Safety and efficacy of acetylcholinesterase inhibitors for Alzheimer's disease: A systematic review and meta-analysis

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Abstract

Alzheimer's disease (AD) affects millions of people worldwide. The most commonly used drugs are acetylcholinesterase inhibitors, i.e., donepezil, galantamine and rivastigmine, which increase levels of acetylcholine. However, the exact efficacy and safety of acetylcholinesterase inhibitors in the treatment of AD is still unclear. The main objective of the current study was to determine the exact safety and efficacy profile of acetylcholinesterase inhibitors in the treatment of AD by conducting a systematic review and meta-analysis of clinical trials according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We conducted a web-based literature search of PubMed and clinical trial websites using relevant keywords. Data were extracted from eligible records and pooled as mean difference (MD) or risk ratio (RR) values with their 95% confidence interval (95% CI) using Review Manager software (v. 5.3 for Windows). Heterogeneity was calculated using χ^2 and I^2 tests. The standard mean difference (SMD) was –0.33 [–0.52, –0.13] for donepezil, –0.48 [–0.58, –0.38] for galantamine and –0.65 [–1.06, –0.23] for rivastigmine, indicating a significant effect of these drugs on cognitive outcomes. Here we show the significant effects of all available acetylcholinesterase inhibitors on cognitive function in patients with AD. However, further studies are needed to draw valid conclusions about the effects of acetylcholinesterase inhibitors on functional outcomes and adverse events.

Key words: Alzheimer's disease, galantamine, donepezil, rivastigmine, acetylcholinesterase inhibitors

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that affects millions of peoples across the globe. Many researchers have documented the abnormal aggregation of β-amyloid in the brains of patients with AD. This abnormal aggregation leads to the activation of various inflammatory and oxidative stress signaling pathways, ultimately leading to neuronal degeneration. Structural and functional abnormalities have been observed in specific regions of the brain, particularly the hippocampus and prefrontal cortex, in patients with AD.[1–3] Mitochondrial dysfunctions also play a significant role in the neurodegenerative diseases, including AD. Tanaka et al. reviewed the functions of mitochondria in the central nervous system (CNS) and their alterations in neurodegenerative diseases.[4]

In normal brain physiology, there is a balance between excitatory and inhibitory neurotransmitters. The major excitatory neurotransmitter in the CNS is glutamate, while the major inhibitory neurotransmitter is gamma-aminobutyric acid (GABA). Glutamate acts on NMDA receptors, while GABA acts on GABA receptors. In neurodegenerative diseases, levels of excitatory neurotransmitters increase, leading to excitotoxicity.[5]

There are a number of mechanisms involved in the pathogenesis of AD. Oxidative stress is one of the major mechanisms involved in the development of AD. Under normal physiological conditions, reactive oxygen species (ROS), reactive nitrogen species (RNS), etc., are generated in mitochondria and scavenged by endogenous antioxidant enzymes such as glutathione, superoxide dismutase (SOD), catalase, etc. Overall, there is balance between generation of reactive species and anti-oxidant enzymes. However, the imbalance (increase in level of reactive species and decrease in level of endogenous antioxidant enzymes) results in the activation of oxidative stress signaling pathways.[6,7]

Increased oxidative stress results in the alteration of the mitochondrial membrane potential.[8,9] The altered mitochondrial potential causes increased expression of apoptotic proteins such as BAX and decreased expression of anti-apoptotic proteins such as Bcl-2. This imbalance activates the caspase-dependent and caspase-independent pathways, which ultimately leads to cell death.[10–15]

Reports in the literature have indicated cognitive dysfunctions in patients with AD.[15–20] The exact etiology of AD is unclear; however, it is known that there is an impairment of central cholinergic neurons in patients with AD.[21] Common AD-associated neuropsychiatric symptoms include depression, anxiety, agitation, aggression, and apathy.[22–24] Currently, very few drugs are available for the AD treatment. The majority of available drugs inhibit the enzyme cholinesterase, which is responsible for degradation of acetylcholine into choline and acetic acid. Inhibition of cholinesterase results in the increased level of acetylcholine. The well-known cholinesterase inhibitors used to treat AD are donepezil, rivastigmine and galantamine.[25] These have been used alone and in combination with memantine.[26] However, the exact efficacy and safety of acetylcholinesterase inhibitors in the treatment of AD is still unclear.

