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Original Article

Efficacy of galantamine in treatment of Alzheimer's disease: an update meta-analysis

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Abstract: Alzheimer's disease (AD) is the common cause of dementia affecting the elderly people. Among the various therapeutic approaches, cholinesterase inhibitors (ChEIs) are the first group of compounds that have produced modest improvements in cognitive function of AD patients. Galantamine, one of the ChEIs, has been approved by the US FDA for the treatment of mild or moderate AD. The objective of this study was to systematically evaluate the efficacy and safety of galantamine in AD. We searched for randomized control trials comparing galantamine with placebo in the treatment of patients with AD in the online electronic database of CNKI (China National Knowledge Infrastructure), PubMed, Embase and Medline. The strength of association was estimated by the odds ratio (OR), mean difference (MD) with their 95% confidence interval (CI). The primary outcome measures were Cognitive outcomes on the ADAS-cog subscale (change from baseline). Overall, data were extracted from eight randomized clinical trials and analyzed using standard meta-analysis. The results showed that cognitive effects were significant increased for 24 mg daily in galantamine group when compared with placebo group (MD=-3.15, 95% CI=-3.70 to -2.60, P<0.00001). This effect was also found in the Clinicians' Global Impression of Change scale (OR=1.30, 95% CI=1.06-1.60, P=0.01). Most adverse events were cholinergic in nature and no serious adverse events occurred. Our results suggested that galantamine might be a well-tolerated drug which could play a significant role in improving cognitive performance of patients with AD.

Keywords: Alzheimer's disease, cholinesterase inhibitors, galantamine, meta-analysis

Introduction

Alzheimer's disease (AD) is a progressive and fatal brain disorder among elderly individuals [1]. It is characterized by memory loss, steady deterioration of cognition, and dementia [2, 3]. AD affects approximately 10% of people worldwide [4]. It is the sixth leading cause of all deaths in the United States and is the fifth leading cause of death in Americans aged ≥65 years [5]. According to Alzheimer's disease facts and figures, an estimated 5.2 million AD cases will be emerged, and 700,000 death will be occurred in older Americans in 2014 [6]. Furthermore, patients with AD have lost the independent living skills and died because of its complications after disease occurrence [7].

Cholinesterase inhibitors (ChEIs) were firstly introduced for symptomatic treatment of clinical Alzheimer's disease (AD) in the early 1990s, with the introduction of the tacrine, donepezil, rivastigmine, and galantamine [8, 9]. These drugs significantly improved cognitive performance and global status of AD patients at early and moderate stages of the disease as compared to placebo in randomized clinical trials (RCTs) [10-12]. Galantamine was approved in Sweden in 2000 characterized as specific, competitive and reversible ChEI [13]. It is licensed for treating mild to moderate AD and is administered at maintenance doses of 16 or 24 mg daily [14]. Moreover, it potentiates cholinergic nicotinic neurotransmission, and provides ChEI agent with a dual mechanism of action [15]. The half-life of galantamine is 7 to 8 hours. Therefore, researchers have developed a once-daily prolonged-release capsule of galantamine to simplify dosing and enhance compliance [16].

In our present study, we performed an updated meta-analysis of placebo-controlled randomized clinical trials of galantamine in patients

with AD. The aim of this meta-analysis was to determine whether galantamine has super degrees of efficacy on the cognitive, behavioral, and functional impairment of AD patients in progressive different stages of severity.

Materials and methods

Identification and eligibility of relevant studies

To identify the efficacy of galantamine in AD, we systematically searched the English- and Chinese-language literature using the CNKI (China National Knowledge Internet), PubMed, Cochrane Library, Medline, Embase, ALOIS, Wiley Online Library and Elsevier to retrieve relevant studies published between January 2000 and June 2015. The following key terms were used: "galantamine", "Alzheimer's disease or AD" and "efficacy". When the same authors or laboratories reported the same issue on the same population, only the recent full-text articles were included in this meta-analysis.

