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REVIEW ARTICLE

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A review of clinical treatment considerations of donepezil in severe Alzheimer's disease

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Summary

Background: Alzheimer's disease (AD) is a neurodegenerative disorder that affects over 45 million people worldwide. Patients with severe AD require help with daily activities and show severe memory impairment. Currently, donepezil is one of two drugs approved by FDA and Health Canada for the treatment of severe AD (MMSE score <10). It is prescribed as 5 or 10 mg/d and an FDA-approved 23-mg/d dose.

Method: This review will discuss risks and benefits of donepezil at these doses in severe AD. Articles were identified using PubMed using the MeSH terms "donepezil" AND "Alzheimer Disease" AND "severe." Three double-blind, placebo-controlled, randomized studies, one post hoc analysis, and one subgroup analysis were selected.

Results: Donepezil was found to benefit patients in cognition and global functioning. The most consistent improvement was in severe impairment battery (SIB) scores. However, more patients treated with high dosage of donepezil discontinued their treatment due to various adverse events (AEs).

Conclusion: Clinicians must weigh benefits against adverse events when determining the course of therapy, as recommendations for cholinesterase inhibitors in advanced AD remain unclear and vary with different guidelines.

KEYWORDS

Alzheiemr's disease, cognition, dementia, donepezil, dose, severity, treatment considerations

1 | INTRODUCTION

1.1 | Background

Dementia is a progressive disease that damages the brain and ultimately becomes severe enough to interfere with daily activities. Alzheimer's disease (AD) is the most common form of dementia (*ca.* 65-80%).[1–3] A report from Alzheimer's Disease International (ADI) estimates that 46.8 million people worldwide were living with dementia in 2015, and the prevalence is expected to double by 2030 and more than triple by 2050.[4,5] Economically, AD is a very expensive disease and affects both patients and their caregivers. According to the World Alzheimer Report 2015, the estimated worldwide cost of dementia was $ 818 billion USD in 2015 and will become two trillion by 2030.[5,6] There is currently no cure for AD. However, there are some pharmacological therapies that can assist in alleviating some of the symptoms of AD and slow the progression of the disease.[7,8] The treatment will be more effective if the drug is introduced in the early stages of the disease.

Adlimoghaddam and Neuendorff equally contributed to this work.

1.2 | Diagnosis and assessment

Memory deficiency (episodic memory, executive function, language, visual and spatial skills, and attention) is utilized for the diagnosis of disease, using both cognitive and neurological

tests.[9,10] For example, the Mini-Mental State Examination (MMSE) is a tool that can be used to measure global cognitive efficiency and evaluate the progression and severity of dementia.[11] It is a recommended test that is easy to manage, and is required by several provincial drug formularies in assessing severe dementia.[10] However, some concerns have risen regarding the use of the MMSE in evaluating severe dementia. For instance, it is believed that the MMSE may become less sensitive for detecting clinically important changes as the disease develops.[10] Additional sets of tests are used to evaluate cognitive and behavioral impairment in more severe disease, which include the Severe Impairment Battery (SIB), the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL), the Functional Assessment Test (FAST), the Clinician's Interview-Based Impression of Severity/Change-Plus Caregiver Input (CIBIS+/CIBIC+), the Neuropsychiatric Inventory (NPI), and the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) (Tables 1–5). In these tests, information is gleaned via caregivers, because in later stages of disease, the patients might not be able to report their symptoms.

1.3 | Treatment of Alzheimer's disease

Currently, there is no cure for AD and all available medications show only modest benefit at best in some individuals. The Food and Drug Administration (FDA) has approved two types of medications for treatment of cognitive symptoms in AD. The first type includes the cholinesterase inhibitors (such as donepezil, galantamine, and rivastigmine) that reversibly bind enzyme and prevent the hydrolysis of acetylcholine, in order to enhance cholinergic neurotransmission.[15–17] Acetylcholine is a key neurotransmitter in the nervous system that interacts with receptors associated with processes of learning and memory. Biopsy of tissue taken from the brain of patients with AD 3.5 years after the onset of symptoms has shown that neurotransmitter pathology occurs early in the course of the disease, and reductions in acetylcholine synthesis and choline acetyltransferase activity are correlated strongly with cognitive impairment.[18] Therapeutic interventions are designed to partially correct for loss of presynaptic cholinergic function.[19] A few of these compounds have confirmed efficacy in temporarily delaying the deterioration of function in patients with AD as well as improvement in cognition, general clinical impression, activities of daily living, and behavioral symptoms. Currently, all commonly prescribed AChE inhibitors (AChEIs) are approved to treat AD in mild-to-moderate stages; however, donepezil is the only selective AChEI that is permitted to treat all stages (mild, moderate, and severe) of AD. Additionally, donepezil, compared to other ChEIs, includes a long half-life that permits once-daily dosing, increased tolerability due to increased specificity for central AChE inhibition, no significant effects of food on pharmacokinetics of the drug, and has minimum interaction with other drugs. Also, donepezil is relatively well-absorbed orally with 100% of relative oral bioavailability compared to other drugs. Another approved medication for AD treatment is memantine. This drug modulates N-methyl-D-aspartate (NMDA) receptor complexes that mediate processes of learning and memory. The National Institute for Health and Care Excellence (NICE) states that memantine is recommended in moderate AD only if AChEIs are contraindicated or not tolerated by AD patients.

TABLE 1 Black, 2007

Methods	24-wk double-blind, parallel-group, placebo-controlled, randomized study
Patients	343 patients from 98 sites across the USA, Canada, France, the UK, and Australia. Ambulatory or ambulatory-aided, 50 y or older
	Inclusion criteria: MMSE 1-12, FAST ≥6, modified Hachinski ≤6, reliable caregiver contact min. 3 d/wk
	Exclusion criteria: skilled nursing home or requiring skilled nursing home within 6 mo, known sensitivity to piperidine derivatives or cholinesterase inhibitors, clinically significant obstructive pulmonary disease or asthma left untreated within 3 mo of study entry, hematologic or oncologic disorder within 2 y, significant active GI/renal/hepatic/endocrine/cardiovascular disease, current primary psychiatric diagnosis (including major depressive disorder) other than AD, dementia complicated by other organic disease, dementia due to primary syphilis, known or suspected history of alcohol or drug abuse within 10 y, patients on most prescription or over-the-counter medications with known psychotropic activity or cholinergic or anticholinergic activity
	AD diagnosis: DSM-IV, NINCDS-ADRDA
Interventions	Placebo vs 5 mg/d for 6 wk, and then 10 mg/d thereafter
Outcome measures	Primary: SIB, CIBIC-Plus
	Secondary: ADCS-ADL-severe, NPI, MMSE, CBQ, RUSP
Notes	Treatment with cholinesterase inhibitors, memantine, or propentofylline was allowed previously if discontinued no <3 mo before screening.

