

The comparative efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate Alzheimer's disease: a Bayesian network meta-analysis

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Background: Comparative evidence for efficacy and safety of second-generation cholinesterase inhibitors (ChEIs) is still sparse.

Objectives: The purpose of this research is to compare three ChEIs, donepezil, galantamine and rivastigmine, in patients with mild-to-moderate Alzheimer's disease (AD).

Methods: We conducted a systematic review for published articles and included randomised, double-blind, placebo-controlled trials and head-to-head randomised trials evaluating the efficacy and safety of ChEIs in patients with AD. We examined Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Clinician's Interview-Based Impression of Change plus caregiver's input (CIBIC+) and Clinical Global Impression of Change (CGIC) as efficacy endpoints. Withdrawals due to adverse events and number of patients experiencing nausea, vomiting, diarrhoea and dizziness were examined as safety profiles. Network meta-analyses were sequentially performed for efficacy and safety outcomes based on drug/dose treatment conditions.

Results: Among the 21 trials included, network meta-analysis showed that all treatments were significantly more efficacious than placebo in cognition measured by ADAS-Cog. All treatments except galantamine were significantly more efficacious than placebo in global change in CIBIC+ or CGIC. Across all conditions, no significant efficacy was observed in neuropsychiatric symptoms measured by NPI. Derived hierarchies in the efficacy of treatment conditions were variables across efficacy and safety.

Conclusions: Our analysis is the first attempt to incorporate available direct and indirect evidence. The results suggest that ChEIs should have significant efficacy for cognition and global change assessment, but the efficacy on neuropsychiatric symptoms is questionable in patients with mild-to-moderate AD.

Key words: Alzheimer's disease; cholinesterase inhibitors; meta-analysis

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Introduction

Alzheimer's disease (AD) is the most common form of dementia. At present, there are no therapeutic interventions that halt or reverse disease progression, and the currently available medications, typically acetylcholinesterase inhibitors (ChEIs), are just palliative therapy for AD symptoms. Regarding

patients with mild-to-moderate AD, the American Psychiatric Association recommends second generation ChEIs, donepezil, galantamine and rivastigmine for mild-to-moderate AD (Rabins *et al.*, 2007). The National Institute for Health and Clinical Excellence guideline also recommends these three second-generation ChEIs as options for managing mild-to-moderate AD (NICE, 2011).

To date, several reviews and meta-analyses have been published summarising the efficacy and safety of second-generation ChEIs for treatment of AD (Trinh *et al.*, 2003; Birks, 2006; Hansen *et al.*, 2008; Tan *et al.*, 2014; Wang *et al.*, 2014). However, comparative evidence is still sparse. Despite the slight variations in the mode of action of the three ChEIs, the Cochrane Dementia and Cognitive Improvement Group concluded that there is no evidence of any difference between them with respect to efficacy (Birks, 2006). On the other hand, a later meta-analysis including adjusted indirect comparison revealed no significant differences between these drugs regarding cognition, but found the relative risk of global response to be better with donepezil and rivastigmine than galantamine and favoured donepezil over galantamine regarding neuropsychiatric symptoms (Hansen, *et al.*, 2008). However, adjusted indirect comparisons did not combine results of direct and indirect comparisons. The network meta-analysis (NMA) is a meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator (Salanti *et al.*, 2008). The analysis is useful when investigators are interested in summarising results from more than two treatments and the hierarchy of these treatments. Although there are concerns about methodological issues of sample size, power, sources of bias and heterogeneity, for many comparisons, the network meta-analysis may yield more reliable and definitive results than would a pairwise meta-analysis (Mills *et al.*, 2013).

We conducted a systematic review and Bayesian NMA of three ChEIs, donepezil, galantamine and rivastigmine, for the treatment of mild-to-moderate AD. Our intention was to provide comparative evidence and hierarchies for efficacy and safety between ChEIs in patients with mild-to-moderate AD.

Methods

Literature search

The initial literature search was conducted with using PubMed and EMBASE. Search keywords included: Alzheimer's disease, cholinesterase inhibitor, donepezil, galantamine and rivastigmine. The search covered English-language reports published as full-text articles before September 2014. Previously published systematic reviews, meta-analyses and the Specialized Register of the Cochrane Dementia and

Cognitive Improvement Group were also manually reviewed.

Inclusion/exclusion criteria and data extraction

We included results from randomised, double-blinded, placebo-controlled trials (RCTs) evaluating the efficacy of ChEIs in patients with mild-to-moderate AD with at least one of the following assessments: (1) Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog; Rosen and Mohs, 1984), (2) Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994), (3) Clinician's Interview-Based Impression of Change scale plus caregiver's input (CIBIC+; Knopman *et al.*, 1994) and (4) Clinical Global Impression of Change (CGIC; Schneider *et al.*, 1997). Results from randomised comparative trials, directly comparing one drug with another, were also included in the analysis. These "head-to-head" trials were not required to be double-blinded in our inclusion criteria. Studies were excluded from the analysis if they examined patients with severe AD (defined as the Mini-Mental State Examination < 10 or specifically indicated in the study design) or mild cognitive impairment. Studies that specifically examined high-dose or low-dose treatment were also excluded from the analysis.

Two authors (H. K., R. N.) independently reviewed identified articles during the initial literature search according to the above inclusion and exclusion criteria. The two reviewers discussed any discrepancies on article retrieval. When agreement between the two reviewers was not achieved, a third reviewer (T. O.) made the final decision. For each study included, patient characteristics, study design, drug name, dosage, sample size, efficacy outcomes and adverse event (AE) occurrences were extracted. In addition, the data were extracted from the results of the intent-to-treat population with last observation carried forward method, if it was available. The data extraction process was also independently conducted by two authors (H. K., R. N.), and any discrepancy was discussed and resolved.

Outcome measures

The efficacy for cognition was evaluated by assessment of ADAS-Cog and neuropsychiatric symptoms were assessed by NPI. The means and standard deviations of the change from baseline were extracted. The efficacy for clinical global change was evaluated by assessment of CIBIC+ and CGIC. Patients who was judged at least "minimal/slightly improved" (i.e. ≤ 3

points in CIBIC+ or CGIC) were counted. We also extracted the number of patients who withdrew from the study because of AEs. Finally, we extracted the numbers of patients with specific AEs: nausea, vomiting, diarrhoea and dizziness.

