Donepezil: A Review of Pharmacological Characteristics and Role in the Management of Alzheimer Disease

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ABSTRACT: We reviewed the literature on the pharmacological characteristics and role of donepezil in Alzheimer disease. We performed an evidence-based review of randomized controlled trials by searching sources such as PubMed, MEDLINE, Google Scholar, and Clinical Key. In total, 18 randomized clinical trials were identified. In amnestic mild cognitive impairment (MCI), data showed that donepezil delays progression to Alzheimer disease. However, for mild-to-moderate and moderate-to-severe Alzheimer disease, it proved effective in slowing cognitive and global function decline. Discontinuation of donepezil results in acceleration of disease progression. The effects of donepezil on behavioral symptoms have shown mixed outcomes. Donepezil is the standard of care in Alzheimer disease as it is well tolerated and has self-limiting gastrointestinal adverse effects. In amnestic MCI, off-label use of donepezil can be considered after risk stratification of conversion to Alzheimer disease.

KEYWORDS: Alzheimer disease, donepezil, randomized controlled trials, adverse effects

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Background

Alzheimer disease (AD) is the most common form of dementia in the elderly.[1,2] The disease is a marked by a slow progressive and irreversible decline in the neurocognitive function over the years that effects memory, language, problem solving, and eventually the ability to do simple tasks. In 2015, there were approximately 5.3 million people in the United States affected by AD, of which 5.1 million were aged 65 or older. Barring development of medical breakthroughs to prevent or cure the disease this number is expected to rise to 13.8 million in 2050.[3]

The diagnostic criteria for AD continuum were updated in 2011 based on clinical features, along with spinal fluid and neuroimaging biomarkers. Alzheimer disease is divided into 3 phases: a preclinical phase, a predementia phase, and a dementia phase. The preclinical phase is characterized by measurable changes in biomarkers such as neuroimaging and spinal fluid beta amyloid and tau changes, with no apparent symptoms. It is followed by the predementia phase referred to as "mild cognitive impairment (MCI) due to AD," in which the patient has mild changes in memory and thinking abilities with positive biomarkers, but activities of daily living (ADL) and functioning are mainly preserved. The third phase is the dementia phase in which there are cognitive and behavioral symptoms that impair a person's ability to function in daily life in the context of positive biomarkers.[4–6]

The cholinergic hypothesis was coined by Bartus et al[7] in 1982. It was the result of the idea that memory dysfunction in AD was caused by a cholinergic deficit.[8] Significant age-related decline in the number of neurons in the Nucleus basalis of Meynert was detected in AD patients compared with age-matched controls. The nucleus basalis of Meynert was believed to be the main source of cholinergic input to the cortical mantle, and loss of this connection was thought to be a major event in the pathogenesis of AD.[9] The cholinergic hypothesis proposed that cholinomimetic drugs would improve cognition in AD patients. There were 2 ways to increase brain acetylcholine (Ach) levels. The primary way involved increasing the brain Ach levels by administering Ach or one of its precursors. The other was to inhibit the enzyme acetylcholinesterase (AChE), which was responsible for breaking down Ach in nerve synapse. Due to difficult pharmacological management and no significant increase in brain Ach using the above methods, an additional option of inhibiting AChE to increase Ach in the nerve synapse was considered. The first AChE inhibitor (AChEI) that was tested in clinical trials was tacrine.[10] However, tacrine was taken off the market soon after its introduction in 1993 because of its hepatotoxicity and poor tolerability. In 1996, donepezil was approved by the Food and Drug Administration (FDA) after randomized, double-blind, placebo-controlled studies demonstrated its efficacy and safety in AD patients. The cholinergic hypothesis explains only part of the complex neurodegenerative mechanism in AD[7]; however, treatment efficacy was proven, and thus AChEIs remain the gold standard for treatment of AD.

Donepezil

Chemistry and preclinical studies

Donepezil (Aricept; E 2020) is a hydrochloride salt of piperidine that is a reversible and noncompetitive inhibitor of AChE. Acetylcholinesterase is an enzyme found in the nerve synapse and is the enzyme involved in the hydrolysis of the neurotransmitter Ach. Donepezil inhibits the hydrolytic activity of AChE and increases the concentration of Ach in the nerve synapse. In AD, there is decreased activity of choline acetyltransferase leading to decreased presynaptic synthesis of ACh and

decreased cholinergic transmission across the synapse. Donepezil increases the synaptic ACh and improves the cholinergic transmission.

The reversible noncompetitive AChE inhibiting action of donepezil has been demonstrated in numerous experimental models. The earliest animal studies in rats used physostigmine (PHY) and tacrine as reference compounds. Tacrine and PHY demonstrated nonselective inhibition of both AChE and butyrylcholinesterase (BuChE). However, the in vitro and in vivo studies showed donepezil to be more selective for AChE than BuChE.[11] As BuChE is found in the peripheral tissues and AChE is found primarily in the brain, it was expected that donepezil would be more tissue-specific as compared with the reference compounds. This hypothesis was later proven through further experimentation. Ogura et al conducted a series of in vitro experiments in which they compared the inhibitory potency of donepezil with other drugs. Of the AChEIs that were tested, donepezil was found to be the most selective. The order of inhibitory potency (IC50) toward AChE is as follows: PHY > rivastigmine > donepezil > TAK-147 > tacrine > ipidacrine.[11] Experiments carried out in rats revealed dose- and time-dependent increases in concentration of Ach in various parts of rat brain, including the cerebral cortex, striatum, and hippocampus.[12] Another set of experiments to study cholinergic hypofunction in rat models was performed by injecting ibotenic acid, or AF64A, in the lateral ventricles to destroy parts of the brain, including nucleus magnocellularis. These experiments yielded similar results.[12] Using different experimental models including sham-operated animals with lesions in nucleus basalis and scopolamine-induced 8 arm radial maze performance, donepezil improved performance in behaviorally impaired animals.[12]

