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REVIEW ARTICLE

A Systematic Review of the Effectiveness of Acetylcholinesterase Inhibitors on Cognition for Patients with Alzheimer's Disease

Lena Meziou[1]* | Kevin Haubrick[1]

Abstract

This systematic review evaluates the effectiveness of acetylcholinesterase inhibitors (AChEIs) including donepezil, galantamine, and rivastigmine in delaying cognitive decline in Alzheimer's disease (AD) patients. It addresses three primary objectives: overall efficacy assessment, comparison of cognitive benefits across AChEI types, and identification of research gaps. The review, comprising 45 selected articles, reveals consistent evidence of AChEI efficacy in improving cognitive outcomes in AD. While higher AChEI doses show potential for greater cognitive improvement, they also elevate the risk of adverse effects. Donepezil is noted for memory enhancement and slowing cognitive decline, galantamine for memory and attention, and rivastigmine for executive function improvement.

Key words: acetylcholinesterase inhibitors, Alzheimer's disease, cognition, donepezil, galantamine, rivastigmine 2

1 | INTRODUCTION

Dementia is a clinical syndrome of progressively worsening cognitive impairment and functional deterioration (Duong et al., 2017). There are roughly 47 million people with dementia around the world, of whom 5.5 million live in the United States. By 2030, this figure is predicted to reach 75 million people around the world, and it is projected to triple by 2050 (Ulep et al., 2018). The health and long-term care systems have been estimated to have spent $259 billion on dementia care in 2017 (Olivari et al., 2018).

Alzheimer's disease (AD), the sixth most prevalent cause of mortality in the US, is the most common type of dementia (Skaria, 2022). Several factors increase the risk of developing AD such as cerebrovascular disorders, diabetes, hypertension, obesity, dyslipidemia, cognitive reserve, physical activity, and dietary habits (Silva et al., 2019). Extracellular amyloid plaques, intracellular neurofibrillary tangles, deteriorated synapses, and neuronal death are the main neuropathologic indicators of AD (Ulep et al., 2018). An accumulation of amyloid plaques disrupts synaptic activity and sets off a chain of subsequent events that lead to intraneuronal and intraneuronal dysfunction and eventually result in cell death (Ulep et al., 2018).

For the screening, diagnosis, and management of Alzheimer's disease patients, healthcare providers must be able to quickly and accurately identify the symptoms and pathology of the disease that are associated with Alzheimer's disease (Porsteinsson et al., 2021). Additionally, this allows patients as well as caregivers to make necessary lifestyle modifications that may prolong the enhancement of the patient's quality of life. Thus, more effective research is required on AD-modifying methods of treatment, such as acetylcholinesterase inhibitors, along

[1]The University of Houston.

Address correspondence to: Lena, Meziou, The University of Houston, *Email: @lena.meziou*

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with risk-reduction strategies to improve or stabilize AD symptoms. This review aims to examine the effectiveness of acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) in delaying the worsening of cognitive functions associated with the disease.

Objectives

1. To determine the overall efficacy of acetylcholinesterase inhibitors in improving cognitive functions among individuals with Alzheimer's disease

2. To compare the cognitive benefits of different types of acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) in Alzheimer's disease patients.

3. To identify gaps in current literature related to the cognitive effects of acetylcholinesterase inhibitors in Alzheimer's disease, suggesting areas of future research and study improvement.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are used in this systematic review to assess qualitative information on the effectiveness of acetylcholinesterase inhibitors on Alzheimer's disease patients (Page et al., 2021).

2.1 | Protocol and Registration

This systematic review was registered with PROSPERO, the International Prospective Register of Systematic Reviews (registration #443631).

2.2 | Search Strategy

A thorough scientific literature search was conducted using online databases to find peer-reviewed research articles published between 2003 to 2024 for this systematic review. Two online databases were used, PubMed and EMBASE. Table 1 lists a combination of keywords and MeSH terms that were employed. The search strategy was designed to find studies relevant to Alzheimer's disease and acetylcholinesterase inhibitors. The search terms were strategically combined and expanded using Boolean operators (AND, OR) as shown in Table 2. Some reference lists of relevant articles were searched as well to find any additional research articles that might have been overlooked.

Table 1. Keywords and MeSH terms

OLDER ADULTS, SENIORS, ELDERLY, AGED, GERIATRIC	ALZHEIMER'S, ALZHEIMERS, ALZHEIMER, DEMENTIA, COGNITIVE IMPAIRMENT, COGNITIVE DECLINE, NEURODEGENERATIVE DISORDER	ACETYLCHOLINESTERASE INHIBITORS, CHOLINESTERASE INHIBITORS, DONEPEZIL, GALANTAMINE, RIVASTIGMINE	COGNITIVE FUNCTIONS, COGNITIVE ABILITIES, MEMORY, DECISION MAKING, ATTENTION

Table 2. Boolean Operators(AND, OR)

Search equation using Boolean operators
(``older adults'' OR ``seniors'' OR ``elderly'' OR ``aged'' OR ``geriatric'') AND (``Alzheimer's'' OR ``Alzheimers'' OR ``Alzheimer'' OR ``dementia'' OR ``cognitive impairment'' OR ``cognitive decline'' OR ``neurodegenerative disorder'') AND (``acetylcholinesterase inhibitors'' OR ``cholinesterase inhibitors'' OR ``donepezil'' OR ``galantamine'' OR ``rivastigmine'') AND (``cognitive functions'' OR ``cognitive abilities'' OR ``memory'' OR ``decision making'' OR ``attention'')

2.3 | Eligibility Criteria

Research articles were included based on specific eligibility criteria which are outlined in Table 3. Only primary research studies were considered for inclusion in this systematic review. Clinical trials and randomized controlled trials (RCTs) were eligible for inclusion while case studies, systematic

reviews, and meta-analysis were excluded. Participants involved female and male older adults aged 55+ years diagnosed with Alzheimer's disease. Patients aged less than 55 years old without a diagnosis of cognitive impairment or Alzheimer's disease are excluded. Studies that evaluated the effects of acetylcholinesterase inhibitors were eligible while studies that evaluated other medications/inhibitors were excluded. Studies that reported outcomes related to cognitive functions were included since cognitive impairment causes several cognitive changes that negatively affect the patient's quality of life. Studies that failed to report any type of cognitive function were excluded. Only studies published in the English language between 2003 to 2024 were considered for inclusion.

Table 3. Inclusion/ExclusionCriteria

Criteria	Inclusion	Exclusion
Study Design Preference	Clinical trials and RCT	Case studies and systematic reviews
Participants' Age	Older adults (55+ years)	Less than 55 years
Participants' Condition	Patients with Alzheimer's disease	Other than Alzheimer's (such as Parkinson's disease)
Size of Study Groups	>= 10 in each study group	< 10 in each study group
Exposure	Acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine)	Medications/inhibitors other than Acetylcholinesterase inhibitors
Outcomes	Cognitive functions (such as attention, memory, and decision making)	Non-cognitive functions
Language	Limited to articles in English	
Publication Year Range	2003-2024	

2.4 | Data Extraction and Quality Assessment

The articles' titles and abstracts were evaluated by the primary author for their applicability to the research question. Full-text articles of potentially pertinent research were then assessed for their eligibility. A study was included based on the predetermined criteria. Studies were excluded if they failed to meet the inclusion criteria or if they were duplicate articles. To represent the study selection process, including the number of records identified, screened, and included, a PRISMA flowchart, shown in Figure 1, was created (Moher et al., 2009).

A data extraction table was adapted from the Cochrane template (Ryan et al., 2016). Information extracted included the author, date of publication, study design, the purpose of the study, participants' characteristics, study methods, description, intervention description, outcome measures, conclusions, and bias rating. Additional research articles from the same study were used to find any missing data.