Objectives

The main objective of this study was to determine the exact safety and efficacy profile of acetylcholinesterase inhibitors in the treatment of AD by conducting systematic review and meta-analysis of clinical studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The overall estimate measure was calculated in terms of standard mean difference (SMD) for continuous data, whereas the odds ratio (OR) or relative risk was calculated for dichotomous data to examine overall safety and efficacy of acetylcholinesterase inhibitors in clinical trials.

Materials and methods

Search strategy

Relevant studies were searched in PubMed from inception to October 2022. The followings MeSH terms were used: "Alzheimer disease" or "AD," "donepezil," "galantamine," and "rivastigmine," with a proper use of Boolean operators.

Selection criteria

The studies were selected based on inclusion and exclusion criteria. The inclusion criteria were as follows: 1) double-blind randomized clinical trials (RCTs) testing at least 1 acetylcholinesterase inhibitor; 2) treatment duration at least 52 weeks; 3) one of the cognitive, functional changes or adverse events were reported. Both sexes and all age groups were included. Non-randomized clinical trials, case reports, case series, narrative reviews, and meta-analyses were excluded. Studies published in languages other than English were also excluded. Two authors (YG and YL) screened the studies based on titles and abstracts. The full text of selected studies was downloaded into a folder. The quality assessment of each study was also assessed to reduce the risk of bias in the estimate of effects.

Data extraction

Data from selected studies were extracted by 2 authors (YG and YL) into a suitable Excel spreadsheet. The columns of Excel spreadsheets were as follows: authors and type of the study.

Data analysis

All data were analyzed using Rev Man 5 (Cochrane Collaboration, London, UK). For continuous data, the overall estimate was calculated as the SMD with 95% confidence interval (95% CI). For dichotomous data, overall estimate was calculated as ORs. The SMD was preferred to the mean difference (MD) due to variations among scales used for cognitive and functional outcomes between the studies. Dichotomous data were in terms of adverse events; therefore, OR was preferred. Heterogeneity was assessed using the Cochran's Q statistic and I^2 tests. The random effects model was used due to variations among included studies. The inverse variance method was used for continuous data and the Mantel–Haenszel method was used for dichotomous data.

Results

Selection of studies

A total of 2,300 studies were found in PubMed, which were further screened based on inclusion and exclusion criteria. A total of 16 studies were selected for quantitative analysis regarding efficacy of acetylcholinesterase inhibitors, while 15 studies were found relevant regarding safety of acetylcholinesterase inhibitors. Of the 16 studies, 6 were related to donepezil,[27–32] 6 were related to galantamine[33–37] and the remaining 4 studies were related to rivastigmine.[38–42] Among the 15 studies related to safety, 9[17–31,43–46] were related to donepezil and the remaining 6 were related to galantamine.[33–38] The flow of study selection is presented in Fig. 1. The characteristics of the included studies are provided in Table 1.

Efficacy of acetylcholinesterase inhibitors

The efficacy of individual acetylcholinesterase inhibitors is compiled below.

Donepezil

Cognitive function

The SMD was found to be −0.33 [−0.52, −0.13], indicating a significant effect of donepezil on cognitive outcome. The forest plot along with the pooled effect, i.e., SMD, is presented in Fig. 2A. The heterogeneity between studies was 38%, as indicated by the I^2 statistic.

