Cognitive symptoms of Alzheimer's disease: clinical management and prevention

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid β in the form of extracellular plaques and by intracellular neurofibrillary tangles, with eventual neurodegeneration and dementia. There is currently no disease-modifying treatment though several symptomatic medications exist with modest benefit on cognition. Acetylcholinesterase inhibitors have a consistent benefit across all stages of dementia; their benefit in mild cognitive impairment and prodromal AD is unproven. Memantine has a smaller benefit on cognition overall which is limited to the moderate to severe stages, and the combination of a cholinesterase inhibitor and memantine may have additional efficacy. Evidence for the efficacy of vitamin E supplementation and medical foods is weak but might be considered in the context of cost, availability, and safety in individual patients. Apparently promising disease-modifying interventions, mostly addressing the amyloid cascade hypothesis of AD, have recently failed to demonstrate efficacy so novel approaches must be considered.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of extracellular amyloid β in the form of plaques and the intracellular accumulation of hyperphosphorylated tau proteins as neurofibrillary tangles, with progressive neuronal loss and cerebral atrophy.[1] AD typically affects memory initially, but atypical presentations can occur, particularly in younger patients.[2] AD eventually progresses to involve diffuse cortical functions, leading to the inability to manage activities of daily living. AD also causes a number of psychological and behavioral changes which can cause significant distress to both patients and care givers.[3-5]

The pathogenesis of AD is quite complex, though genetic[6] and neuropathological studies[7] suggest that elevations of amyloid β plays a central role. To date, however, interventions intended to prevent amyloid β accumulation have failed to demonstrate clinical efficacy in preventing or slowing AD progression despite biomarker evidence of target engagement.[8 9] No disease-modifying treatment for AD currently exists. Existing medications are symptomatic and have only modest benefit. However, appropriate treatment of cognitive symptoms may prolong functional independence,[10] delay institutionalization[11] and improve quality of life.[12] While it is discouraging that there has not been a new medication approved by the US Food and Drug Administration (FDA) since memantine in 2003,[13] a large literature has developed surrounding the specific clinical situations in which medications are most useful. This review discusses the status of existing therapies for cognitive symptoms of AD with an emphasis on how to tailor management to the individual patient.

Incidence and prevalence of Alzheimer's disease

AD is the most common cause of dementia. In a systematic review of 119 studies, the point prevalence of AD overall was 4% among community-dwelling people aged ≥60 years, and the incidence in community settings was 15.8 per 1000 person years.[14] However, the authors noted significant heterogeneity among studies and that prevalence varied depending on the diagnostic criteria used. These estimates are in line with a 2015 systematic review by Alzheimer Disease International (ADI), which estimated a global prevalence of 5.2% for all types of dementia for adults ≥60 years old and an incidence of 17.3 per 1000 person years. ADI further estimated that there were 46.8 million people with dementia worldwide in 2015, with this number projected to rise to 54 million by 2020 and 131 million by 2050.[15] Regional prevalence ranged from 4.7% in central Europe to 8.7% in north Africa and Middle East.

In the US, AD affects 5.8 million people, or approximately 10% of the population >65 years old.[16] This number is projected to grow to 13.8 million by 2050, primarily due to a growing population of older adults, particularly those ≥85 years old.[16]

Sources and selection criteria

We identified sources through a search of PubMed from January 2004 through March 2019 for keywords including "Alzheimer's disease," "cognition," "cognitive," "neuropsychological," "treatment," "medication," and "therapy." Because of the large number of search results, we initially limited our results to studies that were randomized controlled trials (RCTs), systematic reviews, or meta-analyses. After reviewing the resultant 4000 titles, we discarded those that were clearly irrelevant, such as those focused on other conditions; for the remainder, we reviewed abstracts and categorized the relevant ones by topic before selecting articles for inclusion. For each section, we included the strongest available evidence, prioritizing large phase III trials and systematic reviews when available, and including the results of smaller studies when of particular interest or when other evidence was unavailable. To ensure comprehensiveness, we also reviewed, and included when appropriate, the results categorized by Medline as expert (that is, non-systematic) reviews published in Medline core clinical journals, which is a Medline-designated set of 118 journals that are clinically focused and of high impact factor. We also reviewed the reference lists of selected articles and included relevant articles, including those from before 2004 if relevant. We included articles in English only.

Diagnosis of AD for research and prevention studies

Most clinical trials before 2011 used either the DSM-IV criteria for dementia of the Alzheimer type[17] or the NINCDS-ADRDA criteria for probable or possible AD[18] as inclusion criteria. Both of these standards for clinically diagnosed AD require the presence of a multi-domain amnestic syndrome that impairs a person's ability to live fully independently, without other obvious cause.[19] NINCDS-ADRDA criteria for definite AD require neuropathological confirmation of the presence of amyloid plaques and neurofibrillary tangles. The clinical criteria are relatively simple for use in clinical practice but have a sensitivity and specificity of only 81% and 73% respectively.[20] Clinical trials basing enrollment on the NINCDS-ADRDA criteria therefore routinely included patients without AD pathology: in one large trial of bapineuzumab, a monoclonal antibody to amyloid β, 36% of participants who were non-carriers of the apolipoprotein E ε4 allele (*APOE* ε4) had negative amyloid positron emission tomography (PET) scans of the brain,[21] indicating the absence of fibrillar amyloid β pathology.

