Donepezil in Severe Alzheimer's disease: A Review of Treatment Considerations with Disease Progression

Melanie Neuendorff PA-S, B.Sc.

Supervisor: Dr. Benedict C. Albensi, Ph.D. Associate Professor, University of Manitoba Dept. of Pharmacology & Therapeutics, Faculty of Medicine

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects 35 million people worldwide, with the prevalence expecting to double by 2030. Patients with severe AD (Mini-Mental State Examination (MMSE) score <10) require extensive help with daily activities, show severe memory impairment, and exhibit major personality and behavioral changes. Donepezil is one of only two drugs currently approved by the US Food and Drug Administration (FDA) and Health Canada for use in severe AD. The drug is currently available in 5mg, 10mg, and a controversial more recently FDA approved 23mg daily dose. This review will provide a brief background on AD, and discuss the risks, benefits, and current recommendations for donepezil use in severe disease, with an emphasis on Canadian and US practices. **Methods:** Randomized Controlled Trials (RCTs) concerning the efficacy and safety of various doses of donepezil (Aricept) use in severe AD were identified using PubMed. Three original double blind, parallel-group, placebo-controlled, randomized studies, one post-hoc analysis, and one sub-group analysis were selected for review. **Results:** Donepezil benefits patients with severe AD in areas of cognition and global function. Increased benefits of treatment correlated with escalading dose in patients with more advanced baseline disease, as measured by Severe Impairment Battery (SIB) scores. However, more patients assigned to donepezil discontinued their treatment due to an adverse event (AE) than placebo, and AEs occurred more frequently and with increasing severity as dose increased. **Conclusion**: Donepezil treatment shows small but measurable benefits in severe AD. 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.

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INTRODUCTION

Problem

Alzheimer's disease (AD) is an irreversible, progressive disease that impairs memory, rendering one unable to reason, communicate, or perform daily activities. It is the most common cause of dementia; a group of brain disorders that cause memory loss. There are an estimated 35 million people worldwide living with AD, and the prevalence is expected to double by 2030(1). Nearly 750,00 Canadians were living with Alzheimer's disease and other dementias as of 2011(2).

Since 2006, the Canadian Institutes of Health Research has invested more than $220 million towards research into AD and related dementias(3). Despite the scientific progress that has been made, there is still no "cure" for AD. Treatments that are currently available have been shown to temporarily slow progression of memory loss and help with cognitive and behavioral symptoms, but all patients inevitably succumb to the disease.

Background

Biology of Alzheimer's disease

Acetylcholine is an integral neurotransmitter in the autonomic nervous system, acting both peripherally and centrally on many targets. AD shows progressive degeneration of the cholinergic neuronal pathways projecting from the basal forebrain to the cerebral cortex and hippocampus, a component of the limbic system that plays an important role in spatial navigation and the consolidation of short-term to long-term memory. Many years of studies have focused on neurofibrillary tangles (containing an abnormally phosphorylated form of tau protein) and extracellular β-amyloid plaques (derived from the precursor protein APP) with subsequent loss

of neuronal synapses and pyramidal neurons as being potential causative agents (4). However, these processes are still not fully understood. Biopsy of tissue taken from the brain of patients with Alzheimer's disease 3.5 years after onset of symptoms has shown that neurotransmitter pathology happens early in the course of the disease, and reductions in acetylcholine synthesis and choline acetyltransferase activity are believed to be associated with cognitive impairment(5).

Therapeutic interventions have emerged that are designed to partially offset loss of presynaptic cholinergic function. A few of these compounds have shown efficacy in temporarily delaying the deterioration of function in patients with AD. Donepezil enhances cholinergic function by reversibly binding the enzyme acetylcholinesterase (AChE) and inhibiting the hydrolysis of acetylcholine. It is more potent and selective than tacrine, the first AChE inhibitor (AChEI) approved for symptomatic treatment of AD. Benefits of the second generation AChEI donepezil include its long half-life that permits once-daily dosing, increased tolerability due to improved specificity for central AChE inhibition, and lack of significant effects of food on pharmacokinetics of the drug(6).

Symptoms of Alzheimer's disease

Altered behavior may sometimes be the presenting feature of AD, prior to cognitive impairment. Behavioral disturbances in dementia can be broken down into four categories; activity-associated, depressive, psychotic, and anxiety-related. Activity-associated behaviors include wandering, agitation, restlessness, eating and sexual disorders, sleep disturbances, rummaging, aggression, and hoarding. Depressive symptoms include withdrawal, tearfulness, apathy, listlessness, and other manifestations of unhappiness. Psychotic features commonly displayed are delusions, hallucinations, and paranoia(7). Anxiety commonly presents as an anxious or worried appearance, fearfulness, tension, restlessness, or fidgeting(8).

Language dysfunction found in AD includes anomia, word-finding difficulties, reduced vocabulary in spontaneous speech, and circumlocution(9). Motor signs are often absent until later in progression of disease. Extrapyramidal symptoms (EPS) such as tremor, bradykinesia, dystonia, and postural instability can be associated with more severe cognitive impairment and rapid cognitive decline, although they may be present in very early stages of AD, prior to diagnosis(10). Sleep disturbances are common, and generally involve more fragmented sleep. Memory impairment follows a distinctive pattern in AD, with insidious onset. Declarative memory usually deteriorates much earlier than procedural memory and motor learning in the course of disease(11). Within declarative memory, episodic memory (specific events and contexts) is affected more significantly than semantic memory (concepts and vocabulary)(12). Specifically, memory for recent events is more profoundly affected than long-term memory(13). This correlates with the finding that mesial temporal and neocortical structures are affected prior to subcortical structures. The mesial temporal lobe is comprised of the hippocampus, amygdala, dentate gyrus, parahippocampal gyrus, and uncus. Consolidation of short-term memories and spatial learning is encoded in these structures(14).

Social impact of Alzheimer's disease

According to the 2012 World Health Organization's report *Dementia: a Public Health Priority,* the estimated worldwide cost of the disease was US$ 604 billion in 2010(1). Within Canada, the combined direct (medical) and indirect (lost earnings) costs of dementia totals $33 billion annually, with this value estimating to increase to $293 billion by 2040(2). AD accounts for over 60% of all dementias in Canada(15).

The Canadian Study of Health and Aging (CSHA) exemplified the importance of delaying progression of dementia in order to prolong time to institutionalization. It was found

that 46% of patients with dementia in the community were categorized as mild in severity. However, only 11% of the institutional population were considered mild, whereas 89% of patients with dementia were categorized as moderate or severe(16). The cost of caring for a patient with AD increases significantly as the disease progresses, and is related closely to institutionalization. In 1998, analysis of data from the CSHA found that the annual cost per patient with AD was an estimated $9,451 for mild disease, $16,054 for mild to moderate disease, $25,724 for moderate disease, and $36,794 for severe disease(17).

Since 2008, donepezil prescriptions filled in community pharmacies in Canada have been increasing at a rate of approximately 10% annually. It is estimated that over 2 million prescriptions of donepezil, both brand name and generic, were dispensed in 2013(18). In Canada, 5mg and 10mg donepezil is covered for the treatment of mild to moderate AD under all ten provincial drug plans, provided that individuals meet specific clinical criteria for entitlement. It is also covered by most private insurance plans. The medication costs approximately $5 day. At the present time, this medication is not covered by provincial drug plans for the treatment of severe Alzheimer's disease(19). Currently in the US, the cost of brand name Aricept is approximately US$ 500 for a one month supply, and approx. US $230-$340 for the generic equivalent. Interestingly, when comparing the cost of the three Aricept dose options, the new 23mg dose costs less than the 5mg or 10mg dose for a one-month supply(20).

Beyond the direct financial costs of AD, one must consider the effect on caregivers who often have their own comorbid medical problems. Caregivers face rising levels of depression and stress associated with the handling of their loved ones increasing dependency and psycho-behavioral symptoms in advanced disease. Although these indirect consequences are difficult to measure, they cannot be ignored. Therefore, any successful therapeutic intervention that not only

provides benefit to the patients quality of life, but also alleviates caregiver burden is significant and contributes to the efficacy of the drug.