Criteria for inclusion

Eligible articles should meet the following criteria: 1) a randomized placebo-control design with more than 50 participants in each arm; 2) patients were diagnosed on the basis of the diagnostic criteria of probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA) [17]; 3) patients without any other psychiatric or neurological disorder; and 4) outcome focused on the function, behavior, cognition, or clinical global assessment of change.

Quality assessment and data extraction

Two investigators assessed the quality of the included studies according to the data extracted from each study independently. Disagreements were resolved by discussion with another reviewer. For each trial, the following data were documented: first author, publication year, patient population, sample size, mean age, treatment regimen, duration time and mini mental state examination (MMSE) at baseline. The efficacy of galantamine was evaluated based on patient cognitive performance. All the efficacy data were collected if trials reported results at more than one follow-up time. Wherever possible, outcomes from the intention-to-treat (ITT) population were used, and if this was not possible per protocol outcomes were extracted.

Outcome measures and cognition

The studies used a range of scales and measures to record changes in participants. We assessed the global assessment of change, cognition, function and behavior. MMSE was selected as the primary variable to evaluate the effects of galantamine on cognitive function [18]. It uses a scale of 0-30 with a higher score indicating less impairment. Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-cog) was chosen as the secondary measure of cognition [19]. These two scales are objective measures of cognitive function.

Safety evaluation

The mean incidence with its 95% confidence intervals (CI) was employed to calculate data on adverse events from each included trial. Safety was assessed by the monitoring of treatment-emergent adverse events, clinical laboratory evaluations and the recording of vital signs.

Meta-analysis

The trial duration and the time for evaluation were not the same in the different studies. The outcome data at endpoint in each study were chosen for meta-analysis, because the endpoint selected according to clinical protocol is more reliable and the endpoints of individual trials cannot be changed in a meta-analysis. We tested for heterogeneity of treatment effects using I^2 statistic [20]. We used funnel plots to estimate whether each published studies would affect the results and cause publication bias [21]. Furthermore, the pooled OR and 95% CI were calculated with both a fixed-effects model (the inverse variance-weighted method) and a random effects model (DerSimonian and Laird method) [22, 23]. The fixed-effects model is used when the effects are assumed to be homogenous, while the random effects model is used when they are heterogenous. Analyses were performed using the statistical software ReviewManange5 (Oxford, England, UK).

Results

Trails and patients

Through literature search and selection based on the inclusion criteria, eight studies were