The lack of specificity of clinically diagnosed AD is also relevant for trials of lifestyle modifications conducted before the advent of AD biomarkers. Since many changes in diet and physical activity also promote vascular health, it is unclear to what extent any benefit noted may have resulted from an effect on a vascular contribution to cognitive impairment. However, since postmortem studies show that AD and vascular cognitive impairment commonly co-occur,[22] and vascular pathology may be implicated in AD pathogenesis,[23 24] such modifications should nonetheless be recommended to patients with concerns about their cognitive health.

The development of in vivo biomarkers of AD pathology have demonstrated that the pathological changes of AD begin years to decades before the presence of diagnosable dementia.[25] Biomarkers for amyloid pathology include decreased levels of amyloid β42 in the cerebrospinal fluid (CSF) and the presence of fibrillar amyloid on PET scans of the brain. Biomarkers for neurodegeneration include hippocampal volume loss on structural magnetic resonance imaging (MRI), increased CSF total and phosphorylated tau proteins, and detection of tau on PET scans.[1] Use of these biomarkers allowed for the development in 2011 of research criteria for AD, mild cognitive impairment, and presymptomatic AD,[26-28] the ability to track AD pathology in preclinical individuals, and increased homogeneity among clinical trial participants.

Symptomatic treatment

Cholinergic enhancers

Loss of cholinergic neurons from the nucleus basalis of Meynert is an early pathological finding in AD.[29] Modulation of cortical function by cholinergic innervation originating from the basal forebrain enhances focused attention.[30] As a result, attempts to facilitate cholinergic neurotransmission represented an early approach to treating AD. Though agonists of muscarinic receptors have previously been unsuccessful in human trials, and a trial of a nicotine patch is currently under way (ClinicalTrials.gov Identifier: NCT02720445), inhibitors of acetylcholinesterase are the only examples of this approach that have thus far shown some success.

Cholinesterase inhibitors

Acetylcholinesterase inhibitors work by inhibiting acetylcholinesterase (the enzyme primarily responsible for synaptic recycling of acetylcholine in gray matter), thereby prolonging the action of endogenous acetylcholine. Three such inhibitors are currently in clinical use: donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). A fourth, tacrine, is no longer in use, largely due to hepatotoxicity.[31]

Donepezil

Donepezil is a relatively pure acetylcholinesterase inhibitor and was approved by the FDA in 1996 and by the European Medicines Agency (EMA) in 1997. A systematic review and meta-analysis on the efficacy of donepezil in AD found a benefit for both 5 mg and 10 mg daily dosing compared with placebo, with a consistent effect size ranging from 2 to 3 points on the Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog, a 70 point scale) and about 1 point on the mini-mental state examination (MMSE, a 30 point scale)[32] at 3, 6, and 12 months of use (table 1). This effect was sustained across dementia stages. Both doses showed additional mild benefits

on activities of daily living and global assessments compared to placebo, but did not show a consistent benefit on behavioral symptoms or quality of life. In comparison of 10 mg and 5 mg, the higher dose showed mild additional benefit on cognition but no additional benefit on global status, and with somewhat higher incidence of adverse effects.

Donepezil is also available in a 23 mg daily, sustained release formulation that was approved by the FDA in 2010. A randomized controlled trial of 1371 patients with moderate to severe AD showed a small but statistically significant benefit on cognition (2.2 points on the severe impairment battery (SIB)) compared with 10 mg daily, but not global status (clinician's interview-based impression of change with caregiver input (CIBIC+)). Post hoc subgroup analysis did show a benefit for global status and a slightly larger effect on cognition for patients with more severe dementia (MMSE score ≤16). However, the incidence of gastrointestinal side effects was significantly higher (21% in the high dose group *v* 5.9% in the standard dose group).[33] The additional

Table 1 | Administration, pharmacology, and adverse effects of currently approved cognitive enhancing medications