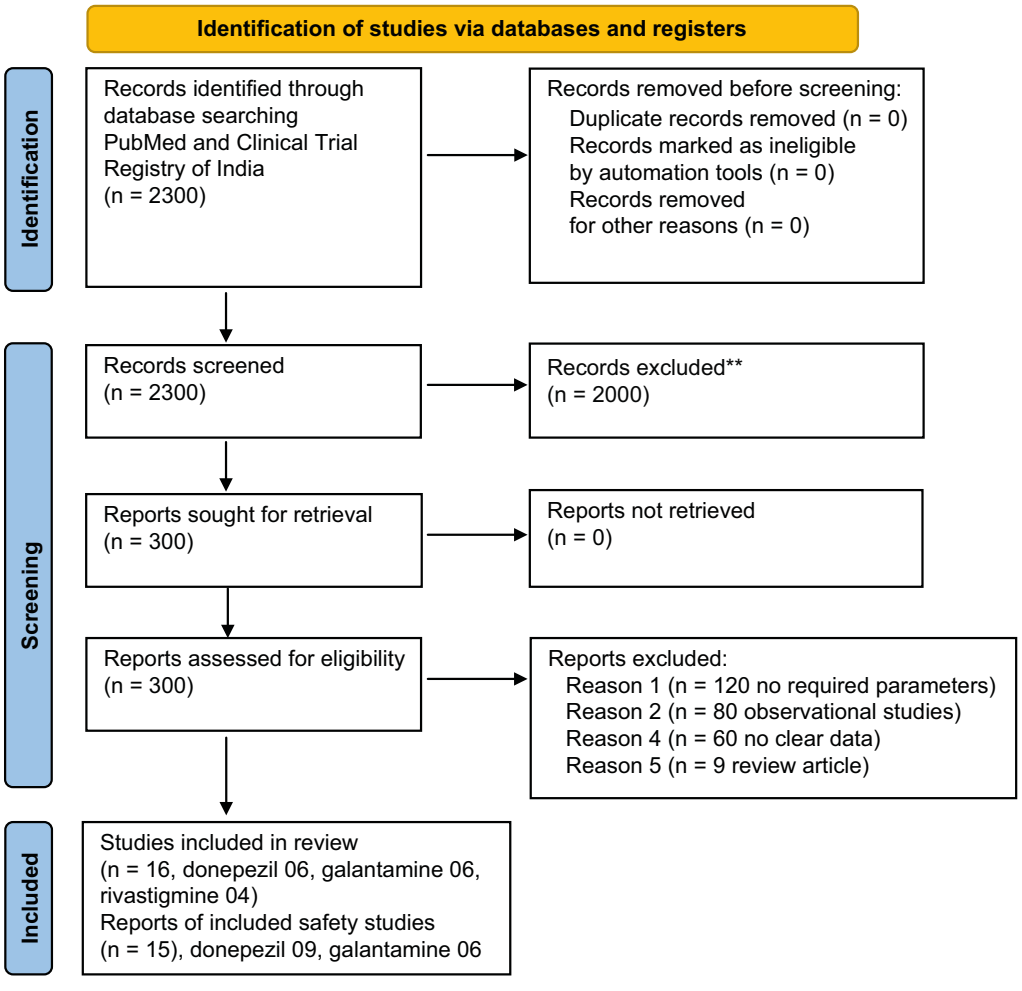

Fig. 1. Selection of studies as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Table 1. Characteristics of included studies