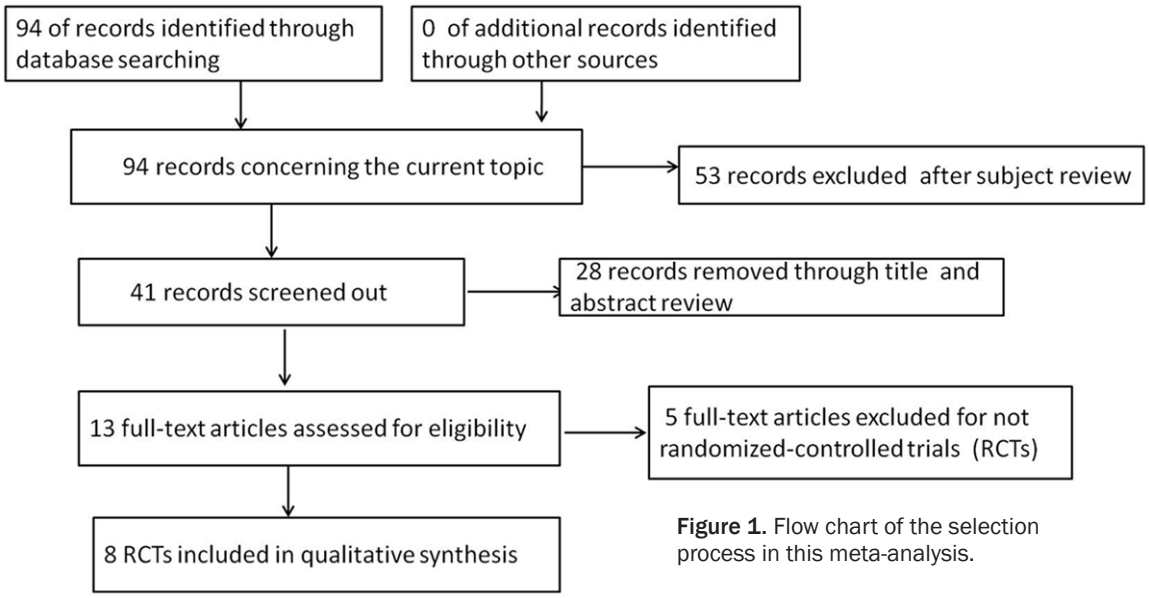

Figure 1. Flow chart of the selection process in this meta-analysis.

Table 1. Study characteristics of all included clinical trials

First author	Year	Country	Disease severity	Dose number of patient	Age year (SD)	Sample size	Duration (week)	Baseline MMSE (SD)
Tariot PN	2000	Belgium	Mild-to-moderate	Placebo	77.1 (0.5)	286	20	17.7 (0.2)
				Galantamine (8 mg)	76.0 (0.6)	140		18.0 (0.3)
				Galantamine (16 mg)	76.3 (0.5)	279		17.8 (0.2)
				Galantamine (24 mg)	77.7 (0.4)	273		17.7 (0.2)
Wilcock GK	2000	Belgium	Mild-to-moderate	Placebo	72.6 (7.6)	215	24	19.3 (3.5)
				Galantamine (24 mg)	71.9 (8.3)	220		19.5 (3.4)
				Galantamine (32 mg)	72.1 (8.6)	218		19.0 (3.8)
Liu FG	2003	China	Mild-to-moderate	Placebo	72 (6)	50	12	18 (4)
				Galantamine (8-16 mg)	71 (6)	47		18 (4)
Brodaty H	2005	USA	Mild-to-moderate	Placebo	76.3 (8.03)	320	24	18.08 (4.08)
				Galantamine (24 mg)	76.5 (7.77)	326		17.80 (4.14)
Rockwood K	2006	Canada	Mild-to-moderate	Placebo	78 (8)	66	16	19.9 (4.2)
				Galantamine (24 mg)	77 (8)	64		20.8 (3.3)
Burns A	2009	Mixed	Severe	Placebo	83.5 (5.8)	200	24	9.1 (2.4)
				Galantamine (4-12 mg)	83.7 (5.7)	207		8.8 (2.4)
Scarpini E	2011	Mixed	Mild-to-moderate	Placebo	74.4	63	48	-
				Galantamine (4-12 mg)	74.5	76		-
Hager K	2014	USA	mild to moderately severe	Placebo	73 (8.7)	1021	96	19.0 (4.04)
				Galantamine (8-24 mg)	73 (8.9)	1024		19.0 (4.12)

MMSE, Mini-Mental State Examination.

found and were ultimately analyzed [13, 24-30] as shown in **Figure 1**. **Table 1** listed the main characteristics of each included study. A total of 5095 patients were included in the study, with 2874 in the galantamine-treated group and 2221 in the placebo-treated group. All three studies enrolled male and female patients according to the diagnosis of AD. The number of patients ranged from 97 to 2045. Trial durations ranged from 12 to 96 weeks. All trials mentioned the type of randomization in "Methods and materials" section. All of them were randomized, double-blind, placebo-controlled studies.