TABLE 2 Winblad, 2006

Methods	6-mo double-blind, parallel-group, placebo-controlled, randomized study
Patients	248 patients from 50 assisted-care facilities, 50 y or older, ambulatory or ambulatory-aided, with nursing assistants knowing their patient for at least 12 wk, spending at least 4 h with pt on at least 3 d every week.
	Inclusion criteria: MMSE 1-10, FAST 5-7c
	Exclusion criteria: non-AD dementia, primary psychiatric and neurological disorders
	AD diagnosis: DSM-IV, NINCDS-ADRDA
Interventions	Placebo vs donepezil 5 mg/d ×30 d, followed by 10 mg/d thereafter
Outcome measures	Primary: SIB, ADCS-ADL-severe
	Secondary: MMSE, NPI, CGI-I scale
Notes	Patients may have received 5 mg donepezil for the remainder of 6 mo if 10 mg was not well tolerated

TABLE 3 Feldman, 2005

Methods	Subgroup analysis of 24-wk double-blind, parallel-group, placebo-controlled RCT
Patients	145 patients, ambulatory or ambulatory-aided, living in the community or in assisted living facilities but not requiring total nursing care, with minimum 8 h of caregiver contact 3 times per week
	Inclusion criteria: MMSE 5-12, FAST ≤ 6, CT or MRI scan within the previous 24 mo had to be consistent with AD without any other significant comorbid pathologies
	Exclusion criteria: evidence of any cause for their dementia, delirium, depression, other diagnosis that might interfere with their participation, primary neurological or psychiatric diagnoses, clinically significant obstructive airway disease or asthma, hematologic or oncologic disorders within 2 y, B12 or folate deficiency, and active gastrointestinal, renal, hepatic, endocrine, or cardiovascular system disease. Known or suspected history of drug or alcohol misuse within 10 y, known hypersensitivity to AChEIs. Medications with notable cholinomimetic or anticholinergic effects, investigational drugs, initiation of psychoactive medications within the first 4 wk of treatment
	AD diagnosis: DSM-IV, NINCDS-ADRDA
Interventions	Placebo vs 5 mg/d for 28 d, followed by placebo vs 10 mg/d as per the clinician's judgment, with the ability to reduce the dose back to 5 mg/d to improve tolerability
Outcome measures	Primary: CIBIC-Plus
	Secondary: MMSE, SIB, DAD, IADL+, PSMS+, NPI
Notes	Treatment differences at each post-baseline visit assessed using ANCOVA methods
	A last observation carried forward (LOCF) analysis was used when there were missing data values
	Antipsychotics and benzodiazepines were allowed provided that patients were on a stable dose of these drugs for a minimum of 4 wk before the baseline visit and were to remain on the same dose for 4 wk after the start of study medication

1.4 | Current recommendations and cautions for donepezil use

Donepezil is an FDA-approved drug for the treatment of severe AD in the USA and Canada. The adverse events (AE) are significantly greater in higher-dosage (10 mg/d) forms as compared to lower-dosage (5 mg/d) forms. Overall, AEs in the higher-dosage group include symptoms such as anorexia, vomiting, nausea, diarrhea, and rhinitis.[20] Although lower dosage levels might be a better option in terms of AEs, in 2010, the FDA approved the higher-dose (23 mg/d) donepezil formulation for the treatment of patients suffering from moderate-to-severe AD. This was based on positive results from a phase 3 clinical trial that compared switching to donepezil 23 mg/d against continuing treatment with daily dose of 10 mg/d donepezil (Table 4). The trial indicated that greater cognitive benefits and functional outcomes (mean change in Severe Impairment Battery score, 2.11 points; $P < 0.001$) were found in the 23-mg/d group compared to the lower dosage (10 mg/d).[21] Additionally, the analyses showed that the cognitive benefits were significant irrespective of concomitant memantine use. The recommended starting dose for daily donepezil is 5 mg/d, and after four to six weeks, it can be increased to 10 mg/d. Patients with moderate-to-severe AD who are recognized on a regimen of Aricept 10-mg tablet daily for at least 3 months are candidates for dose escalation to Aricept 23-mg tablet daily. Although statistically significant differences have been noted in cognition (a 2.2-point improvement compared to the lower dosage of Aricept on the SIB 100-point scale), no statistically significant differences were found in global functioning (a 0.06 improvement on the seven-point CIBIC-Plus scale).[22,23]

Of note, drugs such as donepezil with cholinergic properties usually have gastrointestinal side effects. Discontinuation of the drug has also been reported (Table 6), followed by more severe AEs. A multicenter research trial from 529 patients with mild-to-severe

TABLE 4 Farlow, 2010

Methods	24-wk double-blind, randomized study
Patients	1467 patients, ambulatory or ambulatory-aided, aged 45-90 y, receiving donepezil 10 mg once daily for ≥12 wk before the start of the study (detected by plasma concentrations). Otherwise, physically healthy, clinical laboratory values WNL or deemed by clinician to be insignificant if abnormal. Stable and well-controlled hypertension, cardiovascular disease, diabetes mellitus, non-insulin dependent diabetes, and hypothyroidism eligible if meets specific criteria. Caregivers required to have ≥10 h/wk of contact, have an MMSE ≥27 (or ≥25 if illiterate), and found to be not clinically depressed (CESD-R ≤ 15)
	Inclusion criteria: MMSE 0-20, SIB ≤ 90, CSDD < 12
	Exclusion criteria: additional neurological disorders that might, in the investigator's opinion, affect cognition or the assessment of cognition, even if the disorder was distinguishable from AD (Parkinson's disease, multi-infarct dementia, dementia due to cerebrovascular disease, Huntington's disease, frontotemporal dementia, Creutzfeldt-Jakob disease, Lewy body dementia, normal-pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, or multiple sclerosis). Starting memantine within 12 wk of screening. Unstable or supratherapeutic doses of antipsychotics and SSRIs, any additional AChEI use within 12 wk of screening, or any medication known to interfere with clinical effects of donepezil or that could substantially impact cognition
	AD diagnosis: DSM-IV, NINCDS-ADRDA, CT, or MRI within a year before screening (to rule out other causes of dementia other than AD)
Interventions	Randomly assigned, in a 2:1 ratio using computer-generated randomization codes, to receive donepezil 23 mg (test) or donepezil 10 mg (reference) once daily for 24 wk. Previously on 10 mg for ≥12 wk
Outcome measures	Primary: SIB, CIBIC-Plus
	Secondary: ADCS-ADL, MMSE
Notes	If a patient was taking memantine at a stable dose of ≤20 mg/d for ≥12 wk before screening, use was allowed to continue. All cholinesterase inhibitors were required to be discontinued for 12 wk prior to screening