Medication (trade name)	Dosing and administration	Mechanism of action	Pharmacokinetics/ metabolism*	Adverse effects*	Notes
Donepezil (Aricept)	*Oral immediate release and oral disintegrating tablet* Initial dose 5 mg daily Increase after 1 month to maintenance dose 10 mg daily *Oral sustained release* 23 mg film-coated tablet	Reversible non-competitive acetylcholinesterase inhibitor	*Protein binding*: primarily protein-bound *Metabolism:* hepatic, via CYP2D6 and CYP 3A4; 2 active and 2 inactive metabolites *Half-life:* 70 hours	Nausea, vomiting, loss of appetite, weight loss, diarrhea Bradycardia, heart block, QT prolongation Dizziness, syncope Insomnia, abnormal dreams, fatigue, drowsiness Headache Muscle cramps, rare reports of rhabdomyolysis and neuroleptic malignant syndrome	Levels may be increased in patients with hepatic impairment, CYP2D6 slow metabolizers, and with concurrent CYP2D6 or CYP3A4 inhibitors such as sertraline
Rivastigmine (Exelon)	*Oral* Initial dose 1.5 mg BID with meals Increase by 3 mg daily every 2 weeks to maintenance dose of 6 mg BID *Transdermal patch* Initial dose 4.6 mg patch to upper back daily Increase no sooner than 4 weeks to 9.5 mg/day patch and then to maximum dose of 13.3 mg/day patch Rotate patch site to reduce skin irritation	Acetylcholinesterase and butylcholinesterase inhibitor	*Protein binding*: 40% *Metabolism:* hydrolyzed in brain, then metabolite further processed in liver independent of CYP system then eliminated in urine *Half life:* 1.5 hours (oral), 3 hours (after patch removal), but clinical effect ~10 hours due to pseudo-irreversible nature of inhibition	Nausea, vomiting, diarrhea, loss of appetite, abdominal pain, weight loss Irritation at application site (patch) Allergic dermatitis (both formulations) Rare hypersensitivity reaction and Stevens-Johnson syndrome Bradycardia, heart block, dizziness, syncope, falls Insomnia, fatigue Headache Tremor	Avoid with concurrent β blocker therapy Clearance is inc eased in smokers and decreased in liver and moderate renal impairment but increased in severe renal impairment
Galantamine (Razadyne)	*Oral immediate release* Initial dose 4 mg BID Increase by 8 mg daily every 4 weeks to maintenance dose of 12 mg BID *Oral extended release* Initial dose 8 mg daily Increase by 8 mg daily every 4 weeks to maintenance dose of 24 mg daily Also available as oral solution	Reversible, competitive acetylcholinesterase inhibitor and modulator of nicotinic acetylcholine receptor	*Protein binding:* low *Metabolism:* hepatic via CYP2D6 *Half-life:* 7 hours	Nausea, vomiting, decreased appetite, weight loss, diarrhea, abdominal pain Bradycardia, heart block, dizziness, syncope, falls Rare hypersensitivity reactions, Stevens-Johnson syndrome and other rash	Levels increased in hepatic and renal impairment and in CYP2D6 slow metabolizers
Memantine (Namenda)	*Immediate release initial titration* Week 1: 5 mg daily Week 2: 5 mg BID Week 3: 10 mg qam, 5 mg QHS Week 4 and after: 10 mg BID *Sustained release Namenda XR* Initial dose: 7 mg daily Increase weekly in increments of 7 mg to maintenance dose of 28 mg daily Available in combination with donepezil as Namzaric	Non-competitive NMDA antagonist	*Protein binding:* 45% *Metabolism:* almost 50% excreted unchanged in urine; remainder undergoes hepatic metabolism independent of CYP system *Half-life:* 60-80 hours	Generally well tolerated without consistent pattern of adverse effects; for example, package labeling includes both hypertension and hypotension, and constipation and diarrhea Rare hypersensitivity reactions have been reported	Canadian package label recommends periodic eye exams due to worsening of corneal disease Clearance is reduced by alkaline urine and by liver and renal impairment

BID = twice daily; QHS = each night at bedtime; qam = every morning; NMDA = *N*-methyl-D-aspartate receptor.
*Pharmacokinetics and adverse effects adapted from Lexi-Drugs clinical drug monographs for individual agents[1]3

cognitive benefit was independent of whether patients were simultaneously taking memantine.[34] However, a similar multicenter RCT of 351 patients in Japan found no additional benefit with the higher dose,[35] and data from the two studies combined in a meta-analysis showed no additional benefit from the sustained release 23 mg version compared with 10 mg but with a higher incidence of side effects.[32]

Rivastigmine

Rivastigmine is a combined acetylcholinesterase and butyrylcholinesterase inhibitor that achieved FDA approval in 2000 and is available in oral and transdermal forms (table 1). The half-life is 1.5 hours, but the duration of clinical effect from oral administration is approximately 10 hours because of the "pseudo-irreversible" nature of the inhibition, allowing for twice daily dosing. A more slowly absorbed patch form which is applied once daily was subsequently developed.[36] A meta-analysis of seven trials including 3450 patients on the efficacy of rivastigmine in AD found a benefit on cognition of 1.79 points on the ADAS-Cog and 0.74 points on the MMSE at six months in the combined analyses of the recommended doses (6-12 mg total daily dose in capsules and 9.5 mg/24 hour patch).[37] There was also a mild benefit on activities of daily living and global assessments compared with placebo, but no robust benefit on behavioral symptoms or caregiver quality of life. The meta-analysis also found a minor effect on cognition at a lower dose (1-4 mg daily), 0.84 points on the ADAS-Cog and 0.43 points on the MMSE, as well as on a global assessment. The low dose 4.6 mg patch showed no benefit on cognition.

Galantamine

Galantamine is a competitive inhibitor of acetylcholinesterase and therefore theoretically has greater effect in areas of the brain with low levels of acetylcholine. It is also an allosteric modulator that enhances the effect of acetylcholine at nicotinic cholinergic receptors.[38] It is available in immediate and extended release oral formulations (table 1). A 2006 meta-analysis of 10 trials with 6805 patients on the efficacy of galantamine in AD found no additional cognitive benefit above 16 mg daily, but there was a dose-dependent increase in adverse effects above this dose. The effect size, as for other cholinesterase inhibitors, was modest, around 3 points on the ADAS-Cog scale at six months, with a mild benefit on activities of daily living as well. A more recent meta-analysis including 4074 participants confirmed the cognitive benefits (2.95 points on ADAS-Cog) but did not show any effect on activities of daily living. However, the authors note that that the trials that showed benefit on activities of daily living were longer duration[39] and speculate that longer treatment duration may be needed for the functional status in untreated groups to decline enough to allow for any benefit to be measurable.

