RESEARCH ARTICLE

Comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment: systematic review and Bayesian network meta-analysis

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Funding: *The study was supported by the Natural Science Foundation of Liaoning Province of China, No. 20170541036 (to HYL).*

Abstract

Objective: To assess and compare the clinical efficacy and safety of cognitive enhancers (donepezil, galantamine, rivastigmine, and memantine) on cognition, behavior, function, and global status in patients with vascular cognitive impairment.

Data sources: The initial literature search was performed with PubMed, EMBASE, the Cochrane Methodology Register, the Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing & Allied Health (CINAHL) from inception to January 2018 for studies regarding donepezil, galantamine, rivastigmine, and memantine for treatment of vascular cognitive impairment.

Data selection: Randomized controlled trials on donepezil, galantamine, rivastigmine, and memantine as monotherapy in the treatment of vascular cognitive impairment were included. A Bayesian network meta-analysis was conducted.

Outcome measures: Efficacy was assessed by changes in scores of the Alzheimer's Disease Assessment Scale, cognitive subscale, Mini-Mental State Examination, Neuropsychiatric Inventory scores and Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input, Activities of Daily Living, the Clinical Dementia Rating scale. Safety was evaluated by mortality, total adverse events (TAEs), serious adverse events (SAEs), nausea, vomiting. diarrhea, or cerebrovascular accidents (CVAs).

Results: After screening 1717 citations, 12 randomized controlled trials were included. Donepezil and rivastigmine (mean difference (e) = –0.77, 95% confidence interval (CI): 0.25–1.32; *MD* = 1.05, 95% *CI*: 0.18–1.79) were significantly more effective than placebo in reducing Mini-Mental State Examination scores. Donepezil, galantamine, and memantine (*MD* = –1.30, 95% *CI*: –2.27 to –0.42; *MD* = –1.67, 95% *CI*: –3.36 to –0.06; *MD* = –2.27, 95% *CI*: –3.91 to –0.53) showed superior benefits on the Alzheimer's Disease Assessment Scale–cognitive scores compared with placebo. Memantine (*MD* = 2.71, 95% *CI*: 1.05–7.29) improved global status (Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input) more than the placebo. Safety results revealed that donepezil 10 mg (odds ratio (*OR*) = 3.04, 95% *CI*: 1.86–5.41) contributed to higer risk of adverse events than placebo. Galantamine (*OR* = 5.64, 95% *CI*: 1.31–26.71) increased the risk of nausea. Rivastigmine (*OR* = 16.80, 95% *CI*: 1.78–319.26) increased the risk of vomiting. No agents displayed a significant risk of serious adverse events, mortality, cerebrovascular accidents, or diarrhea.

Conclusion: We found significant efficacy of donepezil, galantamine, and memantine on cognition. Memantine can provide significant efficacy in global status. They are all safe and well tolerated.

Key Words: *nerve regeneration; vascular cognitive impairment; vascular dementia; pharmacotherapy; cholinesterase inhibitors; donepezil; galantamine; rivastigmine; memantine; systematic review; Bayesian network meta-analysis; neural regeneration*

Chinese Library Classification No. *R453*

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doi: *10.4103/1673-5374.249228*

Received: *May 17, 2018*
Accepted: *August 21, 2018*

Introduction

Vascular cognitive impairment is the second most common type of dementia accounting for 15–30% of all cases (Schneider et al., 2007; Goodman et al., 2017), which may even be an underestimation because of misclassification of vascular or mixed dementia as Alzheimer's disease (Smith, 2017). Vascular cognitive impairment represents an enormous public health problem and also poses a huge economic burden; of the estimated 50 million cases of dementia worldwide (Global Burden of Disease Study 2013 Collaborators, 2015), vascular dementia may account for up to 17 million cases, with annual costs of up to 200 billion U.S. dollars (Wimo et al., 2013).

Recent work has indicated that vascular cognitive impairment is potentially preventable and treatable (Hachinski et al., 2010; Li et al., 2017), so pharmacotherapy has received increasing attention. Cerebrovascular lesions in patients with vascular cognitive impairment may cause cholinergic dysfunction that is similar to that observed in Alzheimer's disease, which means that vascular cognitive impairment may be partially due to the disruption of cholinergic signaling and glutamatergic toxicity (Grantham and Geerts, 2002; Román and Kalaria, 2006; Denver and McClean, 2018). The cholinergic deficit hypothesis has been a crucial therapy target for Alzheimer's disease, and the efficacy of cholinesterase inhibitors such as donepezil, galantamine, rivastigmine, has been acknowledged (Kobayashi et al., 2016; Aufschnaiter et al., 2017; Tricco et al., 2018). Memantine is a classic and uncompetitive voltage-dependent N-methyl-D-aspartate receptor antagonist (Alam et al., 2017). Since excessive

ischemia-induced N-methyl-D-aspartate stimulation leads to excitotoxicity, memantine may protect against further damage in vascular cognitive impairment by blocking the pathological stimulation of N-methyl-D-aspartate receptors (Zhang, 2016; Farooq et al., 2017). Most of the randomized controlled trials (RCTs) on potential vascular cognitive impairment treatments have described efficacy in cognition, but have less frequently examined other aspects of efficacy such as behavior, function, and global status. Previous Cochrane reviews (Malouf and Birks, 2004; Birks and Craig, 2006; McShane et al., 2006; Birks et al., 2013) and meta-analyses (Kavirajan and Schneider, 2007; Chen et al., 2016) have highlighted the benefits of donepezil, galantamine, and memantine on cognition, while the efficacy of rivastigmine remains unclear. A recent review found that donepezil and galantamine have been reported to have modest benefits on cognition in patients with vascular dementia, while their reported efficacy on function and global status remains inconsistent (Farooq et al., 2017).

Although two pairwise meta-analyses (Kavirajan and Schneider, 2007; Chen et al., 2016) have been published, it is challenging to synthesize present evidence through traditional meta-analysis because the scarcity of head-to-head trials makes direct comparisons of treatments impossible. Network meta-analysis is viewed as an extension of the traditional pairwise meta-analysis; it enables the integration of data from clinical trials and strengthens the inference about the relative efficacy of each treatment by including both direct and indirect comparisons (Lu and Ades, 2004; Salanti et al., 2008). The increasing number of network meta-analysis reflects their powerful and reliable ability to examine all potential treatments (Zarin et al., 2017).

Hence, we performed this systematic review and network meta-analysis. Compared with the previous reviews and meta-analyses, this present network meta-analysis is the first attempt to quantitatively synthesize the hierarchies of the efficacy and safety of all four cognitive enhancers in patients with vascular cognitive impairment using both direct and indirect comparisons of interventions.

Data and Methods

Information source and literature search

The initial literature search was performed using PubMed, EMBASE, the Cochrane Methodology Register, the Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing & Allied Health (CINAHL). The search terms were as follows: "vascular cognitive impairment", "cholinesterase inhibitor", "donepezil", "galantamine", "memantine", and "rivastigmine". The search covered English-language articles from inception until January 2018. Unpublished studies were retrieved through conference proceedings, clinical trial registries, and author contacts. Reference lists of the included RCTs and relevant reviews were also scanned.