The Academy of Nutrition and Dietetics Quality Criteria Checklist was used to assess the quality and risk of bias in primary research (Academy of Nutrition and Dietetics, 2016). Each article was evaluated for objectivity and scientific suitability based on several factors, including research question, participant selection, blinding, outcomes, results, and more. After evaluation, each article was then marked as positive, negative, or neutral. A positive mark shows that concerns of inclusion/exclusion, bias, generalizability, data collection, and analysis have been effectively addressed in the study. A negative mark shows that the issues mentioned have not been fully addressed. A neutral mark shows that the report is neither particularly strong nor particularly weak.

3 | RESULTS

3.1 | Study Selection

Two database searches led to a total of 172 articles. The inclusion criteria were applied to the titles and abstracts and duplicates were removed; 154 articles were selected for full-text screening. Articles were

removed if they did not meet the inclusion criteria (for example, the outcome was not part of cognitive functions, diseases other than Alzheimer's were studied and were irrelevant to the main subject). Forty-five clinical trials and randomized controlled trials met the eligibility criteria, examined the effectiveness of acetylcholinesterase (AChE) inhibitors in delaying the worsening of cognitive functions associated with AD, and were included in this systematic review. A table summary of outcomes including the risk of bias evaluation is included (Tables 5, 6, 7, and 8).

3.2 | Study Characteristics

The selected studies were conducted between 2003 and 2024. Sample sizes ranged from 59 to 784 participants with Alzheimer's disease (AD). The mean age of participants across the studies ranged from 45 to 90 years and the majority were diagnosed with mild to moderate Alzheimer's disease. The duration of treatment varied between six weeks to 12 months, with an average follow-up period of 12 months.

3.3 | Assessment Tools for Cognitive Outcomes

Across the 45 included studies, various assessment tools for cognitive outcomes were used, with the most used tools being the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). The MMSE was the most frequently used tool, used in 67% of the studies, followed by the ADAS-Cog, used in 44% of the studies, followed by the Severe Impairment Battery (SIB), used in 16% of the studies. Other assessment tools such as Clinical Dementia Rating (CDR), Computerized Neuropsychological Test Battery (CNTB), Digit Symbol Substitution Test (DSST), Consortium to Establish a Registry for Alzheimer's Disease Battery (CERAD), and Neuropsychological Test Battery were used in fewer studies. Table 4 provides an overview of the studies using each assessment tool.

3.4 | Donepezil Cognitive Outcomes

Among the included studies, 13 studies examined the effectiveness of donepezil in delaying the worsening of cognitive functions associated with the disease as shown in Table 5. Black et al. (2007), Feldman et al. (2003), and Molinuevo et al. (2009) found patients with severe AD who took donepezil maintained cognitive performance for at least six months while Wallin et al. (2006), showed three years of donepezil medication resulted in significant favorable cognitive and behavioral results ($p<0.001$). Boada-Rovira et al. (2004) noted donepezil treatment resulted in statistically significant improvements ($p<0.0001$) in cognition, patient activity, and social behavior, and was generally well tolerated compared with baseline over 12 weeks. Boada-Rovira and his team (2004) also highlighted donepezil was associated with substantial enhancements in patient social contact and engagement ($p<0.0001$). Similarly, Feldman et al. (2005) reported significant improvement in patient participation in activities of daily living ($p<0.001$) and cognition ($p<0.0002$).

Johannsen et al. (2006), Winblad et al. (2006), and Howard et al. (2012) concluded a definite therapeutic advantage was shown during patients' initial donepezil medication and when the medication period was completed. Johannsen et al. (2006) found at week 12, the donepezil treatment group experienced significantly greater improvement ($p=0.02$) in cognition scores as compared with the placebo group.

Howard et al. (2012) noted significant improvement ($p<0.001$) in cognition and behavior was seen for individuals who kept their donepezil treatment as compared with those assigned to discontinue it.

Sabbagh et al. (2003) and Han et al. (2016) compared donepezil 23 mg/day with 10mg/day and found donepezil 23 mg/d produced statistically significant cognitive gains ($p=0.011$ and $p=0.028$, respectively) as compared to 10 mg/d of donepezil. The cognitive benefits of a higher concentration of donepezil were particularly apparent in patients with more advanced disease stages. Homma et al. (2008) also noted donepezil (5mg/day and 10mg/day) showed statistically significant superiority ($p<0.001$) in cognition compared to placebo at 8, 16, and 24 weeks. On the

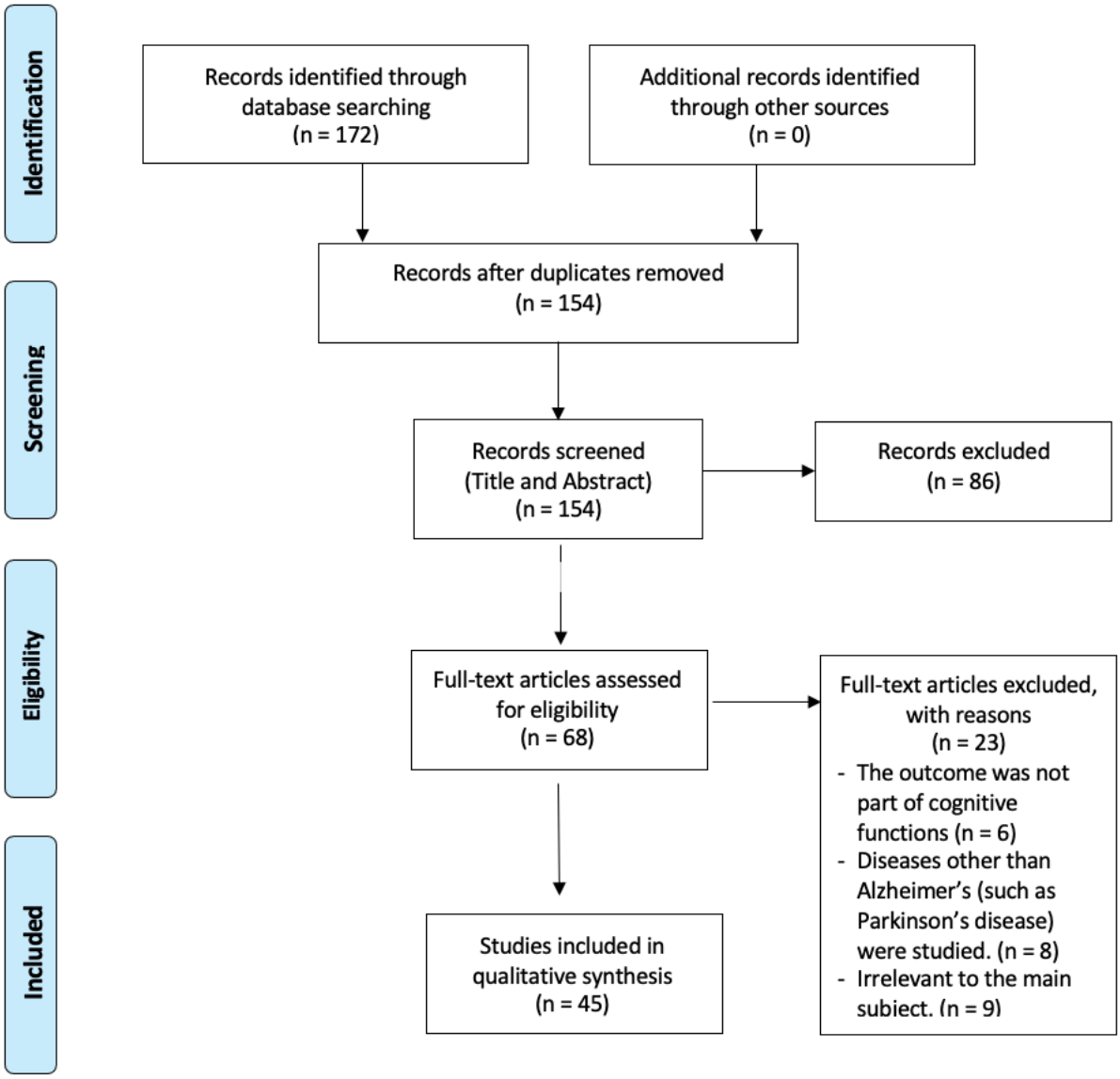

Fig. 1: PRISMA 2020 Flow Diagram

other hand, Doody et al. (2008) suggested there were no significant differences between a higher dose or a standard dose of donepezil on cognitive skills or reasoning. Doody et al. (2009) also found cognitive scores from baseline to week 12 improved ($p<=0.05$) but to week 24, scores worsened ($p=0.05$). Although Sabbagh et al. (2003) and Han et al. (2016) indicate a significant cognitive advantage of a higher dose of donepezil, findings from Doody et al. (2008) suggest no substantial difference between higher and standard doses in cognitive outcomes. Overall, donepezil treatment demonstrated significant cognitive benefits, particularly in maintaining and improving cognitive performance, patient engagement, and activity of daily lives in patients with AD.