Overall, the benefits of the acetylcholinesterase inhibitors on cognition are consistently modest. A meta-analysis of 80 trials that reviewed outcomes on MMSE scores across the cholinesterase inhibitors as a class and across multiple forms of dementia found a mean effect size of 1.08, 1.0, and 1.10 points on the MMSE at 3, 6, and 12 months of treatment respectively.[40] This review did not include any trials of acetylcholinesterase inhibitors on frontotemporal lobar degeneration, for which they have not been shown to be effective.[41]

Timing of initiation of therapy

Although none of the acetylcholinesterase inhibitors is approved for mild cognitive impairment, they are commonly prescribed for this indication in the US. An analysis of 402 participants with mild cognitive impairment in the observational Alzheimer's Disease Neuroimaging Initiative (ADNI) study showed that 44% were taking acetylcholinesterase inhibitors. This group had a higher rate of decline over two years than patients with mild cognitive impairment who were not taking acetylcholinesterase inhibitors; however, 95% of patients in this subgroup were thought by ADNI investigators to have prodromal AD, compared with more heterogeneous etiologies in the mild cognitive impairment group not taking acetylcholinesterase inhibitors.[42]

The utility of acetylcholinesterase inhibitors in mild cognitive impairment is controversial. A randomized controlled trial of 769 participants with amnestic mild cognitive impairment comparing donepezil with placebo and vitamin E found a significantly decreased rate of conversion to dementia at six and 12 months in the donepezil arm, but no difference in the rate of dementia at three years. The cognitive benefit was mild, about 0.5 points on the MMSE scale, but was sustained even after sensitivity analysis that accounted for a higher rate of drop-outs in the donepezil arm.[43] The benefit was greater in carriers of the *APOE* ε4 allele compared with non-carriers, which may imply that some participants had mild cognitive impairment due to non-AD pathology, limiting the study's power. Likewise, another large RCT, of 821 patients, showed a slight cognitive benefit for donepezil but no benefit on the Clinical Dementia Rating scale sum of boxes (CDR SB).[44] A large RCT of 1018 patients (the InDDEx study) of rivastigmine in mild cognitive impairment showed no difference in either co-primary outcome of time to progression to AD or in a composite cognitive measure.[45] In the previously described meta-analysis of galantamine, the pooled analysis of two trials with 2057 patients with mild cognitive impairment showed no benefit on the ADAS-Cog scale but did show an odds ratio of 0.74 for conversion to dementia at 24 months, as well as lower whole brain atrophy. However, there was an unexplained increase in mortality in the galantamine treated group, leading the authors to conclude that the drug should be avoided in mild cognitive impairment.[38] A 2012 meta-analysis of cholinesterase inhibitors as a class, including nine studies of 5149 patients showed a benefit on risk of progression to dementia

at two years, but not at one or three years; however, the authors note that the included studies were done before the 2011 Albert criteria (based on biomarkers) for mild cognitive impairment were widely adopted, and most did not differentiate between amnestic and non-amnestic mild cognitive impairment, which may have influenced the results.[46]

Several studies have investigated if acetylcholinesterase inhibitors have any disease modifying effect. A recent meta-analysis of seven trials including 1708 participants that also included memantine found a small but significant benefit in favor of drug therapy overall and for donepezil in particular on global cerebral atrophy.[47] However, a meta-analysis of 10 trials with 3092 patients at different stages of AD comparing immediate versus delayed (~6 months) initiation of acetylcholinesterase inhibitors or memantine found no benefit for early initiation on cognition or functional status.[48] Overall there is no convincing evidence that acetylcholinesterase inhibitors have any clinically meaningful disease modifying effects, and therefore the decision on timing of initiation of therapy should be individualized based on the preferences of the patient and family.

Duration of therapy

The optimal duration of acetylcholinesterase inhibitor therapy was not resolved by the original efficacy trials, most of which showed cognitive benefit over a six month period. However, all three acetylcholinesterase inhibitors have been shown to be safe and to maintain their cognitive benefits over multiple years.[49-51] The AD2000 trial, a randomized trial of 565 patients with mild-moderate AD treated with donepezil in a real world setting for up to four years, showed a cognitive benefit of about 0.8 points on the MMSE scale over the course of the study, although there was no benefit over placebo in terms of the primary endpoints of time to institutionalization or progression of disability.[52] In contrast, the DOMINO-AD trial, which included 295 patients with moderate to severe AD stable on donepezil, found that discontinuation increased the probability of nursing home placement within the first year; the authors noted that the mean MMSE score in DOMINO-AD was significantly lower than in AD2000 (9 *v* 19), and DOMINO-AD showed a greater difference between donepezil and placebo on MMSE score (1.9 points) and on a measure of daily function than did AD2000.[11]

The acetylcholinesterase inhibitors maintain their efficacy in severe dementia. An open label study of 97 patients living in assisted living facilities found that donepezil was well tolerated and the magnitude of benefit was similar to that reported for populations dwelling in the community, which are studied more often in trials of mild to moderate disease.[53] A pooled analysis of three RCTs involving over 700 patients found a benefit for 6.4 points on the severe impairment battery with donepezil treatment and mild benefit on global impression and activities of daily living.[54] The meta-analysis of donepezil found a benefit on cognition of similar scale to that found in studies of mild to moderate dementia (approximately 1 point on the MMSE) and a small benefit on activities of daily living as well.[32]

Discontinuation of therapy

Several studies have considered acetylcholinesterase inhibitor discontinuation and have generally found a negative impact of drug withdrawal. An analysis of two galantamine withdrawal trials including 841 patients showed a deterioration in cognitive scores in patients switched from the active drug to placebo comparable to that seen in patients who had received placebo alone.[55] A meta-analysis including the smaller of these two trials and four additional discontinuation trials (3 of donepezil, 1 of galantamine) likewise found additional deterioration of cognition in the discontinuation group of 1.6 MMSE points per year. There was a higher rate of study withdrawal in the discontinuation arms overall, suggesting that this represented a clinically noticeable deterioration.[56] Conversely, a small trial that randomized 40 patients with moderate to severe AD in long term care to ongoing treatment with donepezil versus discontinuation showed no difference in global worsening at eight weeks, but the trial was underpowered to detect small differences in deterioration rates. There was a correlation noted between baseline hallucinations and delusions and clinical worsening in the discontinuation arm, suggesting that institutionalized patients with psychosis may be at increased risk of worsening with discontinuation.[57]