Synthesis of results

We first analysed the descriptive data of the studies included and patient characteristics. A set of independent random-effect meta-analyses was then performed for each outcome. These traditional meta-analyses assessed heterogeneities and publication biases across the studies prior to conducting NMA. The heterogeneities were evaluated using I^2 statistic, and the publication biases were evaluated using funnel plots. The meta-analyses were performed using Metafor package (Viechtbauer, 2010) in R.

The NMA was performed on the efficacy in seven arms according to the treatment condition drugs and dose (dose-based comparison: 5 mg donepezil *versus* 10 mg donepezil *versus* 16 mg galantamine *versus* 24 mg galantamine *versus* 6 and 12 mg rivastigmine *versus* 18 mg rivastigmine patch [9.5 cm²] *versus* placebo) and sequentially performed to four arms according to the treatment condition based on drugs (drug-based comparison: donepezil *versus* galantamine *versus* rivastigmine *versus* placebo). The analyses were performed in the Bayesian hierarchical model framework with Markov chain Monte Carlo estimation using the GeMTC package (van Valkenhoef *et al.*, 2012) in R. The number of tuning iterations was set at 1000 and the number of simulation iterations at 10 000. The model convergence was evaluated by visually inspecting the iteration plot and the potential scale reduction factor (Brooks and Gelman, 1997). Finally, tolerability was evaluated as five arms according to the drug (donepezil *versus* galantamine *versus* rivastigmine *versus* rivastigmine patch *versus* placebo). Because a meaningful heterogeneity was expected between rivastigmine and rivastigmine patch, we decided to analyse these two preparations as separate arms.

In the NMA, we summarised ADAS-Cog as the relative empirical mean difference between treatment arms. To evaluate NPI-10 and NPI-12 simultaneously, we examined the standardised mean change (Hedges' adjusted g) from baseline for the NPI scores and again summarised as relative difference. For the dichotomous outcomes, including CIBIC+, CGI and safety data, we evaluated the proportion of these events summarised as the odds ratio between the treatment arms. For each summary statistic, a 95% credible

interval (95% CrI) was computed. The hierarchy between drugs was estimated by the surface under the cumulative ranking (Salanti *et al.*, 2014), which was computed by the ranking probabilities of the frequency table of iteration results.

Because we did not require included randomised comparative trials to be a double-blinded, quality assessment for those studies was essential. We performed a set of sensitivity analyses to test the consistency of results.

Results

Literature search and description of studies

Figure 1 presents the summary of the literature search (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart). A total of 911 potentially relevant articles were identified from initial database search, and 21 met our inclusion criteria, including 18 studies designed as double-blind RCTs and 3 studies exclusively designed as randomised, head-to-head, drug comparisons. Ten studies investigated donepezil, six galantamine and nine rivastigmine. Twenty-one studies assessed ADAS-Cog, six NPI and fourteen CIBIC+ and/or CGIC.

Table 1 presents the details of the 21 trials included. The total sample size was 9509. The studies were mainly conducted in North America and Europe. The mean study duration ranged from 12 to 104 weeks (average, 27.4). The characteristics of the study populations are summarised as follows: mean age at entry ranged from 69.4 to 78.4 years; 62.3% of participants were women. The mean Mini-Mental State Examination score ranged from 15.1 to 21.5. The average scores of ADAS-Cog and NPI at baseline ranged from 20.2 to 34.9 and from 10.3 to 35.2, respectively.

Table 2 summarises all I^2 values from preliminary meta-analysis performed for each efficacy measure of each drug–placebo arm. Cognition and clinical global change gave a hint of heterogeneity among included trials ($I^2 = 44.19\%$ and 52.72% , respectively). For each drug–placebo arm, Rivastigmine-placebo arm in cognition and clinical global change gave a hint of heterogeneity ($I^2 = 63.79\%$ and 51.30% , respectively). All funnel plots (data not shown) showed a fairly symmetric distribution, indicating no hint of publication bias.

Efficacy

Cognition. Across all NMAs, models were well converged (potential scale reduction factor = 1.00–1.03). Of the 21 studies included, 17 reported sufficient data

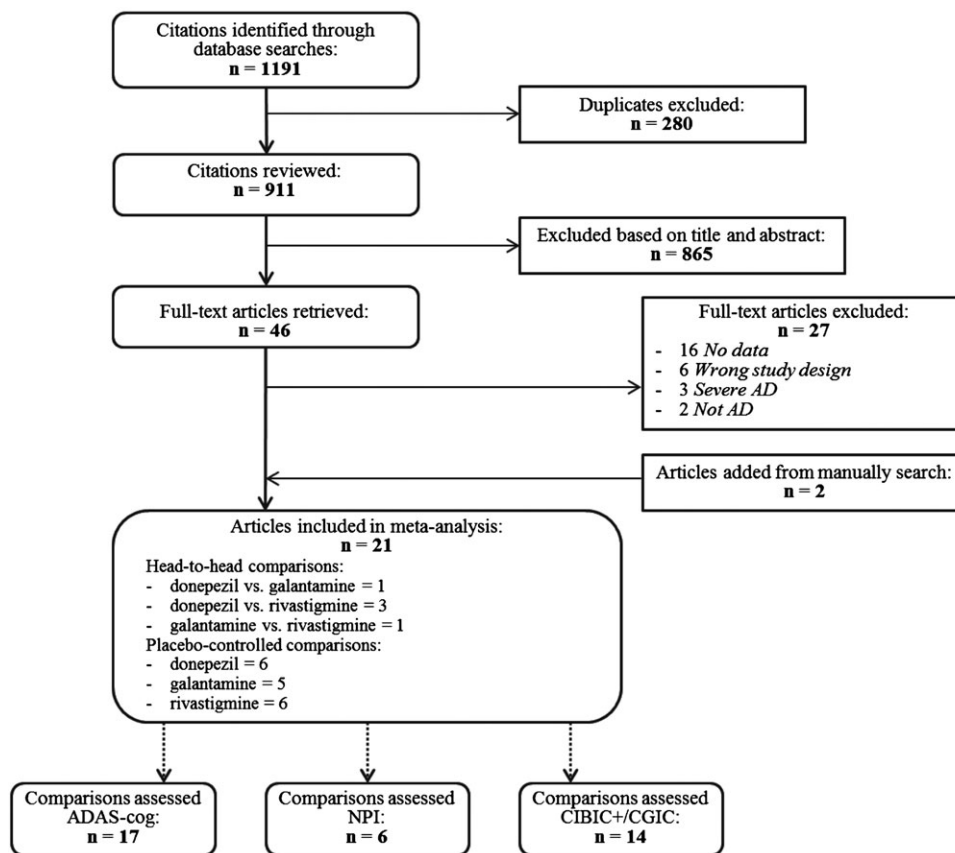


Figure 1 Literature review flowchart. AD, Alzheimer’s disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale, cognitive subscale; CGIC, Clinical Global Impression of Change; CIBIC+, Clinician’s Interview-based Impression of Change plus caregiver’s input; NPI, Neuropsychiatric Inventory.