Table 4. Studies Using Assessment Tools

Assessment Tool	Studies Using the Tool
Mini-Mental State Examination	Sabbagh et al. (2012), Karaman et al. (2004), Wilcock et al. (2003), Johansen et al. (2006), Black et al. (2007), Feldman et al. (2007), Boada-Rovira et al. (2004), Feldman et al. (2005), Brodaty et al. (2006), Baakman et al. (2021), Almkvist et al. (2004), Bullock et al. (2005), Olazaran et al. (2005), Feldman & Lane (2007), Jones et al. (2004), Doody et al. (2008), Howard et al. (2012), Grossberg et al. (2004), Gorus et al. (2007), Molinuevo et al. (2009), Wattmo et al. (2012), Lopez-Pousa et al. (2005), Wallin et al. (2006), Calabria et al. (2008), Aguglia et al. (2004), Cerci et al. (2007), Connelly et al. (2004), Xu et al. (2021), Sun et al. (2007)
Alzheimer's Disease Assessment Scale-Cognitive Subscale	Karaman et al. (2004), Wilcock et al. (2003), Johansen et al. (2006), Feldman et al. (2007), Gaudig et al. (2011), Brodaty et al. (2006), Doody et al. (2009), Olazaran et al. (2005), Feldman & Lane (2007), Richarz et al. (2014), Jones et al. (2004), Doody et al. (2008), Lyketsos et al. (2004), Grossberg et al. (2004), Wallin et al. (2006), Pirttila et al. (2003), Aguglia et al. (2004), Song et al. (2004), Mintzer & Kershaw (2002)
Severe Impairment Battery	Black et al. (2007), Feldman et al. (2005), Winblad et al. (2006), Bullock et al. (2005), Homma et al. (2008), Burns et al. (2009), Ha et al. (2016)
Clinical Dementia Rating	Feldman et al. (2007), Doody et al. (2009), Sun et al. (2007)
Computerized Neuropsychological Test Battery	Caramelli et al. (2004)
Digit Symbol Substitution Test	Connelly et al. (2004)
Consortium to Establish a Registry for Alzheimer's Disease Battery	Crowell et al. (2005)
Neuropsychological Test Battery	Rozzini et al. (2006)

3.5 | Galantamine Cognitive Outcomes

Among the included studies, 11 studies examined the effectiveness of galantamine in delaying the worsening of cognitive functions associated with AD as shown in Table 6. Burns et al. (2009) found galantamine significantly improved cognitive functioning, especially in the domains of memory, visuospatial ability, and attention (p=0.006, p=0.002, p=0.076; respectively). Gaudig et al. (2011), Brodaty et al. (2006), Richarz et al. (2014), and Lyketsos et al. (2004) showed galantamine medication improved patients' cognition with mild to advanced moderate AD. Brodaty et al. (2006) noted 65% of patients' cognitive scores either improved "slightly, much, or very much." Although Gaudig et al. (2011) and Lykestsos et al. (2004) discovered withdrawal of galantamine is associated with a decline in cognitive scores (p=0.001, p=0.0002, respectively), Richarz et al. (2014) found cognition remained improved after three years compared with an untreated population (p<0.05). Like the findings of Richarz and his team (2014), Pirtilla et al. (2003) highlighted the administration of 12 mg/day of galantamine twice a day improved cognitive function for up to three years (p<0.05, p<0.001, respectively).

Although Mintzer & Kershaw (2003) showed patients treated with 16mg/day achieved statistically improved cognitive scores (p=0.003), Baakman et al. (2021) demonstrated patients treated with 16 mg/-day of galantamine led to slow theta and delta waves which are associated with lower cognitive functioning in AD patients (p=0.0001), while Caramelli et al. (2004) discovered no significant differences (p=0.673) in cognition scores between weeks 12 and baseline for those treated with 16mg/day of galantamine. Gorus et al. (2007) noted similar results with individuals suffering from mild to moderate AD receiving galantamine treatment had improved memory and language (p=0.695, p=0.012, respectively) for at least five months. Song et al. (2014) also added galantamine treatment led to improvements in attention (p=0.036) and language cognition areas (p<0.001). Galantamine treatment shows beneficial effects on cognitive functioning, particularly memory, visuospatial ability, and attention, across various stages of AD.

Table 5. Studies Examining the Effectiveness of Donepezil on Cognition Part A

Black et al., 2007	Study Design: 24-week, randomized, double-blind controlled trial. Patients were randomized to donepezil 10mg/day or placebo for 24 weeks. Sample Design: 343 ambulatory or ambulatory-aided individuals, aged 50 or older, with likely AD.	To evaluate the efficacy and safety of donepezil for severe Alzheimer disease.	Patients with severe AD who took donepezil maintained cognitive performance for at least 6 months in contrast to those who took a placebo, who had a 10% decline from baseline (p=0.0001).	R/+; V/+
Boada-Rovira et al., 2004	Study Design: 12-week, open-label trial. Patients received 5mg/day donepezil for the first 28 days, this dose then increased to 10mg/day. Sample Design: 1113 patients with AD, have good eyesight and hearing independently mobile or with assistance.	To evaluate the efficacy, tolerability, and safety of donepezil in a wider and more diverse sample of patients and centers.	Donepezil treatment resulted in statistically significant improvements in cognition, patient activity, and social behavior (p<0.0001) and enhancements in patient social contact, engagement, and participation in ADL (p<0.0001).	R/+; V/+
Doody et al., 2008	Study Design: 24-week, randomized, double-blind controlled study. Patients received either donepezil 10mg/day + 5mg/day for weeks 1-12 or 15mg/day for weeks 1-12; 20mg/day for weeks 12-24. Sample Design: 31 ambulatory or ambulatory-aided patients, 50-86 years old, mild to moderate AD, had been taking donepezil 10 mg/day for 12–30 months.	To evaluate the safety and tolerability of donepezil at doses of 15 and 20 mg/day.	Donepezil is effective in cognition and other impacted domains at higher doses. Higher doses of donepezil were linked to a more significant cognitive effect.	R/+; V/Æ
Doody et al., 2009	Study Design: 51-week randomized controlled study. Patients received either 5 mg/day donepezil for 6 weeks, then 10 mg/day for 42 weeks or a placebo for 48 weeks. Sample Design: 821 patients, 45-90 year-old ambulatory or ambulatory-aided with MCI and no infarctions, infections, or concomitant diseases.	To examine the impact of a 48-week donepezil course in amnestic mild cognitive impairment, Alzheimer's disease.	While there was no change in the major measure of global function, donepezil showed a slight but substantial improvement on the primary measure of cognition (p<=0.5) to week 12 but not to week 24 (p=0.05)	R/+; V/+
Feldman et al., 2003	Study Design: 24-week randomized, double- blind controlled study. Patients received donepezil (5mg/day for 4 weeks and 10mg/day) or placebo for 24 weeks. Sample Design: 290 patients with probable AD, could walk independently or with assistance.	To investigate the efficacy of donepezil treatment on activities of daily living (ADLs) and social functioning in patients with moderate to severe Alzheimer's disease (AD) and the possible benefits of this treatment on caregiving time and stress levels.	Donepezil maintains functional ability and cognition for at least six months in patients with AD. In these patients, donepezil showed a considerably slower decline in instrumental and fundamental ADLs than placebo.	R/+; V/Æ
Feldman et al., 2005	Study Design: Randomized controlled trial. Patients received 5mg/day donepezil followed by an increase to 10mg/day or placebo for 28 days. Sample Design: 290 ambulatory or ambulatory-aided patients with probable AD.	To examine the efficacy and safety of donepezil in patients with more severe Alzheimer's disease	Donepezil had statistically significant improvements on cognitive, functional, and behavioral measures (p=0.0002) as well as patient participation in activities of daily living (p<0.001).	R/+; V/+