Diagnosis and assessment

Dementia is a group of disorders affecting the brain, impairing the daily functioning of an individual. Many different diseases can cause dementia, but the most common cause is AD(15). Others include vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease, Huntington's disease, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, and Wernicke-Korsakoff syndrome. Early-onset AD accounts for less than one percent of all cases of AD, and follows an autosomal dominant inheritance pattern. Mutations in genes that alter production of beta-amyloid (Aβ) protein production or metabolism, including presenilin-1(21), presenilin-2(22), and amyloid precursor protein (APP)(23) are seen in early-onset AD. Typical onset of symptoms in this category is between 30 and 60 years of age.

A US based retrospective study of autopsy-confirmed AD patients found the mean duration of time between onset of clinical symptoms and death to be approximately 8.5 years, in keeping with most literature. They also determined the typical AD patient to be diagnosed at 75 years old, or about 32 months after the onset of symptoms. The average patient was institutionalized 25 months after diagnosis, and died 44 months after institutionalization(24). Although definitive diagnosis of AD is made by post-mortem histopathologic examination of brain tissue, this is hardly useful from a clinician's perspective.

Memory impairment is an essential feature in AD, and is usually the trigger to further workup. A list of clinical criteria guides diagnosis of the disease by a trained professional, and includes a history of insidious onset and progressive course, documented cognitive impairment in one or more domains, a detailed cognitive and neurologic examination, and exclusion of other

etiologies(25,26). The diagnostic Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS- ADRDA) criteria, the Clinical Dementia Rating Scale, and the MMSE are frequently used in diagnosis and staging.

The MMSE is recommended as a formal measure of cognitive function, and may be administered routinely during office visits to monitor changes in cognition. It is a well-recognized test that is easy to use, and is required by many provincial drug formularies as a criteria for reimbursement in trials of severe dementia(26). There have, however, been some concerns raised with the use of the MMSE in assessing severe dementia. The scale may not pick up clinically important changes as the disease progresses, becoming less sensitive with severity(26). Other tests administered to assess cognitive and behavioral decline in more severe disease include the 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 scale (CIBIS+/CIBIC+), the Neuropsychiatric Inventory (NPI), and the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)(Table 4). Many of these tests are based upon information obtained from a caregiver or other informant in close contact with the patient, as the patient may not be able to accurately evaluate and report their symptoms in later stages of disease.

Current recommendations and cautions for donepezil use

In 1996, donepezil was approved for marketing in the US. Canada and the European Union followed suit one year later, with many other countries approving the drug shortly thereafter. Regulatory approval was granted for its use in the treatment of severe AD in the US and Canada in 2006/2007, but remains unapproved in Europe. In Canada, 5mg and 10mg tablets

of donepezil are currently approved for mild (MMSE 18-26), moderate (MMSE 10–18) and severe AD(19).

Target levels of cholinergic enhancement may change with disease progression. It has been argued that in early stages of AD, sufficient cholinergic stimulation may be achieved with lower doses of AChEIs, while higher doses of AChEI may be necessary in patients with more advanced AD(27). The highly respected Cochrane Review published *Donepezil for dementia due to Alzheimer's disease (Review)* in 2006, and concluded that while there is 'slight' evidence for dose-related size of the effect of 10mg/day compared to 5mg/day, the adverse effects are 'significantly greater' in the 10mg/day dose than the 5mg/day dose. Significant differences were found between the two doses for withdrawals, number of patients who suffered at least one AE, and withdrawals due to an AE, favoring 5mg/day. AEs deemed to be more frequent in the higher dose group included anorexia, nausea, vomiting, diarrhea, and rhinitis(28). Therefore, it was concluded that the lower dose might be the better option. Despite this, in July of 2010 Eisai Inc. and Pfizer Inc. announced that the FDA approved a new 23 mg dose for the treatment of patients with moderate to severe AD. This was based on a large, 6-month, phase 3 clinical trial by Farlow et al. (2010) that compared switching to donepezil 23 mg/day against continuing treatment with donepezil 10 mg/day in patients with moderate to severe AD (Table 4.4). The trial summarized that greater cognitive benefits (mean change in Severe Impairment Battery score, 2.11 points; $P < 0.001$) were seen in the 23 mg/day group(29). Analyses showed that benefits were significant irrespective of concomitant memantine use. Based on the approved label, the recommended starting dose of Aricept is 5 mg once daily, and can be increased to 10 mg once daily after four-to-six weeks. Moderate-to-severe AD patients who are established on a regimen of 10 mg for at least three months are candidates for dose escalation to the 23 mg tablet(30). Some contest that it

is more than coincidence that the FDAs approval for the new 23mg dose came just four months prior to the drug becoming generic in November of 2010, as is the inability to multiply and produce a 23mg dose using the generic 5mg and 10mg pills(31). It has been noted that the statistically significant improvement in cognition (a 2.2 point improvement compared to the lower dose on the SIB 100 point scale) but no statistically significant difference in global functioning (a 0.06 improvement on the seven point CIBIC- Plus scale) did not meet the FDA's own regulatory standard, which required statistically significant superiority over the 10mg/day dose of the immediate-release formulation on both primary efficacy measures(32). In 2011, the advocacy group Public Citizen unsuccessfully petitioned to the FDA to withdraw the higher dose, arguing that the drug showed increased toxicity compared to its lower dose counterparts without equivocal evidence for increased benefit(33). Health Canada has yet to approve the 23mg/day dose, and therefore it is not currently covered by provincial drug plans (19,34).

Behavioral disturbances including agitation are seen frequently in patients with AD. There is mixed opinion regarding the effect of donepezil on behavior. A systemic review of the effect of AChEIs on behavioral and psychological symptoms of dementia (BPSD) found that of the fourteen RCTs meeting inclusion criteria, only three showed modest benefit as measured by NPI scores(35). The NPI measures changes in the patient's behavior that have appeared since the onset of the illness, as reported by a caregiver that has spent a significant amount of time with the patient. Frequency and severity are graded on either 10 or 12 measures (two versions available), with higher scores indicating worsening neuropsychiatric disturbances(36). A clinical investigation performed in Japan by Suzuki et al. (2014) evaluated the discontinuation of donepezil in patients with severe AD that had been receiving a stable dose for over three years. In Japan, cholinesterase inhibitors are normally not stopped unless there are serious AEs(37).

Outcome measures of this study were cognitive function and BPSD as represented by MMSE and NPI scores, respectively. Decreases in total NPI score as well as agitation and irritability sub-scores were seen in the donepezil treatment discontinuation group, indicating improvement. They concluded that discontinuation of donepezil may delay the addition or increase of psychotropic drugs, which have been found to have many AEs and are within the STOPP criteria in the elderly(38). However, no significant differences were seen between the treatment discontinuation and control group within this study(37). No changes in MMSE scores were found, although baseline MMSE was ≤ 5 for both groups .It must be stated that this study was open-labeled with a small sample size, and patients had concomitant psychotropic drug use.

AEs can be difficult to attribute to a specific medication in the context of comorbid medical conditions and poly-pharmacy, but there are published studies that have investigated the incidence of donepezil related AEs. Most side effects are gastrointestinal in nature, and are related to the cholinergic properties of the drug. However, more severe AEs requiring discontinuation have also been reported (Table 3). A multicenter study by Carrasco et al. (2011) in mild to moderately severe AD performed at 72 centers throughout Spain found that among the 529 patients enrolled in the trial, 32 AEs were potentially related to donepezil (5mg or 10mg/day). The most commonly reported general events were diarrhea (1.32%), agitation (1.13%), nausea (0.95%), and insomnia (0.95%). At least one neuropsychiatric AE was reported in 5.3% of the participants. No serious AEs or deaths were determined to be attributable to donepezil in this study(39). However, serious AEs attributed to the drug have been documented, and will be discussed within this paper.

A population based cohort study using healthcare databases from Ontario, Canada found community-dwelling older adults with dementia who were prescribed AChEIs had more hospital

visits for syncope than those who were not prescribed AChEIs (31 vs 19 events per 1000 person-years; adjusted hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.57-1.98). They also found an increase in syncope related events such as bradycardia, permanent pacemaker insertion, and hip fracture(40). This data was additionally analyzed using propensity-based matching and comorbidity-based matching, and results remained consistent.