Authors and year of publication	Location	Age years (M ±SD)	Total sample size	Disease severity	Duration [weeks]
Haig et al., 2014[28]	USA	70.3 ±7.94 (placebo) 70.5 ±8.31 (drug)	63 (placebo) 60 (drug)	mild to moderate	12
Johannsen et al., 2006[29]	Denmark	71.4 ±9.3 74.1 ±7.6	103 (placebo) 99 (drug)	mild to moderate	12
Maher-Edward et al., 2011[30]	UK	71.6 ±6.72 (placebo) 71.1 ±8.39	61 (placebo) 67 (drug)	mild to moderate	24
Seltzer, 2004[31]	USA	73.3 ±8.8 (placebo) 73.3 ±9.6	57 (placebo) 96 (drug)	mild to moderate	24
Tune et al., 2003[32]	USA	72.2 ±9.57 (placebo) 73.7 ±5.25 (drug)	14 (placebo) 14 (drug)	mild to moderate	24
Brodaty et al., 2005[33]	Australia	–	296 (placebo) 296 (drug)	mild to moderate	6 months
Raskind et al., 2000[34]	USA	–	207 (placebo) 202 (drug)	mild to moderate	6 months
Rockwood, 2001[35]	USA, Canada, UK, South Africa, Australia, and New Zealand	74.6 ±0.68 75.2 ±0.45	120 (placebo) 239 (drug)	patients with probable Alzheimer's disease	3 months
Gault et al., 2016[44]	USA	73.2 ±7.39 (placebo) 75.1 ±7.75 (drug)	104 (placebo) 76 (drug)	mild to moderate	24
Jia et al., 2017[45]	China	70.0 ±9.57 71.6 ±8.56	156 (placebo) 157 (drug)	severe	24
Tariot et al., 2001[46]	USA	85.9 ±9.25 85.4 ±8.5	105 (placebo) 103 (drug)	mild to moderate	24
Black et al., 2007[47]	Canada	78.0 ±8.04 (placebo) 78.0 ±8.20	167 (placebo) 176 (drug)	severe	24
Gault et al., 2015[48]	USA	73.6 ±8.23 73.9 ±7.92	68 (placebo) 68 (drug)	mild to moderate	12
Homma et al., 2008[49]	Japan	79.7 ±7.5 76.9 ±7.9	102 (placebo) 92 (drug)	severe	24
Winblad et al., 2006[50]	Sweden	85.3 ±5.9 84.5 ±6.0	120 (placebo) 128 (drug)	severe	24
Feldman et al., 2001[51]	Canada	74.0 ±11 73.2 ±10	146 (placebo) 144 (drug)	moderate to severe	24

M ±SD – mean ± standard deviation.

Functional outcome

The effects of donepezil on the functional outcomes were also found to be significant compared to the control group, as indicated by the SMD values, i.e., 0.24 [0.12, 0.36]. The forest plot together with the pooled effect is shown in Fig. 2B. No heterogeneity between studies was found, as indicated by the I^2 statistic.

Adverse events

The overall OR was found to be 1.22 [0.98, 1.52], indicating a non-significant association of donepezil with adverse events. The forest plot together with the pooled effect is shown in Fig. 2C. No heterogeneity between studies was found.

Galantamine

Cognitive function

The SMD was found to be –0.48 [–0.58, –0.38], indicating a significant improvement in cognitive functions in patients with AD compared to the control group. The forest plot together with pooled effect is shown in Fig. 3A. The heterogeneity between studies was 29%, as indicated by the I^2 statistic.

Functional outcomes

The effect of galantamine on functional outcome was not significant, as indicated by the SMD, i.e., 0.17 [–0.08, 0.43]. The forest plot together with the pooled effect is shown in Fig. 3B. However, the heterogeneity between studies was very high (83%) (Fig. 3B).[29,47,48]

