and memantine did not significantly reduce falling. Compared with the placebo, more adverse events occurred in the pooled cholinesterase inhibitors and memantine group than in the placebo group. However, a subgroup analysis indicated that only the rivastigmine group experienced significantly more adverse events than the placebo group, while donepezil and memantine did not produce any significant adverse events.

Consistent with the results of previous meta-analyses, the present study indicated that donepezil was beneficial for DLB



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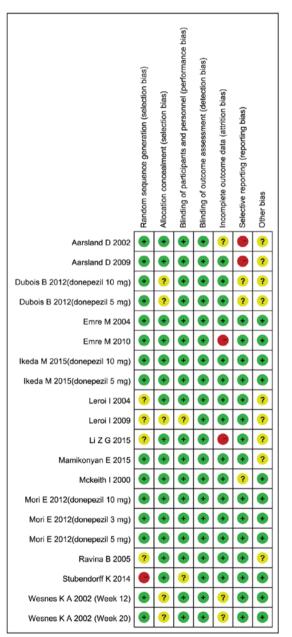


Figure 2. Risk of bias graphs. Review authors' judgments on each risk of bias item (A) presented as percentages across all included studies and (B) for each included study.

regarding cognitive function and global impression, but not in any other aspects. Recently published secondary analyses of donepezil suggest statistically significant advantages of donepezil over placebo regarding aspects of Behavioural

	Exp	eriment	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
1.1.1 DLB,donepezil									
Ikeda M 2015(donepezil 10 mg)	2.2	2.9	49	0.6	3	44	5.1%	0.54 [0.12, 0.95]	
Ikeda M 2015(donepezil 5 mg)	1.4	3.4	43	0.6	3	44	4.9%	0.25 [-0.17, 0.67]	<u>+</u>
Mori E 2012(donepezil 10 mg)	2	3.3	36	-0.4	2.7	31	3.5%	0.78 [0.28, 1.28]	
Mori E 2012(donepezil 3 mg)	1.6	3.8	35	-0.4	2.7	31	3.6%	0.59 [0.10, 1.09]	
Mori E 2012(donepezil 5 mg)	3.4	3.2	32	-0.4	2.7	31	2.9%	1.27 [0.72, 1.81]	
Subtotal (95% CI)			195			181	19.9%	0.63 [0.42, 0.84]	•
Heterogeneity: Chi <sup>2</sup> = 8.96, df = 4 Test for overall effect: Z = 5.88 (P	-	-	55%						
1.1.2 DLB,rivastigmine									
Mckeith I 2000	0.67	4.26	59	-0.57	4.26	61	6.7%	0.29 [-0.07, 0.65]	<u> </u>
Subtotal (95% CI)			59			61	6.7%	0.29 [-0.07, 0.65]	◆
Heterogeneity: Not applicable Test for overall effect: Z = 1.58 (P	= 0.12)								
1.1.3 PDD,donepezil									
Aarsland D 2002	22.8	3.7	12	21	5	12	1.3%	0.40 [-0.41, 1.20]	
Dubois B 2012(donepezil 10 mg)	1.9	2.86	162	0.2	3.16	163	17.7%	0.56 [0.34, 0.78]	
Dubois B 2012(donepezil 5 mg)	1.7	2.85	168	0.2	3.16	163	18.1%	0.50 [0.28, 0.72]	
Leroi I 2004	25.33	3.78	7	25.56	3.75	9	0.9%	-0.06 [-1.05, 0.93]	
Ravina B 2005	24.5	3.2	9	22.5	4.7	10	1.0%	0.47 [-0.45, 1.39]	
Subtotal (95% CI)			358			357	39.0%	0.51 [0.36, 0.66]	•
Heterogeneity: Chi <sup>2</sup> = 1.58, df = 4	(P = 0.8	1); I² =	0%						
Test for overall effect: Z = 6.71 (P	< 0.000	01)							
1.1.4 PDD,rivastigmine									
Emre M 2004	0.8	3.8	335	-0.2	3.5	166	24.9%	0.27 [0.08, 0.46]	
Li Z G 2015	22.97	1.03	41	19.66	2.45	40	3.3%	1.75 [1.24, 2.27]	
Mamikonyan E 2015	1.85	2.25	13	0.21	2.57	14	1.4%	0.66 [-0.12, 1.44]	
Subtotal (95% CI)			389			220	29.6%	0.45 [0.28, 0.62]	•
Heterogeneity: Chi <sup>2</sup> = 28.32, df = 3 Test for overall effect: Z = 5.17 (P			; I² = 93	3%					
1.1.5 DLB and PDD,memantine									
Aarsland D 2009	-1.4	3.2	30	0.5	4.2	33	3.4%	-0.50 [-1.00, 0.00]	
Subtotal (95% CI)			30			33	3.4%	-0.50 [-1.00, 0.00]	
Heterogeneity: Not applicable Test for overall effect: Z = 1.95 (P	= 0.05)								
1.1.6 PDD, memantine									
Leroi I 2009	19.9	6.3	10	20.9	6	14	1.3%	-0.16 [-0.97, 0.66]	
Subtotal (95% CI)			10			14	1.3%	-0.16 [-0.97, 0.66]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.38 (P	= 0.70)								
Total (95% CI)			1041			866	100.0%	0.46 [0.36, 0.55]	•
Heterogeneity: Chi <sup>2</sup> = 58.83, df =	15 (P < 0	0.00001	); l² = 7	75%					-2 -1 0 1 2
Test for overall effect: Z = 9.63 (P	< 0.000	01)							
Test for subgroup differences: Ch	i² = 19.97	7, df = 5	5 (P = (	0.001), I	² = 75.	0%			Favours (control) Favours (experimental)

Figure 3. Forest plot of the meta-analysis of cognitive outcomes determined by Mini-Mental State Examination and Montreal Cognitive Assessment for various drugs and doses. The risk ratio is presented as green squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; IV, inverse variance; SD, standard deviation; df, degrees of freedom; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies.

and Psychological Symptoms of Dementia (BPSD), improvement of cognitive function and visual hallucinations (36-38). Manabe *et al* (36) observed that 10 mg donepezil improved BPSD in DLB. Mori *et al* (37) reported that increasing the dose of donepezil from 5 to 10 mg enhanced the effect in improving cognitive function in DLB with little influence on the safety. Ukai *et al* (38) reported that donepezil was highly effective against visual hallucinations in DLB.