Treatment regimen

In one studies, patients received the galantamine regimen as 8 mg daily for one week, then 16 mg daily for the second week and 24 mg daily for the third week. Patients then continued with their target dose of galantamine for

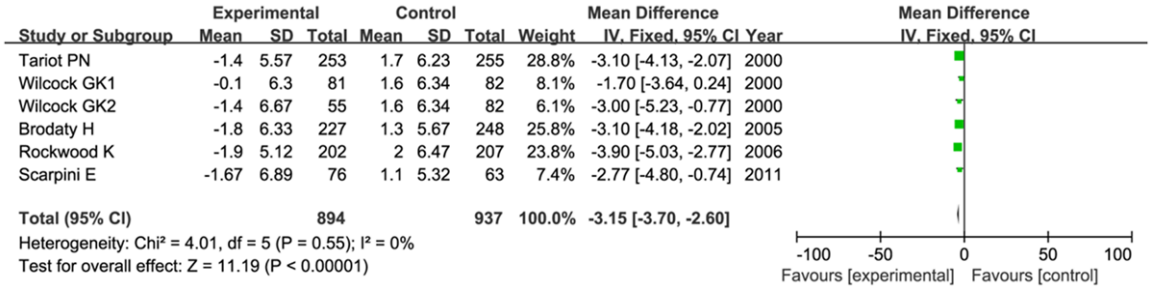

Figure 2. Meta-analysis of cognitive outcome (ADAS-cog) for active treatment compared with placebo.

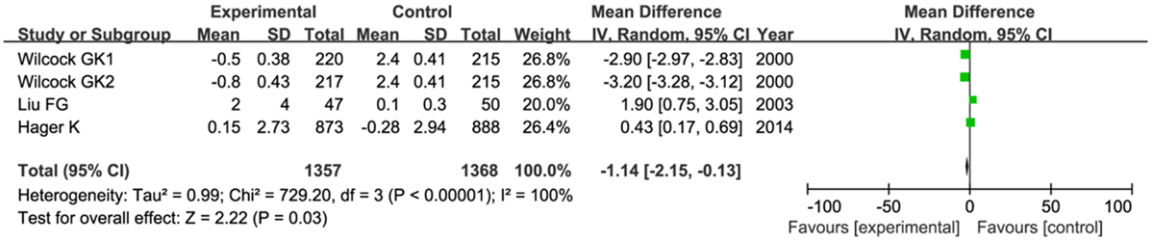

Figure 3. Forest plot of cognitive outcomes comparison on MMSE change from baseline of galantamine relative to placebo in AD patients.

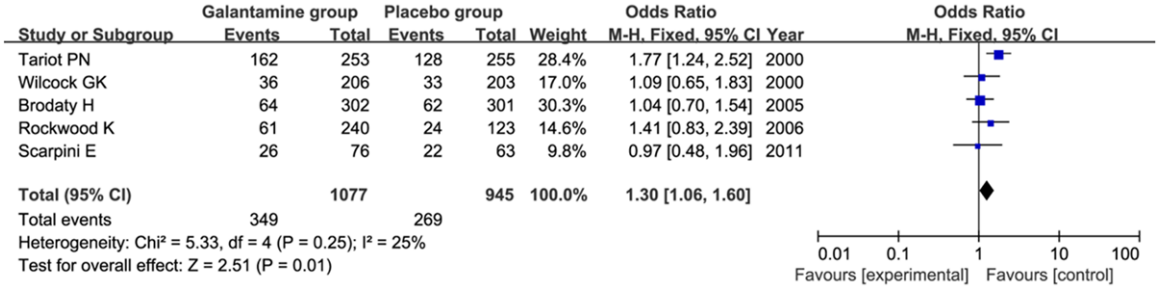

Figure 4. Global change outcomes in AD patients in Galantamine based on CIBIC-plus improvement versus no change or worsening compared to baseline.

a time and then reduce the dose to 16 mg/day. In other four studies, patients in the galantamine group were given 8 mg/day for 4 weeks, followed by 16 mg/day for another 4 weeks. At the end of week 8, the dose could be increased to 24 mg/day depending on tolerability. At week 12, patients were re-evaluated; the dose could then be reduced to 16 mg/day if necessary, after which it could not be changed.