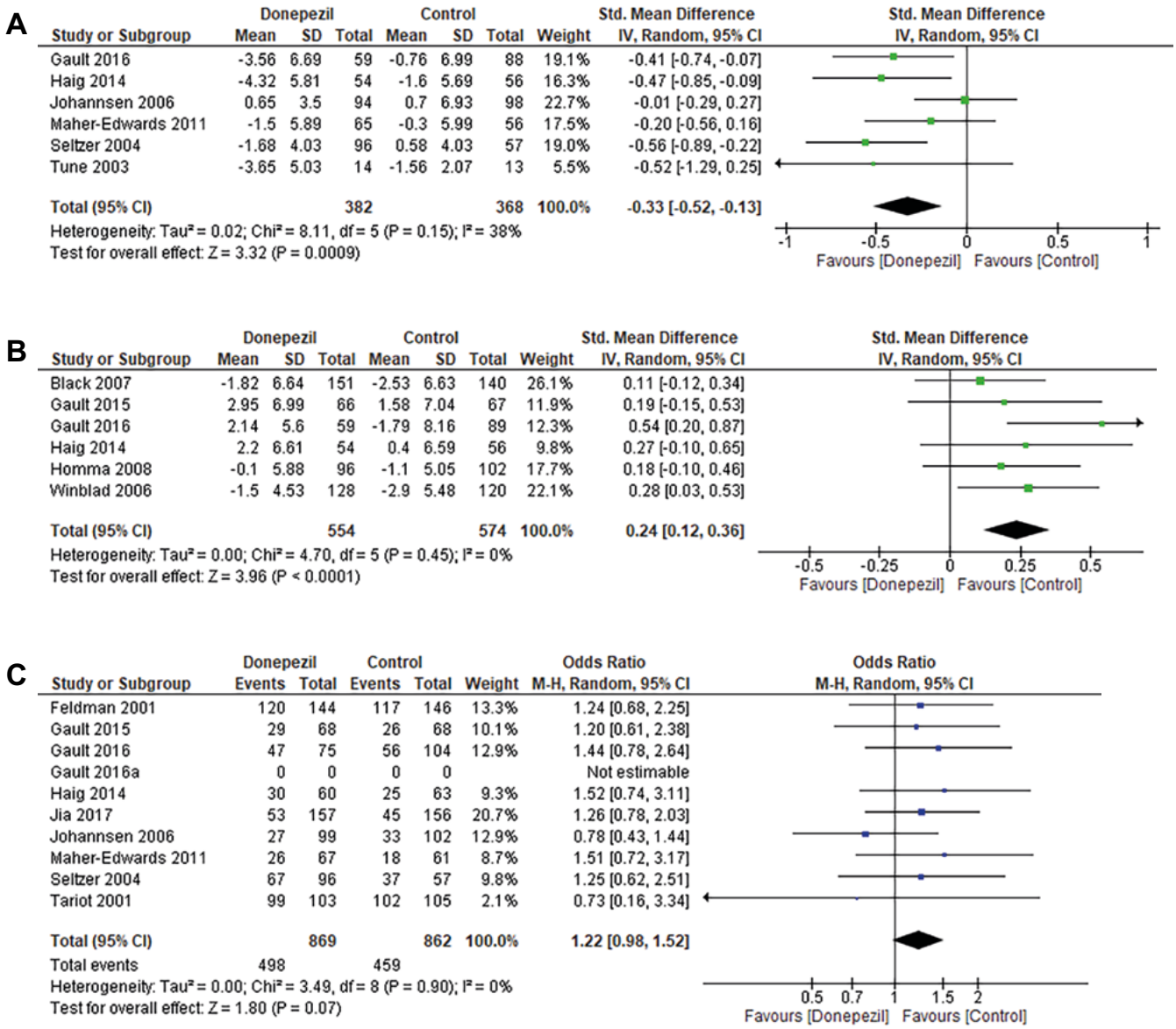

Fig. 2. Effect of donepezil. A. Forest plot + pooled effect on cognitive outcomes, standard mean difference (SMD) with 95% confidence interval (95% CI); B. Forest plot + pooled effect on functional outcomes, SMD with 95% CI; C. Forest plot + pooled effect on adverse events, odds ratio (OR) with 95% CI

Adverse events

The overall OR was found to be 2.34 [1.35, 4.08], indicating a significant association. The forest plot together with the pooled effect is shown in Fig. 3C. The heterogeneity between studies was 73%, as indicated by the I^2 statistic.

Rivastigmine

Cognitive function

The overall estimate, i.e., SMD, was found to be −0.65 [−1.06, −0.23], indicating a significant improvement in cognitive functions in the rivastigmine group compared to the control group. The forest plot together with the pooled effect is shown in Fig. 4. The heterogeneity between studies was very high, i.e., 92% (I^2 statistic).

We did not find sufficient studies for meta-analysis regarding functional outcomes and adverse events related to rivastigmine.