Tolerability of acetylcholinesterase inhibitors

The acetylcholinesterase inhibitors are overall relatively well tolerated. Gastrointestinal side effects—including anorexia, nausea, vomiting, and diarrhea—are fairly common, occurring in 5-33% of patients in clinical trials.[32 58] These side effects may be more common in individuals with lower body weight, at least for the 23 mg sustained release formulation of donepezil.[59 60] Other common adverse effects include dizziness/vertigo, fatigue, insomnia, hallucinations, bradycardia, and muscle cramps. The rivastigmine patch can also cause skin irritation at the application site.[37] To our knowledge, no significant difference in serious adverse effects or deaths compared with placebo has been reported, with the possible exception of increased all cause mortality associated with galantamine treatment for mild cognitive impairment as discussed above.[38]

Tailoring acetylcholinesterase inhibitor therapy and precision medicine

Several studies have looked at whether certain patient groups have a differential response to acetylcholinesterase inhibitors.

A pooled analysis of the donepezil (as an active control) and placebo arms of three phase II trials from 2009 to 2011, including 335 patients, showed no interaction between *APOE* ε4 carrier status and treatment effect.[61] Likewise, a recent

meta-analysis of 38 studies of *APOE* status found no effect of genotype on clinical benefit for either acetylcholinesterase inhibitors as a category or for individual medications.[62]

Donepezil undergoes hepatic metabolism by CYP2D6 and CYP3A4 enzymes.[13] Several small studies have looked at the relationship between drug metabolism, serum levels of the drug, and cognitive response: they found a linear correlation between dose and plasma levels,[63] that plasma levels correlate with the degree of acetylcholinesterase inhibition and with cognitive scores,[63-65] and that CYP2D6 activity modestly influences plasma levels.[64] An open label study of 110 Chinese patients found that carriers of at least one CYP2D6*10 allele, which is common in Asian populations, had a higher response rate to donepezil, defined as improvement or no change in MMSE scores at six months.[66]

Analysis of an open label study of 146 patients on rivastigmine patch monotherapy versus add-on memantine showed that carriers of the common BCHE-K variant of butylcholinesterase had reduced response to rivastigmine.[67] Analysis of samples from 574 participants in the MCI trial of donepezil and vitamin E and found the BCHE-K variant was associated with faster cognitive decline in the donepezil group, suggesting that donepezil is less effective in this genotype.[68]

Routine testing for these variants before starting acetylcholinesterase inhibitor therapy is not widely performed. Although pharmacogenomic testing is becoming more common in certain clinical situations, and at least one commerical service currently provides a patient's predicted response to donepezil as part of their results, the clinical utility of testing for these variants is unproven. In practice, clinicians could instead consider a trial of a higher dose of donepezil (up to 23 mg formulation) for patients who do not derive clinical benefit at 10 mg daily in case of lower serum levels, although the increased rate of adverse effects at higher doses should also be taken into account.

Predictors of good clinical response

A post hoc analysis of 303 patients who received active drug during a large RCT of galantamine in Japan showed that the biggest predictor of sustained clinical response at six months (defined as an improvement of ≥4 points on the Japanese version of the ADAS-Cog scale (ADAS-Jcog)), was the difference on the ADAS-Jcog at four weeks.[69] In a combined analysis of two galantamine withdrawal trials including 841 patients, non-responders in the parent trial (defined as >4 point deterioration on the ADAS-Cog) did not demonstrate a benefit of continued treatment with galantamine.[55] A small open label study of 37 patients with clinically diagnosed mild cognitive impairment or mild dementia due to AD who were treated with donepezil showed that patients with smaller hippocampal volumes at baseline had greater decline on the ADAS-Cog scale.[70]

Comorbid pathology is common in older adults[22] but does not seem to affect response to acetylcholinesterase inhibitors substantively. A post hoc analysis of an RCT of 994 patients comparing donepezil and oral rivastigmine noted a benefit for rivastigmine in patients with possible comorbid Lewy body pathology,[58] possibly because of the subcortical localization of butyrylcholinesterase compared with acetylcholinesterase, which is primarily cortical. A small observational study of patients newly prescribed donepezil found that white matter lesions overall did not affect the likelihood of response to therapy, but periventricular white matter lesions were associated with a good clinical response.[71]

Selecting a acetylcholinesterase inhibitor and switching acetylcholinesterase inhibitors

Overall, any clinical differences among individual acetylcholinesterase inhibitors are modest. The previously mentioned direct comparison of donepezil and oral rivastigmine showed no difference in cognition overall. Oral rivastigmine had a slight benefit overall on activities of daily living and global function, but had a higher rate of adverse effects and study withdrawal, primarily during the titration phase.[58] A randomized, open label study of 120 patients comparing donepezil and galantamine showed higher physician and caregiver satisfaction, the primary outcome, with donepezil; donepezil also showed a benefit on cognition and activities of daily living, and a lower rate of adverse effects.[72] An open label study of 242 patients with mild to moderate AD comparing all three acetylcholinesterase inhibitors showed no difference on cognition and a slight benefit for oral rivastigmine on activities of daily living at three months but not at six months. There was also a higher absolute incidence of death in the donepezil group. However, this study's generalizability is limited by lack of randomization.[73]

If patients do not respond well to the first acetylcholinesterase inhibitor tried—whether due to adverse effects or lack of perceived benefit—clinicians may consider trying an alternative. Given the biological similarities of the three medications, a faster titration of the replacement drug may be successful. This is supported by a study of 89 patients previously receiving donepezil who were randomized to slow or fast titration of galantamine, which showed that both titration regimens were well tolerated.[74] There was similar cognitive benefit from galantamine in this study regardless of duration of prior donepezil treatment.