Pharmacokinetics

Donepezil is absorbed through the gastrointestinal tract with a relative oral bioavailability of 100%.[13] It reaches peak concentration in 3 to 5 hours as compared with <2 hours for other AChEIs. Food bears no effect on the absorption rate nor does it affect the peak concentration (C_{max}), time-to-peak concentration (t_{max}), or area under the curve (AUC).[14,15] Age, however, does increase the t_{max}, which is attributed to decreased gastrointestinal absorption.[16] There exists a linear relationship between donepezil dose and AUC in dose range of 1 to 10 mg/day.[17] In the clinical trials, mean trough plasma concentration (C_{min}) was reported as 25.9 ± 0.7 and 50.6 ± 1.9 µg/L with doses of 5 and 10 mg, respectively.[18] Steady-state concentrations are achieved within 14 to 22 days following repeated administrations of 5 or 10 mg donepezil.[15,17] It is a highly protein-bound drug (96%; 75% to albumin).[14] With the exception of C_{max}, no other pharmacokinetic parameter changes were reported in participants with impaired liver or renal function.[19,20] Its elimination half-life ($t½$) has been reported to be between 60 and 90 hours and may rise up to 104 hours among the elderly.[15,17,18] The longer $t½$ has been attributed to increased volume of distribution. The AUC and clearance did not differ between populations. Considering the clinical insignificance of these changes, no dosage adjustments are recommended.[16] Donepezil clearance is independent of the dose.[15,17]

Pharmacodynamics

Maximum pharmacodynamic effect of donepezil (~70% inhibition) occurs in a cumulative fashion over the first 2 to 3 weeks of its administration. This is consistent with the achievement of steady-state plasma concentration after an equivalent period of time.[17] There is a significant positive correlation between donepezil plasma concentrations and inhibition of AChE in red blood cells. Peak AChE inhibition coincides with t_{max} in plasma.[15,21]

Metabolism

Donepezil undergoes first-pass metabolism. It is primarily metabolized by CYP2D6 and CYP3A4.[14,18] 6-*O*-desmythldonepezil is its major active metabolite and has equal pharmacological activity to its parent drug. Its plasma concentration is 20% that of donepezil.[18]

Dosage

Randomized controlled trials have shown that 5 mg/day dose of donepezil is clinically effective.[22,23] In addition, a dose-response effect is also evident within those participants who were on 10 mg/day dosing regimen, demonstrating greater clinical benefit,[24] with both doses being well tolerated. The higher incidence of cholinergic adverse events experienced in the 10 mg/day dose group in these trials as compared with other groups is thought to be the result of rapid dose increase, ie, 5 mg/day for first 7 days, then 10 mg for the remaining study. When the dose is increased after 4 to 6 weeks of treatment at 5 mg/day, the adverse effects profile for 10 mg/day donepezil is similar to that of the placebo-treated and 5 mg/day donepezil groups.[25]

In moderate-to-severe AD, 23 mg/day donepezil has shown additional cognitive benefit over 10 mg/day dose of donepezil. However, no significant effect was found on global functioning with the increased dosage. Post hoc analysis of severe impairment battery (SIB) in the population suggested that AD patients who are more severely impaired may also experience a global benefit with 23 mg/day donepezil. High-dose group had more adverse events as compared with 10 mg/day of which self-limiting gastrointestinal side effects such nausea, vomiting, and diarrhea were the most common. No serious adverse events were associated with the high-dose group.[26]

Clinical Studies

Cholinesterase inhibitors, used for symptomatic management of AD, have been the mainstay of the treatment for AD. We

review and interpret data from randomized, placebo-controlled double-blind clinical trials to determine when to start, how long to persist with treatment, what are the consequences of stopping and what the realistic expectations are for effect, and how to measure it. Outcome measures and treatment expectations are stage-specific, and most trials study specific stages of the disease.

We review the clinical trials in the following stages of the continuum of AD: amnestic MCI, early AD, mild-to-moderate AD, and moderate-to-severe AD. In addition, trials studying the effect of donepezil on behavioral functions and the effect of discontinuation of donepezil have been discussed separately.

Methods

To critically review the risk/benefit of donepezil, we took an evidence-based approach. Due to the extensive literature, we reviewed all the published class A evidence category for efficacy and behavioral outcomes and all classes for adverse drug reactions. We used the keywords "Alzheimer's disease," "amnestic MCI," "mild to moderate Alzheimer's," "moderate to severe Alzheimer's," "donepezil," "adverse effects," and "randomized controlled trials" for search in PubMed, MEDLINE, Google Scholar, and Clinical Key, without any restriction for language. We also checked the bibliographical information of the publications for further studies which may have been missed by the search parameters.

Amnestic MCI

Three randomized, double-blind, placebo-controlled studies were conducted studying the effects of donepezil therapy in amnestic MCI patients (see Table 1 and Figure 1).

Salloway et al[27] found there to be no significant difference between participants taking donepezil 10 mg vs placebo group in the NYU Paragraph Delayed Recall Test. Donepezil was shown to have beneficial results in a subset of secondary outcome measures, including Alzheimer's Disease Assessment Scale–Cognitive section (ADAS-cog), Wechsler Memory Scale–Revised, Digit Span Backwards test, and Symbol Digit Modalities. However, caution should be used when interpreting the results due to the number of secondary outcome measures observed. The major limitation of the study was the short duration of 24 weeks to detect treatment effects. The primary measure was NYU Paragraph Delayed Recall Test, which is a relatively difficult test and might have limited usefulness in detecting treatment effects in the MCI population due to possible floor effects. In addition, the dropout rate in the donepezil group likely had an effect on the statistical power.

Petersen et al[28] found that donepezil 10 mg delayed conversion of amnestic MCI to AD in the first year with significant beneficial effects on cognition, language, and executive function in the first 18 months as compared with placebo group. For carriers of the APOE4 genotype, the delay in conversion to AD was extended to 3 years. This indicates that although donepezil may not stop the progression of amnestic MCI to AD, it can help improve the quality of life (QoL) for the patients during progression to AD. Furthermore, donepezil modifies the risk of conversion in APOE4 carriers, potentially being especially useful in this population.

In a randomized study of 821 participants, Doody et al[29] found treatment with donepezil 10 mg resulted in a small but significant decrease in ADAS-cog score at the study endpoint but revealed no change in global impairment scale Clinical Dementia Rating–Sum of Boxes (CDR-SB) between the 2 groups.

Subjects and caregivers in both Salloway et al[27] and Doody et al[29] reported significant improvement in cognition and global performance with donepezil treatment compared with the placebo group. This suggests that the outcome measures used to assess the treatment efficacy were not sensitive enough to assess the efficacy of treatment and detect the benefit of donepezil in MCI; these instruments were developed for AD, which has more pronounced deficits in cognition, behavior, and executive functioning compared with MCI. Discontinuation rates were higher in the treatment group in all 3 clinical trials as compared with other clinical trials of mild-to-moderate or moderate-to-severe AD, indicating the subjects might have had less ability or were less willing to tolerate the side effects of donepezil as compared with those with AD.