Overall, the results of our meta-analysis showed that all available acetylcholinesterase inhibitors, i.e., donepezil, galantamine and galantamine, significantly improved cognitive functions in patients with AD. However, the results for galantamine and rivastigmine should be considered with caution due to high heterogeneity of the included studies. Therefore, physicians could consider any of the available acetylcholinesterase inhibitors to improve cognitive function in patients with AD. Nonetheless, only the donepezil group showed a significant improvement in functional outcome. There is also insufficient data on rivastigmine in terms of functional outcomes and adverse events.

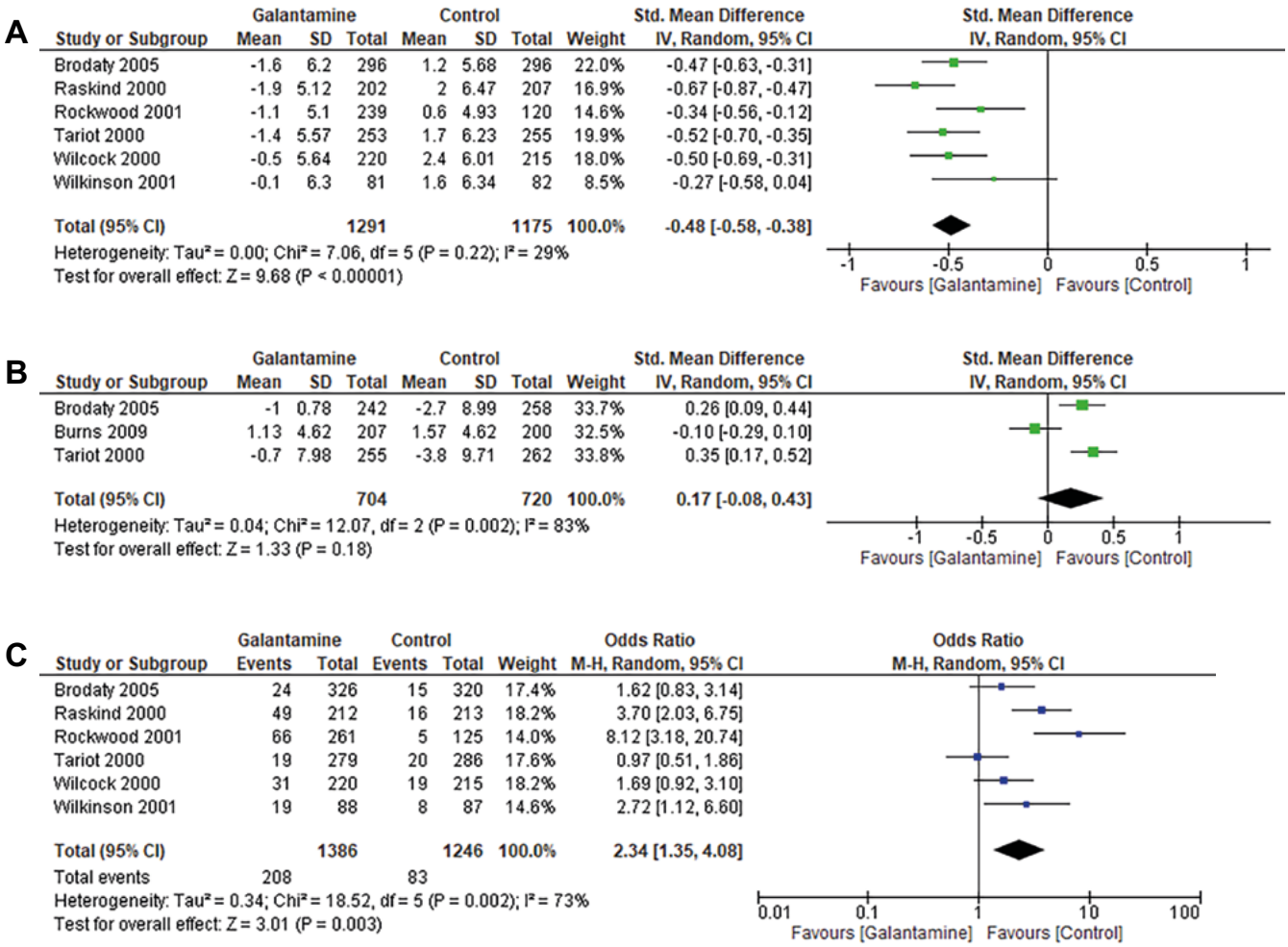

Fig. 3. Effect of galantamine. A. Forest plot + pooled effect on cognitive outcomes, standard mean difference (SMD) with 95% confidence interval (95% CI); B. Forest plot + pooled effect on functional outcomes, SMD with 95% CI; C. Forest plot + pooled effect on adverse events, odds ratio (OR) with 95% CI

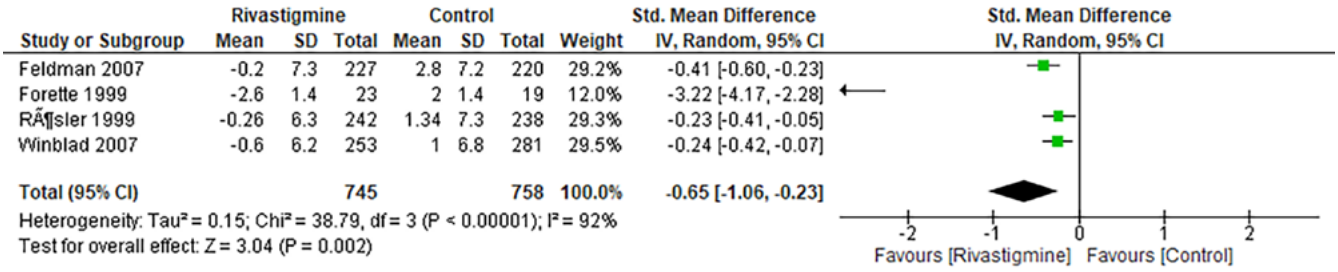

Fig. 4. Effect of rivastigmine on cognitive outcomes (forest plot + pooled effect), standard mean difference (SMD) with 95% confidence interval (95% CI)

Discussion

Despite significant advances in our understanding of the CNS structure and function, the discovery and clinical development of novel medications for many CNS disorders has proven difficult.[53–58] Alzheimer's disease is a CNS disorder that worsens over time.[59,60]