AD indicated that 32 AEs were potentially related to donepezil as following: diarrhea (1.32%), agitation (1.13%), nausea (0.95%), and insomnia (0.95%). The report included at least one in every 3% of patients with neuropsychiatric AEs, but there were no unexpected AEs or death attributable to donepezil in this study.[24]

A cohort study showed that hospital visits for syncope were more *frequent in* those who were prescribed AChEIs than those who were not prescribed the mentioned drugs (31 vs 18.6 events per 1000 person-years; adjusted hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.57-1.98). Additionally, syncope-related outcomes (such as bradycardia, permanent pacemaker insertion, and hip fracture) were higher among participants receiving AChEIs compared with control individuals.[25]

1.5 | Current guidelines for donepezil withdrawal

Although numerous clinical trials have been shown thus far with donepezil, extended use of this medication has not been thoroughly evaluated. There is limited research available concerning evidence-based discontinuation of drugs in severe dementia. The reason for stopping donepezil therapy could be related to either perceived benefits by the hospice medical director or challenges with convincing family to discontinue therapy. Due to the effect of donepezil for severe end-stage dementia, almost 20-30% of patients acquired cognitive (22%), behavioral (28%), and/or functional (22%) benefit. Additionally, it was agreed that donepezil improved patient quality of life (15%) or improved survival (3%). However, discontinuation of donepezil in patients with severe end-stage dementia resulted in accelerated behavioral challenges (32%), functional decline (26%), increased caregiver burden (22%), and decreased quality-of-life measurements (17%).[26]

The Holmes criteria in 2008 evaluated the appropriateness of drugs prescribed for those with advanced dementia (defined by the Cognitive Performance Scale (CPS) score of 4-6).[27] This study was based on 12 geriatrician's opinions, who were all employed within the same institution. These individuals thought that 11 out of 221 drugs were inappropriate medications. AChEIs were in this group; however, 29% of the patients consumed these drugs. In 2012, another study evaluated 1449 nursing home residents with severe cognitive impairment associated with the Services and Health for Elderly in Long Term Care (SHELTER) study. The result of this study indicated that almost 45% of patients consumed inappropriate drugs. Only half of the patients were designated to continue donepezil for the whole period of the study due to either adverse drug effects or perceived lack of effects.[28] More frequently used criteria, such as the START (Screening Tool to Alert Doctors to Right Treatment) and STOPP (Screening Tool of Older Persons' Prescription), are debated to be more globally applicable and sensitive to detecting potentially inappropriate drugs.[29] Additionally, in the STOPP/START criteria, the START criteria address those that should be considered in a given medical condition, and the STOPP tool addresses clinical situations in which a medication is inappropriate. Overall, there is no standard recommendation for discontinuation of AChEI drugs; however, current recommendations are based on weighing risks (more cognitive impairment) versus benefits (avoidance of known AEs).

The overall objective of this article is to review the available evidence of possible benefits and risks for using donepezil in various doses for managing severe AD, thereby utilizing various measurement scales in evaluating cognitive and behavioral impairment outcomes of AD treatment.

TABLE 5 Homma, 2008

Methods	24-wk double-blind, parallel-group, placebo-controlled, randomized study
Patients	325 patients, ambulatory or ambulatory-aided, age 50 or older, residing in the community or assisted living facility but not requiring full-skilled nursing assistance, reliable caregiver at least 3 d/wk (4 h/d)
	Inclusion criteria: MMSE score 1-12, modified Hachinski Ischemic Score ≤ 6 points, FAST ≤ 6
	Exclusion criteria: Non-AD dementia, major depression/other psychiatric illness, severe GI/haptic/renal/endocrine/CV disease, history of severe bronchial asthma or obstructive pulmonary disease, severe extrapyramidal disorders, unstable thyroid dysfunction, poorly controlled hypertension or diabetes, epilepsy or convulsions within 3 mo of study, alcohol or drug dependence within 10 y, treatment with donepezil in 3 mo prior to study, cholinergic or anticholinergic drugs during this study, inability to swallow whole pill
	AD diagnosis: DSM-4, confirmation by neuroimaging (CT or MRI), no significant comorbidities
Interventions	4-wk placebo observation period all groups, then placebo ×24 wk vs 5 mg/d (3 mg/d ×2 wk, then 5 mg/d ×22 wk), vs 10 mg/d (3-mg/d ×2 wk, then 5-mg/d ×4 wk, then 10 mg/d ×18 wk)
Outcome measures	Primary: SIB, CIBIC-Plus
	Secondary: ADCS-ADL-sev, BEHAVE-AD
Notes	AE were standardized according to the *Medical Dictionary for Regulatory Activities—Japanese Version*
	12 patients entering treatment period never received study medication or no post-baseline observation. Therefore, n values taken from Full analysis set