Table 6. Part B

Han et al., 2016	Study Design: 12-month open-label trial. Patients were randomly assigned to donepezil 23 mg or donepezil 10 mg/day for 24 weeks. Sample Design: 223 Asian patients with probable AD and taking donepezil 10 mg/day for 3 months before the study.	To evaluate the safety and effectiveness of donepezil 23 mg/day compared to donepezil 10 mg/day in Asian patients with moderate-to-severe Alzheimer's disease, as well as to examine changes in cognitive and global functioning.	Cognitive improvement was statistically higher with donepezil 23 mg compared to donepezil 10 mg (p=0.028). In terms of global function, there was no distinction between the groupings.	R/+; V/Æ
Homma et al., 2008	Study Design: 24-week, randomized controlled, double-blind trial. Patients were randomly assigned to receive donepezil 5 mg, 10 mg, or a placebo. Sample Design: 302 ambulatory or ambulatory-aided AD patients, >= 50 years old, have a caregiver 3 days/week or more, and swallow pills.	To evaluate the efficacy and tolerability of donepezil in severe Alzheimer's disease (AD).	This study established a significant superiority in cognition (p<0.001) and validated the efficacy of donepezil 5mg/day or 10 mg/day in patients with AD at weeks 8, 16, and 24.	R/+; V/Æ
Howard et al., 2012	Study Design: 52- weeks, double-blind clinical trial. Participants were randomly assigned to 10mg donepezil daily or 5 mg weeks 1-4 or stopping donepezil and starting memantine or continuing donepezil and start memantine. Sample Design: 295 patients with probable AD, have caretakers, prescribed donepezil for >3 months, no severe or unstable medical problems, and not taking memantine.	To assess the continuation of treatment benefits after the progression of Alzheimer's disease to moderate-to-severe.	Patients designated to keep receiving donepezil, as compared with those that stopped receiving donepezil, had a better cognition. Over the course of a year, continuing therapy with donepezil was linked with cognitive advantages (p<0.001) among individuals with moderate or severe Alzheimer's disease.	R/+; V/+
Johannsen et al., 2006	Study Design: 12-24-week open-label donepezil-treatment; 12-week randomized, double-blind phase; and 12-week single-blind phase. Sample Design: Patients with probable AD, >= 50 years old, ambulatory, good eyesight and hearing, and living at home or in an assisted home care facility.	To determine the value of continued donepezil treatment in patients with Alzheimer's disease for whom the therapeutic benefit was first thought to be questionable.	Most patients showed a definite therapeutic advantage during their initial donepezil medication. Improvement in cognition (p=0.02) and behavior was seen for individuals who kept their donepezil treatment compared to the group that switched to placebo at week 12.	R/+; V/+
Molinuevo et al., 2011	Study Design: 6-month prospective, observational, multicenter study. Patients received 1.8 mg/day of donepezil. Sample Design: 408 patients, with probable AD, aged >=55, no prior ChEI treatment, no neurological conditions, and no past alcohol or drug use/abuse.	To compare the cognitive and functional effects of donepezil therapy in individuals with mild vs moderate Alzheimer's disease (AD).	At 6 months, cognition stays steady in patients receiving donepezil monotherapy. The mild AD group benefits more from donepezil than the moderate AD group, with gains in memory and language domains and a more gradual decrease in ADL (p<0.0001).	R/+; V/+

Table 7. Part C

Sab-bagh et al., 2013	Study Design: 24-week, randomized, double-blind, trial. Patients were randomized to donepezil 23mg/day or to continue 10mg/day. Sample Design: 1467 patients with probable AD, taking donepezil 10 mg/d for >= three months, and not taking daily doses of <=20 mg of memantine for >= 3 months before screening.	To investigate relationships between easily observable baseline characteristics/demographics and cognitive improvement in patients treated with either donepezil 23 mg/d or 10 mg/d and to identify factors that might have an impact on response.	Regardless of the patient's age, gender, weight, the length of time they had previously taken donepezil or their functional impairment, donepezil 23 mg/d over 10 mg/d produced cognitive gains (p=-0.011 and p>0.05).	R/+; V/Æ
Wallin et al., 2006	Study Design: Prospective clinical trial. Patients began with 5 mg/day donepezil and increased to 10 mg/day after 4-8 weeks. Sample Design: 430 patients with AD, >= 40, residing at home, have a caregiver, and not having another AChEI.	To investigate the outcome of continuous donepezil long-term treatment on patients with Alzheimer' disease in the typical clinical settings.	Three years of donepezil medication resulted in a favorable behavioral and cognitive results (p<0.001).	R/+; V/+
Win-blad et al., 2006	Study Design: 6-month double-blind, controlled study. Patients were assigned oral donepezil (5mg/day for 30 days then up to 10mg/day) or matched placebo. Sample Design: 248 patients with possible AD, >= 50 years old, and able to walk unassisted or with assistance.	To ascertain the effectiveness of donepezil in patients with severe Alzheimer's disease, by focusing primarily on cognition and activities of daily living.	Overall, the study shows that donepezil is a successful and well-tolerated treatment. Donepezil maintains function and improves cognition in nursing home residents with severe Alzheimer's disease (p=0.008).	R/+; V/Æ

AChEI = Acetylcholinesterase inhibitors
AD = Alzheimer's diseaseADL = Activities of daily living
ChEI = Cholinesterase inhibitors
MCI = Mild cognitive impairment
MMSE = Mini-Mental Stare Examination
R = RelevanceV = Validity

3.6 | Rivastigmine Cognitive Outcomes

Among the included studies, only six studies examined the effectiveness of rivastigmine in delaying the worsening of cognitive functions associated with the disease as shown in Table 7. Karaman et al. (2004) showed patients who received rivastigmine 6–12 mg/day demonstrated significantly improved ($p<0.001$) cognitive performance. Karaman and his team (2004), Feldman & Lane (2007), and Grossberg et al. (2004) discovered long-term rivastigmine therapy looked to be well tolerated and significantly reduced cognitive and functional symptoms of AD patients compared to no treatment ($p<0.001$, $p<0.05$, respectively). Almkvist et al. (2004) and Cecri et al. (2007) noted rivastigmine therapy stabilized cognition with little improvement in cognitive skills ($p<0.05$, $p>0.01$, respectively). Almkvist et al. (2004) also highlighted patients undergoing rivastigmine treatment for Alzheimer's disease showed more improvement ($p<0.05$) over time with a larger dose of 10.5-12 mg/day than with a lower dose of 3-6 mg/day. Feldman et al. (2007) found that over 4 years, rivastigmine had little to no significant impact ($p=0.726$) on cognitive function or on the rate at which AD progressed. Overall, rivastigmine treatment can significantly enhance cognitive performance and alleviate AD symptoms demonstrating tolerability and continuous benefits in managing cognitive decline.