The diagnosis of AD relies mainly on behavioral assessment. Many studies are ongoing to identify specific peripheral biomarkers.[61] The etiology of AD is also unclear.[62] In AD, cells that produce and use acetylcholine are damaged. Acetylcholinesterase is one of the important enzymes that breakdowns acetylcholine into acetic acid and choline in the synaptic cleft. Acetylcholine is a major neurotransmitter that has many important roles, including cognition. It has been observed that the level of acetylcholine is decreased in patients with AD.[50–65] Therefore, drugs that can increase acetylcholine levels are useful in the management of patients with AD. Regulatory authorities across the globe have approved acetylcholinesterase inhibitors for the treatment of patients with AD. Tacrine, donepezil, galantamine, and rivastigmine are

well-known acetylcholinesterase inhibitors approved for the management of patients with AD. However, tacrine has been withdrawn from the market due to its adverse reactions, particularly hepatotoxicity. Recently, monoclonal antibodies have also been approved for the treatment of AD, but their exact role is unclear.[66,67] The efficacy and safety of acetylcholinesterase is also not known so far. Therefore, there is need of updated meta-analysis to find out exact profile of these inhibitors. Meta-analysis is a quantitative analysis that helps to draw a valid conclusion from clinical studies which helps the clinicians to make the right treatment decision.[68–70]