Notes. ADCS-ADL-severe = Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease. This 19-item scale measures basic and complex abilities and validated in patients with moderate-to-severe dementia; total scores range from zero to 54, with the lowest score indicating the greatest functional impairment and the highest no impairment. Items included complex activities of daily living, e.g, operating water taps and switching on lights, as well as basic activities of daily living, e.g, eating and bathing.
BEHAVE-AD = assessment of paranoid and delusional ideations, hallucinations, activity disturbance, aggressiveness, diurnal rhythm disturbances, affective disturbances and anxieties and phobias. Each item is scored from 0 (none) to 3 (severe). Scores range from 0 to 78, with higher scores indicating more severe symptoms.
CBQ = Caregiver Burden Questionnaire evaluates the time and stress associated with assisting the patient with performance of daily tasks. Lower scores indicating less of a burden.
CESD-R = Center for Epidemiologic Studies test for depression Scale Revised, a screening test for depression and depressive disorder. Measures symptoms defined by the American Psychiatric Association' Diagnostic and Statistical Manual (DSM-V) for a major depressive episode, with 20 questions each scored from 0-4, with 4 being most severe.
CGI-I scale = clinical global impression of improvement scale.
CIBIC-Plus = Clinician's Interview-Based Impression of Change-Plus Caregiver input. An independent global assessment of treatment response, covering four domains (general, mental/cognitive state, ADLs, and behavior). Separate interview with caregiver and patient. Scored 1-7 on a Likert scale, with high scores indicating deterioration from baseline, 4 indicating no change, and low scores indicating improvement. CIBIS-Plus =Clinician's Interview-Based Impression of Severity Plus Caregiver Input Scale, a baseline disease severity point of reference for CIBIC-Plus.
CSDD = Cornell Scale for Depression in Dementia, assesses signs and symptoms of major depression in patients with dementia through two semi-structured interviews; an interview with an informant and an interview with the patient. Each of 19 items is rated for severity on a scale of 0-2 (0 = absent, 1 = mild or intermittent, 2 = severe). The item scores are added. Scores above 10 indicate a probable major depression. Scores above 18 indicate a definite major depression. Scores below 6 as a rule are associated with absence of significant depressive symptoms.[12]
DAD = Disability Assessment for Dementia, a 10-domain, 40-item instrument that measures instrumental and basic activities of daily living.
RUSP = Resource Utilization for Severe Alzheimer Disease Patients. Assessment of resources used: visits to the emergency room, hospitalizations, accommodation, visiting nurse, daycare, respite care, home health aid, meal delivery services are included. Less resource used translates to lower scores.
FAST = Functional Assessment Staging.
IADL+ = the modified Instrumental Activities of Daily Living Scale.
MMSE = Mini-Mental State Exam.
NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association.
NPI = Neuropsychiatric Inventory. Two versions assess either 10 or 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, +/−nighttime behavior disturbances, +/− appetite and eating abnormalities. Assessment of frequency, severity, and caregiver distress on each measure is done by a caregiver familiar with the patient spending at least 4 hours per day at least 4 days per week with the patient and who is knowledgeable about the patient's daytime and nighttime behaviors. Measures identify changes in the patient's behavior that have appeared since the onset of the illness, that were not previously present. Scores of frequency and severity are tabulated, with higher scores indicating worsening neuropsychiatric disturbances.[13]
PSMS+ = Physical Self Maintenance Scale.
SIB = Severe Impairment Battery, a 40-item questionnaire designed to assess the severity of cognitive dysfunction in advanced Alzheimer's disease. Nine domains: memory, language, orientation, attention, praxis, visuospatial, construction, orientation to name, and social interaction. Total scores for the questionnaire range from zero (greatest impairment) to 100 (no impairment).[14]

2 | METHODS

2.1 | Selection criteria

Randomized controlled trials (RCTs) evaluating the effectiveness and side effect profile of different dosages of donepezil used in severe AD were identified utilizing PubMed. The search was accomplished using the MeSH terms "donepezil" AND "Alzheimer Disease" AND "severe." The search limits were set for studies in English on humans. Research studies were chosen from clinical trials, multicenter studies, and RCTs on the use of donepezil in patients with severe AD. Additionally, the post hoc use of RCT was utilized to analyze severe AD. For example, one original RCT analysis was used to compare 5 and 10 mg to placebo and two original RCT analyses were selected comparing 10 mg to placebo in severe AD. Other RCT analyses were used to compare 23 to 10 mg in moderate-to-severe AD or severe AD with outcome of (MMSE 0-20) and disease (MMSE 0-16), respectively. Almost 3 years after the aforementioned research studies were published, a *post hoc* analysis was released evaluating the impact of baseline severity on SIB domains and was selected for discussion in this review. All analyses for study design, demographics, and clinical baseline cognitive function of the research studies are summarized in Table 7.

2.2 | Statistical analyses

Analyses of mean changes from the baseline for addressing missing data in clinical trials have relied on various methods such as Last Observation Carried Forward (LOCF), Observed Case (OC), and the Mixed Model for Repeated Measures (MMRM). Aforementioned analytical methods need specific assumptions to analyze the characteristics of the missing data. However, if the assumptions for any of the above methods are not valid, then the interpretation of results can be confusing.

Comparing LOCF and MMRM indicated that LOCF is likely to underestimate within-group mean changes in efficacy (benefit) and safety (risk) for drugs. Unlike LOCF, OC is likely to overestimate within-group changes.[30] Efficacy analysis of data employing the LOCF method of the intent-to-treat (ITT) population was used for calculating missing values from patients with baseline score or ≥1 score after first administration of the study medication. Furthermore, the analysis model of MMRM was utilized in patients who were randomized to the ITT category with missing data being replaced by the mean of observed values for the change from baseline in the placebo group. The analysis method of OC includes completers, those patients that had an observation at the end-point visit.

2.3 | Interpretation of statistical analyses

In this research study, five different articles were chosen to assess various analytical methods for addressing missing data concerning the efficacy and safety of different dosages of donepezil (5 or 10 or 23 mg/d) used to treat severe AD. Random samples were selected in both placebo and treated groups with different periods of time (24-26 weeks). Analytical strategies used in these reviews are LOCF, OC, and MMRM. In the LOCF method of analyses, missing data were assigned by carrying the last observation forward, and analysis of covariance (ANCOVA) model was utilized to assess mean changes at each visit. The model included the categorical effects of treatment and investigator, with baseline value included as a covariate. The analysis of LOCF method expected that the values related to patients who discontinued medication would not have altered from the previous observation to the end of the clinical trial, had they continued in the trial. The OC analyses assessed the same ANCOVA model which was applied to the observed data at each visit. Moreover, the MMRM analysis evaluated data from all visits at the same time via a restricted maximum likelihood-based approach. Various covariates in the model included the fixed categorical effects of treatment, investigator, visit, and treatment by visit interaction, with baseline value and the baseline by visit interaction.