Galanthamine is another cholinesterase inhibitor. To date, the potential benefits of galanthamine have remained insufficiently demonstrated, except for an open-label trial. Litvinenko *et al* (39) reported that galanthamine improved cognitive function, behavioral symptoms, daily activity and the number of falls. Galanthamine treatment was not associated with any significant adverse events when compared with the placebo.

The results of the present meta-analysis revealed that memantine only had a minor side effect on the participants; however, this is in contrast to the meta-analysis by Matsunaga *et al* (6). This discrepancy may have been due to the fact that the analysis of the present study included two further trials, which may have provided more accurate results. Larsson *et al* (40) reported that memantine decreases the probable rapid eye movement sleep behavioral disorder in patients with DLB and PDD.

Safety is as important as the efficacy of the interventions in clinical studies. All of the three drugs assessed in the present study adhered to certain safety standards; however, rivastigmine produced more adverse events compared with those in the placebo group. Of note, donepezil and memantine did not produce any significant adverse events compared with the placebo. None of the drugs improved or Α

	Exp	eriment	al	0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV. Random, 95% CI
9.1.1 Attention, Processing speed and Executive fun	ctions								
Aarsland D 2009 - AQT colour	-5.2	32.2	27	6.9	16.5	30	0.2%	-12.10 [-25.60, 1.40]	
Aarsland D 2009 - AQT colour-form	15.8	67	22	14.7	49.1	24	0.0%	1.10 [-33.10, 35.30]	•
Aarsland D 2009 - AQT form	-5.5	40.9	25	6.9	25.1	28	0.1%	-12.40 [-30.93, 6.13]	·
Dubois B 2012(donepezil 10mg) - BTA	0.61	2.14	105	-0.39	2.14	111	4.2%	1.00 [0.43, 1.57]	~
Dubois B 2012(donepezil 10mg) - Category fluency	1.97	6.31	148	-2.25	6.31	152	3.4%	4.22 [2.79, 5.65]	-
Dubois B 2012(donepezil 10mg) - Category switching	0.6	3.03	148	-2.25	3.03	152	4.1%	1.20 [0.51, 1.89]	~
Dubois B 2012(donepezil 10mg) - Letter fluency	2.57	7.03	148	-0.55	7.03	152	3.2%	3.12 [1.53, 4.71]	
	0.39	2.14	116	-0.39	2.14	111	4.2%		~
Dubois B 2012(donepezil 5mg) - BTA			159			152		0.78 [0.22, 1.34]	-
Dubois B 2012(donepezil 5mg) - Category fluency	1.42	6.33		-2.25	6.33		3.4%	3.67 [2.26, 5.08]	-
Dubois B 2012(donepezil 5mg) - Category switching	0.53	3.04	159	-0.6	3.04	152	4.2%	1.13 [0.45, 1.81]	
Dubois B 2012(donepezil 5mg) - Letter fluency	2.01	7.05	159	-0.55	7.05	152	3.2%	2.56 [0.99, 4.13]	1
Emre M 2004 - Attention	-0.031	0.99	328	0.14	1.8	158	4.4%	-0.17 [-0.47, 0.13]	
Emre M 2004 - Verbal fluency	1.7	6.8	258	-1.1	6.4	144	3.5%	2.80 [1.47, 4.13]	-
Leroi I 2004 - BTA	5.5	1.76	7	4.57	2.7	9	2.6%	0.93 [-1.26, 3.12]	<u>+-</u>
Leroi I 2004 - Category fluency	36	14.4	7	30.5	10.46	9	0.2%	5.50 [-7.17, 18.17]	
Leroi I 2004 - DRS attention	35.2	1.3	7	35.44	1.33	9	3.5%	-0.24 [-1.54, 1.06]	+
Leroi I 2004 - DRS conceptual planning	5.4	0.89	7	5.56	0.53	9	4.1%	-0.16 [-0.90, 0.58]	†
Leroi I 2004 - DRS initiation	31	9.42	7	33.44	3.57	9	0.5%	-2.44 [-9.80, 4.92]	
Leroi I 2004 - TMT-A	-41.81	93.87	7	29.87	81.67	9	0.0%	-71.68 [-159.33, 15.97]	·
Leroi I 2004 - TMT-B	-44.83	253.3	7	42.71	230.09	9	0.0%	-87.54 [-327.97, 152.89]	·
Leroi I 2004 - Verbal fluency	30.83	16.67	7	39.5	19.56	9	0.1%	-8.67 [-26.44, 9.10]	
Mori E 2012(donepezil 10mg) - Category fluency	-0.5	2.7	35	0.3	3.4	31	3.3%	-0.80 [-2.29, 0.69]	-+
Mori E 2012(donepezil 10mg) - Letter fluency	1.7	4.3	35	0.3	4.5	31	2.6%	1.40 [-0.73, 3.53]	
	3.7	7.9	33	0.3	5.9	30	1.6%		
Mori E 2012(donepezil 10mg) - Symbol digit test								3.40 [-0.02, 6.82]	
Mori E 2012(donepezil 10mg) - WMS-R attention	4.8	7.4	33	-0.9	7.9	31	1.4%	5.70 [1.94, 9.46]	
Mori E 2012(donepezil 3mg) - Category fluency	1.2	4	34	0.3	3.4	31	3.0%	0.90 [-0.90, 2.70]	
Mori E 2012(donepezil 3mg) - Letter fluency	1.1	4.5	34	0.3	4.5	31	2.6%	0.80 [-1.39, 2.99]	
Mori E 2012(donepezil 3mg) - Symbol digit test	6.4	7.9	34	0.3	5.9	30	1.6%	6.10 [2.71, 9.49]	
Mori E 2012(donepezil 3mg) - WMS-R attention	3.1	9.9	34	-0.9	7.9	31	1.1%	4.00 [-0.34, 8.34]	
Mori E 2012(donepezil 5mg) - Category fluency	1.6	3.4	32	0.3	3.4	31	3.1%	1.30 [-0.38, 2.98]	<u>–</u>
Mori E 2012(donepezil 5mg) - Letter fluency	3.1	5.8	32	0.3	4.5	31	2.2%	2.80 [0.24, 5.36]	
Mori E 2012(donepezil 5mg) - Symbol digit test	6.9	8	32	0.3	5.9	30	1.5%	6.60 [3.12, 10.08]	
Mori E 2012(donepezil 5mg) - WMS-R attention	5.6	7.8	32	-0.9	7.9	31	1.3%	6.50 [2.62, 10.38]	
Ravina B 2005 - Attention	31	5.1	9	31.1	5.2	10	1.0%	-0.10 [-4.74, 4.54]	
Ravina B 2005 - Initiative	25.9	6.3	9	25.5	7	10	0.7%	0.40 [-5.58, 6.38]	
Wesnes K A 2002(Week 12) - Attention	-0.84	3.3	38	0.61	1.7	47	3.7%	-1.45 [-2.61, -0.29]	
Wesnes K A 2002(Week 12) - DSST	1.55	4.84	37	0.6	2.76	47	3.0%	0.95 [-0.80, 2.70]	+
Wesnes K A 2002(Week 12) - Processing speed	-0.5	3.8	29	3.15	6.9	39	2.2%	-3.65 [-6.22, -1.08]	
Wesnes K A 2002(Week 12) - Processing speed Wesnes K A 2002(Week 12) - Stroop Congruent Test	-3.63	50.82	34	9.04	53.41	43	0.1%	-12.67 [-36.05, 10.71]	·
Wesnes K A 2002(Week 12) - Stroop Congruent Test	-3.03	99.5	29	-4.56	102	43	0.1%	-12.67 [-36.05, 10.71] -20.66 [-69.56, 28.24]	· · · · · · · · · · · · · · · · · · ·
									·
Wesnes K A 2002(Week 12) - Trails A	-53.9	114.1	24	-11.74	122.5	27	0.0%	-42.16 [-107.11, 22.79]	
Wesnes K A 2002(Week 12) - Trails B	101	329.6		-123.3	70.72	6	0.0%	224.30 [-45.43, 494.03]	·
Wesnes K A 2002(Week 12) - Word Association Test	0.68	2.91	36	0.06	2.77	46	3.6%	0.62 [-0.62, 1.86]	
Wesnes K A 2002(Week 20) - Attention	-0.86	3.3	38	0.43	1.5	45	3.7%	-1.29 [-2.43, -0.15]	
Wesnes K A 2002(Week 20) - DSST	1.9	5.67	34	1	3.41	43	2.6%	0.90 [-1.26, 3.06]	<u>+</u> -
Wesnes K A 2002(Week 20) - Processing speed	-0.19	7.2	28	0.75	6	35	1.6%	-0.94 [-4.27, 2.39]	. —
Wesnes K A 2002(Week 20) - Stroop Congruent Test	-16.39	51.55	31	14.39	56.92	37	0.0%	-30.78 [-56.58, -4.98]	·
Wesnes K A 2002(Week 20) - Stroop Incongruent Test	-82.29	171.8	26	8.21	91.07	29	0.0%	-90.50 [-164.39, -16.61]	
Wesnes K A 2002(Week 20) - Trails A	-52.4	109.5	25	-13.76	113	23	0.0%	-38.64 [-101.69, 24.41]	·
Wesnes K A 2002(Week 20) - Trails B	69.17	150.7	9	-75.6	110.2	7	0.0%	144.77 [16.87, 272.67]	I —
Wesnes K A 2002(Week 20) - Word Association Test	0.33	3.5	34	-0.77	2.94	44	3.3%	1.10 [-0.36, 2.56]	
Westles K A 2002(Week 20) - Word Association Test	0.33	3.5	34	-0.77	2.94	44	3.3%	1,10 [-0.36, 2.56]	
Total (95% CI)			2734			2534	100.0%	1.19 [0.65, 1.73]	•
Heterogeneity: Tau <sup>2</sup> = 1.68; Chi <sup>2</sup> = 227.11, df = 50 (P < 0	.00001);	l² = 78%	6						-20 -10 0 10 20
Test for overall effect: Z = 4.35 (P < 0.0001)									-20 -10 0 10 20
1 est 101 overall effect. Z = 4.35 (P < 0.0001)									