Early AD

One randomized, double-blind, placebo-controlled study of early AD patients was conducted by Seltzer et al.[30] The participants had to meet the inclusion criteria consisting of a modified Hachinski Ischemia Scale score of 4 or less, a global Clinical Dementia Rating (CDR) Scale score of 0.5 or 1.0, a Mini-Mental State Examination (MMSE) score of 21 to 26, and only mild impairment in ADL, defined by a summed score of 2 to 4 on the 3 functional domains (home and hobbies, community affairs, and personal care) of the CDR, with no more than 1 functional domain with a score of 2 or more. Patients were excluded if the decline in memory was possibly attributable to a psychiatric or neurologic disorder or to cognitive deficits following head trauma. Previous treatment with cholinesterase inhibitors, whether approved or in development, was not permitted. The study lasted for 24 weeks with a 2:1 randomization of participants to donepezil (n = 96) and placebo (n = 57) groups; 5 mg donepezil was given for the first 6 weeks followed by an escalation to 10 mg for the remaining duration. Modified ADAS-cog was used as the primary outcome measure, whereas MMSE, CDR-SB, Computer Memory Battery Test (CMBT), Apathy Test, and Patient Global Assessment Scale (PGAS) were the secondary outcome measures.

Table 1. Summary of placebo controlled double blind clinical trials of donepzezil in aMCI.

AUTHOR	NO. OF SUBJECTS	DOSE	MMSE RANGE OF PARTICIPANTS INCLUDED	DURATION	PRIMARY OUTCOME MEASURE	SECONDARY OUTCOME MEASURE	COGNITION BENEFIT IN DONEPEZIL VS PLACEBO GROUP	APOE4 POSITIVE STATUS EFFECT ON COGNITIVE BENEFIT
Salloway et al[27]	270	5 mg for 6 wk then 10 mg for 18 wk	24-30	24 wk	NYU Paragraph Delayed Recall Test, ADCS CGIC-MCI	ADAS-cog, WMS-R DSB test, Symbol Digit Modalities, Boston Naming task, Verbal Fluency test, Maze test, Number Cancellation Test, PGA	NYU Paragraph Delayed Recall Test showed insignificant benefit ($P > .05$), whereas ADAS-cog showed significant benefit ($P < .05$)	Not reported
Petersen et al[28]	512	10 mg	24-30	3 y	ADAS-cog	MMSE, CDR-SB, GDS, Modified ADAS-cog	Significant in 0 to 12 mo ($P = .004$), in 0 to 24 mo ($P = .03$), insignificant in all 36 mo ($P = .21$)	Significant in 0 to 12 mo ($P = .003$), in 0 to 24 mo ($P = .009$), in all 36 mo ($P = .04$)
Doody et al[29]	821	5 mg for 6 wk then 10 mg for 42 wk	24-28	48 wk	ADAS-cog, CDR-SB	MMSE, SDMT, DSB, PDQ, PDQ-R, NPI, PGA, CGIC-MCI	ADAS-cog showed significant benefit ($P = .01$), CDR-SB was insignificant	No difference on the basis of APOE4 status

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive section; CDR-SB, Clinical Dementia Rating–Sum of Boxes; DSB, Digit Span Backwards test; GDS, Global Deterioration Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PDQ, Perceived Deficits Questionnaire; PDQ-R, Perceived Deficits Questionnaire for Relatives; PGA, patient global assessment; SDMT, Symbol Digit Modalities Test; WMS-R, Wechsler Memory Scale–Revised NYU, New York University; ADCS-CGIC-MCI, Alzheimer's Disease Cooperative Study Clinical Global Impression of Change-Mild Cognitive Impairment; APOE4, Apolipoprotein E4; PGA, Patient Global Assessment.

There were improvements with donepezil on the modified ADAS-cog scale as early as week 12 ($P = .03$). The donepezil-placebo difference was approximately 2.3 points at week 24 ($P = .008$) and at the endpoint ($P = .001$). During the 24-week period, 70% of participants on donepezil did not experience cognitive worsening compared with 47% of those in the placebo group.

Improvements were observed in MMSE score favoring donepezil as early as week 6 ($P = .02$), and were sustained through week 24 ($P = .03$). The donepezil-placebo difference at the endpoint was 1.8 points in favor of donepezil ($P = .002$). Improvements favoring donepezil on CMBT tasks testing verbal and visual memory were noted. Donepezil group scored higher on the Apathy scale, but the difference was not significant. The lack of change on CDR-SB and PGAS was expected as there was minimal functional impairment in these patients.

The safety data showed that donepezil was well tolerated and safe among the study participants. In addition, the study showed minimal or no decline in ADAS-cog and MMSE as opposed to mild-moderate AD studies, where a decline of 1 to 1.8 on ADAS-cog was reported in 24 weeks.[22,23] This suggests a different treatment response in early AD as compared with advanced stages.

Mild-to-moderate AD

Four randomized, double-blind, placebo-controlled studies were conducted to study the effects of donepezil therapy in mild-to-moderate AD patients (see Table 2 and Figures 2 and 3).

Rogers et al[23] showed statistically significant improvements in cognitive function of donepezil-treated groups during a 24-week randomized controlled trial, as measured by the ADAS-cog (3.2-point 10 mg donepezil-placebo difference at 24 weeks), as well as in global function, as measured by the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+), relative to placebo. Benefits were also found using the MMSE, CDR-SB, and to a lesser extent QoL, confirming cognitive and functional improvements associated with donepezil treatment. This study also showed a statistically significant dose-response effect, which became apparent during the 12th week of the trial. Pharmacokinetic and pharmacodynamic substudy demonstrated that 10 mg/day donepezil inhibits AChE on the upper asymptote of the enzyme inhibition curve, suggesting that further increases in dose would only result in marginal increases in activity. In addition, safety data showed that donepezil is safe and well tolerated in the mild-to-moderate AD population.