on the efficacy for cognition, 7 for donepezil, 5 for galantamine and 6 for rivastigmine. Because a sign of heterogeneity was observed, a post-hoc analysis was performed to further investigate the potential source of the heterogeneity. A linear regression analysis revealed that there was a significant time trend between the efficacy for cognition and the publication year in the placebo group ($p=0.017$), but not in the treatment group ($p=0.606$) (Figure 2A).

Figure 3A presents a network comparing 17 eligible studies as a dose-based comparison. The analysis revealed that all drugs and dosages were associated with a significantly greater improvement than placebo (Figure 4A), and 24 mg galantamine showed a significantly greater improvement than rivastigmine patch (Figure 5A). The derived hierarchy across dosages was 24 mg galantamine > 15 mg galantamine > 12 mg rivastigmine > 5 mg donepezil > 10 mg donepezil > rivastigmine patch. NMA for a drug-based comparison revealed that all drugs had a significantly greater improvement than placebo (Figure 4B), and the derived hierarchy was galantamine > rivastigmine > donepezil (Figure 5B).

Neuropsychiatric symptoms. Six studies reported sufficient data for the efficacy of neuropsychiatric symptoms, three for donepezil, three for galantamine and three for rivastigmine. Preliminary meta-analysis did not indicate a significant heterogeneity ($I^2 < 0.01\%$) across through the extracted data for neuropsychiatric symptoms. The funnel plot showed a fairly symmetric distribution, indicating no hint of publication bias.

Figure 3B presents a network comparing six eligible studies as a dose-based comparison. The analysis revealed that none of the drugs and dosages had a significantly greater improvement than placebo (Figure 4C), and the derived hierarchy across dosages was 16 mg galantamine > 24 mg galantamine > 12 mg rivastigmine > 10 mg donepezil > rivastigmine patch (Figure 5C). NMA for a drug-based analysis revealed that none of drugs had a significantly greater improvement than placebo (Figure 4D). The derived hierarchy was galantamine > donepezil > rivastigmine (Figure 5D).

Clinical global change. Fourteen studies reported sufficient data on the efficacy for clinical global change; five for donepezil, four for galantamine and five for

Table 1 Baseline characteristics of studies included

Drug(s)	Study	Daily dose	Gender (Female, %)	Age (years)	Study duration (weeks)	Baseline MMSE	Outcomes		
							Cognition	Behaviour	Global
Donepezil	Rogers <i>et al.</i> , 1998a	Placebo 5 mg	61	74	12	19.8 19.39	ADAS-Cog	—	CIBIC+
	Rogers <i>et al.</i> , 1998b	10 mg Placebo 5 mg	69 61 61	73.8 73.4 72.6	24	19.35 19.4 19.44	ADAS-Cog	—	CIBIC+
	Burns <i>et al.</i> , 1999	10 mg Placebo 5 mg	62 55 61	72.9 74.6 71	24	19.17 20 20	—	—	CIBIC+
	Homma <i>et al.</i> , 2000	10 mg Placebo 5 mg	57 66 68	72 69.4 70.1	24	20 16.6 17.8	ADAS-Cog	—	CGIC
	Frölich <i>et al.</i> , 2011	Placebo 10 mg	55 66	73.5 73.9	12	—	ADAS-Cog	—	—
	Maheer-Edwards <i>et al.</i> , 2011	Placebo 10 mg	70 63	71.6 71.1	24	18.3 19.2	ADAS-Cog	—	CIBIC+
	Haig <i>et al.</i> , 2014	Placebo 10 mg	62 60	70.3 70.5	12	18 17.9	ADAS-Cog	NPI	—
	Raskind <i>et al.</i> , 2000	Placebo 24 mg	62 66	75.3 75.9	24	19.2 19.5	ADAS-Cog	—	CIBIC+
	Tarot <i>et al.</i> , 2000	Placebo 16 mg	62 62	77.1 76.3	21	17.7 17.8	ADAS-Cog	NPI	—
	Wilcock <i>et al.</i> , 2000	24 mg Placebo 24 mg	67 61 63	77.7 72.7 71.9	24	17.7 19.3 19.5	ADAS-Cog	—	CIBIC+
Rivastigmine	Wilkinson and Murray 2001	Placebo 18 mg 24 mg	59 56 59	74.2 72.7 72.9	12	18.7 18.8 18.2	ADAS-Cog	—	CGIC
	Brodaty <i>et al.</i> , 2005	Placebo 16–24 mg	64 64	76.3 76.5	26	18.08 17.8	ADAS-Cog	NPI	CIBIC+
	Corey-Bloom <i>et al.</i> , 1998	Placebo 6–12 mg	58 68	74.8 73.8	26	20 19.62	ADAS-Cog	—	CIBIC+
	Forette <i>et al.</i> , 1999	Placebo 6–12 mg	-	72.5 70.7	18	19.2 19.6	ADAS-Cog	—	CIBIC+
	Rösler <i>et al.</i> , 1999	Placebo 6–12 mg	-	—	26	—	ADAS-Cog	—	CIBIC+
	Feldman and Lane 2007	Placebo 2–12 mg	59 60	71.7 71.2	26	19.9 18.8	ADAS-Cog	—	—
	Winblad <i>et al.</i> , 2007	Placebo 3–12 mg (P) 18 mg	67 66 68	73.9 72.8 73.6	24	16.4 16.4 16.7	ADAS-Cog	NPI	CGIC
	Nakamura <i>et al.</i> , 2011	Placebo (P) 18 mg	68	74.5	24	16.6	ADAS-Cog	—	CIBIC+
	Cumbo and Ligori 2014	(D) 18 mg (G) 10 mg (S) 24 mg (R) 12 mg	68 55 52 54	75.1 78.4 78.2 78.3	52	16.5 16.3 16.4 16.2	—	NPI	—

(Continues)

Table 1 (Continued)

Drug(s)	Study	Daily dose	Gender (Female, %)	Age (years)	Study duration (weeks)	Baseline MMSE	Outcomes		
							Cognition	Behaviour	Global
Donepezil versus Rivastigmine	Bullock <i>et al.</i> , 2005	(D) 5–10 mg (R) 3–12 mg	69	75.8	104	15.13	—	NPI	—
	Wilkinson <i>et al.</i> , 2002	(D) 5–10 mg (R) 3–12 mg	69 54 64	75.9 74 74.9	12	15.15 21.5 20.7	—	ADAS-Cog	—

ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale; CIBIC+, Clinician's Interview-Based Impression of Change with caregiver's input; CGIC, Clinical Global Impression of Change; (D), donepezil; (R), rivastigmine; (G), galantamine; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; (P), rivastigmine patch; (R), rivastigmine.