Table 8. Studies Examining the Effectiveness of Galantamine on Cognition Part A

Baakman et al., 2022	Study Design: 6-month double-blind, randomized cross-over study. The challenge phase, 1 dose of 16mg galantamine. In the treatment phase, open-label galantamine. Sample Design: 50 participants with AD, never used of ChEIs, and no history of psychiatric illnesses.	To examine the potential for determining long-term treatment response as well as the immediate pharmacodynamic (PD) effects of a single dose of galantamine on the activity of the central nervous system (CNS) in patients with mild to severe Alzheimer's disease.	Patients with AD show a decrease in theta and delta waves following a single administration of galantamine 16 mg leading to lower cognitive functions (p=0.0001).	R/+; V/+
Brodaty et al., 2006	Study Design: 6-month prospective study. Participants were given galantamine. Sample Design: 345 patients with mild to moderate AD related dementia, currently reside at home, have a caregiver, and speak enough English.	To collect detailed information about galantamine's use in treating Alzheimer's disease under realistic circumstances.	Most galantamine-treated participants who finished the trial kept their cognition, behavior, or function stable. At six months, most of the individuals had an improvement in cognition compared to baseline.	R/+; V/Æ
Burns et al., 2009	Study Design: 6-month, double-blind, randomized trial. Patients randomly received 24mg/day galantamine or placebo. Sample Design: 407 ambulatory patients with probable AD, aged 40-95, have a history of cognitive decline for >= 6 months, good vision and hearing.	To assess the efficacy of galantamine in patients with severe AD.	Galantamine significantly improved cognitive functioning, especially in the domains of practice, memory, and visuospatial ability (p=0.006, p=0.002, p=0.076, respectively).	R/+; V/+

Table 9. Part B

Caramelli et al., 2004	Study Design: 12-week prospective, open-label, study. Galantamine started at 4mg for 4 weeks, 8 mg/day for 4 weeks, then 12 mg/day for 4 weeks. Sample Design: 33 patients with probable AD, age 56-87 years, high education level, reside with or get visits from a caregiver, no blood circulatory problems, no AChEI >= 60 days prior to inclusion.	To assess the impact of galantamine on the cognitive abilities of individuals with mild to severe Alzheimer's disease (AD) on a computerized neuropsychological test battery (CNTB).	After 12 weeks of treatment with galantamine at a dose of 16 to 24 mg/day, individuals suffering from mild to moderate Alzheimer's disease did not improve significantly (p=0.003) in cognition scores.	R/+; V/Æ
Gaudig et al., 2011	Study Design: 6-week, double-blind study. Patients received placebo, galantamine 8mg/day, or 16mg/day, or 24mg/day. Sample Design: Outpatients with probable AD, have been in good health, and have a caregiver.	To evaluate the effects of galantamine withdrawal and compare this with uninterrupted therapy. To compare the effects of discontinuation of galantamine therapy after 3- 5 months with those of continuing it for an additional 6 weeks.	Galantamine treatment have shown cognitive gains from galantamine treatment for up to 5 months (p=0.001). Patients with advanced moderate AD may benefit from continuing their galantamine.	R/+; V/Æ
Gorus et al., 2007	Study Design: 22-weeks open-label prospective trial. Galantamine was administered at 2x4 mg/day, then 2x12 mg/day max. Sample Design: 41 mild-severe AD outpatients, with probable AD.	To investigate the impact of galantamine on reaction time, selective attention, alternating attention, errors, and interindividual and intraindividual variability in seniors with moderate to severe Alzheimer's disease.	There was an improvement in memory and language (p=0.695, p=0.012, respectively) after 22 weeks. There was also a decrease in the number of mistakes.	R/+; V/+

Table 10. Part C

Lyketsos et al., 2004	Study Design: 12 month, open-label extension of a previous 5-month, double-blind, trial. Patients increased to a 24-mg galantamine over two weeks for an additional 12 months. Sample Design: 699 patients with probable AD, score of >= 18 on AD Cognition Assessment Scale, and have a caregiver.	To assess the long-term safety, effectiveness, and tolerance of galantamine 24 mg/day in the treatment of Alzheimer's disease.	Patients using galantamine consistently demonstrated persistent cognitive improvements on cognition part (p<0.001).	R/+; V/+
Mintzer & Kershaw, 2003	Study Design: 5-month double-blind study. Participants received placebo, galantamine 8 mg/day, 16 mg/day, or 24 mg/day. Sample Design: 975 patients with probable AD, and discontinued AChEI for >= 60 days prior to study admission.	To assess the effects of galantamine in patients with AD who had previously been exposed to AChEIs to those patients with AD who had not previously been exposed.	Patients treated with galantamine 16 mg/day and 24 mg/day experienced statistically significant improvements in cognitive performance when compared to placebo (p=0.003, p<0.001, respectively).	R/+; V/+
Pirttila et al., 2004	Study Design: 36-month open-label extension study. Patients took 12mg galantamine twice/day for up to 24 months. Sample Design: 491 patients with probable AD had galantamine <= 12 months, had a history cognitive deterioration, and have a caregiver.	To assess long-term effectiveness and safety of galantamine in individuals with mild-to-moderate Alzheimer's disease	In individuals with mild-to-moderate Alzheimer's disease, 12 mg of galantamine twice day for 36 months is efficacious, safe, and well tolerated. Cognitive scores improved significantly (p<0.001).	R/+; V/Æ

Table 11. art C

Richarz et al., 2014	Study Design: A 36-month prospective, clinical trial. Patients began with galantamine 8mg/day then 4mg/day increments for 2 weeks until 16mg/day. Sample Design: 75 patients had a possible or probable AD, >= 45 years old, and not taking anticholinergic medications.	To assess long-term effectiveness of galantamine in community-dwelling persons with mild Alzheimer's disease.	During the three years of observation, galantamine was typically well tolerated and safe. During the 12-month treatment, improvements were made in cognition, behavior, and daily living skills (p<0.05).	R/+; V/+
Song et al., 2014	Study Design: 52-week open-labeled, clinical study. During the 1st 4 weeks, patients were given 8 mg of galantamine/day, then a max of 24 mg/day at 4-week intervals. Sample Design: 66 patients who had probable AD, a history of progressive cognitive decline, and a caregiver.	To examine at the impact of galantamine on cognitive subdomains in Alzheimer's disease (AD).	Galantamine is particularly useful in boosting memory and language cognition areas (p<0.001) and attention (p=0.036)	R/+; V/+

AChEI = Acetylcholinesterase inhibitors
AD = Alzheimer's diseaseADL = Activities of daily living
ChEI = Cholinesterase inhibitors
MCI = Mild cognitive impairment
MMSE = Mini-Mental Stare Examination
R = RelevanceV = Validity

Table 12. Studies Examining the Effectiveness of Rivastigmine on Cognition Part A

Almkvist et al., 2004	Study Design: 12-month study. Every 2 weeks, the dosage was increased by 1.5 mg, low dose was 3-6mg/day and high dose was 10.5-12 mg/day. Sample Design: 54 participants with probable AD. 1st control had AD patients from the past. 2nd control group had MCI diagnosis.	To explore the effects of a 12-month rivastigmine medication on overall cognitive performance, visuospatial ability, attention, and memory in mild AD patients. The results were compared with groups of matched untreated AD patients as well as individuals with MCI.	When rivastigmine-treated AD patients were compared with untreated AD and MCI patients over time, a general pattern of stabilized cognitive performance was observed. Higher dose of rivastigmine showed more improvements than a lower dose ($p<0.05$).	R/+; V/+
Cecri et al., 2007	Study Design: Rivastigmine 3 mg/day was administered for the first four weeks of therapy before being raised to 6 mg/day. Sample Design: 15 patients, ages 64-95, had probable mild to severe AD.	To look for alterations in cerebral perfusion, assessing cognition, and the effects of rivastigmine on single photon emission computed tomography prior to and following treatment.	Rivastigmine therapy didn't significantly modify brain perfusion, except in the inferior frontal lobe. Cognitive function was stable or improved a little throughout the treatment ($p<0.01$).	R/+; V/Æ
Feldman et al., 2007	Study Design: Double-blind, randomized clinical trial. Patients were randomized to rivastigmine (3–12 mg/day) or placebo. Sample Design: 1526 patients, had MCI, no depression, and not having severe medical condition.	To assess the effect of rivastigmine in patients with mild cognitive impairment (MCI) on the time to clinical diagnosis of Alzheimer's disease (AD) and the rate of cognitive decline.	Over a 4-year period, rivastigmine had little to no significant impact ($p=0.726$) on the rate at which AD progressed or on cognitive function.	R/+; V/+