In a separate 15-week randomized controlled trial, Rogers et al[13] found donepezil to be more beneficial compared with placebo in improving cognitive and global function as measured by improvement in ADAS-cog and CIBIC+, respectively. The difference in mean ADAS-cog at endpoint between 5 and 10 mg donepezil from placebo group was 2.5 and 3.1 points, respectively. As for CIBIC+, the difference was 0.3 and 0.4 for

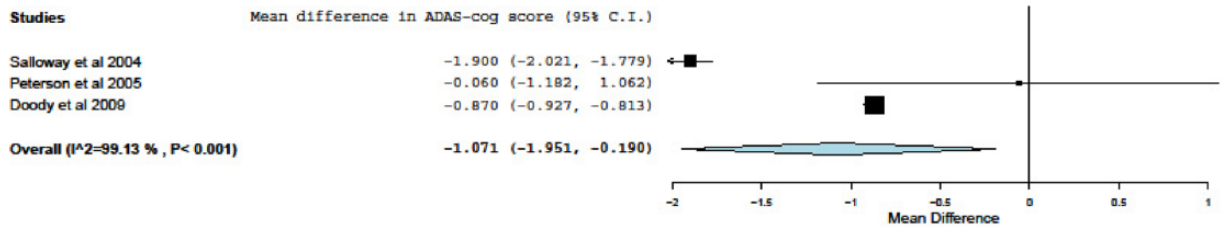

Figure 1. Forest plot showing the mean difference in ADAS-cog score between the donepezil and placebo groups in amnestic MCI randomized controlled trials. Lower ADAS-cog scores with donepezil in Salloway et al and Doody et al clinical trials. ADAS-cog indicates Alzheimer's Disease Assessment Scale–Cognitive section; CI, confidence interval; MCI, mild cognitive impairment.

5 and 10 mg, respectively. There was a mean difference of 1.1 and 1.3 points in MMSE between 5 and 10 mg in the donepezil and placebo groups. No significant difference was noted on the CDR-SB, likely due to the shorter duration of 15 weeks of the study. Pharmacokinetic and pharmacodynamics substudy established a statistically significant correlation between plasma concentrations of donepezil and AChE inhibition in red blood cells as well as improvement in ADAS-cog and CIBIC+. Safety data showed that donepezil is safe and well tolerated in mild AD patients.

In a study performed by Burns et al,[22] significant benefit from donepezil compared with placebo in improving cognitive and global function was reported. In addition, this study also assessed the effect of donepezil on ADL (Interview for Deterioration in Daily Living Activities in Dementia [IDDD] self-care and IDDD complex tasks). For IDDD complex task, there was a statistically significant improvement. This is consistent with the fact that complex tasks are impaired earlier in the disease, whereas ability to care for self is not impaired until late in the disease. A statistically significant dose-response effect was also noted. Safety data showed that donepezil is safe and well tolerated in mild AD patients. As this was a multinational trial, it demonstrated that despite variations in local diagnostic and treatment practices, donepezil therapy is an effective and well-tolerated symptomatic treatment for patients with mild to moderately severe AD.

Mohs et al[31] showed that the beneficial effects of donepezil on cognition, behavior, and function in AD patients extend to 1 year and possibly beyond. The donepezil-treated group retained their function 72% longer as compared with the placebo group. The median time to clinically evident functional decline for the placebo group was 208 days (95% confidence interval [CI], 165-252 days) and 357 days (95% CI, 280-434 days) for donepezil-treated group. The probability of survival with no clinically evident functional decline for participants in the donepezil group was 51% at 48 weeks (95% CI, 43%-58%) compared with 35% (95% CI, 27%-42%) in the placebo group. The hazard ratio for reaching endpoint was 0.62. Thus, participants treated with donepezil were 38% less likely to decline over a 1-year period. Safety data showed that donepezil is safe and well tolerated in mild-to-moderate Alzheimer patients.

Moderate-to-severe AD

The effects of donepezil therapy in moderate-to-severe AD patients was investigated in 1 randomized, double-blind, placebo-controlled studies (Table 3).

In 1 study, Feldman et al[32] showed significant difference in CIBIC+ scale, which suggests clinical response to donepezil may be much more evident in advanced AD than in milder disease. To assess cognition, standardized Mini-Mental State Examination (sMMSE) and SIB were used. Severe impairment battery was sensitive to change with a difference of 5.7 points between the donepezil and placebo groups, whereas sMMSE showed a floor effect in the placebo group. Stabilization of function was achieved with donepezil. Previously, it has been shown that using Disability Assessment for Dementia, patients with more advanced AD declined more rapidly than those with mild AD, and baseline severity was important in predicting subsequent rate of change. Donepezil-treated participants maintaining their baseline ADL became even more significant with the placebo decline ($P < .002$). Furthermore, given the functional loss in the advanced stages, stabilization of function was the best possible functional outcome. Positive results across all the measures indicate that this was a treatment effect and not due to instrumentation or measurement. Safety data showed that there was no difference in safety profile of donepezil compared with what was observed in the previous mild-moderate stage AD clinical trials as it was well tolerated in these advanced stage AD patients.

Severe AD

The effects of donepezil therapy in severe AD patients were investigated in 3 randomized, double-blind, placebo-controlled studies (Table 3).

In a trial performed by Winblad et al,[33] donepezil-treated participants had improved results as compared with placebo group in SIB and Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) inventory for severe Alzheimer's Disease Scale. There was a 4.5-point difference ($P = .01$) on the SIB scale and 1.4-point difference ($P = .03$) on the ADCS-ADL scale in favor of donepezil. A 1.4-point difference ($P = .009$) on the MMSE in favor of donepezil was shown among the secondary measures. Clinical Global

Table 2. Summary of placebo controlled double blind clinical trials of donepzezil in Mild-Moderate AD.

AUTHOR	NO. OF SUBJECTS	DOSE	MMSE RANGE OF PARTICIPANTS INCLUDED	DURATION	PRIMARY ENDPOINT	SECONDARY ENDPOINT	RESULTS (DIFFERENCE BETWEEN TREATMENT AND PLACEBO GROUP)	CONCLUSION
Rogers et al[23]	473	5 and 10 mg	10-26	24 wk	ADAS-cog, CIBIC+	MMSE, CDR-SB, QoL	Significant ($P < .05$) improvement in ADAS-cog, CIBIC+, MMSE, and CDR-SB in both donepezil groups. No overall effect on QoL	These data indicate that donepezil is a well-tolerated drug that improves cognition and global function in patients with mild-to-moderate AD
Rogers et al[13]	468	5 and 10 mg (5 mg for 1 wk, then 10 mg for remaining part of the study)	10-26	15 wk	ADAS-cog, CIBIC+	MMSE, CDR-SB, QoL	Significant ($P < .05$) improvements in ADAS-cog, CIBIC+, and MMSE in both donepezil groups compared with placebo	Donepezil is well tolerated and efficacious in treating the symptoms of cognitive loss and in improving global functioning in patients with mild-moderate AD
Burns et al[22]	818	5 and 10 mg (5 mg for 1 wk, then 10 mg for remaining part of the study)	10-26	24 wk	ADAS-cog, CIBIC+	CDR-SB, QoL, IDDD	Significant ($P < .05$) improvement in ADAS-cog, CIBIC+, IDDD, and CDR-SB for both donepezil groups. No overall effect on QoL	Results confirm previous findings that donepezil is well tolerated and efficacious in treating the symptoms of cognitive loss and in improving global functioning in patients with mild-moderate AD
Mohs et al[31]	431	5 mg for 4 wk, then 10 mg thereafter	12-21	54 wk	Clinically evident functional decline	ADFACS, CDR-SB, MMSE	Clinical functional decline was delayed and less likely with donepezil. Significant benefit ($P < .05$) noted with donepezil compared with placebo group on ADFACS, CDR-SB, and MMSE	There is detectable disease progression in patients over time, but compared with donepezil treatment for 1 year is associated with a 38% reduction in the risk of functional decline