Inclusion/exclusion criteria and data extraction

Our network meta-analysis only included RCTs that reported the efficacy or safety of any of the four cognitive enhancers (donepezil, galantamine, memantine, and/or rivastigmine) as monotherapy in the treatment of vascular cognitive impairment. Vascular cognitive impairment was defined as the cognitive impairment associated with clinical stroke or subclinical vascular brain injury, ranging from mild to severe cognitive impairment, according to American Heart Association and American Stroke Association (Gorelick et al., 2011). We also included two more recent criteria including the International Society of Vascular Behavioral and Cognitive Disorders (Sachdev et al., 2014) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). The eligible RCTs had to report results from at least one of the following assessments: (1) the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog) (Rosen et al., 1984), (2) the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), (3) the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), (4) the Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input (CIBIC+) (Knopman et al., 1994), (5) activities of daily living (ADL) (Lawton and Brody, 1969), (6) the Clinical Dementia Rating (CDR) scale (Morris, 1993), (7) mortality, and (8) adverse events, including total adverse events, serious adverse events, nausea, vomiting, diarrhea, or cerebrovascular accidents. We excluded studies in which patients' diagnoses of vascular cognitive impairment were potentially confused with mixed dementia, Alzheimer's disease, or Alzheimer's disease with cerebral vascular diseases. Studies that used control groups that were not treated with any of the four cognitive enhancers or did not use an appropriate placebo were also excluded.

Two of the authors independently screened articles for inclusion eligibility after the initial literature search. If there was still any controversy after discussion, a third reviewer intervened to make the final decision. Extracted data included the results of the intention-to-treat population using the Last-Observation-Carried-Forward method, unless it was unavailable. We also collected baseline characteristics of each study, such as age and sex ratio of patients, design and sample size of trials, name and dosage of treatments, efficacy outcomes, and occurrences of adverse events.

Outcome measurements

The efficacy of treatments on cognition was assessed by ADAS-Cog and MMSE scores, and efficacy on function through the ADL evaluation. The efficacy of treatments on behavior was evaluated using the NPI, and that on global status by the CIBIC+ and CDR. The means and standard deviations of the change from baseline were extracted for all measures except the CIBIC+, for which we counted the number of "improved" patients to represent the efficacy of treatments on global change. To assess safety, we recorded the number of cases of total adverse events and frequent adverse events, including mortality, serious adverse events, cerebrovascular accidents, diarrhea, nausea, and vomiting.

Statistical analysis

First, we analyzed baseline data and patient characteristics

of the included RCTs. Traditional pair-wise meta-analyses were performed using a random effects model to examine the treatments effects comparing to placebo, which also helped anticipate the heterogeneities and publication biases among the trials before the network meta-analysis. The heterogeneities were evaluated using the I^2 statistic, and the publication biases were judged using funnel plots. These analyses above were performed using Revman version 5.3 (https://community.cochrane.org/help/tools-and-software/revman-5). The Cochrane risk of bias tool was used to assess the individual heterogeneity and risk of bias, which included adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and others.

Second, a network meta-analysis was conducted for each collected outcome of studies and connected network diagrams were constructed using the GeMTC and JAGS packages in R, version 3.0.3, which was initially written by Robert Gentleman and Ross Ihaka of the Statistics Department of the University of Auckland in Auckland, New Zealand, and the current R is the result of a collaborative effort with contributions from all over the world (https://cran.r-project.org/bin/windows/base/old/3.0.3/) (R Development Core Team, 2015). Considering the between-study heterogeneities, random-effect model was adopted for it perhaps being the most appropriate and advisable methodology (Dias et al., 2013; Mills et al., 2013). Within the Bayesian hierarchical model frameworks, Markov chain Monte Carlo estimation was applied using four chains to calculate the median treatment effects and 95% confidence intervals (*CI*s). The number of turning iterations was set to 50,000 and the number of simulation iterations to 100,000. The surface under the cumulative ranking curve indicated the rank of treatments and demonstrated in rank plots. The convergence was estimated by visually inspecting the iteration plot and the potential scale reduction factor (Brooks and Gelman, 1998).

Finally, we synthesized the comparative efficacy and safety of cognitive enhancers for treating vascular cognitive impairment using a network meta-analysis.

The network meta-analysis was based on the assumption that between-study variance (τ^2) was common given that all the interventions were pharmacological. Meanwhile, the transitivity was estimated by inspecting potential efficacy modifiers and reviewing all outcomes and participants' characteristics. The design-by-treatment interaction model (Jackson et al., 2016) was applied to examine the consistency for entire network meta-analysis, and if there is global inconsistency, further detection of any closed loop will be declared in the method of loop-specific with common within-loop τ^2 (Veroniki et al., 2013). If an inconsistency was identified, and no causes were identified, additional analyses would be conducted. These included a subgroup analysis on influential difference, meta-regression of duration, and sensitivity analysis on the study characteristics, including study design, allocation concealment, dose, imputation, and publication year.

Results

Literature search and description of studies

The electronic literature search yielded 1717 potentially relevant articles. Of these, 896 titles and abstracts were reviewed after deleting 821 duplicates. After excluding 847 articles that did not meet the inclusion criteria, we carefully reviewed 49 full-text articles. Eventually, 12 RCTs were identified after full-text review. These included 4 trials for donepezil (Black et al., 2003; Wilkinson et al., 2003; Dichgans et al., 2008; Román et al., 2010), 2 for galantamine (Erkinjuntti et al., 2002; Auchus et al., 2007), 2 for memantine (Orgogozo et al., 2002; Wilcock et al., 2002), and 4 for rivastigmine (Moretti et al., 2003; Mok et al., 2007; Ballard et al., 2008; Narasimhalu et al., 2010). A summary of the literature search is presented in **Figure 1**, and the weighted network is shown in **Figure 2**.

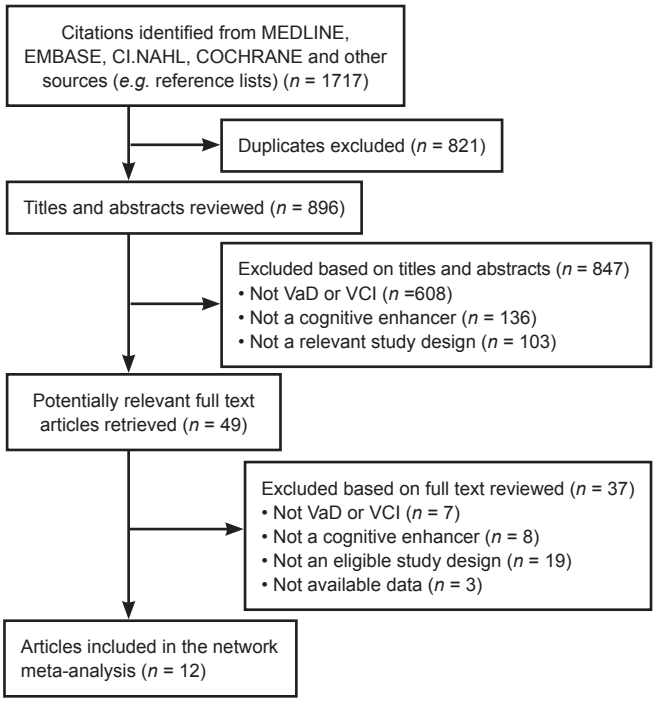

Figure 1 Literature review flow chart.
CINAHL: Cumulative Index to Nursing & Allied Health; COCHRANE: the Cochrane Methodology Register and the Cochrane Central Register of Controlled Trials; VaD: vascular dementia; VCI: vascular cognitive impairment.