Cognition

Six trials including 1831 patients measured the mean change in ADAS-cog score from baseline to end-point for intervention compared with placebo. As shown in **Figure 2**, our result found that galantamine treatment significantly decreased ADAS-cog score when compared with the placebo treatment (MD=-3.15, 95% CI= -3.70 to -2.60, P<0.00001) in a fixed-effect model. In addition, four trials containing 2725 participants measured the MMSE. Compared with the placebo group, MMSE score was not significant improved in the galantamine group (OR=-1.14, 95% CI=-2.15 to -0.13, p=0.03) in a random-effect model as shown in **Figure 3**.

Global assessment

Five studies measured and reported the number of patients with improvement on CIBIC+. Our results found that 24 mg daily galantamine had significant effect on the Clinicians' Global Impression of Change scale (OR=1.30, 95% CI=1.06-1.60, P=0.01) as shown in **Figure 4**.

Table 2. Treatment-emergent adverse events

Adverse event	Number of subjects		Odds ratio (95% CI)
	Galantamine (n=1060)	Placebo (n=680)	
Nausea	17	7	1.57 (0.65, 3.80)
Headache	15	6	1.60 (0.60, 4.18)
Agitation	11	3	2.37 (0.66, 8051)
Abdominal pain	18	2	5.86 (1.35, 25.32)
Somnolence	20	1	4.34 (1.28, 14.66)
Anorexia	14	5	1.81 (0.65, 5.04)
Vomiting	19	7	1.75 (0.73, 4.20)
Dizziness	15	6	1.61 (0.62, 4.18)
Weight loss	13	7	1.19 (0.47, 3.01)
Upper respiratory tract infection	8	2	2.58 (0.55, 12.18)
cough	7	12	0.37 (0.14, 0.94)

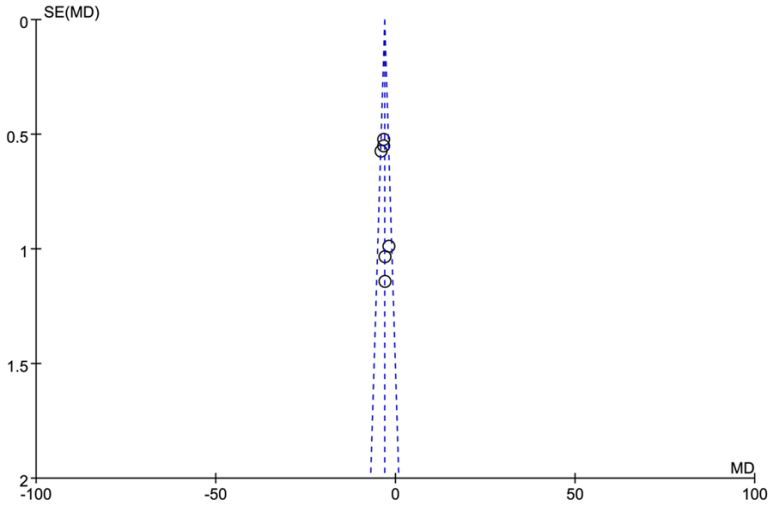

Figure 5. The funnel plot analysis for publication bias in this meta-analysis.

Efficacy of outcomes on other galantamine dosage

One study reported the galantamine regimen was 8 mg, 16 and 24 mg daily respectively, the results showed that 16 and 24 mg daily significantly benefits the cognitive, functional, and behavioral symptoms of AD as compared with placebo. One study showed that long-term treatment with galantamine (8-24 mg) significantly reduced mortality and the decline in cognition and daily living activities, in mild to moderate AD patients.

Safety and tolerability

A total of 1740 patients with AD received at least one dose of study medication in the three clinical trials included in the meta-analysis. No adverse effects on vital signs, blood test results or electrocardiogram results were seen. Most adverse effects were mild, only occasionally moderate in intensity and generally diminished with time despite continuation of treatment (**Table 2**). Of those adverse effects, some mild peripheral cholinergic side effects such as nausea or vomiting and diarrhea were more likely occur in the galantamine group than in the placebo group; however, differences were not significant. Most other non-cholinergic-induced adverse effects were considered unrelated to the study drug. There were no clinically significant differences in abnormal laboratory test parameters, vital signs or cardiovascular parameters between the study groups.