Current guidelines for donepezil withdrawal

Although nearly 230 clinical trials on donepezil have been conducted(41), extended use of the drug has not been evaluated thoroughly. Most trial periods have spanned 3,6, or 12 months(28). Furthermore, there is limited research regarding evidence-based withdrawal of medications in advanced dementia. Discontinuation of medication by clinicians is often empiric, as there is a lack of literature available(42). This is in part due ethical considerations in performing randomized controlled trials on a vulnerable palliative care population, who may be unable to make informed decisions regarding their care.

A report by Shega et al.(2009) surveyed 152 hospice medical directors in the US for the use and recommendations made to families on whether to discontinue donepezil and memantine therapy for end-stage dementia patients. Upon hospice admission, nearly half of respondents stated that between 21%-50% of their patients were still being prescribed donepezil, and for another 25% of respondents this reported value was between 51%-100%. While a sound majority (81%) of these physicians recommended discontinuing therapy for this subset of patients, only 1 in 4 physicians discontinued therapy in 76%-100% of their patients. In fact, approximately one-half of physicians discontinued therapy in 50% or less of their patients. Whether this is due to challenges with convincing family to discontinue therapy or perceived benefits by the hospice medical directors is unknown. Almost three-quarters of physicians agreed

to the statement that ‘families have a difficult time stopping donepezil therapy’. In regard to observed effectiveness of donepezil among patients with end-stage dementia, 20%-30% agreed to cognitive, behavioral, and/or functional benefits (dichotomous category with always or sometimes vs rarely or never). The highest responses were for: decreases patient challenging behaviors (28%), helps maintain patient function (22%), stabilizes patient cognition (22%), and reduces caregiver burden/improves caregiver quality of life (20%). Less were convinced of improving patient quality of life (15%), or improving patient energy (4%) or survival (3%). When asked about experiences with discontinuation of donepezil among persons with end-stage dementia, some physicians surveyed agreed to (always or sometimes) emergence of patient challenging behaviors (32%), patient withdrawal from family or activities (25%), decreased patient time awake (22%), increased caregiver burden (22%), decreased patient quality of life (17%), and accelerated patient cognitive (30%) and functional (26%) decline(43).

There are several different guidelines available providing recommendations for discontinuation of drug therapy in the elderly. The Holmes criteria was published in 2008, based on the opinions of 12 geriatricians at the University of Chicago who evaluated the appropriateness of medications prescribed to 34 patients with advanced dementia (defined by a Cognitive Performance Scale (CPS) (44) score of 4-6). They deemed 11 of the 221 medications as ‘never appropriate’, but found 29% of the patients to be taking at least one of these drugs. AChEIs were within this category. Limitations to this study include small sample size, a variety of dementia subtypes (59% with a primary diagnosis of AD), and possible homogeneity in the opinion of geriatricians surveyed due to practice within the same institution(45). This paper was published after the FDA approved AChEIs for the treatment of severe AD in 2006, but has not adopted this recommendation.

A cross-sectional analysis by Colloca et al. (2012) evaluated 1449 nursing home residents with severe cognitive impairment participating in The Services and Health for Elderly in Long Term Care (SHELTER) study, and found that the use of inappropriate drugs was common (45%). Inappropriate drugs were defined as those classified as rarely or never appropriate in patients with severe cognitive impairment according to the aforementioned Holmes criteria. Donepezil is categorized as never appropriate, but was used in 7.2% of patients regardless. Of note, only half of patients assigned to receive donepezil for the duration of the study did in fact do so. This was attributed to a perceived lack of efficacy and adverse effects(46).

Beers criteria and the STOPP (Screening Tool of Older Persons' Prescriptions)/ START (Screening Tool to Alert doctors to Right Treatment) criteria are more frequently used, with the latter argued to be more globally applicable and sensitive to identifying potentially inappropriate medication(47). The most updated version of Beers criteria discusses AChEIs in the context of syncope and recommends avoiding AChEIs if syncope is present, as the drug increases the risk of orthostatic hypotension and bradycardia. The quality of this evidence is graded as 'moderate', but the strength of this recommendation is 'strong'(48); this is based on an 11-member interdisciplinary expert panel that independently rated the quality and strength of evidence based on the American College of Physicians' Guideline Grading System, which uses the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) scheme(49). The START/STOPP criteria were developed in Ireland, using two rounds of the Delphi process on a consensus panel of 18 experts. It includes two sets of European based criteria. START addresses prescribing omissions (those that should be considered in a given medical condition), and STOPP addresses clinical situations in which a drug is potentially inappropriate. Version 1 of the STOPP/START criteria, created in 2008 and updated as recently as February 2013, does not

make specific STOPP/START recommendations for AChEIs or memantine(50). Version 2.0 was published in October of 2014, and has thoroughly re-assessed new evidence available since the 2008 version was released. This new version rejected memantine for moderate-severe AD as a new START criteria, and no recommendations were added for AChEIs(51).

The National Health Service (NHS) in the UK refers to guidelines from the National Institute for Health and Care Excellence (NICE). NICE CG42 states AChEIs and memantine should be started by a specialist and reviewed by a specialist team to determine whether continuing them is indicated. AChEIs are recommended in the management of mild-moderate AD, while memantine is indicated in moderate AD only if AChEIs are contraindicated or not tolerated. Memantine, but not donepezil, is recommended as an option for managing severe AD(52). The document was issued in November 2006, revised in March 2011, and has been amended as recently as February 2014(52).

The recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCDTD4) were created in May of 2012. Recommendations for symptomatic treatments state, "…all three cholinesterase inhibitors have demonstrated efficacy for mild to severe AD. We recommend a trial of a cholinesterase inhibitor for most patients with AD (Grade1A)"(23, p125). Special emphasis was placed on rules for discontinuation of AChEIs that were lacking in the past. However, the recommendations are Grade 2B; defined as a weak recommendation where benefits and risks are closely balanced and/or uncertain, and moderate-quality evidence is from randomized trials with important limitations; further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate(49). The recommendations for discontinuation of AChEIs emphasize weighing risks and benefits of cessation of treatment; the risks being worsening cognitive function and greater

functional impairment, and the benefits being avoidance of known side effects and drug costs. They suggest discontinuation for medication non-adherence, cognitive/behavioural/functional decline worse than prior to treatment initiation, intolerable side effects determined to be definitely or likely caused by the drug, comorbidities that make the drug futile or unacceptably risky, or progression of dementia to Global Deterioration Scale stage 7. It is advised to taper the drug slowly and monitor for an observable decline, and to consider re-initiating therapy if this occurs(25).

There is no clear consensus on recommendations for if and when donepezil should be discontinued. Some guidelines recommend a trial in mild throughout severe disease with discontinuation based on risk and benefit assessment(25), or specify AEs such as syncope that should prompt cessation of the drug(48). Others state the drug is never appropriate in advanced dementia (CPS score 4-6)(45) or severe AD (MMSE <10)(52). Some medication guidelines fail to comment on donepezil use in the elderly at all(51). Therefore, a clinicians prescribing practice for donepezil may depend on their country of origin, which guideline they decide to follow, or their personal experiences with the drug.

METHODS

Selection criteria

Relevant articles concerning the efficacy and side effects of various doses of donepezil (Aricept) use in severe AD were identified using PubMed. The database search was performed using the MeSH terms “donepezil” AND “Alzheimer Disease” AND “severe”, with search limits set for studies in English on humans. Articles that were selected contained primary research from clinical trials, multicenter studies, and RCTs on the use of donepezil in patients with severe AD. Post hoc analysis of RCTs were also considered, if the analysis was of ‘severe Alzheimer’s

disease". One RCT comparing 10mg and 5mg to placebo in severe AD, two RCTs comparing 10mg donepezil to placebo in severe AD, one sub-group analysis of a RCT comparing 10mg to placebo in severe AD, and one paper comparing 23mg to10mg donepezil in moderate to severe AD (MMSE 0-20) with a subsequent post hoc further isolating SIB scores by severity strata were selected for analysis. Table 1 summarizes study design, demographics, and clinical baseline outcome measures of the papers chosen for analysis.