We conducted a meta-analysis of clinical studies to determine the exact role of acetylcholinesterase inhibitors in the treatment of AD. We have found significant differences between the donepezil and placebo groups, between the galantamine and placebo groups and between the rivastigmine and placebo groups. The results of the current meta-analysis have shown significant improvement in cognitive functions of patients with AD in the donepezil, galantamine and rivastigmine groups compared with the control groups. To the best of our knowledge, very few meta-analyses have been conducted so far to examine the efficacy and safety profile of available acetylcholinesterase inhibitors. Kobayashi et al. have conducted a Bayesian network meta-analysis to compare the efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate AD.[71] The results of the analysis also indicated the significant efficacy of acetylcholinesterase inhibitors on cognitive functions of patients with mild-to-moderate AD. The effects on functional outcome and adverse events are different across the acetylcholinesterase inhibitors. Donepezil has shown a significant effect on functional outcome in patients with AD, whereas galantamine has shown nonsignificant effects. Furthermore, donepezil was not significantly associated with adverse events, whereas galantamine was significantly associated with adverse events. The meta-analysis of RCTs of galantamine in schizophrenia was conducted by Koola et al. and reported significant cognitive improvement.[72]

The results of a meta-analysis conducted by Lanctôt et al. reported modest efficacy of acetylcholinesterase inhibitors and significantly higher rates of adverse events and treatment discontinuation. Cognitive outcomes were reported from randomized, double-blind, placebo-controlled, parallel-group trials of currently marketed cholinesterase inhibitors (ChEIs; donepezil, rivastigmine and galantamine) administered at therapeutic doses for at least 12 weeks. The proportions of participants who responded, experienced adverse events, discontinued treatment for any reason, or discontinued treatment due to adverse events were determined. Treatment with ChEIs produces a small but considerable therapeutic effect, as well as small but considerably increased rates of adverse events and treatment discontinuation.[73] Dou et al. conducted a network meta-analysis to compare the safety and efficacy of ChEIs and memantine in AD. The results of their analysis indicated a beneficial effect of acetylcholinesterase inhibitors on cognition, function and global changes, but not on neuropsychiatric symptoms. They observed that the severity of the disease and its clinical symptoms may have a major impact on the treatment selection.[74]

As only studies that show a substantial difference are usually published, some completed researches were not released and therefore could not be included in the meta-analysis, which could lead to publication bias. Meta-analyses of other treatments, such as like glucagon-like peptide-1 receptor agonists and negative allosteric modulators of 5-hydroxytryptamine 2A receptors, were also conducted by the researchers across the globe.[75,76]

Our meta-analysis showed that all 3 acetylcholinesterase inhibitors now in use, i.e., donepezil, galantamine and galantamine, significantly enhance patients' cognitive abilities. However, given to the substantial heterogeneity among the included trials, caution should be exercised in interpreting the results of galantamine and rivastigmine. To improve cognition of patients with AD, physicians can prescribe any of the currently approved acetylcholinesterase inhibitors. However, patients in the donepezil group showed considerable improvement in functional outcomes. Functional outcomes and adverse events are not adequately covered by the available data on rivastigmine. Therefore, in our opinion, based on current clinical evidence, among the available acetylcholinesterase inhibitors, donepezil should be considered by the physicians in the management of patients with AD unless contraindicated.

Limitations

We included only studies published in English. We also searched only 1 database, i.e., PubMed, for relevant studies. The heterogeneity among studies was quite high. There is a risk of publication bias in all the meta-analyses presented, but this could not be determined due to the small number of studies. The analysis was based on the strength of the drugs; dosage forms were not analyzed due to data unavailability. All available acetylcholinesterase inhibitors are effective in improving cognitive function, but further RCTs are required to find out the exact effects of available acetylcholinesterase inhibitors on functional outcomes or other AD parameters.

Conclusions

A meta-analysis of clinical data was conducted for the current study to determine the precise function of acetylcholinesterase inhibitors in the management of AD. We observed significant differences between the donepezil and placebo groups, the galantamine and placebo groups, and the rivastigmine and placebo groups. According to the current meta-analysis, donepezil, galantamine and rivastigmine significantly improved the cognitive abilities of patients with AD when compared to control groups. Based on current clinical evidence, donepezil has shown

significant improvement in cognitive and functional outcomes. We also found non-significant association of donepezil with adverse events. However, more RCTs are required to test the effects of galantamine and rivastigmine, particularly on functional outcomes and adverse events.

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