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive section; ADFACS, Alzheimer's Disease Functional Assessment and Change Scale; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CIBIC+, Clinician's Interview-Based Impression of Change Plus Caregiver Input; IDDD, Interview for Deterioration in Daily Living Activities in Dementia; MMSE, Mini-Mental State Examination; QoL, quality of life.

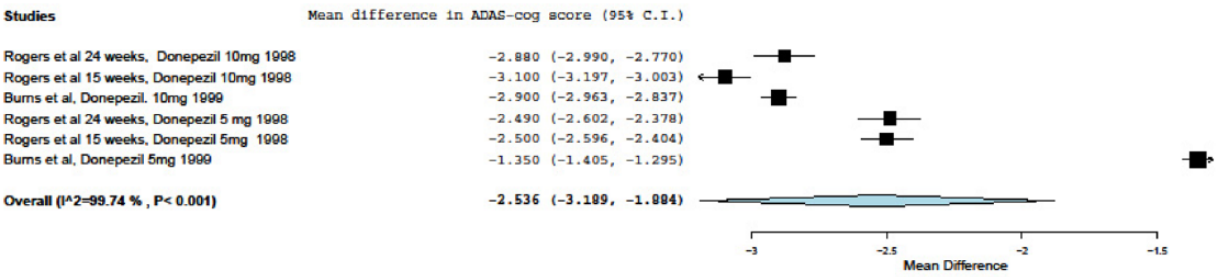

Figure 2. Forest plot showing the mean difference in ADAS-cog score between the donepezil and placebo groups in mild-to-moderate randomized controlled trials. Direction to lower ADAS-cog score is consistent between the clinical trials and demonstrates a dose-response effect. ADAS-cog indicates Alzheimer's Disease Assessment Scale–Cognitive section; CI, confidence interval.

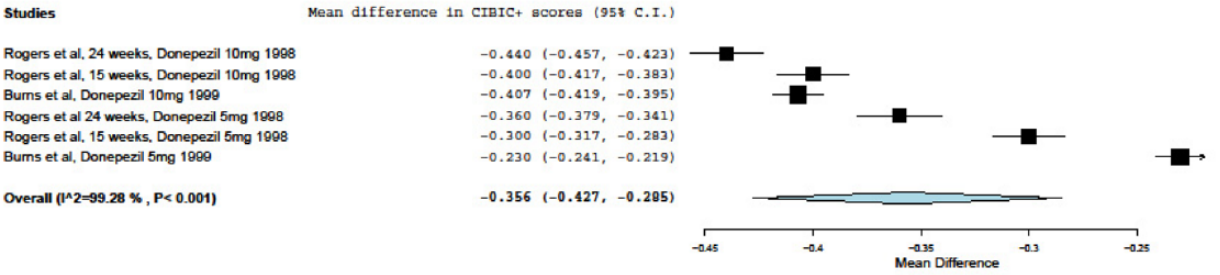

Figure 3. Forest plot showing the mean difference in CIBIC+ score between the donepezil and placebo groups in mild-to-moderate randomized controlled trials. Direction to lower CIBIC+ is consistent between the clinical trials and demonstrates a dose-response effect. CI indicates confidence interval; CIBIC+, Clinician's Interview-Based Impression of Change Plus Caregiver Input.

Impression of Improvement scale revealed an improvement in favor of donepezil. The improvements in cognition seemed to have a positive effect on the functioning of the patients, potentially indicating a direct relationship between these domains. Reviewing the safety data, it can be concluded that donepezil was safe and well tolerated.

Homma et al[24] showed significant difference in SIB scale at both 5 and 10 mg doses compared with placebo group. A significant difference was noted at 10 mg dose on CIBIC+ compared with the placebo group but not with 5 mg dose. Thus, a cognitive response is measurable with the 5 mg dose in severe AD, but a daily dose of 10 mg appears to be required to detect an effect on global function in addition to cognition. This was the first prospective clinical trial that demonstrated a dose-response relationship for donepezil dose of 5 and 10 mg/day on CIBIC+ and SIB. There was no statistically significant difference between the donepezil and placebo groups on ADCS-ADL scale. This is in contrast to results from a study by Winblad et al, which suggests a difference in expectations regarding ADL with severe AD between patients who are in the community vs those who are institutionalized. The results from the study of Homma et al along with the other clinical trials support a 10 mg/day dose of donepezil as treatment for severe AD patients.

Black et al[34] showed that participants with severe AD improved global function, as evidenced by a significant benefit on the CIBIC+ ($P = .047$) and maintained cognitive function with donepezil treatment for at least 6 months as shown on the SIB compared with an approximate 10% decline from baseline in participants receiving placebo. The benefits of donepezil over placebo were not evident on measures of ADL and behavior in this population. No changes were noted on Caregiver Burden Questionnaire (CBQ) and Resource Utilization for Severe Alzheimer Disease Patients (RUSP). For CBQ, it is surprising but less so than RUSP because of the shorter duration of the study (6 months), and they might reflect the relative stability of the patients who are still living in the community.

Behavioral studies

Most randomized controlled clinical trials studying the effect of donepezil incorporated behavioral function as a secondary outcome measure. However, the following 3 studies incorporate it as the primary outcome measure (Table 4).

Tariot et al[35] performed a 24-week study in which donepezil was initially given at a dose of 5 mg for 6 weeks and then 10 mg for the remaining period of the study. It showed that there was improvement from baseline in both the treatment and the placebo groups from the fourth week onward on the Neuropsychiatric Inventory (NPI) scale, but there was no statistically significant difference observed in the change from baseline between the treatment groups at any assessment. The overall mean improvements at week 24 were -4.9 ± 1.9 and -2.3 ± 1.9 for placebo and donepezil treatment groups, respectively.