Statistical Analyses

Different analytical strategies for addressing missing data in clinical trials can be utilized in reporting results, including the last observation carried forward (LOCF), observed case (OC) and the mixed model for repeated measures (MMRM). Each method requires certain assumptions regarding the characteristics of the missing data. If the assumptions for any particular method are not valid, results from that method may be biased. Results based on these different analytical methods can therefore be inconsistent, making interpretation of clinical study results confusing. LOCF tends to underestimate within-group mean changes in efficacy (benefit) and safety (risk) for drugs compared with MMRM, whereas OC tends to overestimate within-group changes(53). All of the studies reported efficacy analysis of data using the LOCF method of the intent-to-treat (ITT) population, which includes all patients as long as the baseline score and ≥1 score was available after the administration of the first dose of study medication, computing missing values. The MMRM model was also incorporated by Winblad et al. (2006), where data collected from all patients who were randomized to the intention-to-treat category (those who dropped out as well as those who completed the study) were used, with missing data being replaced by the mean of observed values for the change from baseline in the placebo

group. The OC method was used by Black et al. (2007) and Winblad et al. (2006). This is an analysis using only completers (those patients that had an observation at the end-point visit).

RESULTS

Outcome measures

The only test that was consistently administered across all five studies was the SIB, which has been found to be reliable and valid in differentiating patients with moderate or severe dementia(54,55). The SIB is 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) are tested using simple one-step commands and gestural cues. Total scores for the questionnaire range from zero (greatest impairment) to 100 (no impairment). SIB LS mean differences were calculated by subtracting the LS mean change from baseline of the placebo group from the LS mean change from baseline of the donepezil group in the ITT population. The exception to this is the post-hoc analysis by Ferris et al. (2013), which calculated LS mean treatment differences and standardized effect sizes between 23mg/d and 10mg/d rather than placebo. This study dissected the nine SIB domain scores for stratified baseline MMSE score sub-populations. Data from the severe subgroups as defined by this paper with MMSE scores of 0-5 and 6-10 were selected for discussion.

The SIB LS mean differences varied from 4.5 to 8.9 depending on the study, dose, and statistical analysis used (Table 2), with all studies showing an improvement in score in the treatment group and a clinical decline in placebo. Homma et al. (2008) was the only study to evaluate the lower 5mg dose; the SIB LS mean difference of 6.7 ($p=0.001$) was found to be inferior to the 10mg dose (8.9($p=0.001$)), with a significant dose-response relationship compared

to placebo(56). When the previously stated 5mg dose is compared to the SIB LS mean difference of 10mg by Feldman et al. (2005), the higher dose remains superior (7.42 (p= 0.0017))(57), but this is not found when compared to Winblad et al. (2006) or Black et al. (2007) (5.6 (p=0.008) and 5.32(p=0.0001), respectively)(58,59). However, one must be cautious when comparing data between studies, as patient demographics and study inclusion/exclusion criteria may vary (Table 4).

Ferris et al. (2013) reported a SIB LS mean treatment difference (95% CI) of 6.048 (1.04 to 11.05) and 3.258 (0.30 to 6.21) for MMSE scores at baseline of 0-5 and 6-10, respectively(60). This translates to an approximated 3-6 point difference on the 100-point SIB scale in favor of 23mg over 10mg. Further investigation of subdomains of the SIB showed improvement or less decline in LS mean change from baseline in favor of the higher dose in areas of language, memory, praxis, visuospatial ability, attention, and construction for both severe MMSE subgroups. Mixed values were reported for social interaction and orienting to name. Negative values were reported for orientation in both MMSE subgroups. Unfortunately, p values are not reported for subgroup LS mean treatment differences in this study, and the impact of the actual values is difficult to interpret, as each SIB domain is weighted differently (ranging from 2 to 46 points). However, standardized effect sizes are given, with the authors stating "positive standardized effect sizes represent superiority of donepezil 23mg/day dose over 10 mg/day dose" (Table 2, pg. 6). In Cohen's terminology, an effect size of 0.2 to 0.3 is considered a "small" effect, 0.5 a "medium" effect, and 0.8 or greater a "large" effect (61). In assessing the data by this definition, none of the individual domains show donepezil to reach a medium effect in severe disease. Language, memory, praxis, and construction showed the highest individual effect sizes (between 0.3 and 0.4), with the most severe MMSE scores (0-5) showing the highest

effect sizes compared to all other strata. The effect size for total SIB scores in the MMSE 0-5 and 6-10 subgroups were 0.460 and 0.273, respectively.

A pooled cohort study from 3 AD clinical trials found that the average - MMSE score declines by 3.5 points over an 18 month period(62). Within this paper, the 3 studies that analyzed MMSE change showed slight LS mean differences varying from 0.68 to 1.4 when comparing 10mg donepezil to placebo, with all scores being slightly higher than baseline for the treatment group. However, these values are relatively small when taking into consideration the scoring of the MMSE. Although Ferris et al. (2013) did not comment on changes in MMSE scores within their post hoc review, the original data from Farlow et al. (2010) showed no statistically significant change from 23mg donepezil to 10mg donepezil in MMSE scores. Homma et al. (2008) did not analyze changes in MMSE scores within their paper. Regardless, there have been questions raised regarding the validity of the MMSE in severe disease(63,55). There are only 11 items in total, with some having markedly higher weight (0-5 vs 0-1) towards the final score of 30 than others. A floor effect is observed for lower values, and it has been argued that the SIB measurement properties in the lower score region are better suited for differentiating poor performances than the MMSE(54,55) .

In general, the studies analyzed reported statistically significant improvements in SIB scores. Higher dose donepezil in severe disease showed the most benefit in areas of language, memory, praxis, and construction, with small-medium effect sizes. MMSE scores showed small differences in favor of donepezil to placebo.

Adverse events

Feldman et al. (2005) reviewed AEs within the more severe subclass (MMSE 5-12) of patients from their original study in 2001. The treatment group had a higher percentage of

patients with at least one AE than placebo (82% vs 78%), more serious AEs (15% vs 14%), and more patients withdraw due to an AE (7% vs 5%). However, the serious AEs were deemed unrelated to the study medication by the investigator, and there were no deaths. The study states that vital signs were "generally within normal limits during the course of the study", but does not report rates of bradycardia, syncope, or falls. It is unknown whether these incidences, or accidental injury/contusion/bone fracture were recorded. AEs reported in ≥5% of donepezil treated patients and at twice the incidence of placebo 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 urinary tract infection (6% vs 3%). However, within the safety/tolerability discussion the paper instead states that "there were no AEs occurring in more than 5% of patients receiving placebo that were twice the incidence in donepezil-treated patients". Weight decrease, asthenia, insomnia, and anorexia were also reported at slightly higher rates in the treatment group. Interestingly, although vomiting was reported in 7% of donepezil patients versus 1% of placebo, nausea was reported in 4% of both groups. Apart from stating that some AEs including diarrhea and vomiting were cholinergic-related, this study does not attempt to discuss causality of AEs.

AEs from the original study by Farlow et al. (2010) are discussed, as the further subgroup analysis (MMSE 0-16) and post hoc by Ferris et al. (2013) evaluate outcome measures, but do not comment on AEs. However, it is important to assess AEs associated with the 23mg dose regardless. A higher percentage of patients discontinued donepezil due to a treatment-emergent adverse event (TEAE) in the 23mg/d group (19%) than the 10mg/d group (7.9%). The majority of discontinuations in the higher dose group happened during the first month of treatment (60%).