Table 13. Part B

Feldman & Lane, 2007	Study Design: 26 week, randomized double blind study. Patients were given rivastigmine 2-12 mg/day 2 or 3 times/day or placebo. Sample Design: 678 patients, >= 50 years old, had probable AD, had a responsible caregiver, and have no concurrent conditions.	To assess the effectiveness and safety of rapidly titrated rivastigmine administered twice or three times daily in patients with mild to moderate Alzheimer's disease (AD).	Rivastigmine was found to significantly improve cognitive, functional, and overall performance in AD patients when taken twice or three times per day ($p<0.05$).	R/+; V/+
Karaman et al., 2004	Study Design: 12-month randomized study. Patients were randomly assigned to placebo or rivastigmine treatment (tablet twice/day, dose increased by 1.5mg every 2 weeks). Sample Design: 44 ambulatory or ambulatory-aided patients, had probable AD, and sufficient vision and hearing.	To analyze the long-term outcome of rivastigmine treatment and to determine the efficacy of rivastigmine in patients with advanced moderate AD.	Patients who took rivastigmine for 1 year saw significant improvements compared placebo ($p<0.001$). By 52 weeks, patients using rivastigmine 6–12 mg/day significantly improved cognitive performance compared to those taking a placebo ($p<0.001$).	R/+; V/Æ
Grossberg, 2004	Study Design: For 26 weeks, patients were randomly assigned to rivastigmine 1mg-6mg bid or placebo. Sample Design: Patients with probable mild to moderate AD, and had a MMSE score 10-26.	To investigate whether rivastigmine remained therapeutically beneficial after up to 2 years of therapy in individuals with probable Alzheimer's disease.	Rivastigmine was safe and improved cognitive function in individuals with AD for up to 2 years, compared to placebo ($p<0.05$).	R/+; V/Æ

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3.7 | Acetylcholinesterase Inhibitors Comparison on Cognitive Outcomes

Among the included studies, 12 studies compared the effectiveness of different AChE inhibitors (donepezil, galantamine, and rivastigmine) in delaying the worsening of cognitive functions associated with the disease as shown in Table 8. Wilcock et al. (2003) favor galantamine in the early and long-term management of mild-to-moderate Alzheimer's disease over donepezil, citing a significant between-group difference ($p<=0.05$). The authors emphasized the AChE inhibitors' efficacy in maintaining cognition. In contrast, Jones et al. (2004) favor donepezil, highlighting the drug's substantial advantages in cognition ($p<0.05$) as compared to galantamine in week 12. Both medications were well tolerated, but the donepezil group reported fewer gastrointestinal adverse events than the galantamine group. Aguglia et al. (2004) highlighted cognitive functions improved significantly in the rivastigmine group ($p<0.05$) and galantamine groups ($p<0.05$). Bullock et al. (2005) discovered rivastigmine showed superior efficacy over donepezil on cognition ($p=0.007$). Meanwhile, Xu et al. (2021) and Lopez-Posa et al. (2005) noted there were no significant differences ($p>0.05$) among different AChE inhibitors' effects on cognition.

Olazran et al. (2005) found patients receiving 5-10mg of donepezil or 6-12mg of rivastigmine in addition to a cognitive-motor intervention, further cognitive advantages were seen in months one and six ($p=0.05$, $p=0.95$, respectively). Loewenstein et al. (2004) showed improvement in face-name memory ($p<0.001$) and orientation ($p=0.006$), Crowell et al. (2005) noted enhancements in recognition memory ($p<0.05$), while Rozzini et al. (2006) discovered improvements in episodic memory ($p<0.01$) and abstract reasoning ($p<0.02$) in mildly impaired Alzheimer's disease patients taking an AChE inhibitor and neuropsychological training. Calabria et al. (2008) added patients' cognition after receiving AChE inhibitors improved after three months of therapy ($p<0.001$) and then dropped at month 21 ($p=0.006$). Like Calabria et al., Connelly et al. (2004) noted statistically significant improvements in cognition ($p<0.0005$) and activities of daily living ($p=0.025$) after 3 months. Wattmo et al. (2012) demonstrated patients who improved or remained stable in cognitive functions had superior cognition states, were younger, and took fewer antidepressants ($p<0.001$). Sun et al. (2007) highlighted while gender ($p=0.07$) and types of medicine ($p=0.62$) were not significant factors, age was the only significant associated factor with treatment duration ($p=0.0006$). While different opinions exist regarding the preferred choice of AChEI in the management of AD, most studies agree on the efficacy of AChEI in maintaining cognitive function.

4 | QUALITY/RISK ASSESSMENT

Each article's quality/risk assessment demonstrated an overall positive result in the relevant questions. This systematic review used 45 studies in total. Mixed validity was observed, with primarily positive or neutral results. All the articles that were part of this review were adequately addressed because no article received a negative validity rating. Twenty-five of those studies had a "+" rating, which indicated that the articles addressed inclusion/exclusion, bias, generalizability, and data collection and analysis (Academy of Nutrition and Dietetics, 2016). Twenty studies had a rating of " ", which indicated the articles were neither exceptionally strong nor exceptionally weak (Academy of Nutrition and Dietetics, 2016). Overall, all articles were considered relevant, and some showed positive validity while others showed neutral validity.

Table 14. Studies Examining the Effectiveness of Different AChEI on Cognition Part A

Aguglia et al., 2004	Study Design: 6-month comparison research. Patients were given rivastigmine 1.5 mg twice/day then 3 mg, or donepezil 5 mg once/day then 10 mg, or galantamine 4 mg twice/day then 8 mg. Sample Design: 242 participants with AD for at least 6 months and not taking AChEI.	To investigate the effects of donepezil, rivastigmine, and galantamine, which are used to treat Alzheimer's disease, in a real-world context.	Cognition improved in the rivastigmine and galantamine groups with significant differences between both but decreased in the donepezil ($p<0.05$, $p<0.05$, respectively)	R/+; V/Æ
Bullock et al., 2005	Study Design: 24-month double-blind, randomized controlled trial. Participants were randomly assigned to receive donepezil 5-10 mg/day or rivastigmine 3–12 mg/day. Sample Design: 994 outpatients, 50-85 years old, had AD or probable AD, have a caregiver once/ day.	To assess over a 2-year period the effectiveness and tolerability of cholinesterase inhibitor therapy in individuals with moderate to moderately severe Alzheimer's disease.	For cognitive functioning, neither rivastigmine nor donepezil demonstrated a comparative advantage. Rivastigmine medication may be more effective for specific patient subpopulations ($p=0.007$).	R/+; V/Æ
Calabria et al., 2009	Study Design: 21-months. Patients assigned to 5 or 10 mg/day donepezil- therapy or 3 to 12 mg/day rivastigmine. Sample Design: 427 patients with probable mild-to-moderate AD.	To investigate cognitive and functional results in 427 AD patients during a 21-month period.	The findings demonstrate that patients' cognition improved after 3 months ($p<0.001$), remained steady for 15 months, and then dropped at month 21 ($p=0.006$).	R/+; V/Æ