Gauthier et al[36] showed benefits with donepezil treatment group compared with placebo group for all individual items on the NPI, with significant treatment differences for depression/

Table 3. Summary of placebo controlled double blind clinical trials of donepzezil in Moderate-Severe AD.

AUTHOR	NO. OF SUBJECTS	DURATION	MMSE RANGE OF PARTICIPANTS INCLUDED	DOSE	PRIMARY END POINT	SECONDARY ENDPOINT	RESULTS	CONCLUSION
Feldman et al[32]	290	24 wk	5-17	5 mg for 4 wk, then 10 mg for 20 wk	CIBIC+	sMMSE, SIB, NPI, DAD, FRS, IADL, PSMS	Significant benefit ($P < .05$) with donepezil as compared with placebo shown by all primary and secondary efficacy measures	Donepezil is effective as well as safe and tolerated in advanced stages of AD
Winblad et al[33]	248	24 wk	1-10	5 mg for 30 d, then 10 mg for the remainder of 6 mo	SIB, ADCS-ADL severe[a]	MMSE, NPI, CGI-I	Significant benefit ($P < .05$) with donepezil as compared with placebo shown with SIB, ADCS-ADL, MMSE, and CGI-I (completer population). No benefit shown by NPI	Donepezil improves cognition and preserves function in individuals with severe AD who live in nursing homes. It is safe and well tolerated in this population
Homma et al[24]	302	24 wk	1-12	5 and 10 mg	SIB, CIBIC+	ADCS-ADL, BEHAVE-AD	Significant benefit ($P < .05$) with donepezil as compared with placebo shown with SIB and CIBIC+ (10 mg). No benefit shown by CIBIC+ (5 mg), ADCS-ADL, and BEHAVE-AD	Study confirmed the effectiveness of donepezil 10 mg/d in patients with severe AD and demonstrated a significant dose-response relationship. Donepezil at both doses is safe and well tolerated
Black et al[34]	343	24 wk	1-12	10 mg	SIB, CIBIC+	MMSE, NPI, ADCS-ADL, CBQ, RUSP	Significant benefit ($P < .05$) with donepezil as compared with placebo shown with SIB, CIBIC+, and MMSE. No benefit shown by NPI, ADCS-ADL, CBQ, and RUSP	Patients with severe AD showed greater efficacy with donepezil compared with placebo on measures of cognition and global function. It is safe and well tolerated in patients with severe AD

Abbreviations: AD, Alzheimer disease; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; CBQ, Caregiver Burden Questionnaire; CGI-I, Clinical Global Impression of Improvement; CIBIC+, Clinician's Interview-Based Impression of Change Plus Caregiver Input; DAD, Disability Assessment for Dementia; FRS, Functional Rating Scale; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; RUSP, Resource Utilization for Severe Alzheimer Disease Patients; SIB, severe impairment battery; sMMSE, standardized Mini-Mental State Examination.
[a]Modified instrumental activities of daily living.

Table 4. Summary of placebo controlled double blind clinical trials of donepzezil focusing on behavioral symptoms.

AUTHOR	NO. OF SUBJECTS	DOSE	DURATION	NPI	EFFECT ON BEHAVIORAL FUNCTION	RESULTS
Tariot et al[35]	280	5 mg for 4 wk, then 10 mg thereafter	24 wk	Primary outcome measure (NPI-NH)	No significant difference on NPI-NH between the donepezil and placebo groups	Significant improvement ($P < .05$) in both CDR-SB and MMSE. No significant improvement on PSMS
Gauthier et al[36]	290	5 mg for 4 wk, then 10 mg thereafter	24 wk	Primary outcome measure	NPI showed benefits with donepezil treatment compared with placebo for all items, with significant treatment differences for depression/dysphoria, anxiety, and apathy/indifference ($P < .05$)	Behavioral symptoms of the magnitude observed in moderate-to-severe AD population improved with donepezil
Holmes et al[37]	96	10 mg	3 mo	Primary (NPI) and secondary (NPI-D) outcome measures	Significant improvement in both NPI and NPI-D in those who continued on donepezil vs worsening in discontinuation group	Discontinuation of donepezil is not safe and well tolerated and leads to worsening of behavioral symptoms
Feldman et al[32]	290	5 mg for 4 wk, then 10 mg for 20 wk	24 wk	Secondary outcome measure	Significant benefit ($P < .05$) with donepezil as compared with placebo shown with NPI	Donepezil is effective in reducing behavioral symptoms in advanced stages of AD
Winblad et al[33]	248	5 mg for 30 d, then 10 mg for the remainder of 6 mo	24 wk	Secondary outcome measure	No significant benefit ($P > .05$) with donepezil as compared with placebo shown with NPI	Donepezil does not have significant benefit on behavioral function in individuals with severe AD living in nursing homes
Black et al[34]	343	10 mg	24 wk	Secondary outcome measure	No significant benefit ($P > .05$) with donepezil as compared with placebo shown with NPI	Donepezil does not have significant benefit on behavioral function in individuals with severe AD
Johannsen et al[38]	202	10 mg	3 mo	Secondary outcome measure	Significant improvement ($P < .05$) in NPI in those who continued on donepezil vs worsening in discontinuation group	Discontinuation of donepezil is not safe and well tolerated and leads to worsening of behavioral symptoms
Howard et al[39]	146	10 mg	12 mo	Secondary outcome measure	No clinically significant difference ($P > .05$) in NPI between the 2 groups	Discontinuation of donepezil does not lead to worsening of behavioral symptoms
Herrmann et al[40]	40	10 mg	8 wk	Secondary outcome measure	No clinically significant difference ($P > .05$) on NPI in the 2 groups apart from hallucinations and delusion in the discontinuation group	Discontinuation of donepezil is safe and well tolerated and does not lead to worsening of behavioral symptoms

Abbreviations: AD, Alzheimer disease; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI-D, Neuropsychiatric Inventory–Distress; NPI-NH, Neuropsychiatric Inventory–Nursing Home; PSMS, Physical Self-Maintenance Scale.

dysphoria, anxiety, and apathy/indifference ($P < .05$). Symptoms present at baseline that improved significantly with donepezil compared with placebo-treated participants at week 24 included anxiety, apathy/indifference, and irritability/lability ($P < .05$). Significant improvement in NPI score was observed with donepezil compared with placebo at week 24 ($P < .05$) when a separate analysis was carried out for patients not taking psychoactive medications at baseline.