Table 2 I^2 values for heterogeneity analysis

	ADAS-cog	NPI	CIBIC+/CGIC
Overall	44.19	<0.00	52.72
Donepezil	30.47	na*	<0.00
Galantamine	<0.00	<0.00	<0.00
Rivastigmine	63.79	<0.00	51.3

ADAS-cog, Alzheimer's Disease Assessment Scale, cognitive subscale; CIBIC+, Clinician's Interview-Based Impression of Change with caregiver's input; CGIC, Clinical Global Impression of Change.

*Heterogeneity test was not conducted, because only a single NPI-Placebo arm evaluated NPI.

rivastigmine. Because a sign of heterogeneity was observed, the same analysis performed in the analysis of cognition was applied. The responder rate was arc-sin transformed to normalise the distribution. A significant time trend between the efficacy and the publication year in the placebo group ($p=0.044$) was observed, but not in the treatment group ($p=0.950$) (Figure 2B).

Figure 3C presents a network comparing 14 eligible studies as a dose-based comparison. The analysis revealed that 5 mg donepezil, 10 mg donepezil and 12 mg rivastigmine had a significantly greater improvement than placebo and 24 mg galantamine (Figure 4E). The derived hierarchy was 10 mg donepezil > 5 mg donepezil > 12 mg rivastigmine > 16 mg galantamine > rivastigmine patch > 24 mg galantamine (Figure 5E). NMA for a drug-based analysis revealed that all drugs except galantamine had a significantly greater improvement than placebo (Figure 4F), and the derived hierarchy was donepezil > rivastigmine > galantamine (Figure 5F).

Tolerability

Withdrawals from study due to adverse events. Nineteen studies provided data on withdrawals from study due to AEs. NMA revealed that all drugs except donepezil had a significantly higher risk of AEs than placebo (Figure 4G). The risk of AEs with donepezil was also significantly less than with rivastigmine (Figure 5G). The derived hierarchy across drugs was donepezil > galantamine > rivastigmine patch > rivastigmine.

Nausea. Twenty-one studies provided data on nausea. NMA revealed that all drugs had a significantly higher risk than placebo. The risk associated with rivastigmine patch was significantly less than with

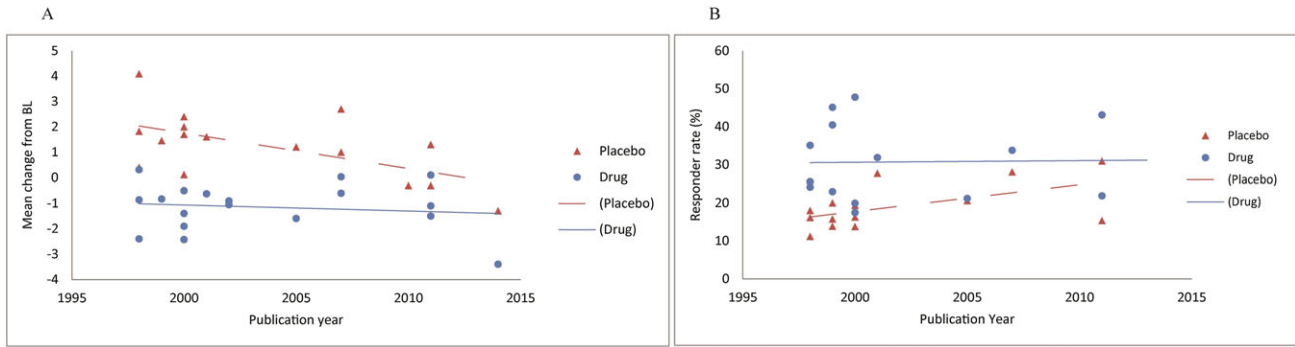


Figure 2 Association between efficacy ((A) ADAS-Cog; (B) CIBIC+/CGIC) and publication year. ADAS-Cog, Alzheimer’s Disease Assessment Scale, cognitive subscale; CGIC, Clinical Global Impression of Change; CIBIC+, Clinician’s Interview-Based Impression of Change plus caregiver’s input.