Memantine

Memantine is a low affinity N-methyl-D-aspartate (NMDA) receptor antagonist; the exact mechanism of action in AD is uncertain but has been hypothesized to involve mitigation of glutamate-induced excitotoxicity. It is available as immediate and extended release formulations; a combination pill of memantine XR 28 mg daily and donepezil 10 mg daily (Namzaric) was approved by the FDA in 2014 (table 1).

A recent meta-analysis of 29 trials including 7885 patients with AD found with a high degree

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of certainty that memantine showed a clear but modest benefit on global impression, cognition, and activities of daily living for moderate to severe AD.[75] Subgroup analyses showed an effect of memantine compared with placebo that persisted with or without concurrent treatment with a cholinesterase inhibitor. The meta-analysis also found an effect on behavior with patients randomized to the memantine arm being significantly less likely to develop agitation during the treatment period compared with those randomized to placebo. However, this was only true for those without agitation at baseline; meta-analysis of trials with patients with agitation at baseline showed that they were twice as likely to develop worsening of agitation during the study period.

For mild AD, the meta-analysis found there was probably no difference between memantine and placebo for cognition, activities of daily living, or behavior; there was also no significant difference on global impression, but with a lower degree of certainty.[75] Despite this evidence, memantine is—like the acetylcholinesterase inhibitors—widely prescribed in the US outside of its indication for moderate to severe disease, with 46% of patients with mild AD in the ADNI study taking it. Similar to the mild cognitive impairment group, the mild AD group taking memantine showed a higher rate of decline, suggesting that clinicians are prescribing it off label to patients with more aggressive disease.[42]

The clinical benefit of memantine is smaller than that of the acetylcholinesterase inhibitors. The previously mentioned meta-analysis of 80 trials that reviewed the effect of cognitive enhancing medications on MMSE scores across multiple forms of dementia found a mean effect size of memantine of 0.65 and 0.4 points at three and six months respectively. The effect size at 12 months did not reach statistical significance.[40] Notably, this meta-analysis included two trials of memantine for treating frontotemporal lobar degeneration, both of which were negative. This may have weakened the magnitude of the effect observed.

In the memantine meta-analysis the drug was generally well tolerated, with no difference from placebo in discontinuation overall or stopping due to adverse effects. Notably, in an analysis of patients with mild AD only, there was a higher rate of withdrawal in patients receiving memantine, which may suggest the lack of clinical efficacy alters the perceived tolerability of any adverse effects. Side effects that were statistically significant between groups included dizziness, confusion, and headache.[75]

Combination therapy

The benefit of adding memantine to acetylcholinesterase inhibitor therapy has been studied with mixed results. In the previously mentioned DOMINO-AD study, 295 patients with moderate to severe AD stable on donepezil therapy were randomized both to continuing *v* discontinuing donepezil and to initiation of active memantine *v* placebo. Both drugs showed a benefit on MMSE scores as well as on the Bristol ADL scale. Subgroup analysis did not show an additional cognitive benefit in the dual active treatment arm, although there was an additional benefit on behavioral symptoms measured using the neuropsychiatric inventory (NPI), a secondary outcome measure. However, the study was stopped early due to difficulty with recruitment, so it may have been underpowered. The rate of withdrawal was lower in the dual active treatment arm than in either monotherapy group, suggesting that caregivers may have perceived additional benefit.[76] Another large RCT, of 404 community dwelling patients with moderate to severe AD (MMSE scores 5-12) taking a stable dose of donepezil, found a benefit of memantine on the severe impairment battery, global impression, and activities of daily living, as well as on behavioral symptoms.[77]

A recent meta-analysis of 11 trials found that the combination of donepezil and memantine showed a moderate benefit compared with donepezil monotherapy on cognition and a significant benefit on global function and behavioral symptoms without a significant difference in adverse effects.[78] In the previously discussed memantine meta-analysis, subgroup analysis showed a persistent benefit of memantine on cognition regardless of status of cholinesterase therapy.[75] Another recent meta-analysis including seven studies including 2182 participants found that the cognitive benefit of combination therapy did not quite reach statistical significance when including patients with mild to moderate AD, but subgroup analysis of patients with moderate to severe dementia only did show a benefit in cognition. There was also an overall benefit with combination therapy on activities of daily living, global impression, and behavioral symptoms without corresponding increase in adverse effects.[79] Conversely, another meta-analysis including 14 studies of 5019 patients found no benefit of combination therapy overall, and subgroup analysis showed only a benefit on NPI scores in moderate to severe dementia[80]; this discrepancy may have been in part due to the authors' choice of inclusion criteria for relevant studies.