The study conducted by Holmes et al[37] included a 12-week randomized, double-blind, placebo-controlled phase (randomized controlled trial [RCT] phase). The RCT phase was preceded by a 12-week period of donepezil administration to all participants (5 mg for 6 weeks, then 10 mg for remaining 6 weeks) after which the participants were randomized into donepezil or placebo group. The results demonstrated that participants who continued on donepezil 10 mg had improvements in NPI (mean change −2.9 vs 3.3 points; ITT-LOCF $P = .02$) and in Neuropsychiatric Inventory–Distress scores (median change −2.0 vs 1.0 points; intention to treat- last observation carried forward [ITT-LOCF] $P = .01$) when compared with the placebo group.

In addition to the aforementioned studies, NPI was a secondary outcome measure in 6 randomized, double-blind controlled trials. Feldman et al[32] showed significant improvement in NPI scores in the donepezil treatment group as opposed to slight decline in the placebo group (mean difference = 5.64; $P < .05$). Winblad et al[33] showed no significant benefit in NPI in the donepezil group compared with the placebo group. This concurs with a study conducted in mild-to-severe AD patients in nursing home.[35] In contrast to studies that were conducted in the community setting,[32] which found improvement on NPI, there might be an inherent difference between studying behavioral aspects of AD in patients residing in different settings and a differential sensitivity of the NPI in these settings. Black et al[34] demonstrated that changes in NPI scores were not significantly different in the donepezil treatment group compared with the placebo group (mean difference = 1.4; $P = .46$). Johannsen et al[38] showed an improvement in NPI scores in the donepezil treatment group as opposed to slight decline in the placebo group after 12 weeks of the double-blind phase (mean difference = 2.870; SE = 1.227; $P = .02$). Howard et al[39] did not show a significant improvement in NPI in the donepezil continuation group as opposed to the discontinuation group (mean difference = 2.3; 95% CI, −1.1 to 5.7; $P = .08$). Herrmann et al[40] showed no significant improvement in NPI in the donepezil continuation group as opposed to the discontinuation group (mean difference = 3.5; $P = .24$). Hallucinations and delusions were noted in the discontinuation group which may suggest clinical deterioration.

Donepezil discontinuation studies

Four randomized, double-blind, placebo-controlled studies were conducted to study the effects of discontinuation of donepezil therapy in patients (Table 5).

Holmes et al[37] addressed the question whether discontinuation of donepezil has an acute effect on behavioral symptoms. The participants were followed up for 3 months following discontinuation of donepezil. There was a fall in the NPI total score in the participants randomized to donepezil 10 mg compared with those who were allocated placebo (−2.9 vs 3.3 points). Thus, discontinuation of donepezil resulted in worsening of behavioral symptoms.

The randomized, double-blind, placebo-controlled study conducted by Johannsen et al[38] was run with open-label components before and after the RCT portion. ADAS-cog/11 was used as the primary endpoint of cognitive function, and there was a small but nonsignificant benefit in the donepezil group compared with the placebo group (0.65 vs 0.70 change from baseline, respectively). ADAS-cog/11 was inconsistent in assessing the treatment affects and there seemed to be a country-specific interaction with the test which may be due, in part, to the inexperience with this test in those countries. There was a difference between the assessment of cognitive function with MMSE vs ADAS-cog/11 because both of these instruments assess different items. This study had the largest number of participants involved in the study among all the discontinuation trials.

The study by Howard et al[39] consisted of multiple participant arms (donepezil discontinuation group, memantine discontinuation group, combined donepezil and memantine and placebo group). The study included 295 participants and a 52-week follow-up duration. All of the participants were taking 10 mg donepezil for at least 3 months before beginning the study. Standardized Mini-Mental State Examination was higher by an average of 1.9 points (95% CI, 1.3-2.5) in the donepezil group when compared with the discontinuation group. Behavioral Pathology in Alzheimer's Disease Rating Scale score was lower (indicating less impairment) by 3.0 points (95% CI, 1.8-4.3) in donepezil group compared with discontinuation group ($P < .001$ for both comparisons). The memantine group, when compared with memantine placebo group, had a score on the sMMSE that was an average of 1.2 points higher (95% CI, 0.6-1.8; $P < .001$) and a score on the Behavioral Pathology in Alzheimer's Disease Rating Scale that was 1.5 points lower (95% CI, 0.3-2.8; $P = .02$). No significant benefits were noted in the combination of donepezil and memantine over donepezil alone. Secondary and post hoc analysis focusing on the nursing home placements of AD patients in these trials showed that donepezil withdrawal resulted in increased risk of nursing home placement during the first 12 months of discontinuation (hazard ratio: 2.09 [95% CI, 1.29-3.39]); however, there was no difference in the following 3 years of follow-up (hazard ratio: 0·89 [95% CI, 0.58-1.35]).

Herrmann et al[40] showed that after adjusting for sMMSE, treatment group was a nonsignificant predictor of Clinical Global Impression–Change scale worsening at 8 weeks (odds ratio for worsening: 1.58 [95% CI, 0.38-6.55], $P = .53$). No

Table 5. Summary of placebo controlled double blind discontinuation clinical trials of donepzezil.

AUTHOR	NO. OF SUBJECTS	DURATION	PREVIOUS DURATION IN THERAPY	DISCONTINUATION OF DONEPEZIL	PRIMARY ENDPOINT	SECONDARY ENDPOINT	EFFECT ON COGNITION	EFFECT ON NPS	SAFETY AND TOLERABILITY
Holmes et al[37]	96	3 mo	3 mo	Direct	NPI	NPI-D	Significant cognitive benefit ($P < .05$) in continuation group	Significant improvement ($P < .05$) in both NPI and NPI-D in those who continued on donepezil vs worsening in discontinuation group	Discontinuation is not safe and well tolerated
Johannsen et al[38]	202	3 mo	3-6 mo	Direct	ADAS-cog/11	MMSE, NPI, DAD	Significant cognitive benefit ($P < .05$) in continuation group	Significant ($P < .05$) worsening in discontinuation group	Discontinuation is not safe and well tolerated
Howard et al[39]	146	12 mo	At least 3 mo	4 wk of tapering followed by discontinuation	sMMSE, BADLS	NPI, GHQ-12, DEMQOL-Proxy	Significant cognitive benefit ($P < .05$) in continuation group	No significant difference ($P > .05$) in NPI between the 2 groups. Significant difference favoring continuation on GHQ-12 and DEMQOL-Proxy	Discontinuation is not safe and well tolerated
Herrmann et al[40]	40	8 wk	≥2 y	2 wk of tapering followed by discontinuation	CGI-C	sMMSE, SIB, NPI-NH, CMAI, AES, QUALID,ADCS-ADL	No clinically significant changes ($P > .05$)	No clinically significant difference ($P > .05$) in the 2 groups apart from hallucinations and delusion in the discontinuation group	Hallucinations and delusions may suggest clinical deterioration when donepezil is discontinued, otherwise it is well tolerated