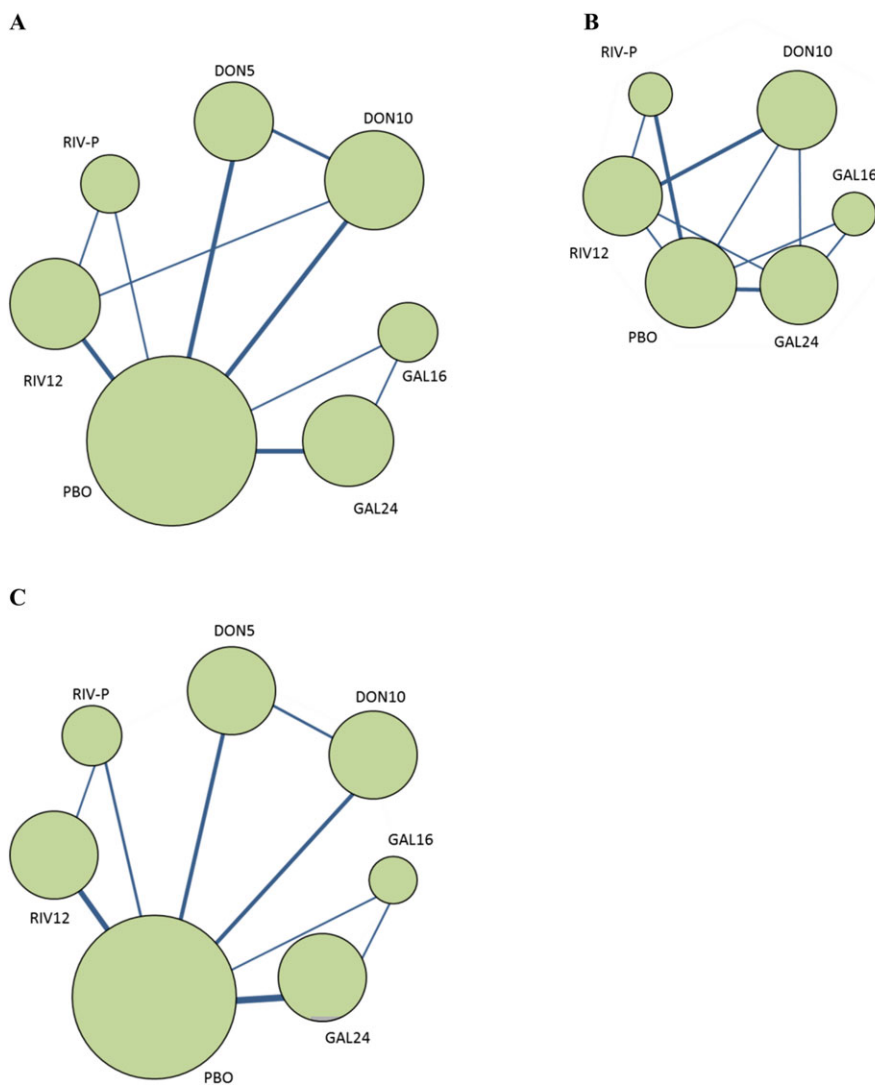


Figure 3 Network diagram of three efficacy measures ((A) ADAS-Cog; (B) NPI; (C) CIBIC+/CGIC). The sizes of the nodes indicate the number of trials that evaluated the treatments. The nodes are linked by a line when the treatments were directly comparable, the thickness of which indicates the number of trials. ADAS-Cog, Alzheimer’s Disease Assessment Scale, cognitive subscale; CGIC, Clinical Global Impression of Change; CIBIC+, Clinician’s Interview-Based Impression of Change plus caregiver’s input; DON5, 5 mg donepezil; DON10, 10 mg donepezil; GAL16, 16 mg galantamine; GAL24, 24 mg galantamine; NPI, Neuropsychiatric Inventory; PBO, placebo; RIV12, 12 mg rivastigmine; RIV-P, rivastigmine patch (9.5 cm²).

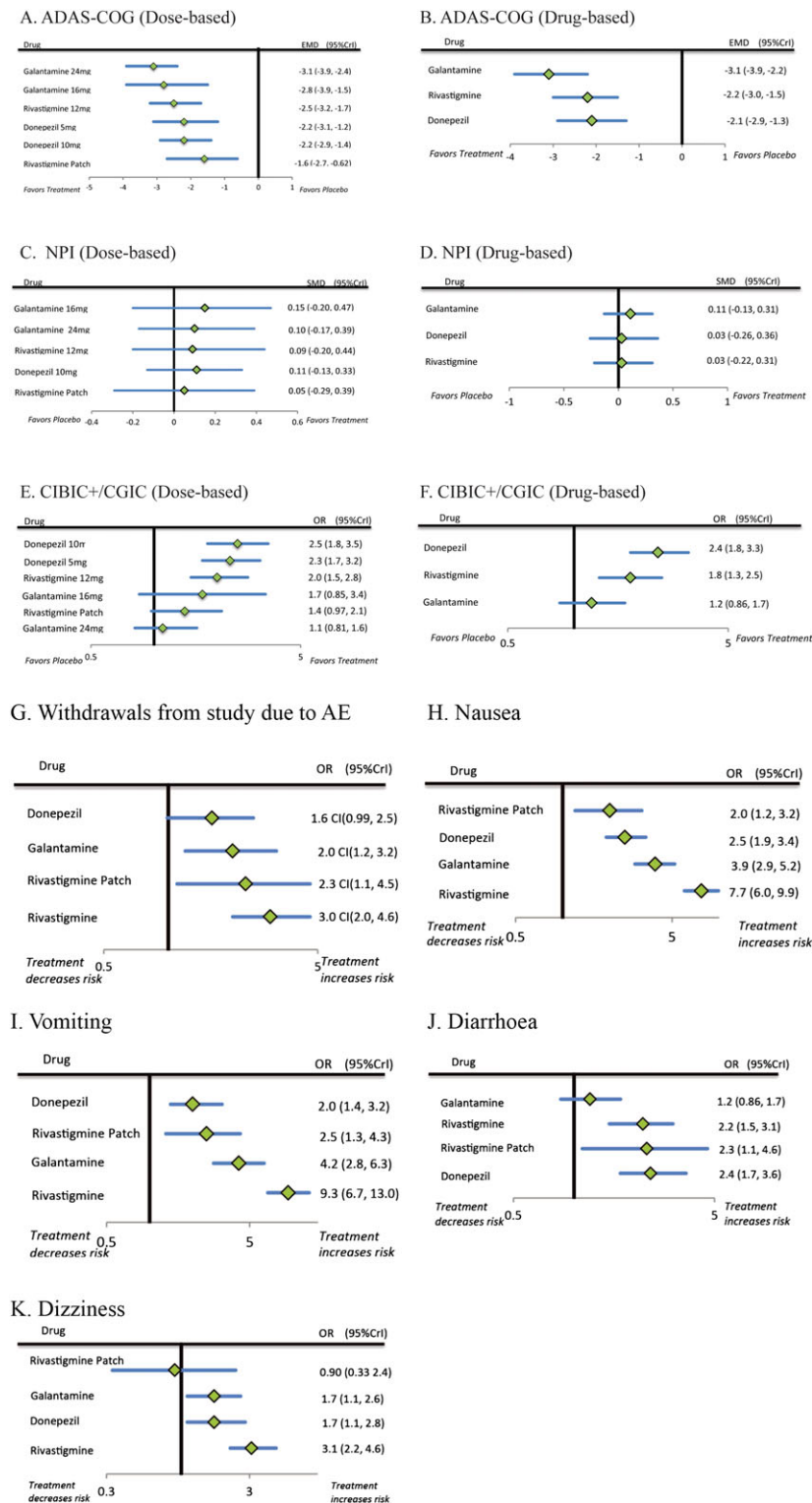


Figure 4 Forest plots of the efficacy and safety of ChEIs ((A) ADAS-Cog [dose-based]; (B) ADAS-Cog [drug-based]; (C) NPI [dose-based]; (D) NPI [drug-based]; (E) CIBIC+/CGIC [dose-based]; (F) CIBIC+/CGIC [drug-based]; (G) Withdrawals from study due to AE; (H) Nausea; (I) Vomiting; (J) Diarrhoea; (K) Dizziness) among patients with mild to moderate AD. ADAS-Cog, Alzheimer’s Disease Assessment Scale, cognitive subscale; AE, adverse event; CGIC, Clinical Global Impression of Change; ChEIs, cholinesterase inhibitors; CIBIC+, Clinician’s Interview-Based Impression of Change plus caregiver’s input; CrI, credible interval; EMD, empirical mean difference of change on total ADAS-Cog score between placebo and treatment; NPI, Neuropsychiatric Inventory; OR, odds ratio; SMD, standardized mean difference.