в		-											
D			rimenta			ontrol			Mean Difference		Mean Differ		
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% CI		IV. Fixed. 9	15% CI	
	9.2.1 Memory												
	Leroi I 2004 - DRS-memory	22.2	4.66	7	19.56	4.28	9	0.1%	2.64 [-1.80, 7.08]		-		
	Leroi I 2004 - HVLT-R Recall	6.3	3.5	7	5.2	4.3	9	0.1%	1.10 [-2.72, 4.92]				
	Leroi I 2004 - HVLT-R Recognition	10.2	2.6	7	10.8	1.3	9	0.4%	-0.60 [-2.71, 1.51]			-	
	Leroi I 2004 - HVLT-R Total	20.83	8.66	7	18.22	8.29	9	0.0%	2.61 [-5.79, 11.01]				
	Mori E 2012(donepezil 10mg) -VPTA form recognition	-1	2.1	34	-1	2.9	31	1.1%	0.00 [-1.24, 1.24]		-		
	Mori E 2012(donepezil 3mg) - VPTA form recognition	0	3.7	34	-1	2.9	31	0.7%	1.00 [-0.61, 2.61]		+		
	Mori E 2012(donepezil 5mg) - VPTA form recognition	-1.1	2.4	32	-1	2.9	31	1.0%	-0.10 [-1.42, 1.22]		-		
	Wesnes K A 2002(Week 12)-Episodic secondary memory	0.131	0.656	34	-0.125	0.526	44	23.6%	0.26 [-0.01, 0.53]		•		
	Wesnes K A 2002(Week 12)-Overall quality of memory	0.424	1.06	34	-0.159	0.72	44	10.0%	0.58 [0.17, 1.00]		-		
	Wesnes K A 2002(Week 12)-Quality of working memory	0.257	0.672	30	-0.008	0.484	40	21.4%	0.27 [-0.02, 0.55]		-		
	Wesnes K A 2002(Week 20)-Episodic secondary memory	-0.023	0.731	33	-0.13	0.512	41	19.8%	0.11 [-0.19, 0.40]		<u>†</u>		
	Wesnes K A 2002(Week 20)-Overall quality of memory	0.0991	1.28	33	-0.141	0.794	41	6.9%	0.24 [-0.26, 0.74]		-		
	Wesnes K A 2002(Week 20)-Quality of working memory	0.105	0.804	30	-0.02	0.56	38	15.0%	0.13 [-0.21, 0.46]		t 1		
	Total (95% CI)			322			377	100.0%	0.24 [0.11, 0.37]		•		
	Heterogeneity: Chi <sup>2</sup> = 7.38, df = 12 (P = 0.83); l <sup>2</sup> = 0%									+ +			——
	Test for overall effect: $Z = 3.58$ (P = 0.0003)									-10 -5	0	5	10
	Test for subgroup differences: Not applicable									Favours (cont	rol) Favo	urs (experimental	1)