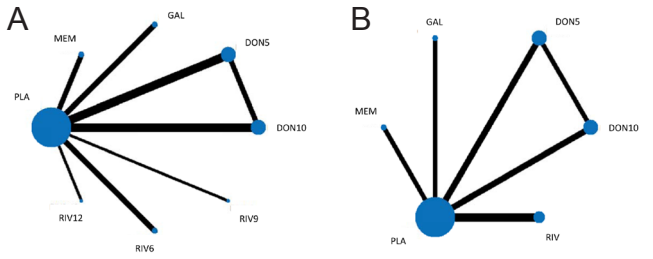

Figure 2 Network of treatments included in the meta-analysis.
(A) The dose-based meta-analysis; (B) The drug-based meta-analysis. The nodes are linked by a line when the treatments were directly comparable. The width of the lines is proportional to the number of randomized controlled trials and the size of each node is proportional to the number of patients (sample size). DON5: Donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg.

The 12 selected studies were all RCTs, and 11 were double-blinded. The characteristics of these trials can be summarized as follows: a publication date from 1991 to 2010, the number of participants ranging from 40 to 974, the average age distribution between 53.8 and 77.6 years old, a baseline MMSE score ranging from 13.0 to 26.89, and a percentage of female participants from 34% to 80%. The total sample size of all RCTs was 5361; the duration of 11 RCTs was from 18 to 28 weeks, and 1 RCT had a duration of 52 weeks. Further details are displayed in **Table 1**.

Quality assessment

In general, the studies showed a low risk of biases across the different measures scored (**Figure 3**).

Meta-analysis results

Efficacy

The statistical significance of results (identified as "superior" herein) of network meta-analysis for each outcome was provided in this analysis. Due to some three-arm studies and dosage differences between RCTs, we performed more than one network meta-analysis on some outcomes, both on dosages and treatments. The network meta-analyses all converged adequately (potential scale reduction factor = 1.00–1.01). The derived hierarchies are described from the most to the least effective.

Cognition

The network meta-analysis on MMSE and ADAS-cog score changes was conducted to estimate the efficacy of treatment on cognition. Sufficient MMSE data were reported in 9 RCTs (Orgogozo et al., 2002; Wilcock et al., 2002; Black et al., 2003; Moretti et al., 2003; Wilkinson et al., 2003; Mok et al., 2007; Ballard et al., 2008; Dichgans et al., 2008; Román et al., 2010), which included three treatments and 3900 patients (**Figure 4A** and **B**). Results of the dosage-based network meta-analysis

Table 1 Baseline characteristics of the included studies

Treatments	Study	Blinding	Number of patients	Daily dose	Gender (female, %)	Age (years)	Study duration (weeks)	Baseline (MMSE)	Outcome assessment			
									Cognition	Behavior	Global	Function
Donepezil	Wilkinson et al. (2003)	Double-blinded	193	Placebo	45.6	74.4	24	22.2	MMSE; ADAS-cog	–	CIBIC+; CDR	ADL
			208	5 mg	37.5	74.7	24	21.8				
			215	10 mg	37.7	75.7	24	21.5				
	Black et al. (2003)	Double-blinded	199	Placebo	42.2	74.2	24	21.7	MMSE; ADAS-cog	–	CIBIC+; CDR	ADL
			198	5 mg	43.9	73.7	24	21.9				
			206	10 mg	48.1	73.9	24	21.8				
	Román et al. (2010)	Double-blinded	326	Placebo	44	72.3	24	23.57	MMSE; ADAS-cog	–	CIBIC+; CDR	–
			648	5 mg	38.6	73.4	24	23.49				
	Dichgans et al. (2008)	Double-blinded	82	Placebo	39	55.8	18	26.89	MMSE; ADAS-cog	–	CDR	–
			86	10 mg	53.5	53.8	18	26.69				
Galantamine	Erkinjuntti et al. (2002)	Double-blinded	196	Placebo	46	75.2	26	20.2	ADAS-cog	NPI	–	–
			396	24 mg	48	75	26	20.7				
	Auchus et al. (2007)	Double-blinded	390	Placebo	34	72.2	26	20.2	ADAS-cog	NPI	–	ADL
			396	24 mg	38	72.3	26	20.3				
Memantine	Wilcock et al. (2002)	Double-blinded	284	Placebo	49	77.6	28	17.7	MMSE; ADAS-cog	–	–	ADL
			295	20 mg	48	77.2	28	17.5				
	Orgogozo et al. (2002)	Double-blinded	156	Placebo	43	76.1	28	16.9	MMSE; ADAS-cog	–	CDR	ADL
			165	20 mg	51	76.6	28	16.9				
Rivastigmine	Ballard et al. (2008)	Double-blinded	345	Placebo	36.5	72.7	24	19.2	MMSE; ADAS-cog	NPI	–	ADL
			365	3–12 mg	38.9	72.9	24	19.2				
	Mok et al. (2007)	Double-blinded	20	Placebo	55	74.1	26	13.4	MMSE	NPI	CDR	ADL
			20	6 mg	65	75.7	26	13				
	Narasimhalu et al. (2010)	Double-blinded	25	Placebo	52	69.4	24	23.9	ADAS-cog	NPI	–	ADL
			25	3–9 mg	80	68.1	24	23.7				
	Moretti et al. (2003)	Unclear	104	Placebo	–	–	52	20.23	MMSE	–	–	–
			104	3–6 mg	–	–	52	19.75				

ADAS-Cog: Alzheimer's Disease Assessment Scale, cognitive subscale; MMSE: Mini-Mental State Examination; ADL: activities of daily living; NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating; CIBIC+: Clinician's Interview-Based Impression of Change scale plus caregiver's input.

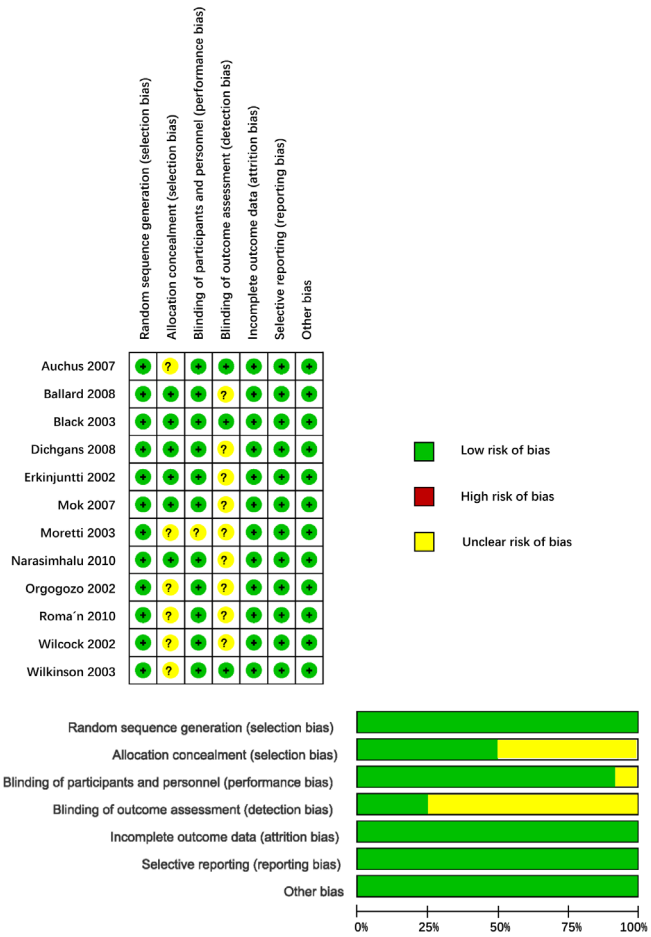

Figure 3 Quality assessment for the risk of bias of included studies.

revealed that donepezil 10 mg (*MD* = 0.84, 95% *CI*: 0.14–1.57) and rivastigmine 6 mg (*MD* = 1.37, 95% *CI*: 0.22–2.53) were superior compared with the placebo (**Figure 5A**). Results of the drug-based network meta-analysis on MMSE score changes showed that donepezil (*MD* = 0.77, 95% *CI*: 0.25–1.32) and rivastigmine (*MD* = 1.05, 95% *CI*: 0.18–1.79) were superior to the placebo (**Figure 5B**). The derived hierarchy across dosages was rivastigmine 6 mg > donepezil 10 mg > donepezil 5 mg > rivastigmine 12 mg > memantine 20 mg > placebo (**Figure 6A**), and that of the drug-based analysis was rivastigmine > donepezil > memantine > placebo (**Figure 6B**).