In comparison with MMRM, the LOCF method is likely to yield smaller within-group mean changes in efficacy and safety for medications which leads to a "conservative" analysis. For instance, if patients drop out of medication due to AE, mean change to end point using LOCF is assumed to lead to smaller mean changes. This is because patient dropout happened before much improvement could occur. Likewise, the bias in OC is assumed to lead to overestimation of within-group changes. Patients who are not responding are more likely to drop out, leaving only patients who were responding well to complete the trial.

The LOCF method was used in all of the studies in which the baseline and ≥1 scores were considered for computing missing values after first administration of the medication. The MMRM model was employed only by Winblad et al,[31] where data were obtained from all patients who were randomly selected to be classified as intention-to-treat group (those who dropped out and those who completed the study), with missing data being substituted by the mean of observed values for the change from baseline in the placebo group. The OC method of analysis has been applied to some studies that made use of completers (those patients that had an observation at the end-point visit). In this review article, "significant" or "statistically significant" refers to comparisons with $P \leq 0.05$.

3 | RESULTS

3.1 | Outcome measures

The SIB test is considered a reliable cognitive measure across all five research studies for differentiating patients with.[14] In addition, the SIB is a 40-item scale created for the evaluation of the severity of cognitive dysfunction in advanced AD. In SIB, 9 subscales (memory, social interaction, orientation language, attention, visuospatial, praxis, construction, and orientation) are tested. Scores from questionnaires (zero and one hundred) indicated the greatest and no impairment, respectively. SIB least-square

TABLE 6 Adverse events

Study	Black, 2007		Winblad, 2006		Feldman, 2005		Farlow, 2010		Homma, 2008		
	Treatment group, n (%)										
	Donepezil 10 mg (n = 176)	Placebo (n = 167)	Donepezil 10 mg (n = 128)	Placebo (n = 120)	Donepezil 10 mg (n = 72)	Placebo (n = 73)	Donepezil 10 mg (n = 471)	Donepezil 23 mg (n = 963)	Donepezil 5 mg (n = 101)	Donepezil 10 mg (n = 96)	Placebo (n = 105)
Any AE	140 (80)	117 (70)	105 (82)	91 (76)	59 (82)	57 (78)	300 (64)	710 (74)	79 (78)	80 (83)	77 (73)
Any treatment-related AE	74 (42.0)	51 (30.5)	—	—	—	—	Possibly: 97(21) Probably: 33 (7.0)	Possibly: 301 (31) Probably: 173[21]	—	—	—
Diarrhea	18 (10)	7 (4.2)	12 (9)[a]	3 (3)	8 (11)	2 (3)	25 (5.3)	80 (8.3)	6 (5.9)	8 (8.3)	4 (3.8)
Anorexia	12 (6.8)	7 (4.2)	—	—	2 (3)	1 (1)	8 (1.7)	51 (5.3)	1 (1.0)	7 (7.3)	2 (1.9)
Nausea	12 (6.8)	3 (1.8)	8 (6)	5 (4)	3 (4)	3 (4)	16 (3.4)	114 (12)	—	—	—
Vomiting	11 (6.3)	4 (2.4)	—	—	5 (7)	1 (1)	12 (2.5)	89 (9.2)	7 (6.9)	14 (15)	7 (6.7)
Loss of appetite	—	—	—	—	—	—	—	—	5 (5.0)	4 (4.2)	2 (1.9)
Weight loss	—	—	—	—	3 (4)	2 (3)	12 (2.5)	45 (4.7)	—	—	—
Insomnia	—	—	—	—	3 (4)	2 (3)	11 (2.3)	33 (3.4)	—	—	—
Restlessness	—	—	—	—	—	—	—	—	6 (5.9)	2 (2.1)	1 (1.0)
Bradycardia	—	—	—	—	—	—	3(0.6)	27(2.8)	—	—	—
Accidental injury/ fall	—	—	Injury: 7 (6) Fall: 17 (13)	Injury: 6 (5) Fall: 15 (13)	—	—	Serious: 2 (0.4) Total: 18 (3.8) Syncope: 5 (1.1)	Serious: 6 (0.6) Total: 39 (4.0) Syncope: 2 (0.2)	7 (6.9)	6 (6.3)	6 (5.7)
Accidental bone fracture	—	—	7 (6)	4 (3)	—	—	—	—	—	—	—
Contusion	—	—	—	—	—	—	1 (0.2)	20 (2.1)	5 (5.0)	3 (3.1)	3 (2.9)
Agitation/ Aggression/ hostility	11 (6.3)	10 (6.0)	—	—	12 [20]	5 (7)	Agitation: 18 (3.8) Aggression: 12 (2.5) Serious: 4 (0.8)	Agitation: 38 (3.9) Aggression: 26 (2.7) Serious: 2 (0.2)	—	—	—
Confusion	—	—	—	—	8 (11)	4 (5)	—	—	—	—	—
Hallucination	—	—	8 (6)[b,c]	1 (1)[d]	—	—	—	—	—	—	—
Serious/severe AE	19 (11)	26 (16)	31 (24)	31 (26)	9 (13)/9 (13)	7 (10)/12 (16)	45 (9.6)/34 (7.2)	80 (8.3)/81 (8.4)	12 (12)/2 (2.0)	10 (10)/5 (5.2)	15(14)/10(9.5)
Discontinuation due to AE	34 [22]	18 (11)	20 (16)	8 (7)	5 (7)	4 (5)	39 (7.9)	182 (19)	8 (7.9)	13 (14)	11(11)
Death	2 (1.1)	8 (4.8)	18 (14)	19 (16)	0 (0)	0 (0)	5 (1.1)	8 (0.8)	2 (2.0)	2 (2.1)	1 (1.0)

[a]Possibly treatment related in 8(6%) patients.
[b]Possibly treatment related in four (3%) patients.
[c]Present before start of study in three patients.
[d]Present before start of study in one patient.