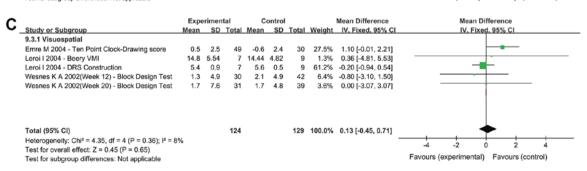


Figure 4. Forest plot of the meta-analysis for the cognitive domains of (A) attention, processing speed and executive functions, (B) memory for donepezil, rivastigmine and memantine, and (C) visuospatial cognition. The risk ratio is presented as green squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds.

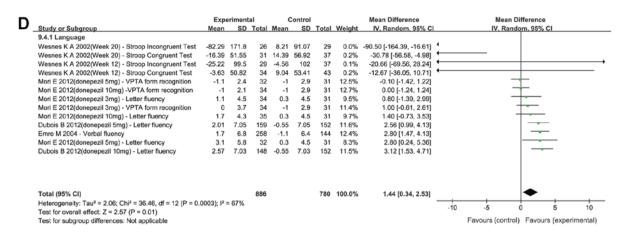


Figure 4. Continued. Forest plot of the meta-analysis for the cognitive domain of (D) language for donepezil and rivastigmine. The risk ratio is presented as green squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; IV, inverse variance; SD, standard deviation; df, degrees of freedom; VPTA, Visual Perception Test for Agnosia; AQT, A Quick Test of Cognitive Speed; WMS-R, Wechsler Memory Scale-Revised; BTA, Brief Test of Attention; DRS, Dementia Rating Scale; TMT, Trial Making Test; DSST, Digit Symbol Substitution Test; HVLT-R, Hopkins Verbal Learning Test-Revised.

	Exporim	ontal	Contro	а		Risk Ratio	Risk Ratio
Study or Subgroup	Experim Events				Weight	M-H. Fixed. 95% Cl	MISK Ratio M-H. Fixed. 95% Cl
2.1.1 DLB,donepezil	Lveins	TOTAL	Lvents	Total	Weight	M-H, FIXed, 55% CI	M-H, FIXed, 55% CI
Mori E 2012(donepezil 10 mg)	18	28	10	30	3.2%	1.93 [1.08, 3.43]	
Mori E 2012(donepezil 10 mg)	22	32	10	30	3.4%	2.06 [1.18, 3.60]	· · · · ·
Mori E 2012(donepezil 5 mg)	22	31	10	30	3.3%	2.13 [1.22, 3.70]	
Subtotal (95% CI)		91	10	90	9.9%	2.04 [1.48, 2.83]	•
Total events	62		30				
Heterogeneity: Chi <sup>2</sup> = 0.06, df = 2		l <sup>2</sup> = 0%					
Test for overall effect: Z = 4.31 (P		,.					
2.1.2 PDD,donepezil							
Dubois B 2012(donepezil 5 mg)	70	177	68	170	22.7%	0.99 [0.76, 1.28]	+
Dubois B 2012(donepezil 10 mg)	85	170	68	170	22.3%	1.25 [0.99, 1.59]	
Aarsland D 2002	5	12	2	12	0.7%	2.50 [0.60, 10.46]	
Subtotal (95% CI)		359		352	45.6%	1.14 [0.96, 1.35]	•
Total events	160		138				
Heterogeneity: $Chi^2 = 2.89$ , df = 2 Test for overall effect: Z = 1.46 (P		I² = 31%	þ				
2.1.3 PDD, rivastigmine							
Emre M 2004	134	329	49	165	21.4%	1.37 [1.05, 1.79]	<b>—</b>
Subtotal (95% CI)	104	329	40	165	21.4%	1.37 [1.05, 1.79]	◆
Total events	134		49				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.31 (P	= 0.02)						
2.1.4 DLB,memantine							
Emre M 2010	16	33	16	41	4.7%	1.24 [0.74, 2.09]	
Subtotal (95% CI)		33		41	4.7%	1.24 [0.74, 2.09]	
Total events	16		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.82 (P	= 0.41)						
2.1.5 PDD, memantine							
Emre M 2010	31	60	28	56	9.5%	1.03 [0.72, 1.48]	
Leroi I 2009	6	10	6	14	1.6%	1.40 [0.64, 3.08]	
Subtotal (95% CI)		70		70	11. <b>1%</b>	1.09 [0.78, 1.51]	<b>•</b>
Total events	37		34				
Heterogeneity: $Chi^2 = 0.47$ , df = 1 Test for overall effect: Z = 0.50 (P		I <sup>2</sup> = 0%					
2.1.6 DLB and PDD, memantine							
Stubendorff K 2014	12	18	9	14	3.3%	1.04 [0.62, 1.73]	
Aarsland D 2009	19	30	13	33	4.1%	1.61 [0.97, 2.66]	
Subtotal (95% CI)		48		47	7.4%	1.35 [0.94, 1.94]	◆
Total events	31		22				
Heterogeneity: $Chi^2 = 1.50$ , df = 1		l² = 33%					
Test for overall effect: Z = 1.63 (P			-				
Total (95% CI)		930		765	100.0%	1.29 [1.15, 1.45]	◆
Total events	440		289				
Heterogeneity: Chi <sup>2</sup> = 15.86, df =	11 (P = 0.15	5);  ² = 3					
Test for overall effect: Z = 4.39 (P							0.1 0.2 0.5 1 2 5 10
Test for subgroup differences: Chi	² = 11.03, d	if = 5 (P	= 0.05), I <sup>2</sup>	= 54.	7%		Favours (control) Favours (experimental)

Figure 5. Forest plot of the meta-analysis of Clinical Global Impression of Change by drug and dose. The risk ratio is presented as green squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; M-H, Mantel-Haentzel; df, degrees of freedom; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies.