Medical foods

Medical foods are regulated differently than drugs by the FDA. They generally require ongoing physician supervision and are intended for conditions with altered nutritional requirements that require dietary management that cannot be achieved by modification of a regular diet.[81]

AC-1202 (Axona) is an FDA-approved medical food that consists of medium chain triglycerides, which are ketogenic and for which there is not a dietary source except for coconut and palm kernel oil. Since uptake of ketone bodies is normal in mild to moderate AD, increasing levels circulating ketone bodies could correct dysregulated energy metabolism that may underlie decreased glucose uptake on

fluorodeoxyglucose positron emission tomography (FDG-PET), in addition to neuronal loss.[82] A RCT of 140 patients with mild to moderate AD found a statistically significant difference on ADAS-Cog scores at 45 and 90 days for participants negative for the *APOE* ε4 allele compared with isocaloric placebo powder.[83] The main side effect was gastrointestinal distress, which was alleviated by consumption with food. A small RCT of a different ketogenic drink in mild cognitive impairment showed increased plasma and brain ketone uptake, but the only between-group cognitive measure that reached statistical significance was a naming task.[84]

Patients with AD and mild cognitive impairment also have reduced levels of plasma phospholipids, which can also be seen in the serum of cognitively normal older adults who go on to develop the disorder.[85] Souvenaid with Fortasyn Connect is a nutritional drink with active ingredients that include uridine monophosphate, docosahexaenoic acid, eicosapentaenoic acid, choline, phospholipids, folic acid, vitamins B6, B12, C, and E, and selenium, which are precursors for membrane phospholipids.[85] In a 24 week trial of 259 patients with mild AD, there was a statistically significant benefit in favor of Souvenaid on the primary outcome, a memory composite score,[86] as well as on quantitative electroencephalography; treatment also increased serum phospholipid concentration.[85] Given the proposed mechanism, there are theoretical benefits to earlier treatment, but a 24 month trial in participants with biomarkers for AD and episodic memory impairment did not show a benefit on the primary outcome, performance on a composite neuropsychological battery. There was, however, a benefit in favor of Souvenaid for the CDR-SB dementia scale as well as on MRI volumetric measures. The authors noted that, because of a smaller than expected decline in the control group, the study may have been underpowered.[87]

Although these medical foods are likely safe, overall, the evidence for their efficacy in AD is weak.

Evidence for specific approaches for slowing or preventing cognitive decline

Exercise

Prospective cohort studies have shown that physical activity is inversely associated with dementia risk.[88 89] Some of this decreased risk is likely related to decreased vascular cognitive impairment, which is supported by a more consistent evidence of benefit on executive function than memory, as in a small RCT of six months of aerobic exercise in previously sedentary people with amnestic mild cognitive impairment.[90]

However, there is evidence that midlife exercise is associated with reduced risk of AD in particular.[91] Much of the evidence for a direct benefit on AD pathology comes from animal studies, which show increased levels of brain derived neurotrophic factor and decreased amyloid and tau accumulation with both voluntary and forced exercise[92 93]; however, the dose and duration of exercise interventions in these studies are generally significantly more than what may be feasible for older adult humans.[93] In the handful of existing observational studies that have examined the relationship between physical activity (either self reported or measured via actigraphy) and biomarkers for AD, most have found an association between higher levels of physical activity and decreased amyloid β burden. However, the largest of these, with 271 people with either subjective cognitive decline or mild cognitive impairment, showed no relationship.[94] A single intervention trial of exercise in mild to moderate AD showed no effect on either cerebrospinal fluid biomarkers or cerebral blood flow from exercise[95 96]; other biomarker-based exercise intervention trials are ongoing (for example, the LEARNit study, ClinicalTrials.gov identifier NCT02726906).

The benefits of exercise after onset of dementia are also unclear, and the data are limited by the lack of consistent use of biomarkers. A 2014 meta-analysis of studies involving a total of 116 people with AD found a benefit from exercise on the rate of cognitive decline.[97] A 2015 meta-analysis of exercise in dementia including 409 participants was unable to draw any conclusions on the cognitive effects because of the diversity of studies in terms of characteristics of both participants and exercise programs.[98] Nonetheless, a slight benefit was found for activities of daily living. However, both of these reviews were published before the negative results of recent large RCTs. In the Dementia and Physical Activity (DAPA) trial, a four month, aerobic and strength training intervention followed by a maintenance home exercise program showed no benefit on any measure at one year, including activities of daily living.[99] The intervention arm actually showed worsening of cognition compared with the control group. A Finnish trial of 210 community-dwelling AD patients randomized to home based versus daycare based exercise showed no benefit of either exercise program compared with controls with the exception of a possible slight benefit on executive function at 12 months only for the home based exercise group.[100] In the ADEPT trial, a pilot RCT of 76 participants with amnestic mild cognitive impairment or mild dementia showed a slight benefit on activities of daily living and no benefit on cognition from six months of aerobic exercise compared with an active control group of stretching exercises.[101] A RCT of 186 Swedish nursing home residents found that a four month long physical therapy program of supervised exercise with an emphasis on strength training showed no benefit on cognition compared with a control program of occupational therapy-led activities designed to be enjoyable but not deliberately cognitively stimulating.[102] Likewise, an RCT of 87 Dutch nursing home residents found a modest benefit on executive function from training in activities of daily living, but no additional benefit from adding an exercise intervention.[103] Thus, while exercise may be recommended for a patient's overall physical health, the data do not support its prescription to specifically improve cognitive

function in patients with dementia. For patients with mild cognitive impairment, limited evidence suggests that addition of exercise promotes cognitive health and should be recommended, although the direct effect on AD pathology remains uncertain.