A. ADAS-COG (Dose-based)

GAL 24mg					
-0.36 (-1.6 to 0.76)	GAL 16mg				
-0.64 (-1.7 to 0.42)	-0.28 (-1.6 to 1.2)	RIV 12mg			
-0.93 (-2.1 to 0.26)	-0.56 (-2.0 to 1.0)	-0.30 (-1.5 to 0.89)	DON 5mg		
-0.97 (-2.1 to 0.08)	-0.61 (-2.0 to 0.83)	-0.33 (-1.4 to 0.65)	-0.04 (-1.1 to 0.97)	DON 10mg	
-1.5 (-2.8 to -0.21)	-1.1 (-2.6 to 0.53)	-0.87 (-2.0 to 0.29)	-0.57 (-1.9 to 0.82)	-0.54 (-1.7 to 0.77)	RIV-P 9.5mg
-3.1 (-3.9 to -2.4)	-2.8 (-3.9 to -1.5)	-2.5 (-3.2 to -1.7)	-2.2 (-3.1 to -1.2)	-2.2 (-2.9 to -1.4)	-1.6 (-2.7 to -0.62)
					PBO

B. ADAS-COG (Drug-based)

GAL				
-0.95 (-2.1 to 0.15)	RIV			
-0.82 (-1.9 to 0.31)	-0.13 (-1.2 to 0.86)	DON		
-3.1 (-3.9 to -2.2)	-2.2 (-3.0 to -1.5)	-2.1 (-2.9 to -1.3)		PBO

C. NPI (Dose-based)

GAL 16mg					
0.06 (-0.39 to 0.47)	GAL 24mg				
0.04 (-0.28 to 0.38)	-0.06 (-0.40 to 0.28)	RIV 12mg			
0.05 (-0.37 to 0.45)	0.02 (-0.36 to 0.35)	0.01 (-0.25 to 0.26)	DON 10mg		
0.10 (-0.36 to 0.57)	0.07 (-0.35 to 0.44)	0.06 (-0.28 to 0.40)	0.04 (-0.35 to 0.45)	RIV-P	
0.15 (-0.20 to 0.47)	0.10 (-0.17 to 0.39)	0.09 (-0.20 to 0.44)	0.11 (-0.13 to 0.33)	0.05 (-0.29 to 0.39)	PBO

D. NPI (Drug-based)

GAL				
0.08 (-0.31 to 0.40)	DON			
0.08 (-0.27 to 0.37)	0.00 (-0.24 to 0.26)	RIV		
0.11 (-0.13 to 0.32)	0.03 (-0.26 to 0.36)	0.03 (-0.22 to 0.31)		PBO

E. CIBIC+ / CGIC (Dose-based)

DON 10mg					
1.1 (0.76 to 1.5)	DON 5mg				
1.3 (0.77 to 2.0)	1.2 (0.75 to 1.8)	RIV 12mg			
1.5 (0.68 to 3.2)	1.4 (0.64 to 3.0)	1.2 (0.55 to 2.6)	GAL 16mg		
1.7 (1.0 to 2.9)	1.6 (0.99 to 2.7)	1.4 (0.91 to 2.2)	1.2 (0.53 to 2.6)	RIV-P	
2.2 (1.4 to 3.5)	2.1 (1.3 to 3.3)	1.8 (1.1 to 2.8)	1.5 (0.74 to 3.1)	1.3 (0.76 to 2.1)	GAL 24mg
2.5 (1.8 to 3.5)	2.3 (1.7 to 3.2)	2.0 (1.5 to 2.8)	1.7 (0.85 to 3.4)	1.4 (0.97 to 2.1)	1.1 (0.81 to 1.6)
					PBO

F. CIBIC+ / CGIC (Drug-based)

DON				
1.4 (0.87 to 2.1)	RIV			
2.0 (1.3 to 3.2)	1.5 (0.96 to 2.4)	GAL		
2.4 (1.8 to 3.3)	1.8 (1.3 to 2.5)	1.2 (0.86 to 1.7)		PBO

G. Withdrawals from study due to AE

DON					
0.80 (0.41 to 1.5)	GAL				
0.70 (0.31 to 1.6)	0.88 (0.39 to 2.0)	RIV-P			
0.53 (0.31 to 0.88)	0.67 (0.35 to 1.3)	0.76 (0.36 to 1.6)	RIV		
1.6 (0.99 to 2.5)	2.0 (1.2 to 3.2)	2.3 (1.1 to 4.5)	3.0 (2.0, 4.6)		PBO

H. Nausea

RIV-P					
0.79 (0.46 to 1.3)	DON				
0.50 (0.29 to 0.90)	0.64 (0.44 to 0.98)	GAL			
0.26 (0.16 to 0.41)	0.32 (0.25 to 0.43)	0.50 (0.34 to 0.74)	RIV		
2.0 (1.2 to 3.2)	2.5 (1.9 to 3.4)	3.9 (2.9 to 5.2)	7.7 (6.0 to 9.9)		PBO

I. Vomiting

DON					
0.77 (0.43 to 1.7)	RIV-P				
0.47 (0.27 to 0.90)	0.59 (0.28 to 1.2)	GAL			
0.21 (0.15 to 0.34)	0.27 (0.14 to 0.47)	0.45 (0.26 to 0.76)	RIV		
2.0 (1.4 to 3.2)	2.5 (1.3 to 4.3)	4.2 (2.8 to 6.3)	9.3 (6.7 to 13.0)		PBO