	E		4-1	~				Maan Difference	Maca Difference
Study or Subgroup	Mean	erimen ne	tai Total		ontrol ne	Total	Weight	Mean Difference IV. Random. 95% CI	Mean Difference IV. Random. 95% Cl
3.1.1 DLB,donepezil	Wiedii	30	TUtal	Weall	30	Total	Weight	TV, Kandoni, 55/6 Ci	
Ikeda M 2015(donepezil 10mg)	-5.5	9.89	49	-6.4	9.9	44	6.7%	0.90 [-3.13, 4.93]	
Ikeda M 2015(donepezil 5mg)	-3.3		45	-6.4	9.9	44	6.7%	3.10 [-0.91, 7.11]	+
Mori E 2012(donepezil 10mg)	-8		35		17.5	32	2.2%	-8.30 [-15.70, -0.90]	
Mori E 2012(donepezil 3mg)	-3.9	22	35		17.5	32	1.3%	-4.20 [-13.68, 5.28]	
Mori E 2012(donepezil 5mg)	-5.5		32		17.5	32	2.8%	-5.80 [-12.29, 0.69]	
Subtotal (95% CI)	0.0	0.1	196	0.0		184	19.7%	-1.98 [-6.26, 2.29]	
Heterogeneity: Tau <sup>2</sup> = 14.20; Chi	<sup>2</sup> = 10.97	df = 4	(P = 0.)	03); l² =	64%				
Test for overall effect: Z = 0.91 (F	P = 0.36)								
3.1.2 DLB,rivastigmine									
Mckeith I 2000	-5	16.2	47	-1.2	10.7	53	3.9%	-3.80 [-9.25, 1.65]	
Subtotal (95% CI)			47			53	3.9%	-3.80 [-9.25, 1.65]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.37 (F	P = 0.17)								
3.1.3 PDD,donepezil	4.0	0.0	470		0.0	470	00.084	4 70 / 0.00 0.001	
Dubois B 2012(donepezil 10mg)	-1.3	9.3	173	0.4	9.2	170	20.2%	-1.70 [-3.66, 0.26]	
Dubois B 2012(donepezil 5mg)	-1.6	8.6	183 7	0.4	9.2	170 9	21.5%	-2.00 [-3.86, -0.14]	
Leroi I 2004 Subtotal (95% CI)	8.8	12.4	363	7.8	10.7	349	0.9% <b>42.6%</b>	1.00 [-10.54, 12.54] -1.82 [-3.16, -0.48]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	-0.00 d	( - 0 / P		12 - 0	0/	349	42.0%	-1.02 [-3.10, -0.40]	•
Test for overall effect: Z = 2.66 (F		`	- 0.07	); 1 0	70				
Test for overall effect. 2 = 2.00 (F	- 0.000	,							
3.1.4 PDD, rivastigmine									
Emre M 2004	-2	10	334	0	10.4	166	20.8%	-2.00 [-3.91, -0.09]	
Subtotal (95% CI)			334			166	20.8%	-2.00 [-3.91, -0.09]	$\bullet$
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.05 (F	P = 0.04)								
3.1.5 DLB,memantine									
Emre M 2010	-4.3	14	33	1.7	13.3	41	3.0%	-6.00 [-12.28, 0.28]	
Subtotal (95% CI)			33			41	3.0%	-6.00 [-12.28, 0.28]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.87 (F	P = 0.06)								
3.1.6 PDD, memantine									
Emre M 2010	-1.6	13	60	0.1	13.6	56	4.8%	1 50 [ 6 25 2 25]	
Leroi I 2009		11.5	10		12.4	56 14	4.8%	-1.50 [-6.35, 3.35] -2.00 [-11.64, 7.64]	
Subtotal (95% CI)	11.5	11.5	70	13.5	12.4	70	6.1%	-1.60 [-5.93, 2.73]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	= 0.01 d	f = 1 (P		)· I² = 0'	%	10	0.170	-1.00 [-0.00, 2.10]	
Test for overall effect: Z = 0.72 (F		(1	0.00	,,, = 0					
	0,								
3.1.7 DLB and PDD,memantine									
Aarsland D 2009	1.5	10.8	29	1.4	10.6	33	4.0%	0.10 [-5.24, 5.44]	
Subtotal (95% CI)			29			33	4.0%	0.10 [-5.24, 5.44]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.04 (F	P = 0.97)								
Total (95% CI)			1072			896	100.0%	-1.73 [-2.84, -0.62]	
Heterogeneity: Tau <sup>2</sup> = 0.60; Chi <sup>2</sup>	-		(P = 0.3	30); l² =	: 14%				-10 -5 0 5 10
Test for overall effect: $Z = 3.04$ (F		,	(D	05) 12	001				Favours (experimental) Favours (control)
Test for subgroup differences: Ch	II <sup>+</sup> = 2.67	, at = 6	(P = 0.8	50), I* =	0%				

Figure 6. Forest plot of the meta-analysis of behavioral symptoms according to the 10-Item Neuropsychiatric Inventory by drug and dose. The risk ratio is presented as green squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; IV, inverse variance; SD, standard deviation; df, degrees of freedom; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies.

aggravated the symptoms of Parkinsonism compared with the placebo. Emre *et al* (41) reported that in a 76-week, prospective, open-label, randomized study in PDD patients aged 50 to 85 years, rivastigmine exhibited long-term safety.

Of note, the present meta-analysis had several limitations. First, even though 15 trials were included, the number of participants was small, and the results may not sufficiently allow for making any final conclusions. Furthermore, a complete evaluation of all interventions applied was impossible due to a lack of data. In addition, most of the trials included were relatively short, and more long-term trials with relatively longer follow-up periods similar to that by Li *et al* (10) lasting 12 months, are required for further evaluation. In addition, in the cognitive domains analysis with  $I^2=78\%$ , variation in at times overlapping interventions, heterogeneity in outcomes assessed and low number of controls were of greatest concern. The studies examined were performed across multiple countries with instruments that may appear to be similar, prima facie, but may substantially differ in how they sequentially remove individual studies (42). The authors of the current study combined different doses of the same drug for analysis, thus this may lead to biased results; this must be taken into consideration and eliminated in future studies.