The network meta-analysis of ADAS-cog score changes on cognition included 10 RCTs (Erkinjuntti et al., 2002; Orgogozo et al., 2002; Wilcock et al., 2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Ballard et al., 2008; Dichgans et al., 2008; Narasimhalu et al., 2010; Román et al., 2010), which included four treatments and 4729 patients (**Figure 4C** and **D**). The analysis revealed that donepezil (*MD* = –1.30, 95% *CI*: –2.27 to –0.42), galantamine (*MD* = –1.67, 95% *CI*: –3.36 to –0.06), and memantine (*MD* = –2.17, 95% *CI*: –3.91 to –0.53) were associated with a significantly greater improvement than the placebo, for both dosage-based and drug-based analyses (**Figure 5C** and **D**). The derived dose-based hierarchy was memantine 20 mg > galantamine 24 mg > donepezil 10 mg > donepezil 5 mg > rivastigmine 12 mg > placebo > rivastigmine 9 mg, and the drug-based hierarchy was memantine > galantamine > donepezil > rivastigmine > placebo (**Figure 6C** and **D**).

Function

The network meta-analysis of ADL score changes on function included 6 RCTs (Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Mok et al., 2007; Ballard et al.,

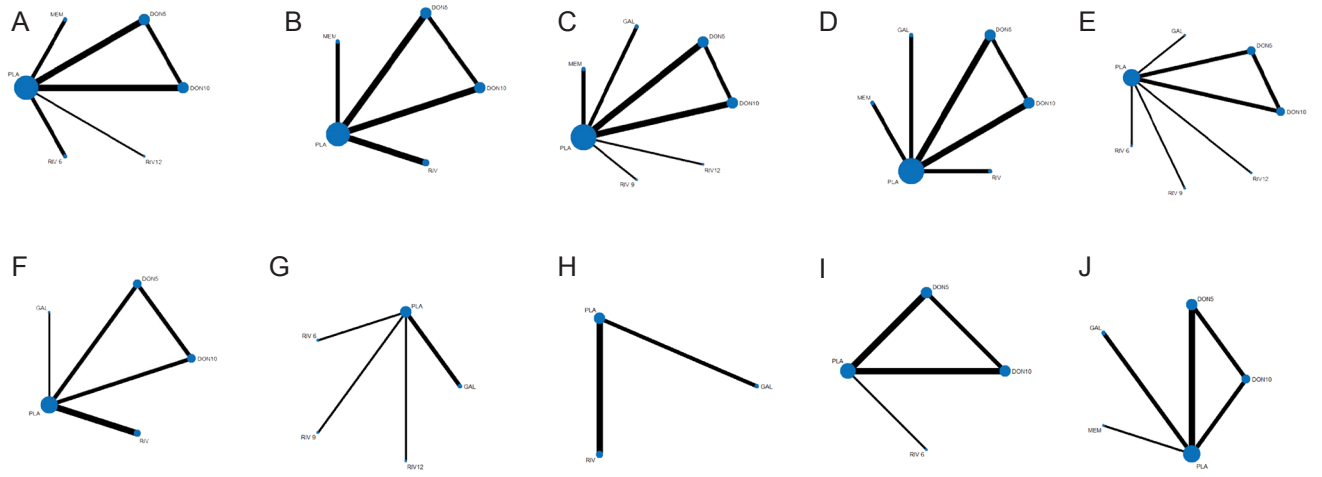

Figure 4 Network diagram of the efficacy of cognitive enhancers.
(A) MMSE (dose-based); (B) MMSE (drug-based); (C) ADAS-cog (dose-based); (D) ADAS-cog (drug-based); (E) ADL (dose-based); (F) ADL (drug-based); (G) NPI (dose-based); (H) NPI (drug-based); (I) CDR; (J) CIBIC+. ADAS-Cog: Alzheimer's Disease Assessment Scale, cognitive subscale; MMSE: Mini-Mental State Examination; ADL: activities of daily living; NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating; CIBIC+: Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input; DON5: donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg. The nodes are linked by a line when the treatments were directly comparable. The width of the lines is proportional to the number of randomized controlled trials and the size of each node is proportional to the number of patients (sample size).

2008; Narasimhalu et al., 2010), which included three treatments and 2677 participants (**Figure 4E** and **F**). No treatments were superior to the placebo (**Figure 4E** and **F**). The derived dose-based hierarchy was rivastigmine 12 mg > donepezil 5 mg > donepezil 10 mg > placebo > rivastigmine 6 mg > galantamine 24 mg > rivastigmine 9 mg, and the drug-based hierarchy was donepezil > placebo > rivastigmine > galantamine (**Figure 5E** and **F**).

Behavior

The network meta-analysis of NPI score changes on behavior included five RCTs (Erkinjuntti et al., 2002; Auchus et al., 2007; Mok et al., 2007; Ballard et al., 2008; Narasimhalu et al., 2010), which included two treatments and 2317 participants (**Figure 4G**). None of the treatments were superior to any other or to the placebo (**Figure 5G** and **H**). The derived hierarchy was rivastigmine > placebo > galantamine. Rivastigmine 6 mg was the most likely to be associated the greatest improvement in NPI scores (**Figure 6G** and **H**).

Global status

Efficacy of treatment on global status was evaluated by CDR and CIBIC+ score changes. The network meta-analysis of CDR scores used data from five RCTs (Black et al., 2003; Wilkinson et al., 2003; Román and Kalaria, 2006; Mok et al., 2007; Dichgans et al., 2008), which included two treatments and 2037 participants. There were no significant differences between treatments and the placebo (**Figure 5I**). The derived hierarchy was donepezil 10 mg > donepezil 5 mg > placebo > rivastigmine 6 mg (**Figure 6I**).

The network meta-analysis of CIBIC+ score changes used data from five RCTs (Erkinjuntti et al., 2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Román et al., 2010), which included three treatments and 3182 participants (**Figure 5J**). Only memantine 20 mg (*OR* = 2.71, 95% *CI*: 1.05–7.29) was found to be superior to the placebo (**Figure 5J**). The de-