The most common TEAEs causing discontinuation for 23mg/d and 10mg/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%). It is notable that the percentages of individual TEAEs leading to discontinuation were over 4 times the frequency in the higher dose group, although the absolute values are relatively small. Similarly, the most common TEAEs overall for the 23mg/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%). Overall, gastrointestinal (GI) TEAEs occurred within the first month in 21% of patients in the 23mg/d group, and in 5.9% of the 10mg/d patients. This is the only study that commented on bradycardia and weight loss. The higher dose group had recorded bradycardia in 2.8% of patients versus 0.6% in the lower dose group. Furthermore, the higher dose group had a higher rate of falls, contusions, fatigue, dizziness, and headache. Weight loss as an AE was reported in 4.7% of the 23mg/d group and in 2.5% of the 10mg/d group, and was observed as a weight decrease of ≥7% in 11% of 23mg/day patients versus 7.4% of 10mg/d patients.

Black et al. (2007) had more people in the treatment group discontinue intervention than placebo (19% vs 11%), and a higher percentage that discontinued due to AE/intercurrent illness (19% vs 11%). The most common AEs leading to discontinuation were anorexia, agitation, pneumonia, and somnolence. More patients were described as discontinuing due to ‘other’ reasons unspecified in the treatment group than placebo (7.4% vs 5.4%). More AEs considered related to study medication were observed in the donepezil group (42% vs 31%), which included diarrhea, nausea, vomiting, anorexia, and agitation. AEs recorded in the treatment group at greater than or equal to twice the frequency of placebo were diarrhea, insomnia, nausea, infection, urinary incontinence, and pain. Placebo patients had more recorded severe AEs (16%

vs 11%) and serious AEs (15% vs 11%) than the treatment group. However, eight patients in the placebo group (4.8%) but only 2 in the donepezil group (1.1%) died due to an AE; these were all deemed unrelated to treatment. This is likely the reason for the discrepancy in the aforementioned results. The authors state that there were no 'clinically meaningful' changes in laboratory tests or 'significant changes' in vital signs. Abnormal electrocardiogram (ECG) values emerged in the same percentage of patients in each group. No mention of falls or fall-related injuries was made.

Homma et al. (2008) had an overall discontinuation rate of 18%, with those attributed to an AE/concurrent illness being 11% of placebo, 7.9% of 5mg, and 14% of 10mg. AEs resulting in discontinuation during the treatment period were highest in the 10mg group. However, the highest percentage of AEs categorized as serious or severe were found in the placebo group (14% vs 10%, respectively). Two people in each of the treatment groups and 1 person from placebo died during the treatment period. The authors could not rule out causality in 2 of the 5 people, whom were on a 5mg dose at the time of death (by arrhythmia and myocardial infarction). A clinically meaningful increase in blood creatine kinase (CK) levels at the end of the study was noted in the donepezil group (5mg; 4.0%, 10mg; 9.4%) compared to placebo (2.9%). Most of the patients with increased values in the 10mg group in fact had shown elevations when still on the 5mg dose. These values improved with time. One incidence of ST elevation on ECG was possibly attributed to treatment in the 10mg/day group. Other less serious AEs recorded at greater than or equal to twice the frequency of placebo were: decreased appetite, restlessness and pyrexia (5mg and 10mg), constipation (5mg only), anorexia, diarrhea, vomiting, and excoriation (10mg only).

Winblad et al. (2006) had a similar percentage of deaths and serious AEs between treatment and placebo, and did not consider either to be treatment related. The overall incidence of AEs was 82% for donepezil and 76% for placebo, with most being 'transient and mild or moderate in severity'. The most common AEs reported were urinary tract infection, accidental fall, diarrhea, and pneumonia. However, the authors did not distinguish AEs as likely versus not likely due to medication as other studies have. Any AEs that were reported in at least 5% of patients in either treatment group were listed. This study did not list vomiting within its AEs, although this is a main side effect commented on by other studies. They do instead list nausea and gastroenteritis, but how they distinguished this from vomiting or diarrhea due to medication is unclear, as gastroenteritis is often a clinical diagnosis. Those AEs that occurred in at least twice the frequency of the treatment compared to placebo group were diarrhea, accidental bone fracture, and hallucinations. The latter was stated as "possibly treatment related" in 4 (3%) of donepezil treated patients. Anorexia/loss of appetite were not recorded. There were substantially more patients that discontinued their treatment due to an AE in the donepezil group than placebo (16% [20] vs 7% [n=8]).

The five studies listed were compared for emergence of AEs in patients treated with donepezil at doses of 5mg, 10mg, and 23mg. In general, the most common AEs were diarrhea, nausea, vomiting, and anorexia (with associated weight loss or loss of appetite), which are predominantly due to increased parasympathetic cholinergic activity. There were increased rates of AEs with higher doses on most outcome measures, with the 23mg dose trending towards the most frequent amount of AEs (Table 3).

In January 2015, the Government of Canada released an alert from Health Canada warning the public of two new potentially serious AEs with the use of Aricept. The first,

rhabdomyolysis involves the breakdown of muscle tissue. Symptoms include weakness, muscle pain, fever, nausea, and dark urine. Kidney failure and arrhythmias may result. The second, Neuroleptic Malignant Syndrome (NMS), is a life-threatening neurological disorder that involves marked reduction in dopamine activity. Symptoms include muscle rigidity, delirium, fever, autonomic instability, and may develop into rhabdomyolysis; verified by elevated plasma CK(18). Pfizer has received a total of 88 cases reports of rhabdomyolysis and 67 of NMS with Aricept use internationally. Of these, three episodes of rhabdomyolysis and 9 occurrences of NMS proved to be fatal. Health Canada has only received one reported case of rhabdomyolysis, which was considered 'possibly' related to the drug(18). Caution should therefore be taken when 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(64). Prescribing updates have been made accordingly to both Aricept and its generic equivalents.

DISCUSSION

Considerations

Overall, there is not sufficient homogeneity towards reporting AEs among the discussed papers. Farlow et al. (2010) listed TEAEs that occurred in ≥2% of patients who received donepezil 23 mg/d and that occurred at a higher frequency with donepezil 23 mg/d than with donepezil 10 mg/d. Black et al. (2007) listed AEs if they were reported by ≥5% of patients in the donepezil group, and considered possibly or probably related to treatment by the investigator. Feldman et al. (2001) included those that were reported in ≥5% of donepezil treated patients and

at twice the incidence of placebo, but also reported other selected AEs. Winblad et al. (2006) and Homma et al. (2007) discussed AEs reported in ≥5% of patients in either treatment group.

All of the papers allowed for concomitant medications during the study that included analgesics, hypnotics, anxiolytics, antidepressants, sedatives, antipsychotics laxatives, diuretics, etc. Some studies specified that antipsychotics and antidepressants must have reached steady state prior to initiation of treatment(57,59), antihistamines or sympathomimetics were allowed for only 3 days out of every 2 weeks but not given within 48 hours of a testing visit(59), or psychoactive medications and SSRIs were allowed to be started after a minimum of 4 weeks following initiation of study medication(57). Others allowed atypical antipsychotics and SSRIs within stable therapeutic ranges, but did not allow "any medication known to interfere with the clinical effects of donepezil…or that could substantially impact cognition, either by enhancing alertness or causing sedation"(29, p.1236).

Three of the studies allowed clinicians to reduce the dose back to 5mg/d following titration to 10mg/d in order to improve tolerability(58,59,65). Winblad et al. (2006) reported that the mean daily dose of donepezil in the treatment group was 8.2mg (SD 1.5). Black et al. (2007) stated the maximum dose of 10mg/d was maintained by 85% of participants in the treatment group. The original study by Feldman et al. (2001) found that 82% of donepezil treatment patients attained the 10mg/day dose, but 10% subsequently lowered back to 5mg/d due to decreased tolerability. However, the data collected from these patients appears to contribute towards the 10mg/d treatment group that is compared to placebo. Therefore, results from these papers are in fact for doses slightly less than 10mg.

Concurrent use of the *N*-methyl-D-aspartate antagonist memantine was allowed in some of the studies reviewed, although it has been shown that in moderate-to-severe AD,

administration of memantine with donepezil resulted in significantly better outcomes than placebo on measures of cognition, activities of daily living, global outcome, and behavior(66). Although Winblad et al. (2006) acknowledges this within the paper's introduction, there is no further mention of memantine within the exclusion criteria. Farlow et al. (2010) declared concomitant use of memantine in 36.6% and 35.7% of 23mg and 10mg groups, respectively. It is unclear whether Feldman et al. (2001) or Homma et al. (2007) allowed memantine use. Black et al. (2007) required discontinuation a minimum of three months prior to screening.