In conclusion, cholinesterase inhibitors provide a benefit not only regarding global cognitive function, CGIC and behavioral symptoms, but also in cognitive domains.

	-							N	N
		eriment			control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	lotal	Mean	SD	lotal	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
4.1.1 DLB,donepezil									
Ikeda M 2015(donepezil 10mg)	-0.9	6.1	46	-1.7	6.17	47	5.5%	0.80 [-1.69, 3.29]	
Ikeda M 2015(donepezil 5mg)	0.4	6.3	49	-1.7	6.17	47	5.5%	2.10 [-0.39, 4.59]	
Mori E 2012(donepezil 10mg)	-1	6.7	33	0.7	3.8	31	4.9%	-1.70 [-4.35, 0.95]	
Mori E 2012(donepezil 3mg)	-0.5	7.4	34	0.7	3.8	31	4.3%	-1.20 [-4.02, 1.62]	
Mori E 2012(donepezil 5mg)	-0.5	5.4	32	0.7	3.8	31	6.5%	-1.20 [-3.50, 1.10]	
Subtotal (95% CI)			194			187	26.6%	-0.20 [-1.33, 0.94]	<b>T</b>
Heterogeneity: Chi <sup>2</sup> = 6.32, df =		· ·	37%						
Test for overall effect: Z = 0.34 (	P = 0.73)	1							
4.1.2 PDD,donepezil									
Aarsland D 2002	31.8	15.4	12	35.1	8.1	12	0.4%	-3.30 [-13.14, 6.54]	
Leroi I 2004	37.14	19.67	7	32.89	10.08	9	0.1%	4.25 [-11.74, 20.24]	· · · · · · · · · · · · · · · · · · ·
Ravina B 2005	40.3	13.6	21	40.5	13.7	20	0.5%	-0.20 [-8.56, 8.16]	
Subtotal (95% CI)			40			41	1.0%	-0.71 [-6.63, 5.21]	
Heterogeneity: Chi <sup>2</sup> = 0.65, df =	2 (P = 0.7	72); l² =	0%						
Test for overall effect: Z = 0.24 (	P = 0.81)								
4.1.3 PDD, rivastigmine									
Li Z G 2015	1.82	1.99	41	4.26	1.63	40	54.6%	-2.44 [-3.23, -1.65]	
Mamikonyan E 2015	-3.38	4.31	13	-3	4.23	14	3.3%	-0.38 [-3.60, 2.84]	
Subtotal (95% CI)	-0.00	4.51	54	-5	4.25	54	57.8%		•
Heterogeneity: $Chi^2 = 1.48$ , df =	1/P = 0.2	22)· I2 =	• • •			04	01.070	2.02 [ 0.00, 1.00]	
Test for overall effect: Z = 5.92 (			JZ /0						
		,							
4.1.4 DLB, memantine									
Emre M 2010	-0.7	9.2	33	0.7	8.6	41	2.0%	-1.40 [-5.50, 2.70]	
Subtotal (95% CI)			33			41	2.0%	-1.40 [-5.50, 2.70]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.67 (	P = 0.50)	l.							
4.1.5 PDD, memantine									
Emre M 2010	1.5	9.9	60	1	9.9	56	2.6%	0.50 [-3.11, 4.11]	
Leroi I 2009	24.3	8.8	10	21.9	9.1	14	0.7%	2.40 [-4.84, 9.64]	
Subtotal (95% CI)			70			70	3.3%	0.88 [-2.35, 4.10]	
Heterogeneity: Chi <sup>2</sup> = 0.21, df =	1 (P = 0.6	35); l² =	0%						
Test for overall effect: Z = 0.53 (	P = 0.59)								
4.1.6 DLB and PDD ,memantin	e								
Aarsland D 2009	0.3	3.1	28	0	4.3	30	9.3%	0.30 [-1.62, 2.22]	
Subtotal (95% CI)	0.5	0.1	28	5	4.5	30	9.3%		
Heterogeneity: Not applicable			20				0.070	0.00 [ 1.02, 2.22]	Ī
Test for overall effect: Z = 0.31 (	P = 0.76)	)							
Total (95% CI)			419			422	100 0%	-1.38 [-1.96, -0.79]	•
, ,	= 12 /D	0.041		,		423	100.0%	-1.30 [-1.80, -0.79]	-++
Heterogeneity: Chi <sup>2</sup> = 23.50, df =			- 43%	D					-20 -10 0 10 20
Test for overall effect: Z = 4.61 (			E (D =	0.04) 12	- 66 00				Favours (experimental) Favours (control)
Test for subgroup differences: C	nr = 14.8	14, df =	5 (P =	0.01), I²	= 66.3%	/o			

Figure 7. Forest plot of the meta-analysis of motor function on the Unified Parkinson's Disease Rating Scale-motor by drug and dose. The risk ratio is presented as green squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; IV, inverse variance; SD, standard deviation; df, degrees of freedom; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies.

	Experim	ental	Conti	ol		<b>Risk Ratio</b>		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% Cl	
Dubois B 2012(donepezil 10mg)	1	182	2	173	4.2%	0.48 [0.04, 5.19]				
Dubois B 2012(donepezil 5mg)	2	195	2	173	4.3%	0.89 [0.13, 6.23]				
Emre M 2004	21	362	11	179	29.9%	0.94 [0.47, 1.91]		_		
Emre M 2010	6	62	5	58	10.5%	1.12 [0.36, 3.48]			-	
Leroi I 2009	1	10	1	14	1.7%	1.40 [0.10, 19.82]				-
Li Z G 2015	13	41	24	40	49.4%	0.53 [0.32, 0.88]				
Total (95% CI)		852		637	100.0%	0.74 [0.51, 1.08]		•		
Total events	44		45							
Heterogeneity: Chi <sup>2</sup> = 3.02, df = 5	(P = 0.70);	$I^{2} = 0\%$					0.02	0.1	10	50
Test for overall effect: Z = 1.54 (P	= 0.12)						0.02	Favours (control)		

Figure 8. Forest plot of the meta-analysis of falling by drug and dose for Parkinson's disease with dementia and cognitive impairment in Parkinson's disease. The risk ratio is presented as blue squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; M-H, Mantel-Haentzel; df, degrees of freedom.