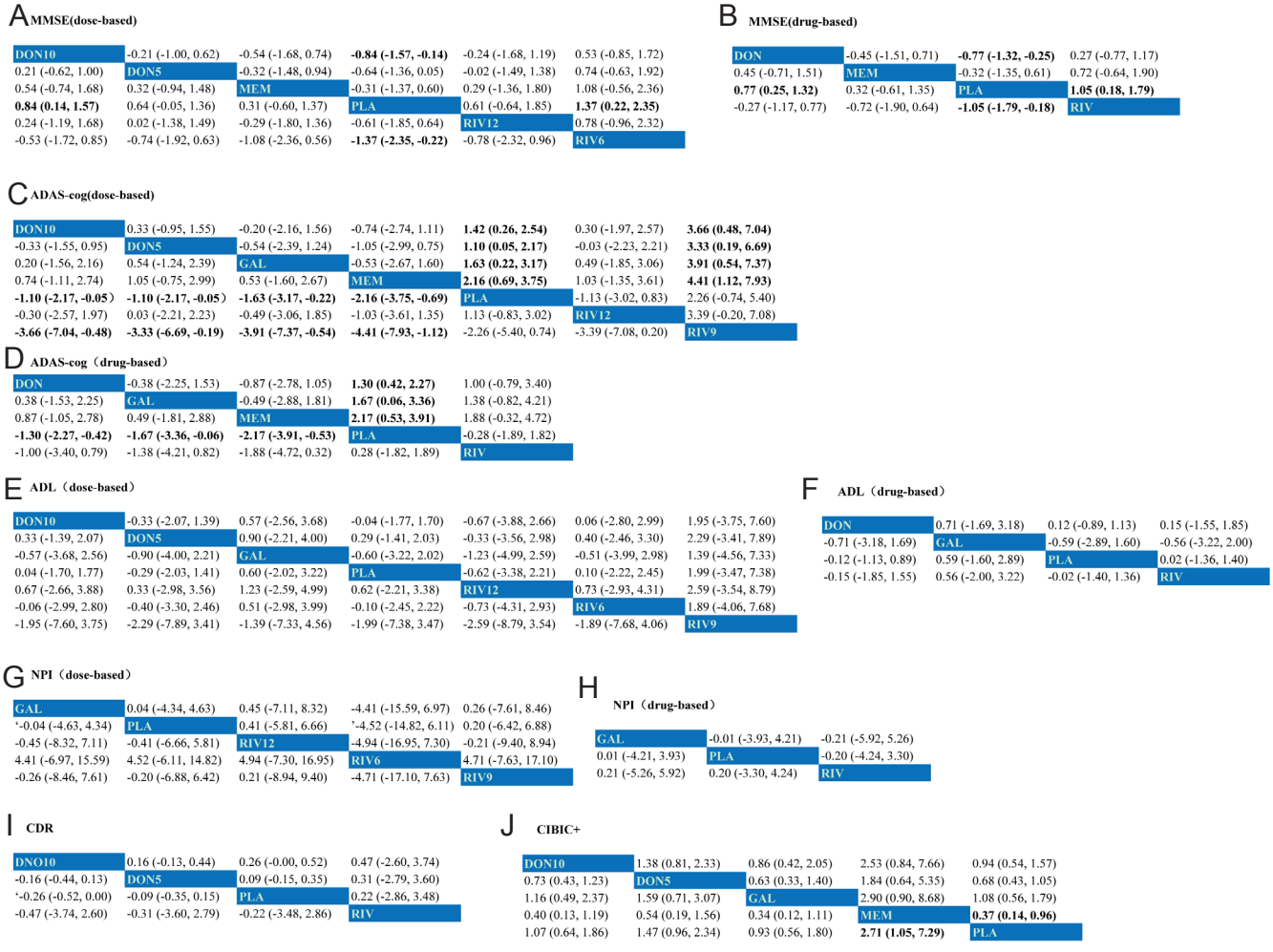

Figure 5 League tables of the efficacy of cognitive enhancers.
(A) MMSE (dose-based); (B) MMSE (drug-based); (C) ADAS-cog (dose-based); (D) ADAS-cog (drug-based); (E) ADL (dose-based); (F) ADL (drug-based); (G) NPI (dose-based); (H) NPI (drug-based); (I) CDR; (J) CIBIC+. When the mean difference with 95% CI displayed above blue grid is positive, the efficacy of the column-defining treatment is identified as better than the row-defining treatment, and vice versa. ADAS-Cog: Alzheimer's Disease Assessment Scale, cognitive subscale; MMSE: Mini-Mental State Examination; ADL: activities of daily living; NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating; CIBIC+: Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input; DON5: donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg.

rived hierarchy was memantine 20 mg > donepezil 10 mg > donepezil 5 mg > placebo > galantamine 24 mg (**Figure 6J**).

Safety

The network meta-analysis converged adequately (potential scale reduction factor = 1.00–1.01). Unlike the network meta-analysis on efficacy, we only performed the safety network meta-analysis across treatments and ignored all dosage differences except for those of donepezil because of its three-arm studies.

Total adverse events

The network meta-analysis on total adverse events included 10 RCTs (Erkinjuntti et al., 2002; Orgogozo et al., 2002; Wilcock et al., 2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Mok et al., 2007; Dichgans et al., 2008; Narasimhalu et al., 2010; Román et al., 2010), which included four treatments and 4378 patients (**Figure 7A**). Results indicated that only the risk of donepezil 10 mg was significantly associated with a higher risk than placebo (*OR* = 0.33, 95% *CI*: 0.18–0.54), donepezil 5 mg (*OR* = 0.40, 95% *CI*: 0.22–0.70) and memantine (*OR* = 0.37, 95% *CI*: 0.17–0.73) (**Figure 8A**). The rivastigmine was the only one owing the possibility of being safer than placebo. The derived hierarchy of the risk of total adverse events was donepezil 10 mg > galantamine > donepezil 5 mg > memantine > placebo > rivastigmine (**Figure 9A**).

Mortality

The network meta-analysis on mortality included 11 RCTs (Erkinjuntti et al., 2002; Orgogozo et al., 2002; Wilcock et al., 2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Mok et al., 2007; Ballard et al., 2008; Dichgans et al.,