Another consideration when comparing studies is patient demographics. Older age at baseline has been associated with a slower rate of decline in several different measurements of cognitive testing(62). This highlights the fact that subject age at entrance of a study is an important fact to consider in comparing AD clinical trials. The studies discussed within this paper vary in age at entrance from 73-84 years old, with anywhere from 59-80% of participants being female (table 2). When considering nutrition status, increased AE were seen more frequently in patients with lower initial weight (<55kg)(29).

In summary, weaknesses to these studies include the possibility for different interpretations of assessment scales with baseline disease severity, variance in exposure to donepezil prior to study initiation, allowance of concurrent memantine use, and lack of directly observed medication intake.

Conclusion

No cure for AD currently exists, and all available medications are modest at best. Donepezil treatment shows small but statistically significant benefits in severe AD. Clinicians must weigh these benefits against the possible AEs when determining an appropriate course of therapy, as recommendations for discontinuation of cholinesterase inhibitors in advanced disease

remain unclear and vary with different guidelines. Continued research is required for a better option of treatment. After ten years of disappointing trials for monoclonal antibodies directed against β-amyloid, one promising study for a novel drug named Aducanumab has recently sparked media attention. The human recombinant monoclonal antibody that selectively binds aggregated forms of β-amyloid showed statistically significant dose- and time-dependant reduction in amyloid plaques on PET imaging, with corresponding slowing of cognitive decline(67). Where the future lies for this new mechanism of action is currently unclear, but the AD research community is hard-working to seek out new treatment options and possibly one day a cure for this tragic disease that strips one of their vocabulary, independence, and memories of loved ones once cherished.

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REFERENCES

1. World Health Organization and Alzheimer's Disease International. Dementia: A public health priority [Internet]. 2012 p. 112. Available from: http://www.who.int/mental_health/publications/dementia_report_2012/en/
2. A new way of looking at the impact of dementia in Canada [Internet]. Alzheimer Society of Canada. 2012. Available from: http://www.alzheimer.ca/~/media/Files/national/Media-releases/asc_factsheet_new_data_09272012_en.pdf
3. Information about Alzheimer's and related dementias [Internet]. Canadian Institutes of Health Research. [cited 2015 Jan 21]. Available from: http://www.cihr-irsc.gc.ca/e/45554.html
4. Francis PT, Palmer a. M, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry [Internet]. 1999 Feb 1;66(2):137–47. Available from: http://jnnp.bmj.com/cgi/doi/10.1136/jnnp.66.2.137
5. Francis PT, Sims NR, Procter AW, Bowen DM. Cortical Pyramidal Neurone Loss May Cause Glutamatergic Hypoactivity and Cognitive Impairment in Alzheimer's Disease: Investigative and Therapeutic Perspectives. J Neurochem [Internet]. 1993 May;60(5):1589–604. Available from: http://doi.wiley.com/10.1111/j.1471-4159.1993.tb13381.x
6. Shintani EY, Uchida KM. Donepezil: An anticholinesterase inhibitor for Alzheimer's disease. Am J Heal Pharm. 1997;54:2805–10.
7. Esiri MM. The basis for behavioural disturbances in dementia. Neurol Psychiatry. 1996;61(2):127–30.

8. Ferretti L, Mccurry SM, Gibbons L, Teri L. Anxiety and Alzheimer ' s Disease. J Geriatr Psychiatry Neurol. 2015;52–8.

9. Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, et al. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol [Internet]. 2004 Mar;55(3):335–46. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2362399&tool=pmcentrez&rendertype=abstract

10. Portet F, Scarmeas N, Cosentino S, Helzner EP, Stern Y. Extrapyramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study. Arch Neurol. 2009;66(9):1120–6.

11. Hirono N, Mori E, Ikejiri Y, Imamura T, Shimomura T, Ikeda M. Procedural memory in patients with mild Alzheimer's disease. Dement Geriatr Cogn Disord. 1997;8(4):210–6.

12. Markowitsch HJ, Staniloiu A. Amnesic disorders. Lancet [Internet]. Elsevier Ltd; 2012 Oct 20 [cited 2014 Dec 14];380(9851):1429–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22503117

13. Heyman A, Fillenbaum GG, M. G, S. MS, Welsh-Bohmer, K. A., Peterson B. Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to Establish a Registry for Alzheimer's Disease, Part XIX. Neurology,. 1999;52(9):1839–44.

14. Scoville WB, Milner B, Scoviille WB. Loss of recent memory after bilateral hippocampal lesions. 1957. J Neuropsychiatry Clin Neurosci. 1957;12(1):103–13.

15. Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging : study methods and prevalence of dementia. 1994;150(6):899–913.

16. Group CS of H and AW. Patterns of caring for people with dementia in Canada. Can J Aging. 1994;13:470–87.

17. Hux MJ, Brien BJO, Iskedjian M, Goeree R, Gagnon M, Gauthier S. Relation between severity of Alzheimer's disease and costs of caring. CMAJ. 1998;159(5):457–65.

18. Health Canada. Summary Safety Review - ARICEPT (donepezil) - Risk of Rhabdomyolysis and Neuroleptic Malignant Syndrome [Internet]. 2015. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/aricept-eng.php

19. Aricept® and Aricept® rdt [Internet]. Alzheimer Society of Canada. 2007. Available from: http://www.alzheimer.ca/~/media/Files/national/Drugs/Drug_Aricept_e.pdf

20. Lexicomp. Donepezil (Dental Lexi-Drugs) Monograph [Internet]. Lexicomp Online®. 2015. Available from: http://online.lexi.com.proxy2.lib.umanitoba.ca/lco/action/doc/retrieve/docid/dental_f/46726?hl=6068

21. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995;375(6534):754–60.

22. Renbaum P, Levy-Lahad E. Monogenic determinants of familial Alzheimer's disease: Presenilin-2 mutations. Cell Mol Life Sci. 1998;54(9):910–9.

23. Goate A, Chartier-Harling M, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991;349(6311):704–6.

24. Jost B, Grossberg G. The natural history of Alzheimer's Disease: a brain bank study. J Am Geriatr Soc. 1995;43(11):1248–55.

25. Gauthier S, Patterson C, Chertkow H, Gordon M, Herrmann N. CLINICAL PRACTICE GUIDELINES / CONCENSUS STATEMENTS Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4). Candian Geriatr J. 2012;15(4):120–6.

26. Herrmann N, Gauthier S. Diagnosis and treatment of dementia: 6. Management of severe Alzheimer disease. CMAJ [Internet]. Canadian Medical Association; 2008 Dec 2 [cited 2015 Feb 20];179(12):1279–87. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2585109&tool=pmcentrez&rendertype=abstract

27. Sabbagh M, Cummings J. Progressive cholinergic decline in Alzheimer's Disease: consideration for treatment with donepezil 23 mg in patients with moderate to severe symptomatology. BMC Neurol [Internet]. 2011 Jan;11:21. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3042005&tool=pmcentrez&rendertype=abstract

28. Birks J, Harvey R. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev [Internet]. 2006 [cited 2015 Mar 12];(1):Art. No.: CD001190. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001190/full

29. Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, Wang Q, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. Clin Ther [Internet]. Excerpta Medica Inc.; 2010 Jul [cited 2014 Dec 10];32(7):1234–51. Available from:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3068609&tool=pmcentrez&rendertype=abstract