J. Diarrhoea

GAL					
0.55 (0.33 to 0.91)	RIV				
0.53 (0.24 to 1.3)	1.0 (0.48 to 2.04)	RIV-P			
0.50 (0.29 to 0.81)	0.90 (0.59 to 1.3)	-0.95 (0.41 to 2.0)	DON		
1.2 (0.86 to 1.7)	2.2 (1.5 to 3.1)	2.3 (1.1 to 4.6)	2.4 (1.7 to 3.6)		PBO

K. Dizziness

RIV-P					
0.53 (0.19 to 1.6)	GAL				
0.53 (0.17 to 1.6)	0.99 (0.51 to 1.8)	DON			
0.29 (0.11 to 0.72)	0.55 (0.29 to 0.95)	0.55 (0.31 to 1.0)	RIV		
0.9 (0.33 to 2.4)	1.7 (1.1 to 2.6)	1.7 (1.1 to 2.8)	3.1 (2.2 to 4.6)		PBO

Figure 5 League tables of efficacy and safety of ChEIs ((A) ADAS-Cog [dose-based]; (B) ADAS-Cog [drug-based]; (C) NPI [dose-based]; (D) NPI [drug-based]; (E) CIBIC+/CGIC [dose-based]; (F) CIBIC+/CGIC [drug-based]; (G) Withdrawals from study due to AE; (H) Nausea; (I) Vomiting; (J) Diarrhoea; (K) Dizziness). Drugs are ordered based on effect size ranking derived from the network meta-analyses. Placebo was listed at the bottom as a comparison. For tolerability, the odds ratio with 95% CrI lower than 1.0 indicates that column-defining treatment decreases the risk of adverse event comparing with the row-defining treatment. ADAS-Cog, Alzheimer’s Disease Assessment Scale, cognitive subscale; AE, adverse event; CGIC, Clinical Global Impression of Change; ChEIs, cholinesterase inhibitors; CIBIC+, Clinician’s Interview-Based Impression of Change plus caregiver’s input; DON, donepezil; GAL, galantamine; NPI, Neuropsychiatric Inventory; PBO, placebo; RIV, rivastigmine; RIV-P, rivastigmine patch.

galantamine (Figure 4H). The risk associated with donepezil was also significantly less than with galantamine and rivastigmine. The risk associated with galantamine was also significantly less than with rivastigmine. The derived hierarchy across drugs was rivastigmine patch > donepezil > galantamine > rivastigmine (Figure 5H).

Vomiting. Nineteen studies provided data on vomiting. NMA revealed that all drugs had a significantly higher risk than placebo. The risk for donepezil was significantly less than for galantamine and rivastigmine. The risk for rivastigmine patch was significantly less than for rivastigmine. The risk for galantamine was significantly less than for rivastigmine (Figure 4I). The derived hierarchy across drugs was donepezil > rivastigmine patch > galantamine > rivastigmine (Figure 5I).

Diarrhoea. Fourteen studies provided data on diarrhoea. NMA revealed that all drugs except galantamine had a significantly higher risk than placebo (Figure 4J). The risk associated with galantamine was significantly less than with rivastigmine and donepezil (Figure 5J). The derived hierarchy across drugs was galantamine > rivastigmine > rivastigmine patch > donepezil.

Dizziness. Fourteen studies provided data on dizziness. NMA revealed that all drugs except rivastigmine patch had a significantly higher risk than placebo (Figure 4K). The risk for rivastigmine patch was significantly less than for rivastigmine (Figure 5K). The risk for galantamine was also significantly less than for rivastigmine. The derived hierarchy across drugs was rivastigmine patch > galantamine > donepezil > rivastigmine.

Discussion

The present analysis demonstrated the modest beneficial effects of all ChEIs on cognition, but not on neuropsychiatric symptoms compared with placebo in patients with mild-to-moderate AD. Beneficial effects on clinical global change were found for donepezil and rivastigmine, but not for galantamine compared with placebo. Regarding hierarchies of efficacy for cognition, 24 mg galantamine showed superior efficacy to rivastigmine patch. In clinical global change, both 5 and 10 mg of donepezil and 12 mg rivastigmine showed superior efficacy to 24 mg galantamine. To our knowledge, this is the first

NMA of ChEIs treatment in patients with AD in which compared using both direct and indirect comparisons of interventions across trials simultaneously. This should strengthen the findings from our analysis over previous meta-analyses (Trinh *et al.*, 2003; Birks, 2006; Hansen *et al.*, 2008; Lockhart *et al.*, 2011; Tan *et al.*, 2014; Wang *et al.*, 2014). The study quality of head-to-head trials might be questionable, because two out of three head-to-head trials were not double-blinded. However, sensitivity analysis without these two trials demonstrated essentially the same results (data not shown).

Previous pair-wise meta-analyses and adjusted indirect comparisons revealed the modest efficacy of ChEIs on cognition, but there has been no evidence of any differences between them (Hansen *et al.*, 2008). The present analysis also demonstrated essentially the same result. A slight difference from previous analyses is that 24 mg galantamine treatment was superior to rivastigmine patch with respect to efficacy for cognition. However, the number of trials of rivastigmine patch was limited, and this might affect the present results. Taken together, ChEIs have modest but robust efficacy on cognition; however, hierarchies of efficacy for cognition among them are still unclear. Although AD is a progressive disease and long-term efficacy on cognition is clinically important, meta-analyses, including this one, mainly selected placebo-controlled RCTs demonstrating relatively short-term efficacy on cognition. Because a long-term placebo-controlled study is ethically questionable, high-quality long-term head-to-head trials are essential to clarify comparative differences between ChEIs.