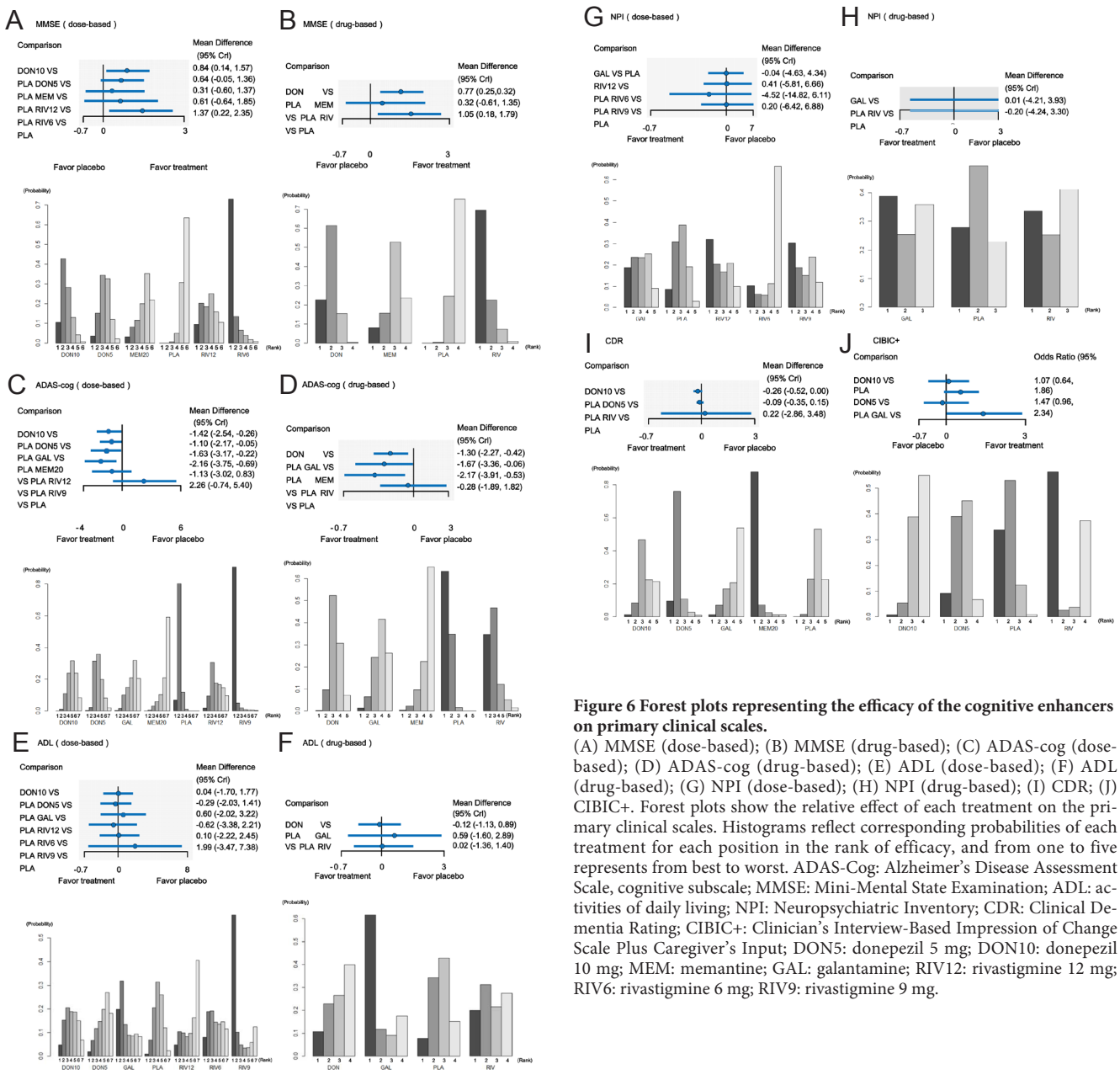

Figure 6 Forest plots representing the efficacy of the cognitive enhancers on primary clinical scales.

(A) MMSE (dose-based); (B) MMSE (drug-based); (C) ADAS-cog (dose-based); (D) ADAS-cog (drug-based); (E) ADL (dose-based); (F) ADL (drug-based); (G) NPI (dose-based); (H) NPI (drug-based); (I) CDR; (J) CIBIC+. Forest plots show the relative effect of each treatment on the primary clinical scales. Histograms reflect corresponding probabilities of each treatment for each position in the rank of efficacy, and from one to five represents from best to worst. ADAS-Cog: Alzheimer's Disease Assessment Scale, cognitive subscale; MMSE: Mini-Mental State Examination; ADL: activities of daily living; NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating; CIBIC+: Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input; DON5: donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg.

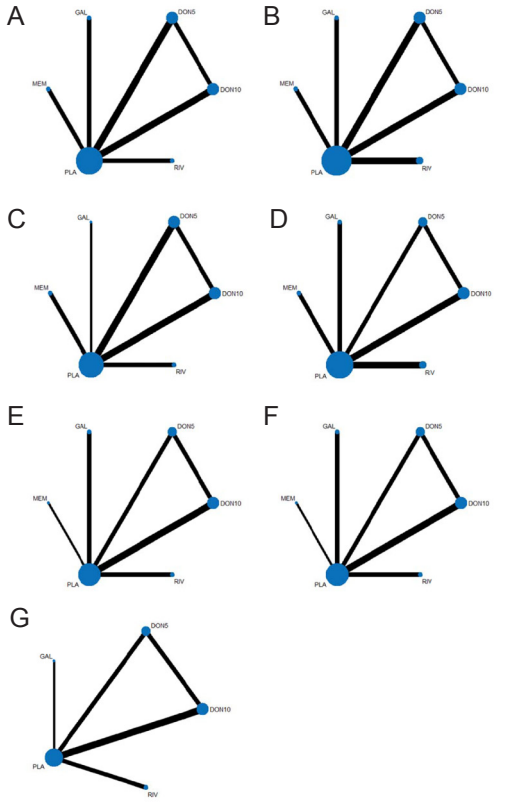

Figure 7 Network diagram of the safety of cognitive enhancers.
(A) Total adverse events; (B) mortality; (C) serious adverse events; (D) nausea; (E) cerebrovascular accidents (stroke); (F) diarrhea; (G) vomiting. DON5: Donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg. The nodes are linked by a line when the treatments were directly comparable. The width of the lines is proportional to the number of randomized controlled trials and the size of each node is proportional to the number of patients (sample size).

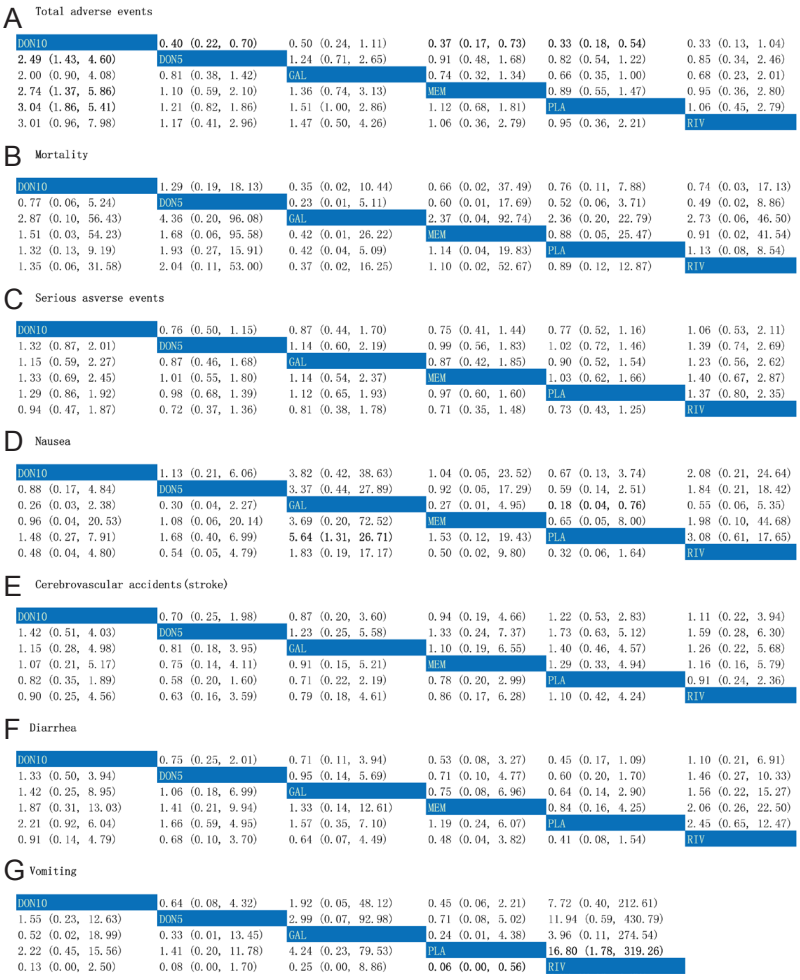

Figure 8 League tables of the safety of cognitive enhancers.
(A) Total adverse events; (B) mortality; (C) serious adverse events; (D) nausea; (E) cerebrovascular accidents (stroke); (F) diarrhea; (G) vomiting. DON5: Donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg. The odds ratio with 95% *CI* above blue grid lower than 1.0 indicates that the column-defining treatment decreases the risk of adverse events compared with the row-defining treatment. CI: Confidence interval.

2008; Narasimhalu et al., 2010; Román et al., 2010), which included four treatments and 5085 patients (**Figure 7B**). There were no significant differences between any drug and the placebo (**Figure 8B**). The derived hierarchy of the risk of mortality was donepezil 5 mg > donepezil 10 mg > placebo > rivastigmine > galantamine > memantine (**Figure 9B**).