Table 15. Part B

Connelly et al., 2005	Study Design: 3-year cohort study. First 3 months, participants took donepezil 5 mg/day, rivastigmine 6 mg/day, or galantamine 16 mg/day. Maintained dosage if improved, if not, greatest tolerable dosage was given. Sample Design: 160 patients with probable AD with a score of 11-26 on the MMSE, and no cerebrovascular illness.	To study the potential that response to cholinesterase inhibitor medication might be predicted by easily measured factors that change because of treatment, such as measures of function and attention.	Although neither of the initial changes were statistically significant at 6 months, there was a statistically significant improvement in cognition ($p<0.0005$) and activities of daily living ($p = 0.025$) after 3 months.	R/+; V/+
Crowell et al., 2006	Study Design: 2-year trial. Patients took donepezil or rivastigmine. Patients who have not taken any ChEI before were used as a comparison group. Sample Design: 28 patients with a probable AD, memory issues, and had been taking AChEI for >= 1 month.	To investigate the effect of cholinesterase inhibitor drugs on recognition memory function in patients with mild to moderate Alzheimer's disease	The principal advantage of ChEI therapy on memory appears to be enhancing retention of new material ($p<0.05$) in memory in mild to severe Alzheimer's disease patients.	R/+; V/Æ
Jones et al., 2004	Study Design: 12-week, randomized clinical trial. Patients were randomly assigned to 5mg/day donepezil then 10 mg/day or 4mg twice/day galantamine then 8 mg twice/day then 12 mg twice/day. Sample Design: 120 patients with possible AD, >= 50 years old, and have a caregiver.	To compare the ease of use and tolerability of donepezil and galantamine in the treatment of Alzheimer's disease (AD) and investigate the effects of both treatments on cognition and activities of daily living (ADL).	Assessments of cognition and ADL demonstrated substantial advantages for donepezil as compared to galantamine ($p<0.05$) in week 12. Donepezil group reported fewer GI adverse events than galantamine group.	R/+; V/+

Table 16. Part C

Loewenstein et al., 2004	Study Design: Random selection to Cognitive Rehabilitation or Mental Stimulation training, with different ChEI dosage in both groups. All participants attended training sessions twice/week. Sample Design: 44 participants with possible AD and a severe increasing deficit in memory.	To assess the effectiveness of a novel cognitive rehabilitation program on memory and functional performance in mildly impaired Alzheimer's disease patients taking a cholinesterase inhibitor.	Improvements in face-name connection memory ($p<0.001$), and orientation ($p=0.001$), and particular functional activities were observed after the intervention and during the 3-month follow-up.	R/+; V/Æ
Lopez-Pousa et al., 2005	Study Design: Open-label, prospective study. Patients were assigned to 5 mg/day donepezil then 10 mg/day, 3mg/day rivastigmine then 6mg/day and 9mg/day, or 8 mg/day then 16 and 24 mg/day for the galantamine group. Sample Design: 147 participants with probable AD, with a caregiver, good hearing and vision, and no serious illness.	To compare the effectiveness of acetylcholinesterase inhibitors to a previous sample of individuals with Alzheimer's disease who were not treated with acetylcholinesterase inhibitors.	There were no significant variations in effectiveness between donepezil, galantamine, and rivastigmine in the investigation ($p>0.05$). At 6 months, patients treated with ChEIs show more improvement than untreated individuals.	R/+; V/+
Olazarán et al., 2004	Study Design: 1-year program. Patients were randomized to receive psychosocial assistance along with cognitive-motor intervention or only psychosocial support. Sample Design: 84 patients with probable AD and have been taking donepezil or rivastigmine for > 1 month.	To evaluate the effectiveness of a cognitive-motor program in patients with early Alzheimer disease (AD) who are treated with a cholinesterase inhibitor (ChEI).	While patients in the control group had dramatically worsened by month 6, cognitive advantages were seen in those in the cognitive motor intervention group in month 1 ($p=0.05$) and month 6 ($p=0.95$).	R/+; V/Æ

5 | DISCUSSION

The systematic review aimed to assess the effectiveness of acetylcholinesterase inhibitors (AChEIs) including donepezil, galantamine, and rivastigmine in delaying the worsening of cognitive function in patients with Alzheimer's disease. The review addressed three primary objectives: Assessing the overall efficacy of AChEIs in improving cognitive functions, comparing cognitive benefits across different types of AChEIs, and identifying gaps in the current literature to guide future research. The findings from the 45 selected articles give important insights into the efficacy and benefits of AChEIs in cognitive improvement.

The review found constant evidence AChE inhibitors improved cognitive outcomes in Alzheimer's disease patients (Black et al. 2007, Boada-Rovira et al. 2004, Brodaty et al. 2006, Burns et al. 2009, Feldman et al. 2003, Feldman & Lane 2007, Gaudig et al. 2011, Grossberg et al. 2004, Han et al. 2016, Homma et al. 2008, Howard et al. 2012, Johannsen et al. 2006, Karaman et al. 2004, Lyketsos et al. 2004, Mintzer & Kershaw 2002, Molinuevo et al. 2009, Pirtilla et al. 2003, Richarz et al. 2014, Sabbagh et al. 2003, Wallin et al. 2006, Winblad et al. 2006). The results of this review match prior research that suggests AChEIs play an important role in improving cognitive decline, particularly in areas such as global cognitive function, memory, decision-making, and attention (Boada-Rovira et al. 2004, Bullock et al. 2005, Burns et al. 2009, Crowell et al. 2005, Feldman et al. 2005, Loewenstein et al. 2004, Rozzini et al. 2006). Studies also demonstrated increasing the AChE inhibitors dose can potentially lead to greater inhibition of the enzyme acetylcholinesterase which can have a positive impact on cognition in some patients with Alzheimer's disease (AD), especially those with early-stage AD (Almkvist et al. 2004,

Table 17. Part D

Rozzini et al., 2007	Study Design: 1-year longitudinal, retrospective study. Patients were distributed to Neuropsychological Training with ChEI, ChEI only, or no therapy. Sample Design: 59 patients with MCI, 63-78 years, live independently and meet the criteria for MCI.	To assess the effectiveness of a neuropsychological training in patients with MCI who receive treatment with cholinesterase inhibitors (ChEIs) to individuals with MCI who are not treated with ChEIs.	The group who received ChEIs and neuropsychological training increased their cognitive abilities, especially their memory (p<0.01) and abstract reasoning (p<0.02).	R/+; V/+
Sun et al., 2008	Study Design: Donepezil was first introduced, followed by rivastigmine, then galantamine including various doses Sample Design: 9877 patients with mild or moderate AD with a comprehensive case study of clinical indications and symptoms.	To assess the duration of acetylcholinesterase inhibitor, use as well as the patients' cognition stability.	AD was highest in ages 70-80 years old with the most cognitive impairment (p=0.0006). This was the age which changes or worsens cognitive ability. Gender (p=0.07) and types of medicine (p=0.62) were not significant factors affecting cognition.	R/+; V/Æ
Wilcock et al., 2003	Study Design: 52-week randomized, rater-blinded study. Patients were randomized to galantamine 8mg twice/day or donepezil 5mg/day. Sample Design: 182 patients with probable AD, cog decline, had a caregiver who resided with patient or visited >= five days/week.	To compare the long-term efficacy and safety of galantamine 24 mg/day and donepezil 10 mg/day in patients with Alzheimer's disease.	Galantamine is better for early and long-term management of individuals with mild-to-moderate AD due to its great efficacy in maintaining cognition when compared to donepezil (p<=0.05).	R/+; V/+
Wattmo et al., 2012	Study Design: 3-year, non-randomized research. Patients were given donepezil, rivastigmine, or galantamine. Sample Design: 784 patients aged >40 with a diagnosis of dementia and possible AD, have been living at home, and have a caregiver.	To determine the socio-demographic and clinical parameters that influence functional and cognitive performance after 6 months of ChEI treatment.	After 6 months of ChEI treatment, patients improved or did not really change in ADL and physical self-care. Patients who improved or remained stable had superior cognitive state (p<0.001).	R/+; V/+
Xu et al., 2021	Study Design: A longitudinal cohort study. Patients received 7.5 mg/day donepezil, or 9mg rivastigmine, or 16 mg galantamine. Sample Design: 39,196 patients, diagnosed with Alzheimer dementia or mixed Alzheimer dementia, no ChEI treatment of more than 3 months.	To examine if cholinesterase inhibitors (ChEIs) are linked to slower cognitive loss in Alzheimer's disease and a lower risk of severe dementia or mortality.	ChEIs have a correlation with moderate cognitive improvements that remain over time. There were no significant differences among different ChEIs effects on cognition (p>0.05).	R/+; V/+