Previous meta-analyses have consistently demonstrated that ChEIs have beneficial effects on neuropsychiatric symptoms (Trinh *et al.*, 2003; Hansen *et al.*, 2008; Lockhart *et al.*, 2011; Tan *et al.*, 2014; Wang *et al.*, 2014). However, differences in efficacy between each ChEI were inconsistent. Furthermore, some systematic reviews suggested that pharmacological therapies are not particularly effective for management of neuropsychiatric symptoms of dementia (Sink *et al.*, 2005; Rodda *et al.*, 2009). Unlike previous meta-analyses, the present analysis demonstrated that none of the currently available ChEIs had beneficial effects on neuropsychiatric symptoms compared with placebo in patients with mild-to-moderate AD. We excluded trials enrolling patients with severe AD. Conversely, recent meta-analyses include severe AD (Hansen *et al.*, 2008; Di Santo *et al.*, 2013; Tan *et al.*, 2014; Wang *et al.*, 2014). Although a previous meta-analysis Di Santo *et al.* (2013) documented no relationship between severity of dementia and efficacy

of ChEIs on neuropsychiatric symptoms, patients with AD deteriorate progressively and may present with varying degrees of severity of disease, which may influence the results from pooled data. Indeed, a recent study demonstrated that NPI total score significantly increased with dementia stage in patients with AD (Hashimoto *et al.*, 2015). Not only severity but also features of neuropsychiatric symptoms might be influenced by dementia stage. Another recent study demonstrated that mood symptoms would be developed in the early course of the disease; on the other hand, psychotic symptoms and agitation would characterise the middle-to-late stages of dementia in patients with AD (Lopez *et al.*, 2003). These data suggest that patients with AD having neuropsychiatric symptoms would have varied clinical manifestations when severity of dementia and feature of symptoms are not optimally controlled. Such heterogeneity might contribute to incongruent results from both each trial and pooled analyses for pharmacotherapy. To verify efficacy of ChEIs on neuropsychiatric symptoms, further placebo-controlled studies targeting individual psychiatric symptoms in targeting subjects in specific should be needed.

Regarding clinical global change, donepezil showed superior efficacy to galantamine. We speculate that differences in the year of study conduct might be associated with the hierarchy of clinical global change. Trials of donepezil and oral rivastigmine were conducted earlier than those of galantamine and rivastigmine patch. There was a significantly positive correlation between when the study was carried out and responder rates of clinical global change assigned to placebo. Namely, placebo effects on global clinical change increased over time. Meanwhile, no significant correlation between when the study was carried out and responder rate of clinical global change assigned to study drugs was noted. Therefore, increasing placebo effects may contribute in decreasing drug-placebo differences in galantamine and rivastigmine patch studies. Increasing placebo effects over time were found in antipsychotic and antidepressant trials (Walsh *et al.*, 2002; Rutherford *et al.*, 2014). We assume that similar phenomena could occur in trials of ChEIs. Increasing placebo effects over time were observed not only for global clinical change but also for cognition. We believe that increasing placebo effects over time should be taken into account in the interpretation of the results of meta-analyses. Further analysis is needed to clarify factors related to increasing placebo effects over time in anti-dementia drug trials. Such effects should be also taken in to consideration forward anti-dementia trials.

In the present analysis, we evaluated nausea, vomiting, diarrhoea, dizziness and withdrawals due to AEs as tolerability profiles of each ChEI, because these AEs are the most common ones in ChEIs trials. A previous meta-analysis documented the frequency with which these events were reported, generally lowest for donepezil and highest for rivastigmine (Hansen 2008). It also documented that the relative risk of withdrawing for any reason or because of AEs was similar for donepezil compared with placebo, but the relative risk was statistically significantly greater for galantamine and rivastigmine compared with placebo. Regarding withdrawal due to AEs, our analysis demonstrated essentially the same result; all drugs, except donepezil, had a significantly higher risk than placebo. Other safety profiles such as nausea, vomiting and dizziness were concordant with safety profiles documented in the previous analysis. A difference from the previous analysis was that diarrhoea was less frequent with galantamine than other ChEIs. In this analysis, we separately analysed oral rivastigmine and rivastigmine patch; rivastigmine patch showed superior tolerability. A study (Winblad *et al.*, 2007) of oral *versus* rivastigmine patch also demonstrated the superior tolerability of the patch. Differences in tolerability of rivastigmine could be explained by differences in formulation. Mortality was generally reported, and most of them have been identified as not related with drugs. The data also distributed fairly even across all drugs and placebo arms (data not shown).

Other limitations that were not discussed previously could restrict the study speculations. First, we examined the effect of publication year as a possible factor of heterogeneity of efficacy, but there might be other factors of heterogeneity that could lead to inconsistency in the NMA, such as the study duration and the quality of the study. While all but one of the studies included were short term, study duration was still a variable and might be a factor to consider. Second, the result on neuropsychiatric symptoms was derived based on relatively small number of trials. This might affect the wider intervals of estimated effect size. Third, our results for tolerability were only based on the studies that reported at least one of the efficacy outcomes, and thus, additional studies reporting safety information, but not eligible for inclusion in our analysis, may exist. Finally, some of our trials used flexible drug doses. Except for the rivastigmine trials, we attempted to estimate and categorise the dosages used in each trial with the information provided in their reports. Despite some limitations, we believe our results are the first attempt to

quantitatively synthesise the hierarchy of the efficacy and tolerability of ChEI treatment for mild-to-moderate AD. Overall, the results indicate benefits in cognition and clinical global change but the efficacy on neuropsychiatric symptoms is questionable in patients with mild-to-moderate AD. Our results might suggest a possible perspective for anti-dementia drug trials, such as increasing placebo effects over time and heterogeneity of neuropsychiatric symptoms in AD.

Transparency

Contributors

T. O. designed the study. HK designed the analysis. H. K., T. O. and R. N. literature searched and abstracted the data. H. K. and R. N. performed the statistical analysis. All authors interpreted the data and drafted the manuscript. All authors reviewed and approved the manuscript publication.

Competing interests

All authors have disclosed that they are full-time employees of Janssen Pharmaceutical K.K. of Johnson & Johnson in Japan.

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Financial declaration

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Ethics approval

This study does not require ethics approval and consent form each participant, because (1) the present meta-analysis does not directly involve human participants as stated in the MRC guidance and (2) the studies used in the present have previously satisfied regulatory requirements and been peer reviewed.

Previous presentation

This study has been presented at the 12th International Conference on Alzheimer's & Parkinson's diseases, March 19, 2015, Nice, France.

Key points

- Comparative evidence for efficacy and safety of cholinesterase inhibitors (ChEIs) in patients with Alzheimer's disease (AD) is still sparse.
- We conducted the network meta-analysis (NMA) to provide comparative evidences and hierarchies for efficacy between three cholinesterase inhibitors (ChEIs) in patients with mild-to-moderate Alzheimer's disease (AD).
- The NMA showed significant, relatively similar, efficacy on cognition in mild-to-moderate AD patients, and all treatments except galantamine were significantly more efficacious than placebo in global change. However, efficacy on neuropsychiatric symptoms in patients with mild-to-moderate AD is questionable.
- The safety profiles of ChEIs were similar across three drugs.

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