TABLE 7 Study design, demographic, and clinical baseline cognitive function of 5 studies

Study	Black, 2007	Winblad, 2006	Feldman, 2005	Farlow, 2010	Homma, 2008
Study Design	Double-blind, parallel-group placebo-controlled randomized study	Double-blind, parallel-group, placebo-controlled, randomized study	Subgroup analysis (Feldman 2001); Double-blind, parallel-group, placebo-controlled RCT	Double-blind, randomized study	Double-blind, placebo-controlled, randomized trial
Donepezil dose (mg/d)	10	10[a]	10[b]	10 or 23	5 or 10
MMSE	1-12	1-10	5-12	1-20[c]	1-12
Country	US, Canada, France, UK, Australia	Sweden	Canada, Australia, France	23 countries within Asia, Europe, Australia, North America, South Africa, and South America	Japan
Sample size (placebo), No. randomized	167	120	73	486 (10 mg)	105
Sample size (treatment arm), No. randomized	176	128	72	981 (23 mg)	197 (5 mg = 101 10 mg = 96)
Duration	24 wk	26 wk	24 wk	24 wk	24 wk
Baseline demographics					
Mean age	78	84	73	74	78
Female, %	70	77	59	63	80
Baseline outcome scores (mean)					
MMSE	7.5	6.1	9.0	13.1	7.5
SIB	64.9	55.5	71.9	74.7	62.2
FAST	6A-6E	—	5-6	—	6A-6E
ADCS-ADL-severe	27.0	14.2	—	34.2	26
CIBIS+/CIBIC+	5.1	—	4.71	4.41	—
NPI	22.5	19.3	20.6	—	—
BEHAVE-AD	—	—	—	—	9.0

[a]5 mg/d for 28 days, then 10 mg/d for duration of study.
[b]5 mg/d for 28 d, then 10 mg/d as per clinician's judgment. Dose could be reduced back to 5 mg/d to improve tolerability.
[c]Post hoc analysis of more severe disease (MMSE 0-16) from this study, as well as Ferris et al[35] (severity strata) to be discussed.

(LS) mean changes were calculated by subtracting the LS mean changes from baseline of the placebo group from donepezil group in the ITT population. Other analyses method, post hoc, calculated LS mean treatment differences and standardized effect sizes between 23- and 10-mg daily doses, but not in placebo group. In this study, all nine SIB domain scores were separated for stratified baseline MMSE subpopulations. For discussion, data from the severe AD subgroups with MMSE scores of 0-5 and 6-10 were chosen. Depending on the particular study, dose, and statistical analysis, the SIB LS mean changes are varied between 4.5 and 8.9. Regardless, all studies show an improvement in scores in the treatment group and a clinical impairment in placebo groups. There is also a study that evaluated a significant dose response relationship between different doses of donepezil (5 mg/d or 10 mg/d) and placebo. The SIB results confirmed that both 5 mg/d and 10 mg/d donepezil were greatly superior to placebo, with a LS mean treatment difference of 6.7 (P = 0.001) and 8.9 (P = 0.001), respectively. Moreover, the SIB LS data confirmed that the dosage of 5 mg/d was significantly inferior to the higher dosage (10 mg/d) of donepezil.[32] Another study by Feldman et al[33] stated that the higher dose (10 mg/d) remains superior (7.42) (P = 0.0017), but not when compared to studies by Winblad et al[31] or Black et al[34] (5.6 (P = 0.008) and 5.32 (P = 0.0001), respectively). A study by Ferris et al[35] also indicated SIB LS mean treatment differences (95% CI) of 6.048 (1.04-11.05) and 3.258 (0.30-6.21) for MMSE scores at baseline of 0-5 and 6-10, respectively. This translates to a 3-6-point difference on the 100-point SIB scale in favor of higher dosage (23 mg/d) over to (10 mg/d). In addition, analysis of subdomains of the SIB showed improvement or at least less decline in LS mean change from baseline in some subscales such as memory, praxis, language, attention, visuospatial ability, as well as construction for both severe MMSE subgroups. Mixed values were presented for orienting to name and social interaction. Negative values were stated for orientation in MMSE subgroups. In this study, p values were not reported for subgroup LS mean treatment differences, and so, interpretation of the impact of the real values is challenging, since each domain of SIB is weighted differently (ranging from 2 to 46 points). However, standardized effect sizes between 23 and 10 mg represent superiority of donepezil at the 23-mg/d dose over 10-mg/d dose (Table 8). In Cohen's terminology, effect size is categorized into small (0.2-0.3), medium (0.5), and large (0.8) groups.[36] Analysis data based on Cohen's terminology reported that none of the individual domains show donepezil reaching a medium size effect in advanced disease. The highest effect size between 0.3 and 0.4 referred to praxis, language, memory, and construction, with the most severe MMSE scores (0-5) indicating the highest effect sizes compared to all other strata. Effect sizes for total SIB scores were also shown in the MMSE 0-5 and 6-10 subgroups that were 0.460 and 0.273, respectively. A pooled cohort study from three Alzheimer clinical trials over an 18-month period reported that the average MMSE score diminished by 3.5 points.[37] Furthermore, analyses of MMSE scores in the same clinical trials presented a slight LS mean change in scores varying from

TABLE 8 Outcome measures of five studies

Analysis	Black, 2007		Winblad, 2006			Feldman, 2005	Homma, 2008		Ferris, 2013	
	LOCF	OC	LOCF	MMRM	OC	LOCF	LOCF		LOCF	
Donepezil dose	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	5 mg	10 mg	23 mg	
SIB LS mean difference[a] (score (p))	5.32 (0.0001)	5.59 (0.0008)	5.6 (0.008)	4.5 (0.01)	5.8 (0.008)	7.42 (0.0017)	6.7 (0.001)	8.9 (0.001)	MMSE 0-5 = 6.048 MMSE 6-10 = 3.258	
MMSE LS mean difference (score (p))	0.68 (0.0267)	0.74 (0.0409)	1.4 (0.009)	1.0 (0.01)	1.4 (0.009)	1.00 (0.0022)	–	–	–	

LS, least squares.
[a]LS mean treatment difference between placebo and donepezil treatment groups, except for Ferris et al,[35] who compared 10 mg with 23 mg donepezil.