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Han et al. 2016, Homma et al. 2008, Mintzer & Kershaw 2002, Pirtilla et al. 2003, Richarz et al. 2014, Sabbagh et al. 2003). Yet, while higher doses can further improve cognition for some patients with AD, these higher doses can also increase the risk of adverse effects such as nausea, vomiting, diarrhea, headaches, and muscle cramps (Bullock et al 2005, Feldman & Lane 2007, Jones et al 2004, Pirtilla et al 2004). AChE inhibitors have also been shown to be well-tolerated and effective in improving cognitive function for several months to years (Baakman et al. 2022, Feldman & Lane 2007, Grossberg et al. 2004, Karaman et al. 2004, Lykettsos et al. 2004, Pirttila et al. 2004, Richarz et al. 2014, Wallin et al. 2006, Wilcock et al. 2003). AChE inhibitors are effective in enhancing cognitive outcomes; however, it should be noted that higher doses may lead to increased inhibition of AChE, which could exacerbate side effects.

The ability of donepezil to increase memory, slow down the onset of cognitive decline, and improve general cognitive performance is well documented in the literature (Black et al. 2007, Boada-Rovira et al. 2004, Feldman et al. 2003, Feldman et al. 2005, Han et al. 2016, Homma et al. 2008, Howard et al. 2012, Johannsen et al. 2006, Molinuevo et al. 2009, Sabbagh et al. 2003, Wallin et al. 2006, Winblad et al. 2006). There is evidence that galantamine is beneficial in enhancing cognitive abilities, specifically in the domains of memory and attention (Brodaty et al. 2006, Burns et al. 2009, Gaudig et al. 2011, Gorus et al. 2007, Lyketsos et al. 2004, Pirtilla et al. 2003, Richarz et al. 2014, Song et al. 2014). With an emphasis on executive function, rivastigmine has demonstrated effectiveness in enhancing cognitive abilities (Almkvist et al. 2004, Cecri et al. 2007, Feldman & Lane 2007, Grossberg et al. 2004, Karaman et al. 2004). The complexity of identifying the best AChEI is increased by the fact different studies in the systematic review identified one AChEI as being more effective than another. Thus, it is unclear from the available data which AChEI offers the greatest significant cognitive advantages. These variations emphasize the significance of adapting treatment options to certain patient demands and cognitive problems. Despite these differences, a recurring theme appears that all AChEIs (donepezil, galantamine, and rivastigmine) are useful in improving cognitive abilities. Variations in acetylcholinesterase inhibitor effectiveness might be attributed to variability in the selected studies, patient groups, and outcome measures. Most included studies revolved around short-term and medium-term treatment periods, necessitating additional research into the long-term cognitive effects of AChEIs. Furthermore, the findings emphasize the necessity of individualized therapy methods and subjects for future study to better understand the potential of AChEIs in cognitive decline management in patients with Alzheimer's disease.

Acetylcholinesterase inhibitors (AChEIs) are recommended for the treatment of Alzheimer's disease by the American Alzheimer's Association (AAA). Cholinesterase inhibitors are given to address problems with language, memory, reasoning, judgment, and other cognitive functions. These medications inhibit acetylcholine, a neurotransmitter crucial to memory and learning, from breaking down (American Alzheimer's Association, 2024). AChEIs also facilitate nerve-to-nerve communication. The three cholinesterase inhibitors most frequently prescribed are donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). According to the American Alzheimer's Association (2024), galantamine and rivastigmine are recommended for mild to moderate dementia, whereas donepezil is for mild to severe dementia caused by Alzheimer's. While generally well-tolerated, adverse effects are occasionally reported to include nausea, vomiting, an increase in the frequency of bowel movements, and loss of appetite (American Alzheimer's Association, 2024).

Quality Assessment/Bias Assessment

Based on the quality assessment conducted using the Academy of Nutrition and Dietetics Evidence Analysis Library's grading table (Academy of Nutrition and Dietetics, 2020), the systematic review is classified as Grade II - Fair. This was based on the quality of the studies, appropriateness of inclusion criteria for studies, adequacy of data extraction methods, and consistency of findings included in the review. Most of the studies received a rating of "+", indicating the articles addressed inclusion/exclusion, bias, generalizability, and data collection and analysis based on the Quality Criteria Checklist for primary research (Academy of Nutrition and Dietetics, 2016). Some studies had small sample sizes, studies

with fewer than 50 participants, which could have potentially impacted the generalizability and robustness of the findings. Additionally, there were some nonsignificant results, particularly in cognition outcomes. Despite these limitations, high methodological qualities, consistency in the findings, and high levels of statistical significance were observed in the included studies. The strengths which increased the reliability and validity of the review, along with the minor limitations contributed to the fair quality rating assigned.

Strengths/Limitations

By including a diverse range of studies, the review provided a comprehensive appraisal of the impact of acetylcholinesterase inhibitors (AChEIs) on cognitive functions in Alzheimer's disease. An inclusive literature search strategy offers an in-depth examination of the available research studies. Other strengths also include the number of studies reviewed and the systematic approach of the review guided by the comprehensive PRISMA guidelines. Despite its strengths, this systematic review has some limitations. Its eligibility criteria had to be broader in terms of the publication date and restricted to English articles. Also, variability in participant characteristics and AD stages made it harder to draw consistent conclusions regarding the comparison between different AChEIs.

Application for Practitioner

Current research demonstrates AChEIs are effective in delaying the worsening of cognitive function in patients with Alzheimer's disease. Tailoring treatment plans according to each patient's unique profile becomes essential when considering the different cognitive benefits associated with different AChEIs. The use of AChEIs requires monitoring to minimize side effects, making sure the selected AChEI fits the patient's overall health. Given that AChEIs can improve a patient's general well-being and maintain cognitive improvement over time, incorporating them into long-term treatment can be considered.

6 | CONCLUSION

The effectiveness of acetylcholinesterase inhibitors (AChEIs) in delaying the worsening of cognitive decline linked to Alzheimer's disease (AD) is thoroughly examined in this systematic review. The review, which was achieved by carefully examining 45 research articles, shows that AChEIs have a consistent beneficial effect on cognitive functions (Black et al. 2007, Boada-Rovira et al. 2004, Brodaty et al. 2006, Burns et al. 2009, Feldman et al. 2003, Feldman & Lane 2007, Gaudig et al. 2011, Grossberg et al. 2004, Han et al. 2016, Homma et al. 2008, Howard et al. 2012, Johannsen et al. 2006, Karaman et al. 2004, Lyketsos et al. 2004, Mintzer & Kershaw 2002, Molinuevo et al. 2009, Pirtilla et al. 2003, Richarz et al. 2014, Sabbagh et al. 2003, Wallin et al. 2006, Winblad et al. 2006). Although individual research revealed varying levels of effectiveness among different AChEIs, the body of evidence highlights the overall advantage of AChEIs in reducing cognitive deterioration in AD patients. The lack of a clear superior AChEI over the other highlights how crucial it is to customize treatment plans to the unique needs of each patient. Physicians should evaluate individual patient characteristics, disease extent, and the areas of cognition impacted.

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AUTHOR BIOGRAPHY

Lena Meziou Houston, TX 77012