30. How ARICEPT 23 mg is taken [Internet]. Eisai Inc. and Pfizer Inc. 2014 [cited 2015 Apr 22]. Available from: http://www.aricept.com/aricept-5-10-23/how-aricept-23mg-is-taken
31. Schwartz LM, Woloshin S. How the FDA forgot the evidence: the case of donepezil 23 mg. BMJ [Internet]. 2012 Jan [cited 2015 Mar 14];344(March):e1086. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22442352
32. Katz R. FDA memorandum of March 19, 2007, meeting minutes. [Internet]. [cited 2015 Apr 19]. p. Web page 42. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022578Orig1s000Admincorres.pdf
33. Barbehenn E, Wolfe SM, Finucane TE. Public Citizen Petition.pdf. 2011.
34. Drugs and Health Products: Aricept [Internet]. Health Canada. 2013 [cited 2015 Apr 25]. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/dispatch-repartition.do?lang=eng
35. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int Psychogeriatr [Internet]. 2009 Oct [cited 2015 Apr 26];21(5):813–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19538824
36. Cummings JL. Neuropsychiatric Inventory: Comprehensive Assessment of Psychopathology in Patients with Dementia. 2009 p. 1–22.
37. Suzuki H, Inoue Y, Mikami K, Gen K. The influence and changes in the dosages of concomitantly used psychotropic drugs associated with the discontinuation of donepezil in

severe Alzheimer's disease with behavioral and psychological symptoms on dementia: a preliminary open-label trial. Ther Adv Psychopharmacol [Internet]. 2014 Feb [cited 2015 Feb 20];4(1):37–42. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3896135&tool=pmcentrez&rendertype=abstract

38. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing [Internet]. 2014 Oct 16 [cited 2014 Oct 17];(October 2014):213–8. Available from: http://www.ageing.oxfordjournals.org/cgi/doi/10.1093/ageing/afu145

39. Carrasco MM, Agu L. Safety and Effectiveness of Donepezil on Behavioral Symptoms in Patients With Alzheimer Disease. Alzheimer Dis Assoc Disord. 2011;25(4):333–40.

40. Sudeep S. Gill, MD, MSc; Geoffrey M. Anderson, MD, PhD; Hadas D. Fischer, MD; Chaim M. Bell, MD, PhD; Ping Li, PhD; Sharon-Lise T. Normand, PhD; Paula A. Rochon, MD M. Syncope and Its Consequences in Patients With Dementia Receiving Cholinesterase Inhibitors. Arch Intern Med. 2009;169(9):867–73.

41. Therapeutics: Donepezil [Internet]. Alzforum. [cited 2015 Apr 25]. Available from: http://www.alzforum.org/therapeutics/donepezil

42. Parsons C, Hughes CM, Passmore AP, Lapane KL. Withholding, Discontinuing and Withdrawing Medications in Dementia Patients at the End of Life. 2010.

43. Shega JW, Ellner L, Lau DT, Ph D, Maxwell TL. Cholinesterase Inhibitor and N-Methyl-D-Aspartic AcidReceptor Antagonist Use in Older Adults with End-Stage Dementia : A Survey of Hospice Medical Directors. J Palliat Med. 2009;12(9):779–83.

44. Morris JN, Fries BE, Mehr DR, Hawes C, Phillips C, Mor V, et al. MDS Cognitive Performance Scale(C). J Gerontol [Internet]. 1994 Jul 1;49(4):M174–82. Available from: http://geronj.oxfordjournals.org/cgi/doi/10.1093/geronj/49.4.M174

45. Holmes HM, Sachs G a, Shega JW, Hougham GW, Cox Hayley D, Dale W. Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. J Am Geriatr Soc [Internet]. 2008 Jul [cited 2015 Feb 20];56(7):1306–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18482301

46. Colloca G, Tosato M, Vetrano DL, Topinkova E, Fialova D, Gindin J, et al. Inappropriate drugs in elderly patients with severe cognitive impairment: results from the shelter study. PLoS One [Internet]. 2012 Jan [cited 2015 Feb 20];7(10):e46669. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3463565&tool=pmcentrez&rendertype=abstract

47. Levy HB, Marcus E-L, Christen C. Beyond the beers criteria: A comparative overview of explicit criteria. Ann Pharmacother [Internet]. 2010 Dec [cited 2015 Feb 20];44(12):1968–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21081709

48. Campanelli CM. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults: The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. J Am Geriatr Soc. 2013;60(4):616–31.

49. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ [Internet]. 2008 Apr 26 [cited 2014 Jul 29];336(7650):924–6. Available from:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2335261&tool=pmcentrez&rendertype=abstract

50. O'Mahony D, Gallagher P, Ryan C, Byrne S, Hamilton H, Barry P, et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. Eur Geriatr Med [Internet]. Elsevier Masson SAS; 2010 Feb [cited 2015 Apr 26];1(1):45–51. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1878764910000112

51. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing [Internet]. 2014 Oct 16 [cited 2014 Oct 17];1–6. Available from: http://www.ageing.oxfordjournals.org/cgi/doi/10.1093/ageing/afu145

52. National Institute for Health and Care Excellence. Dementia: Supporting people with dementia and their carers in health and social care [Internet]. 2006. Available from: guidance.nice.org.uk/cg42

53. Prakash a, Risser RC, Mallinckrodt CH. The impact of analytic method on interpretation of outcomes in longitudinal clinical trials. Int J Clin Pract [Internet]. 2008 Aug [cited 2015 Apr 11];62(8):1147–58. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2658028&tool=pmcentrez&rendertype=abstract

54. Konsta A, Bonti E, Parlapani E, Athanasiadis L, Kechayas P, Karagiannidou M, et al. Development and validation of the Greek severe impairment battery (SIB). Int Psychogeriatr [Internet]. 2014 Apr [cited 2015 Apr 22];26(4):591–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24443975

55. Barbarotto R, Cerri M, Acerbi C, Molinari S, Capitani E. Is SIB or BNP Better Than MMSE in Discriminating the Cognitive Performance of Severely Impaired Elderly Patients? Arch Clin Neuropsychol [Internet]. 2000 Jan 1;15(1):21–9. Available from: http://acn.oxfordjournals.org/cgi/doi/10.1093/arclin/15.1.21

56. Homma A, Imai Y, Tago H, Asada T, Shigeta M, Iwamoto T, et al. Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial. Dement Geriatr Cogn Disord [Internet]. 2008 Jan [cited 2015 Mar 18];25(5):399–407. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18391486

57. Feldman H, Gauthier S, Hecker J, Vellas B, Xu Y, Ieni JR, et al. Efficacy and safety of donepezil in patients with more severe Alzheimer's disease: a subgroup analysis from a randomized, placebo-controlled trial. Int J Geriatr Psychiatry. 2005;20(0885-6230 (Print)):559–69.

58. Winblad B, Kilander L, Eriksson S, Minthon L, Båtsman S, Wetterholm A-L, et al. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet [Internet]. 2006 Apr 1 [cited 2014 Dec 20];367(9516):1057–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16581404

59. Black SE, Doody R, Li H, McRae T, Jambor KM, Xu Y, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology [Internet]. 2007 Jul 31;69(5):459–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17664405

60. Ferris S, Cummings J, Christensen D, Doody R, Farlow M, Sabbagh M, et al. Effects of donepezil 23 mg on Severe Impairment Battery domains in patients with moderate to

severe Alzheimer's disease: evaluating the impact of baseline severity. Alzheimers Res Ther [Internet]. BioMed Central Ltd; 2013 Jan [cited 2014 Dec 19];5(1):12. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4055003&tool=pmcentrez&rendertype=abstract

61. Cohen J. Statistical Power Analysis for the Behavioral Sciences (second ed.). Lawrence Erlbaum Associates; 1988.

62. Bernick C, Cummings J, Raman R, Sun X, Aisen P. Age and rate of cognitive decline in Alzheimer disease: implications for clinical trials. Arch Neurol [Internet]. 2012 Jul [cited 2015 Feb 13];69(7):901–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22431834

63. Salmon D, Thal L, Butters N, Heindel W. Longitudinal evaluation of dementia of the Alzheimer type: a comparison of 3 standardized mental status examinations. Neurology. 1990;40(8):1225–30.

64. Recalls and Alerts: Alzheimer's drug Aricept (donepezil) - New warnings on the serious risks of muscle breakdown and of a neurological disorder [Internet]. Government of Canada. 2015 [cited 2015 Jan 21]. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43469a-eng.php

65. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology. 2001 p. 613–20.

66. Farlow MR, Grossberg GT, Graham SM, Mcdonald S. Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil. JAMA. 2004;291(3):317–24.