Memantine treatment results in a significant improvement in attention, processing speed and executive functions according

to sensitivity analysis. However, cholinesterase inhibitors and memantine do not significantly reduce falling. Finally,

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H. Fixed, 95% Cl	
8.1.1 DLB,donepezil							
Ikeda M 2015(donepezil 10 mg)	34	49	31	46	4.5%	1.03 [0.78, 1.35]	
Ikeda M 2015(donepezil 5 mg)	30	47	31	46	4.4%	0.95 [0.71, 1.27]	
Mori E 2012(donepezil 10 mg)	32	37	24	34	3.5%	1.23 [0.95, 1.58]	
Mori E 2012(donepezil 3 mg)	24	35	24	34	3.4%	0.97 [0.71, 1.33]	
Mori E 2012(donepezil 5 mg)	27	33	24	34	3.3%	1.16 [0.88, 1.52]	
Subtotal (95% CI)		201		194	19.1%	1.06 [0.93, 1.20]	◆
Total events	147		134			• • •	
Heterogeneity: $Chi^2 = 2.61$ , $df = 4$ ( Test for overall effect: $Z = 0.89$ (P	(P = 0.63);	I <sup>2</sup> = 0%					
3.1.2 PDD,donepezil							
Aarsland D 2002	10	14	9	12	1.4%	0.95 [0.60, 1.52]	
Dubois B 2012(donepezil 10 mg)	133	182	123	173	17.7%	1.03 [0.90, 1.17]	<b></b> _
Dubois B 2012(donepezil 5 mg)	150	195	123	173	18.3%	1.08 [0.96, 1.22]	+ <b>-</b> -
_eroi   2004	5	7	4	9	0.5%	1.61 [0.67, 3.83]	
Ravina B 2005	11	21	9	20	1.3%	1.16 [0.62, 2.19]	
Subtotal (95% CI)		419	9	387	39.0%	1.06 [0.97, 1.16]	•
	309	415	268	507	55.070	1.00 [0.07, 1.10]	•
Total events Heterogeneity: Chi <sup>2</sup> = 1.50, df = 4 ( Test for overall effect: Z = 1.36 (P =	(P = 0.83);	l² = 0%	200				
3.1.3 DLB, rivastigmine							
Mckeith I 2000	54	59	46	61	6.3%	1.21 [1.03, 1.43]	
Subtotal (95% CI)		59		61	6.3%	1.21 [1.03, 1.43]	★
Total events	54		46				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.33 (P	= 0.02)						
3.1.4 PDD,rivastigmine							
Emre M 2004	303	362	127	179	23.8%	1.18 [1.06, 1.31]	
Mamikonyan E 2015	12	13	12	14	1.6%	1.08 [0.83, 1.40]	
	12	375		193	25.4%	1.17 [1.06, 1.30]	$\blacksquare$
Subtotal (95% CI)	315		139	193	25.4%	1.17 [1.06, 1.30]	•
Subtotal (95% CI) Total events Heterogeneity: Chi² = 0.41, df = 1 (	315 (P = 0.52);	375	139	193	25.4%	1.17 [1.06, 1.30]	•
Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Test for overall effect: Z = 3.16 (P	315 (P = 0.52);	375	139	193	25.4%	1.17 [1.06, 1.30]	•
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Fest for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine	315 (P = 0.52); = 0.002)	375 I² = 0%					
Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Test for overall effect: Z = 3.16 (P 8.1.5 DLB,memantine Emre M 2010	315 (P = 0.52);	375  ² = 0% 34	139 17	41	2.2%	1.28 [0.79, 2.07]	
Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Test for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI)	315 (P = 0.52); = 0.002) 18	375 I² = 0%	17				
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Test for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable	315 (P = 0.52); = 0.002) 18 18	375  ² = 0% 34		41	2.2%	1.28 [0.79, 2.07]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Fest for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0.99 (P 3.1.6 PDD,memantine	315 (P = 0.52); = 0.002) 18 18	375  ² = 0% 34	17	41	2.2%	1.28 [0.79, 2.07]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Fest for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0.99 (P 3.1.6 PDD,memantine	315 (P = 0.52); = 0.002) 18 18	375  ² = 0% 34	17	41	2.2%	1.28 [0.79, 2.07]	
Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Fest for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 0.99 (P 3.1.6 PDD,memantine Emre M 2010	315 (P = 0.52); = 0.002) 18 18 = 0.32)	375  ² = 0% 34 34 34	17 17	41 41 58 14	2.2% 2.2%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07]	
Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Test for overall effect: Z = 3.16 (P 8.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.99 (P 8.1.6 PDD,memantine Emre M 2010 Leroi I 2009	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28	375 l² = 0% 34 34 34	17 17 26	41 <b>41</b> 58	2.2% 2.2% 3.8%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50]	
Subtotal (95% CI) Fotal events Heterogeneity: $Chi^2 = 0.41$ , $df = 1$ ( Fest for overall effect: $Z = 3.16$ (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: $Z = 0.99$ (P 3.1.6 PDD,memantine Emre M 2010 .eroi   2009 Subtotal (95% CI) Fotal events Heterogeneity: $Chi^2 = 0.19$ , $df = 1$ (	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66);	375   <sup>2</sup> = 0% 34 34 34 62 11 73	17 17 26	41 41 58 14	2.2% 2.2% 3.8% 1.1%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65]	
Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Test for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.99 (P 3.1.6 PDD,memantine Emre M 2010 .eroi   2009 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.19, df = 1 ( Test for overall effect: Z = 0.17 (P	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66);	375   <sup>2</sup> = 0% 34 34 34 62 11 73	17 17 26 9	41 41 58 14	2.2% 2.2% 3.8% 1.1%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65]	
Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0.41$ , $df = 1$ ( Test for overall effect: $Z = 3.16$ (P 8.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: $Z = 0.99$ (P 8.1.6 PDD,memantine Emre M 2010 Leroi   2009 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0.19$ , $df = 1$ (P Test for overall effect: $Z = 0.17$ (P 8.1.7 DLB and PDD,memantine	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66);	375   <sup>2</sup> = 0% 34 34 34 62 11 73	17 17 26 9	41 41 58 14	2.2% 2.2% 3.8% 1.1%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65]	
Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0.41$ , $df = 1$ ( Test for overall effect: $Z = 3.16$ (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: $Z = 0.99$ (P 3.1.6 PDD,memantine Emre M 2010 Leroi   2009 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0.19$ , $df = 1$ (F Fest for overall effect: $Z = 0.17$ (P 3.1.7 DLB and PDD,memantine Aarsland D 2009	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66); = 0.87)	375 1 <sup>2</sup> = 0% 34 34 62 11 73 1 <sup>2</sup> = 0% 35	17 17 26 9 35	41 41 58 14 72 40	2.2% 2.2% 3.8% 1.1% 4.9% 2.6%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65] 0.97 [0.69, 1.37] 0.86 [0.52, 1.40]	
Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0.41$ , $df = 1$ ( Test for overall effect: $Z = 3.16$ (P <b>3.1.5 DLB,memantine</b> Emre M 2010 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: $Z = 0.99$ (P <b>3.1.6 PDD,memantine</b> Emre M 2010 Leroi I 2009 Subtotal (95% CI) Total events Heterogeneity: $Chi^2 = 0.19$ , $df = 1$ ( Test for overall effect: $Z = 0.17$ (P <b>3.1.7 DLB and PDD,memantine</b> Aarsland D 2009 Stubendorff K 2014	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66); = 0.87) 15	375 1 <sup>2</sup> = 0% 34 34 62 11 73 1 <sup>2</sup> = 0%	17 17 26 9 35	41 41 58 14 72	2.2% 2.2% 3.8% 1.1% 4.9%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65] 0.97 [0.69, 1.37]	
Subtotal (95% CI) Fotal events Heterogeneity: $Chi^2 = 0.41$ , $df = 1$ ( Fost for overall effect: $Z = 3.16$ (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Test for overall effect: $Z = 0.99$ (P 3.1.6 PDD,memantine Emre M 2010 Leroi I 2009 Subtotal (95% CI) Fotal events Heterogeneity: $Chi^2 = 0.19$ , $df = 1$ (C Test for overall effect: $Z = 0.17$ (P 3.1.7 DLB and PDD,memantine Aarsland D 2009 Stubendorff K 2014 Subtotal (95% CI)	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66); = 0.87) 15 4	375   <sup>2</sup> = 0% 34 34 62 11 73   <sup>2</sup> = 0% 35 18	17 17 26 9 35 20 3	41 41 58 14 72 40 14	2.2% 2.2% 3.8% 1.1% 4.9% 2.6% 0.5%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65] 0.97 [0.69, 1.37] 0.86 [0.52, 1.40] 1.04 [0.28, 3.90]	
Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.41, df = 1 ( Fost for overall effect: Z = 3.16 (P 3.1.5 DLB,memantine Emre M 2010 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable First for overall effect: Z = 0.99 (P 3.1.6 PDD,memantine Emre M 2010 .eroi   2009 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.19, df = 1 ( Fest for overall effect: Z = 0.17 (P 3.1.7 DLB and PDD,memantine Aarsland D 2009 Stubendorff K 2014 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 0.07, df = 1 (	315 (P = 0.52); = 0.002) 18 18 = 0.32) 28 6 34 (P = 0.66); = 0.87) 15 4 19 (P = 0.79);	375 1 <sup>2</sup> = 0% 34 34 62 11 73 1 <sup>2</sup> = 0% 35 18 53	17 17 26 9 35	41 41 58 14 72 40 14	2.2% 2.2% 3.8% 1.1% 4.9% 2.6% 0.5%	1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.28 [0.79, 2.07] 1.01 [0.68, 1.50] 0.85 [0.44, 1.65] 0.97 [0.69, 1.37] 0.86 [0.52, 1.40] 1.04 [0.28, 3.90]	
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Figure 9. Forest plot of the meta-analysis of adverse events by drug and dose. The risk ratio is presented as blue squares, with the horizontal lines indicating the confidence interval. Combined results for all studies are presented as black diamonds. CI, confidence interval; M-H, Mantel-Haentzel; df, degrees of freedom; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies.