0.68 to 1.4 with 10 mg donepezil compared to placebo group. Collectively, the MMSE scores were slightly higher than baseline for the treatment group. However, these values are relatively small when considering the scoring of the MMSE. Although Ferris et al did not comment on changes in MMSE scores within their *post hoc* analysis, the original data from Farlow et al showed no statistically significant change in MMSE scores from 23 mg donepezil to 10 mg donepezil. Of note, Homma et al did not analyze changes in MMSE scores in their article. Regardless, questions have been raised about the validity of the MMSE in severe disease.[14,38] There are a low overall number of items,[11] with different items having markedly higher weight (0-5 vs 0-1) toward the final score[33] as compared to others. This causes a floor effect for lower values, and therefore it has been argued that the SIB measurement properties in the lower score region are better suited for differentiating poor performance with respect to MMSE.[14,39]

Overall, these analyzed studies stated modest benefits as reported by SIB scores. In particular, domains of language, memory, praxis, and construction seem to be positively affected the most, with effect sizes being small, but statistically significant. MMSE scores showed small differences in favor of donepezil to placebo group.

3.2 | Adverse events

In 2005, Feldman and his colleagues revised AEs within the more severe subclass (MMSE 5-12) of patients from their original study in 2001. Compared to placebo group, the treatment group had a greater ratio of patients with at least one AE (82% vs 78%) and more serious AEs (15% vs 14%), and more patients withdrew due to an AE (7% vs 5%). However, the serious AEs were thought by the investigator to be unrelated to the study medication; there were no deaths. The study reported that vital signs were "generally within normal limits during the course of the study" but did not state bradycardia, syncope, or falls rates. It is not known whether these accidental/non-accidental injury/contusion/bone fracture events were reported. In ≥5% of patients treated with donepezil and at twice the incidence of placebo, AEs included: hostility (17% vs 7%), headache (14% vs 4%), diarrhea (11% vs 3%), confusion (11% vs 5%), fecal incontinence (8% vs 3%), somnolence (7% vs 0%), vomiting (7% vs 1%), back pain (7% vs 3%), flatulence (6% vs 0%), rash (6% vs 3%), and UTI (6% vs 3%). However, the safety or tolerability discussion section in the article instead states that "there were no AEs happening in more than 5% of placebo group that were twice the incidence in donepezil-treated groups." Weight decrease, asthenia, insomnia, and anorexia were also reported at slightly higher rates in the treated group. Although vomiting was stated in 7% of donepezil patients versus 1% of placebo group, nausea was reported in 4% of both treated groups. Aside from stating that some AEs (diarrhea and vomiting) were cholinergic related, this study did not discuss AE causality.

The study by Farlow et al[21] showed that a higher percentage of patients stop treatment due to a treatment-emergent adverse event (TEAE) in the 23-mg/d group (19%) as compared to the 10-mg/d group (7.9%). Most of the discontinuations in the higher treatment group occurred during the first month of treatment (60%). The most common TEAEs causing discontinuation for 23 mg/d and 10 mg/d, respectively, were: vomiting (2.9% vs 0.4%), nausea (1.9% vs 0.4%), diarrhea (1.7% vs 0.4%), and dizziness (1.1% vs 0%). Although the absolute values are fairly small, the individual TEAEs percentages leading to discontinuation were over four times the frequency in the higher-dose group. Also, the most common TEAEs overall for the 23-mg/d and 10-mg/d groups were: nausea (12% vs 3.4%), vomiting (9.2% vs 2.5%), diarrhea (8.3% vs 5.3%), dizziness (4.9% vs 3.4%), and anorexia (5.3% vs 1.7%). Additionally, gastrointestinal (GI) TEAEs occurred during the first month in 21% of the 23-mg/d group, and in 5.9% of the 10-mg/d patients. This is the only study that noted both bradycardia and weight loss. The higher- and lower-dose groups had recorded bradycardia in 2.8% and 0.6% of patients, respectively. Additionally, the higher-dose group had a greater fall, contusion, fatigue, dizziness, and headache rates. Some AEs such as weight loss was reported in 4.7% of patients treated with 23 mg/d and in 2.5% of the 10-mg/d group. Moreover, AEs were observed as a weight decrease of ≥7% in 11% of 23-mg/d patients vs 7.4% of 10-mg/d patients.

A study by Black et al[34] showed more individuals in the treatment group discontinue the drug as compared to placebo group (19% vs 11%), and a greater ratio that discontinued due to AE/intercurrent illness (19% vs 11%). The most common AEs leading to discontinuation were pneumonia, anorexia, agitation, and somnolence. Also, there are other unspecified discontinuation reasons that were designated in the treatment group rather than placebo group (7.4% vs 5.4%). More AEs related to study medication were recorded in the donepezil group (42% vs 31%), which included diarrhea, nausea, vomiting, anorexia, and agitation. AEs (diarrhea, insomnia, nausea, infection, urinary incontinence, and pain) reported in the treatment group were greater than or equal to twice the frequency of placebo group. In general, placebo groups mostly experienced severe AEs (16% vs 11%) rather than the treatment group (15% vs 11%). Notably, due to an AE, eight patients in the placebo group (4.8%) vs only two in the donepezil group (1.1%) died. However, none of these deaths happened due to treatment, and this could be the reason for the inconsistency in the aforementioned results. It is important to state that there were "clinically meaningful" changes in laboratory tests or "significant change" in vital signs. Unusual ECG values appeared in the same percentage of patients in each group and falls or fall-related injuries were not mentioned.

A study by Homma et al[22] revealed an almost 18% discontinuation rate during the treatment period with those attributed to an AE/concurrent illness being 11% of placebo, 7.9% of 5 mg/d, and 14% of 10 mg/d. AEs resulting in discontinuation rate were highest in the 10-mg/d group. However, the maximum percentage of AE, categorized as serious and severe, was observed in the placebo group (14% vs 10%, respectively). Two individuals in each treatment group and one person from placebo died during the treatment period. The authors could not explain causality in two of the five people, who were on a 5-mg/d dose at the time of death (by arrhythmia and myocardial