Sensitivity analysis and publication bias

For this meta-analysis, the influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, respectively. The risk ratio was not significantly influenced by omitting any single study. The funnel plot for this meta-analysis revealed no evidence of asymmetry (**Figure 5**). Thus, there was no publication bias in this meta-analysis.

Discussion

This meta-analysis of eight clinical trials was conducted to determine the effect size of galantamine for the treatment of AD. As patients in the placebo group were generally treated with concomitant treatment, we included trials comparing galantamine with placebo. Our result confirmed that galantamine can be started and used safely in elderly patients with AD and improved cognitive function. Our results were in accord with previous meta-analysis which

showed that administration of galantamine for 8-28 weeks (16-40 mg daily) led to significant improvements in ADAS-cog score [31, 32].

Galantamine is licensed for the treatment of mild to moderate AD and is administered at maintenance doses of 16 or 24 mg daily [33]. The beneficial effects of galantamine in patients with Alzheimer's disease have already been demonstrated in two large 6 month placebo controlled trials [34, 35]. Results in each study were homogenous regardless of timepoint and evaluation instrument adopted or drug doses administered. Our overall results confirmed that galantamine could significantly improve the MMSE score of AD patients. The pooled effect size of galantamine versus placebo was 0.09 (95% CI, 0.03-0.16), indicating a beneficial effect of galantamine. The effect of galantamine on the ADLs of AD patients was detected using the mean difference of change. Galantamine was effective in delaying time to cognitive deterioration in subjects with mild to moderate AD [36, 37]. Richarz et al. showed that galantamine was generally safe and well tolerated during the 3-year observation period, and cognition, behavior, and activities of daily living improved during 12 months treatment [38]. Ohnishi et al. demonstrated that patients who show improvement of episodic memory function during the first 4 weeks of galantamine administration may be likely to particularly benefit from galantamine treatment [39].

Patients on galantamine, compared with those on placebo, experienced benefits in cognitive function and instrumental and basic activities of daily living. Galantamine is effective and well tolerated in AD [40]. The pooled weighted mean difference in change between galantamine treatment group and placebo group was -0.56 (95% CI, -0.83 to -0.38), indicating that galantamine might be a safe drug in elderly patients with severe AD. According to the Okayama Galantamine Study, results revealed a long-term efficacy of galantamine in very elderly AD patients, and suggested a better efficacy for male and baseline lower cognitive, affective, and ADL functions [41].

As expected from the results of randomized controlled trials completed to date, galantamine was shown to be well tolerated. Most adverse effects were related to the well-known cholinergic activity of this class of drug, and were mainly gastrointestinal in nature. Such adverse effects were generally of mild to moderate severity and transient. There were no clinically significant differences between the study groups, and most of these adverse effects were rated as mild. In addition, galantamine might be combined with other therapies, thus playing a beneficial role in AD treatment. Tokuchi et al. found that the combination therapy of galantamine and ambulatory cognitive rehabilitation showed a superior benefit both on cognitive and affective functions than galantamine only therapy in AD patients [42].

In this meta-analysis, several factors limited the current study. Firstly, one study included the small amount of available data for inclusion in the meta-analysis and the small sample size of individual trials. Secondly, treatment duration was not consistent, which has been suggested as a key time point for medication assessment. Finally, only MMSE and ADAS-cog scales were used to evaluate the efficacy of galantamine because the other scales used in the studies were too divergent for a meta-analysis. MMSE has good reliability and validity when used for screening for dementia but is not considered to be an ideal outcome measure for AD drug trials because it is not designed to measure more subtle changes in cognition [43]. Finally, the data for meta-analysis came solely from published scientific literature, so there might be a publication bias. The effect of publication bias was not evaluated owing to the low levels of data.

Conclusions

Our results showed that galantamine might have a cognitive and functional benefit in patients with mild to moderate AD with little adverse effects, indicating that galantamine would have a useful role in the treatment of AD.

Disclosure of conflict of interest

None.

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