cholinesterase inhibitors and memantine are associated with good safety outcomes, with only the rivastigmine group exhibiting significant adverse events compared with the placebo group. However, considering the limitations of the present study, the results may not sufficiently support the use of cholinesterase inhibitors and memantine as treatments for CIND-PD, PDD and DLB. Further clinical trials on a larger scale are imperative to better assess the efficacy and safety of cholinesterase inhibitors and memantine in CIND-PD, PDD and DLB.

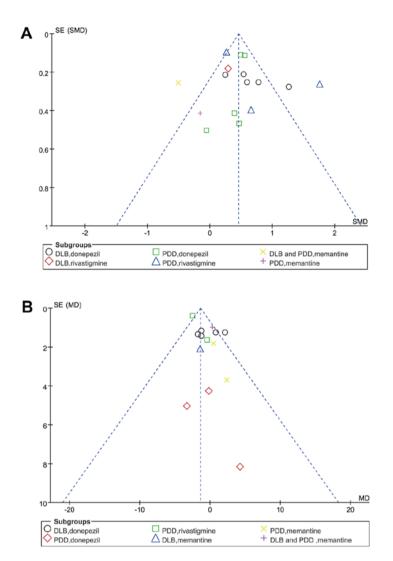


Figure 10. Funnel plot of (A) cognition and (B) motor function. PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; SE, standard error; SMD, standard mean difference; MD, mean difference.

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## Availability of data and materials

All data generated or analysed during this study are included in this published article.

## Authors' contributions

YHM and JHW designed the analysis. YHM and JHW collected and abstracted the data, and performed the statistical analysis. YHM drafted the manuscript. YHM, JHW, PPW and YXS analysed and interpreted the data, and critically revised

the manuscript for important intellectual content. All authors reviewed and approved the final report.

#### Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## **Competing interests**

The authors declare that they have no competing interests.

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