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; BADLS, Behavioral Pathology in Alzheimer's Disease Rating Scale; CGI-C, Clinical Global Impression–Change scale; CMAI, Cohen Mansfield–Agitation Inventory; DAD, Disability Assessment for Dementia; GHQ-12, General Health Questionnaire–12; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI-D, Neuropsychiatric Inventory–Distress; NPI-NH, Neuropsychiatric Inventory–Nursing Home; SIB, severe impairment battery; sMMSE, standardized Mini-Mental State Examination; QUALID, Quality of Life in Late-Stage Dementia; ADAS-cog/11, Alzheimer disease assessment scale-Cognitive scale 11 item; NPS, Neuropsychiatric symptoms; DEMQOL Proxy, Dementia Quality of Life- Proxy; AES, Apathy Evaluation Scale.

significant difference was found between donepezil and the discontinuation group in any of the secondary measures (sMMSE, SIB, Neuropsychiatric Inventory–Nursing Home, Cohen-Mansfield Agitation Inventory 5 [CMAI5], AES, Quality of Life in Late-Stage Dementia, and ADCS-ADL). Major limitations of this clinical trial were that it included a short-term follow-up of just 8 weeks, only 40 subjects, only institutionalized participants, and it allowed concomitant use of antipsychotics which could mask medication effects. In addition, most participants in the study were men who are more prone to psychosis, and thus introduced sampling bias.[41,42]

Side Effects and Drug Interactions

The side effect profile of Donepezil is the lowest of all the AChEIs that are commercially available.[11,13,43,44] In randomized, placebo-controlled clinical trials, only nausea, insomnia, and diarrhea were significantly associated with donepezil use. These events were generally self-limiting and resolved without the need for interruption or adjustment of dosage.[13,22] The other presumed side effects of donepezil including bradyarrhythmias, syncope, sedation, lack of appetite, mild headaches, sialorrhea, and worsening of chronic obstructive pulmonary disease (COPD) have not shown higher incidence when compared with placebo in randomized, placebo-controlled studies.[40,45]

Idiosyncratic adverse effects attributed to donepezil have been reported in various case reports. Rhabdomyolysis is a rare side effect that has been recently attributed to the necrotic myolytic effect of donepezil.[44,46] Other rare side effects that have been attributed to donepezil include hypnopompic hallucinations,[47] violent behavior,[48] mania,[49] pancreatitis,[50] urinary incontinence,[51] seizures,[52] extrapyramidal syndrome,[53,54] purpuric rash in a patient taking atenolol and doxazosin,[55] and Pisa syndrome.[56] While causation has not yet been established, vigilance is a reasonable approach to detect these idiosyncratic reactions.

Various observational and open-label studies have reported adverse effects of donepezil on the cardiovascular autonomic systems, including a significant increase in diastolic blood pressure[57] and decrease in heart rate variability.[58] Another study showed no changes in heart rate variation.[59,60] Several cases of syncope have been reported in patients who have been receiving donepezil treatment[50,57]; 69% of these cases of syncope were associated with carotid sinus syndrome, sinus node dysfunction, complete atrioventricular block, paroxysmal atrial fibrillation, and severe orthostatic hypotension, whereas in 31% of the cases no cause of syncope was found.[57] Isik et al[61] performed an open-label study involving 52 AD patients, a much larger study population as compared with previous works,[58–60] and found no changes in electrocardiogram or blood pressure, and concluded that the previous studies were confounded by comorbidities and medications. However, there is no clear evidence of the effect of donepezil on the cardiovascular autonomic system, and further randomized double-blind controlled studies are needed to assess the full extent of this effect.

Randomized, double-blind, placebo-controlled studies have shown no hepatotoxicity of donepezil alone.[13,22,62] However, hepatotoxicity of donepezil in combination with SSRI has been reported because of CYP2D6 inhibition by selective serotonin reuptake inhibitor (SSRI).[63,64] So careful consideration should be done in prescribing patients donepezil who are already using an SSRI.

Multiple cases of drug interactions between donepezil and other medications have been reported. These include prolonged paralysis as a result of coadministration with suxamethonium,[65] neuroleptic malignant-like syndrome due to combination with maprotiline,[66] and in an AD patient who was undergoing left colectomy under general anesthesia after 14 months of donepezil therapy, succinylcholine-induced relaxation was markedly prolonged and the effect of atracurium besylate was inadequate even at high doses. It was proposed after ruling out atracurium resistance that this was due to donepezil or its metabolites acting on muscle plaque, blocking Ach hydrolysis and antagonizing atracurium.[67] These drug reactions are rare, and causation has not been established.

Discussion

The randomized placebo-controlled trials demonstrated that donepezil is effective in all stages of AD continuum. The beneficial effects are greater on the cognitive function early in the course of AD, whereas behavioral function benefits are greater as the disease progresses to more advanced stages. Donepezil has been approved by the FDA for all stages of AD, with the exception of amnestic MCI. In amnestic MCI, off-label use of donepezil can be considered after risk stratification of conversion to AD. Currently, available data suggest the use of donepezil lifelong due to better ADL, delayed nursing home placement within 1 year after discontinuation; however, this topic remains controversial, and further studies are needed.

Safety data of the randomized, placebo-controlled trials have shown that apart from self-limiting nausea, diarrhea, and insomnia, there are no significant adverse effects associated with donepezil use, and it is safe and well tolerated in all stages of the disease. Rare side effects may occur; however, drug relation is not established from the case reports. In case of patients who are intolerant to donepezil, alternative drugs such as rivastigmine and galantamine should be started.

Further studies are needed to determine the difference in treatment strategies between an elderly and a young AD patient. In addition, there is a need for new trials using more sensitive scales to assess the effects of donepezil in amnestic MCI as the scales used in the randomized, double-blind, placebo-controlled trials were developed for AD and may not be sensitive to change in amnestic MCI.

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Author Contributions

KS conceived and designed the experiments. MWZ analyzed the data. MWZ wrote the first draft of the manuscript. MWZ, AR, and KS contributed to the writing of the manuscript. KS agree with manuscript results and conclusions. KS and MWZ jointly developed the structure and arguments for the paper. KS, MWZ, and AR made critical revisions and approved final version. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication, author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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