67. Biogen Idec. A Randomized, Blinded, Placebo-Controlled Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of BIIB037 in Subjects With Mild to Moderate Alzheimer's Disease.

68. Alexopoulos GS, Abrams RC, Young RC, Shamoian C a. Cornell scale for depression in dementia. Biol Psychiatry [Internet]. 1988 Feb;23(3):271–84. Available from: http://linkinghub.elsevier.com/retrieve/pii/0006322388900388

APPENDIX

Table 1. Study design, demographic, and clinical baseline cognitive function of 5 studies used for analysis					
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/day)	10*	10*	10*	10 or 23	5 or 10
MMSE	1-12	1-10	5-12	1-20†	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 arm, (# randomized)	167	120	73	486 (10mg)	105
Sample size, treatment arm, (# randomized)	176	128	72	981 (23mg)	197 (5mg=101 10mg=96)
Duration	24 weeks	26 weeks	24 weeks	24 weeks	24 weeks
Baseline Demographics					
Age (mean)	78	84	73	74	78
Female (%)	70	77	59	63	80
Baseline Mean Outcomes					
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-sev	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

* Dose could be reduced to 5mg/day to improve tolerability if required.
† post-hoc analysis of more severe disease (MMSE 0-16) from this study, as well as Ferris et. al (2013) (severity strata) to be discussed

Table 2. Outcome measures of 5 studies used for analysis

Study	**Black, 2007**		**Winblad, 2006**			**Feldman, 2005**	**Homma, 2008**		**Ferris, 2013**
Analysis	LOCF	OC	LOCF	MMRM	OC	LOCF	LOCF		LOCF
Donepezil dose	10mg		10mg			10mg	5mg	10 mg	23mg
SIB LS mean difference* (score (*p*))	5.3 (0.0001)	5.6 (0.0008)	5.6 (0.008)	4.5 (0.01)	5.8 (0.008)	7.4 (0.002)	6.7 (0.001)	8.9 (0.001)	MMSE 0-5= 6.0 MMSE 6-10= 3.3
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)	1.0 (0.002)	--	--	--

*LS mean treatment difference between placebo and donepezil treatment groups, except for Ferris et al. (2013) who compared 10mg to 23mg donepezil. LS, least squares.

Table 3. Adverse events

Study	Black, 2007		Winblad, 2006		Feldman, 2005		Farlow, 2010		Homma, 2008		
	Treatment group, n (%)										
	Donepezil 10mg (n=176)	Placebo (n=167)	Donepezil 10mg (n=128)	Placebo (n=120)	Donepezil 10mg (n=72)	Placebo (n=73)	Donepezil 10 mg (n=471)	Donepezil 23mg (n=963)	Donepezil 5mg (n=101)	Donepezil 10mg (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(18)	---	---	---
Diarrhea	18 (10)	7 (4.2)	12 (9) *	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 (17)	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) † ‡	1 (1) §	---	---	---	---	---	---	---
Serious/ severe AE	20 (11)/ 19 (11)	25 (15)/ 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 (19)	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)

*Possibly treatment-related in 8(6%) patients. †Possibly treatment-related in four (3%) patients. ‡Present before start of study in 3 patients. §Present before start of study in one patient

Characteristics of studies

Table 4.1 Black, 2007	
Methods	24-week double-blind, parallel-group, placebo-controlled, randomized study
Patients	343 patients from 98 sites across the US, Canada, France, the UK, and Australia, ambulatory or ambulatory-aided, 50 years or older Inclusion criteria: MMSE 1-12, FAST ≥6, modified Hachinski ≤6, reliable caregiver contact min. 3 days/week Exclusion criteria: skilled nursing home or requiring skilled nursing home within 6 months, known sensitivity to piperidine derivatives or cholinesterase inhibitors, clinically significant obstructive pulmonary disease or asthma left untreated within 3 months of study entry, hematologic or oncologic disorder within 2 years, 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 years, 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 5mg/day for 6 weeks, and then 10mg/day thereafter
Outcome measures	Primary: SIB, CIBIC-Plus Secondary: ADCS-ADL-severe, NPI, MMSE, CBQ, RUSP
Notes	Clinicians were able to reduce the dose back to 5mg/d to improve tolerability as necessary. Treatment with cholinesterase inhibitors, memantine, or propoentofylline was allowed previously if discontinued no less than 3 months before screening.

Table 4.2 Winblad, 2006	
Methods	6 month double-blind, parallel-group, placebo-controlled, randomized study
Patients	248 patients from 50 assisted-care facilities, 50 years or older, ambulatory or ambulatory-aided, with nursing assistants knowing their patient for at least 12 weeks, spending at least 4 hours with patient on at least 3 days 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 5mg/day x30 days, followed by 10mg/day thereafter
Outcome measures	Primary: SIB, ADCS-ADL-severe Secondary: MMSE, NPI, CGI-I scale
Notes	Clinicians were able to reduce the dose back to 5mg/d to improve tolerability as necessary.

Table 4.3 Feldman, 2005	
Methods	Subgroup analysis of 24-week 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 hours of caregiver contact 3 times per week Inclusion criteria: MMSE 5-12, FAST ≤ 6, CT or MRI scan within the previous 24 months 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 neurologic or psychiatric diagnoses, clinically significant obstructive airway disease or asthma, hematologic or oncologic disorders within 2 years, 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 years, known hypersensitivity to AChEIs. Medications with notable cholinomimetic or anticholinergic effects, investigational drugs, initiation of psychoactive medications within the first four weeks of treatment. AD diagnosis: DSM-IV, NINCDS-ADRDA
Interventions	Placebo vs 5mg/d for 28 days, followed by placebo vs 10mg/d
Outcome measures	Primary: CIBIC-Plus Secondary: MMSE, SIB, DAD, IADL+, PSMS+, NPI
Notes	Clinicians were able to reduce the dose back to 5mg/d to improve tolerability as necessary. Antipsychotics and benzodiazepines were allowed provided that patients were on a stable dose of these drugs for a minimum of 4 weeks before the baseline visit and were to remain on the same dose for 4 weeks after the start of study medication.

Table 4.4 Farlow, 2010	
Methods	24-week double-blind, randomized study
Patients	1467 patients, ambulatory or ambulatory aided, aged 45 to 90 years old, receiving donepezil 10 mg once daily for ≥12 weeks 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 hours/week 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 neurologic 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 weeks of screening. Unstable or supratherapeutic doses of antipsychotics and SSRIs, any additional AChEI use within 12 weeks 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 weeks. Previously on 10mg for ≥12 weeks
Outcome measures	Primary: SIB, CIBIC-Plus Secondary: ADCS-ADL, MMSE
Notes	If a patient was taking memantine at a stable dose of ≤ 20mg/d for ≥12 weeks before screening, use was allowed to continue. All cholinesterase inhibitors were required to be discontinued for 12 weeks prior to screening.

Table 4.5 Homma, 2008	
Methods	24-week 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 days/week (4 hours/day) 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 months of study, alcohol or drug dependence within 10 years, treatment with donepezil in 3 months 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-week placebo observation period all groups, then placebo x24 weeks vs 5 mg/day (3mg/ day x2 weeks, then 5mg/day x22 weeks), vs 10 mg/day (3-mg/day x2 weeks, then 5-mg/day x4 weeks, then 10mg/day x18 weeks)
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.

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 validated in patients with moderate- to-severe dementia; total scores range from 0 to 54, with the lowest score indicating the greatest functional impairment and the highest no impairment. Items include both complex and basic activities of daily living.
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 disorders that measures symptoms defined by the DSM-V for a major depressive episode, with 20 questions each scored from 0-4; 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).
DAD= Disability Assessment for Dementia, a 10-domain, 40-item instrument that measures instrumental and basic activities of daily living
DSM-4= Diagnostic Statistical Manual of Mental Disorders, 4th Edition
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 resources used translates to lower scores.
FAST= Functional Assessment Staging
IADL+= the modified Instrumental Activities of Daily Living Scale
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, +/-night-time behavior disturbances, +/-appetite and eating abnormalities. Assessment of frequency, severity, and caregiver distress on each measure is.
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).