Serious adverse events

The network meta-analysis on serious adverse events included nine RCTs (Orgogozo et al., 2002; Wilcock et al., 2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Ballard et al., 2008; Dichgans et al., 2008; Narasimhalu et al., 2010; Román et al., 2010), which included four treatments and 4793 patients (**Figure 7C**). There was no significant difference between any of the treatments and the placebo (**Figure 8C**). The derived hierarchy of the risk of serious adverse events was rivastigmine > donepezil 10 mg > galantamine > placebo > donepezil 5 mg > memantine (**Figure 9C**).

Nausea

The network meta-analysis on nausea included 10 RCTs (Erkinjuntti et al., 2002; Wilcock et al., 2002; Black et al., 2003; Moretti et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Ballard et al., 2008; Dichgans et al., 2008; Narasimhalu et al., 2010; Román et al., 2010), which included four treatments and 4932 patients (**Figure 7D**). Only galantamine (*OR* = 5.64, 95% *CI*: 1.31–26.71) was associated with significantly more risk of nausea than the placebo (**Figure 8D**). The derived hierarchy of the risk of nausea was galantamine > rivastigmine > donepezil 5 mg > donepezil 10 mg > placebo > memantine (**Figure 9D**).

Cerebrovascular accidents (stroke)

The network meta-analysis on cerebrovascular accidents included eight RCTs (Erkinjuntti et al., 2002; Wilcock et al.,

2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Mok et al., 2007; Ballard et al., 2008; Dichgans et al., 2008), which included four treatments and 3742 patients (**Figure 7E**). We found no significant differences between any of the treatments and the placebo (**Figure 8E**), and the derived hierarchy of the risk of cerebrovascular accidents was rivastigmine > placebo > donepezil 10 mg > galantamine > donepezil 5 mg > memantine (**Figure 9E**).

Diarrhea

The network meta-analysis on diarrhea included seven RCTs (Wilcock et al., 2002; Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Ballard et al., 2008; Dichgans et al., 2008; Narasimhalu et al., 2010), which included four treatments and 3501 patients (**Figure 7F**). No treatments showed significant differences with each other (**Figure 8F**). The derived hierarchy of the risk of diarrhea was rivastigmine > donepezil 10 mg > donepezil 5 mg> galantamine > placebo > memantine (**Figure 9F**).

Vomiting

The network meta-analysis on vomiting included six RCTs (Black et al., 2003; Wilkinson et al., 2003; Auchus et al., 2007; Ballard et al., 2008; Dichgans et al., 2008; Narasimhalu et al., 2010), which included three treatments and 2921 patients (**Figure 7G**). Rivastigmine (*OR*: 16.80, 95% *CI*: 1.78–319.26) was the only drug to display more risk of vomiting than placebo (**Figure 8G**). The derived hierarchy of the risk of vomiting was rivastigmine > galantamine > donepezil 10 mg > donepezil 5 mg > placebo (**Figure 9G**).

Discussion

Overall, our network meta-analysis was based on 12 RCTs with low risk of bias that included 25,928 individuals who were randomly assigned to donepezil, galantamine, memantine, rivastigmine treatment and placebo. The objective of this analysis was to determine if these cognitive enhancers could benefit patients with vascular cognitive impairment in terms of cognition, function, behavior, and global status.

Donepezil, galantamine, and memantine all exhibited obvious superiority to the placebo on ADAS-cog score changes, but not MMSE score changes. On the hierarchy of ADAS-cog before placebo, memantine ranked first followed by galantamine and then donepezil indicating a good efficacy of all the three treatments. However, memantine and galantine did not have a significant effect on MMSE score changes. More importantly, donepezil 10 mg displayed the most stable and modest improvement, because it was the

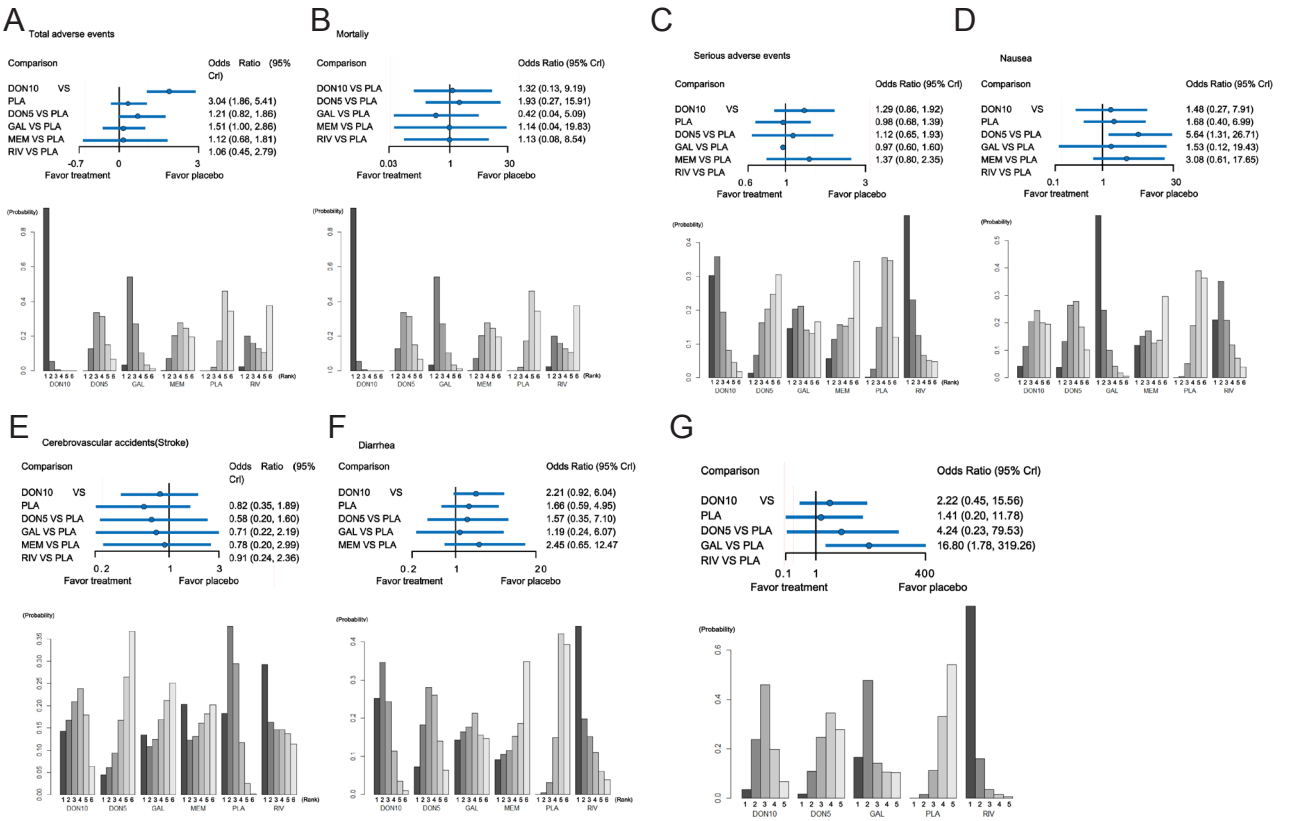

Figure 9 Forest plots representing the safety of cognitive enhancers on primary clinical scales.
(A) Total adverse events; (B) mortality; (C) serious adverse events; (D) nausea; (E) cerebrovascular accidents (stroke); (F) diarrhea; (G) vomiting. Forest plots show the relative safety of each treatment on primary clinical scales. Histograms reflect corresponding probabilities of each treatment for each position in the rank of risk, and the numbers one to five represent the worst to best. ADAS-Cog: Alzheimer's Disease Assessment Scale, cognitive subscale; MMSE: Mini-mental State Examination; ADL: activities of daily living; NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating; CIBIC+: Clinician's Interview-Based Impression of Change Scale Plus Caregiver's Input; DON5: donepezil 5 mg; DON10: donepezil 10 mg; MEM: memantine; GAL: galantamine; RIV12: rivastigmine 12 mg; RIV6: rivastigmine 6 mg; RIV9: rivastigmine 9 mg.