infarction). At the end of the study, a clinical increase in blood creatine kinase (CK) levels was reported in the donepezil (5 mg = 4.0%, 10 mg = 9.4%) group compared to placebo (2.9%) group. Most of the patients with increased values in the 10-mg/d group had shown advancements when still on the 5-mg/d dose; these values developed with time. The ST elevation was probably attributed to treatment in the 10-mg/d group. Other less serious AEs recorded at higher or equal to twice the frequency of placebo group were: decreased appetite, restlessness, and pyrexia (5 and 10 mg), constipation (5 mg only), anorexia, diarrhea, vomiting, and excoriation (10 mg only). Study by Winblad et al stated a similar percentage of serious AEs and death between treatment and placebo groups and did not consider either to be treatment related.[31] The total incidence of AEs was 82% donepezil, 76% placebo, with most being "transient and mild or moderate in severity." The most common AEs reported were categorized as urinary tract infection, accidental fall, diarrhea, and pneumonia. Unlike other studies, the AEs were not distinguished as likely vs not likely due to medication. Any AEs that were stated in at least 5% of patients in either treatment group were recorded. Although vomiting is a main side effect commented on by other studies, it does not list within its AEs. They instead list other AEs such as nausea and gastroenteritis, but how they diagnosed gastroenteritis from drug-induced vomiting is not clear, as gastroenteritis is often a clinical diagnosis. Those AEs (diarrhea, accidental bone fracture, and hallucinations) occurred in at least twice the frequency of the placebo groups. The latter was stated as "possibly treatment related" in four (3%) of donepezil-treated patients. Anorexia/loss of appetite was not recorded. There were noticeably more individuals that stopped their treatment due to AEs in the donepezil group than in the placebo group (16% [20] *vs.* 7% [n = 8]). All five studies listed were compared for the emergence of AEs in patients treated with donepezil at various dosages (5, 10, and 23 mg/d). In general, due to increased parasympathetic cholinergic activity, the most common AEs were diarrhea, nausea, vomiting, and anorexia (with associated weight loss or loss of appetite). There were increased AE rates with higher doses on most outcome measures, with the 23 mg/d trending toward the most frequent amount of AEs.

Health Canada in 2015 released an alert warning the public of two new potentially serious AEs with the use of donepezil.[40] The first one was rhabdomyolysis that involves the breakdown of muscle tissue with symptoms including weakness, muscle pain, fever, nausea, and dark urine. Also, kidney failure and arrhythmias may result. The second one was neuroleptic malignant syndrome (NMS), which is a neurological disorder that involves marked reduction in dopamine activity that is characterized by fever, muscular rigidity, delirium, autonomic instability, and may develop into rhabdomyolysis, verified by elevated plasma creatinine phosphokinase.[40] Due to Health Canada, internationally, a total of 88 cases of rhabdomyolysis and 67 of NMS have been recorded, with only one case of rhabdomyolysis occurring in Canada that was thought to be possibly related to the drug. Three episodes of rhabdomyolysis and nine occurrences of NMS proved to be fatal. Therefore, it is very important to know whether patients are known to be on other medications known to cause rhabdomyolysis, such as statins, antipsychotics, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors, or when risk factors such as muscular disorders, uncontrolled hypothyroidism, or known liver/kidney damage are present.[41] Prescribing updates have been made accordingly to both brand name donepezil and its generic equivalents.

4 | DISCUSSION

This review presented the possible risks and benefits for utilizing various doses of donepezil for managing severe AD. In this study, various measurement scales were utilized in assessing outcomes of AD treatment. Combination of comparative studies assessing dose response with donepezil (5 and 10 mg/d) indicated that higher dosage of donepezil improves cognition and preserves function in individuals with severe AD. The enhancements in cognition seem to have a positive effect on the functioning of the AD individuals. Furthermore, increased benefits of AD treatment via donepezil correlated with escalating dose to 23 mg/d in patients with more advanced baseline disease, as measured by SIB scores. Randomized, double-blind, multicenter, head-to-head clinical trial indicated patients receiving donepezil, 23 mg/d, showed a statistically significant improvement in cognition compared with 10-mg/d group. Additionally, the difference between groups on a measure of global functioning was significant in higher doses as measured by post hoc analysis. However, AEs occurred more frequently and with increasing severity as the dose increased. Due to an AE, some patients assigned to donepezil stopped their treatments; however, more severe AEs requiring discontinuation have also been reported. Another risk of discontinuation was related to worsening cognitive function and greater functional impairment. There is limited research available concerning evidence-based discontinuation of drugs in severe dementia. In this study, almost 81% of physicians recommended discontinuing therapy for a subset of patients. The reason for stopping donepezil therapy could be related to either perceived benefits by the hospice medical director or challenges with convincing family to discontinue therapy. Due to the effect of donepezil for severe end-stage dementia, almost 20-30% of patients acquired cognitive (22%), behavioral (28%), and/or functional (22%) benefit. Additionally, it was agreed that donepezil improved patient quality of life (15%) or improved survival (3%). However, discontinuation of donepezil in patients with severe end-stage dementia resulted in accelerated behavioral challenges (32%), functional decline (26%), increased caregiver burden (22%), and decreased quality-of-life measurements (17%).[26,42] Some medication guidelines fail to reference the prescription of donepezil in the elderly,[43] whereas some guidelines state donepezil as being an inappropriate drug in severe dementia (CPS score 4-6)[44] or severe AD (MMSE <10)).[45] Overall, there is no agreement on recommendations about whether and when donepezil should be discontinued and current recommendations are based on weighing risks versus benefits.

Because very few drugs have been approved for the treatment of severe AD, higher doses of donepezil may be a safer option for treatment of individuals with moderate—severe AD or patients who are no longer responding to lower doses. Clinicians must weigh these benefits against the possible AEs when determining the appropriate course of therapy, as recommendations for discontinuation of cholinesterase inhibitors in advanced AD remain unclear and vary with different guidelines. It is clear that additional research is required for developing better treatment options.

Another option for treatment of AD in moderate-to-severe stage would be concomitant medication. Administration of memantine with donepezil resulted in significantly better outcome than placebo on measures of cognition, activities of daily living, global outcome, and behavior. Although Winblad et al acknowledge this observation in the article's introduction, there is no further mention of memantine in the exclusion criteria. Farlow et al declared concomitant use of memantine in 36.6% and 35.7% of 23-mg and 10-mg groups, respectively. It is unclear whether Feldman et al or Homma et al allowed memantine use. Black et al required discontinuation at a minimum of 3 months prior to screening.

5 | CONCLUSION

Although there is no cure for AD, medications can slow the worsening of symptoms temporarily and improve the quality of life for those with AD. In addition, donepezil treatment shows small but measurable clinical benefits in various stages of AD. The information in this review should allow physicians to improve treatment options for those individuals in various stages of AD.

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