only one found to be statistically superior to the placebo for both MMSE and ADAS-cog scores. However, rivastigmine showed no significant benefit on ADAS-cog scores, and only rivastigmine 6 mg presented little significance on MMSE with limited number of RCTs. Although rivastigmine ranked better than the placebo, there were still discrepancies in the efficacy of rivastigmine due to the finite number of patients. Furthermore, the differences noted between the MMSE and ADAS-cog results should be treated with caution. First, the lack of studies of some treatments was to blame. For example, we failed to find RCTs that investigated the effect of galantamine on MMSE scores. Second, different studies and dosages were included in the network meta-analysis just as that rivastigmine was compared with placebo in two RCTs (Ballard et al., 2008; Narasimhalu et al., 2010) for the ADAS-cog score, but there were three (Moretti et al., 2003; Mok et al., 2007; Ballard et al., 2008) for MMSE. Third, it is possible that intrinsic differences between the MMSE and ADAS-cog mean that they differ in their ability to detect cognitive improvement.

Concerning the network meta-analysis on function, there was no significant difference among treatments or placebo. However, the derived hierarchies confirmed that donepezil (5/10 mg) and rivastigmine 9 mg ranked before the placebo, which means that they may have beneficial effects on function.

Similarly, no treatments were superior to the placebo in terms of their effect on behavior, yet galantamine 24 mg and rivastigmine 6 mg might offer greater benefits than the placebo according to the derived hierarchies.

With respect to the efficacy of the treatments on global status, only memantine 20 mg treatment showed improvements in CIBIC+ scores that were statistically superior to the placebo. However, donepezil also ranked better than the placebo for CDR and CIBIC+ scores and could therefore be more effective than the placebo.

Comparing to placebo, donepezil 10 mg increased the risk of total adverse events, galantamine aggravated the risk of nausea, and rivastigmine did harm the risk of vomiting. For all treatments, there were no other significant differences in adverse events compared with the placebo. More importantly, memantine was the only drug ranked safer than the placebo. Donepezil may own the most stable and appropriate efficacy, whereas its general safety is not so good and even ranked the least safe for mortality and total adverse events.

Four previous Cochrane reviews have reported a good efficacy of donepezil (Malouf and Birks, 2004), galantamine (Birks and Craig, 2006), and memantine (McShane et al., 2006) on cognition, which is consistent with our results. Nevertheless, the review of rivastigmine (Birks et al., 2013) revealed discrepancies in the reported efficacy between studies. This was explained by small sample sizes and the resulting limited and inadequate conclusions. As for the efficacy on other aspects, the Cochrane review of donepezil clearly reported benefits for global status and function compared with the placebo, and the Cochrane review of galantamine found benefits over the placebo on behavior, but we could not conclude such conclusions according to our results. These reviews also reported that the tolerability of memantine was quite good which the same as our conclusion is. It is also reported that the incidence rate of adverse events of donepezil was low, and the risk of adverse events of galantamine was noted to be higher than placebo, but we didn't observe that findings. Another two meta-analyses also discussed the efficacy and tolerability of these four cognitive enhancers in vascular dementia and vascular cognitive impairment. One suggested that all four treatments improved cognition, and that donepezil 10 mg treatment had behavioral or functional benefits (Kavirajan and Schneider, 2007). The other concluded that donepezil and galantamine improve cognition (Chen et al., 2016).

Compared with the previous reviews and meta-analyses, this present network meta-analysis is the first attempt to quantitatively synthesize the hierarchies of the efficacy and safety of all four cognitive enhancers in patients with vascular cognitive impairment using both direct and indirect comparisons of interventions. Simultaneously, both dose-based and drug-based hierarchies were constructed to provide more potential guidance for clinical medication. To strengthen the scientific rigor and evidence-based power of our findings, this study only included RCTs and referred to strict inclusion/exclusion criteria to ensure that included trials were not only the most up-to-date and comprehensive, but also of the best quality. Therefore, several previous conclusions were confirmed in the present analysis. First, we found that no evidence for a superior effectiveness of donepezil on function, behavior, or global status, but we did confirm its modest efficacy on cognition and it might earn more possibility of behaving better than placebo over some other hierarchies. Second, memantine was the only treatment that resulted in improvements in CIBIC+ scores, which has not been previously reported. Third, donepezil did not rank very safely and significantly aggravated the risk of total adverse events. Memantine ranked safer than the placebo in all hierarchies except total adverse events and vomiting, which means it may be the best tolerated. More considerably, despite there being some precious judgments in favor of some cognitive enhancers on behavior or function, actually we failed to verify the benefits of any treatments through our network meta-analysis.

Additionally, dementia is a progressive disease leading to a amount of missing data, and thus the last-observation-carried-forward strategy for intention-to-treat analysis was adopted. There were more drop-outs from participants allocated to receive the cognitive enhancers than the placebo, and this could lead to bias favoring a more positive outcome on cognition (Molnar et al., 2009).

Our study has some limitations that should be noted. First, we were unable to include some eligible studies because the authors did not provide data in a usable format and we could not retrieve these through personal communications. Second, we also excluded studies that investigated cognitive enhancers in patients with mixed types of dementia or Alzheimer's disease, or with cerebral vascular diseases that were not specific to vascular cognitive impairment or vascular dementia (Bullock et al., 2004; Erkinjuntti et al., 2008). More-

over, the behavior outcome could only be assessed for two treatments, which might lower the reliability of our results. Finally, some of the included RCTs used flexible drug doses, especially rivastigmine; we attempted to estimate the efficacy of each dosage through the dosed-based network meta-analysis, but the discrepancies between studies and doses should not be ignored as some of RCTs were performed with a limited number of patients.

In summary, donepezil, galantamine, and memantine seem to provide improvements in patients with vascular cognitive impairment, especially on cognition. Donepezil may have the most stable and modest efficacy, but was associated with an increased risk of total adverse events and did not rank well in other hierarchies of the risk of adverse events. Memantine was the only drug found to show significant difference on global status and demonstrated quite good safety. Unlike previous findings, we did not find any support for the benefits of these treatments on behavior or function. Considering the limitations, we hope to see more studies conducted on the efficacy and safety of cognitive enhancers and updated work on this network meta-analysis in the future.

Author contributions: *Study design, literature search and data analysis: BRJ and HYL; paper writing: BRJ; paper revision: HYL. Both authors approved the final version of the paper.*
Conflicts of interest: *None declared.*
Financial support: *The study was supported by the Natural Science Foundation of Liaoning Province of China, No. 20170541036 (to HYL). The funder had no role in the study design, conduction of experiment, data collection and analysis, decision to publish, or preparation of the manuscript.*
Reporting statement: *This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.*

Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Jiang Li, Qingdao University, China.*

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P-Reviewer: Li J; C-Editor: Zhao M; S-Editors: Yu J, Li CH;
L-Editors: Cason N, Qiu Y, Song LP; T-Editor: Liu XL