Vitamin E

Vitamin E is a fat soluble vitamin that functions as an antioxidant, protecting against free radical damage which is implicated in normal aging and AD.

The previously mentioned trial of vitamin E 2000 IU daily compared with donepezil or placebo in 769 patients with mild cognitive impairment showed no benefit for vitamin E on the primary endpoint of time until conversion to dementia.[43] The TEAM-AD trial, a RCT of vitamin E 2000 IU/day in 613 patients with mild to moderate AD, showed a 19% decrease in the primary outcome, annual rate of decline in activities of daily living, in the vitamin E arm; the authors note that this was equivalent to a six month delay in progression.[104] For secondary outcomes, the increase in caregiving time required was 2 hours higher in the placebo group than in the vitamin E group; there was no benefit on cognition or any of the other secondary outcomes. The other arms of the study included memantine therapy, alone or in combination with vitamin E. No benefit on activities of daily living was seen from memantine, and there was a negative interaction between memantine and vitamin E. In contrast to other reports, which showed an increased rate of serious adverse effects and mortality with high dose vitamin E, the mortality was lower in the vitamin E arm than in placebo. Since this trial was conducted through the US Veterans Administration, the study population was predominantly male, and the results may therefore not be generalizable to women. A meta-analysis of this and two smaller trials found no benefit overall for cognition.[105]

Trials of vitamin E in AD have used α-tocopherol at doses much higher than the recommended daily allowance of 22.4 IU, which have been associated with adverse effects such as increased risks of hemorrhagic stroke,[106] prostate cancer,[107] heart failure[108] and higher mortality.[105] As evidence for the efficacy of vitamin E in AD is limited, its utility must be weighed against these potential adverse effects before its recommendation.

Fish oil

Omega-3 polyunsaturated fatty acids are present in fish as well as vegetable oil and nuts. They are a component of membrane phospholipids in the brain and have antioxidant effects and are also thought to be important for synaptic plasticity.[109] A RCT of docosahexaenoic acid (DHA) 2 g/day supplementation in 402 patients with mild to moderate AD showed no benefit on cognition or dementia severity overall.[110] A meta-analysis of 632 participants of this trial as well as two smaller studies showed no benefit on cognition or any other outcome relevant for mild to moderate AD,[109] and so routine use of DHA supplements cannot be advocated.

In a pre-specified but exploratory analysis stratifying participants by *APOE* status, DHA supplementation produced a significant cognitive benefit for participants negative for *APOE* ε4 on both the ADAS-cog and MMSE scales.[110] As a result, a study of differential DHA delivery to brain among *APOE* genotypes is currently being pursued (ClinicalTrials.gov identifier NCT03613844).

Emerging treatments

Although elevations of amyloid β are observed in AD before the development of cognitive symptoms, anti-amyloid monoclonal antibodies have so far been unsuccessful at slowing cognitive decline in AD and prodromal AD despite demonstrated efficacy at clearing amyloid. Most recently, phase III trials of aducanumab were terminated early because of futility.[21 111 112] Nonetheless, trials of other anti-amyloid immunotherapies are ongoing in selected populations.[113] Trials of several inhibitors of β-secretase 1 (BACE1) enzyme, the first step in cleavage of amyloid precursor protein were also discontinued recently, but two drugs are still in phase III clinical trials.[113] Inhibitors of γ-secretase, which is responsible for the second cleavage step, were unsuccessful due to side effects, but modulators of this enzyme are also in development.[114]

The ongoing failure of anti-amyloid therapies to slow cognitive decline has led to consideration of other targets for disease modification. Monoclonal antibodies to tau protein are in phase II trials, as are several small molecules that inhibit tau synthesis or aggregation.[113] Agents with proposed neuroprotective or anti-inflammatory mechanisms are being studied—including omega-3s and other antioxidants, glutamate modulators including troriluzole, growth factors, and modulators of mast cells—as are non-disease-specific immunotherapies including plasma exchange and intravenous immunoglobulin.[113]

Finally, a variety of approaches to brain stimulation are under development. Non-invasive stimulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), has shown some evidence of benefit on cognition in AD in two recent meta-analyses, although the modality of stimulation, target choice, and frequency used were heterogeneous.[115 116] In deep brain stimulation (DBS), electrodes are implanted to stimulate targeted regions. A phase II trial of DBS of the fornix showed a benefit on regional glucose metabolism and cognitive performance but only in the subgroup >65 years old[117]; a phase III trial is currently in progress (ClinicalTrials.gov identifier NCT03622905). Though an intriguing approach, the specific parameters of the intervention, risks, and long term efficacy of brain stimulation remain to be established.

Guidelines

Consideration of treatment with an acetylcholinesterase inhibitor at time of diagnosis is recommended by the European Federation of

Neurological Societies (EFNS)[118] and for mild to moderate AD by the UK National Institute for Health and Care Excellence (NICE).[119] For patients with moderate to severe dementia, combination therapy with memantine and an acetylcholinesterase inhibitor is recommended in a joint guideline from EFNS and the European Neurological Society (ENS)[120] and by NICE. The German Institute for Quality and Efficiency in Healthcare (IQWiG) also found evidence of cognitive benefit for acetylcholinesterase inhibitors for mild to moderate AD.[121] In their initial review of the evidence for memantine, they did not find a benefit, but this conclusion was revised after the manufacturer submitted additional unpublished data on responder analyses.[122]

Conversely, in May 2018, France announced that all three acetylcholinesterase inhibitors and memantine would no longer be reimbursable[123] by the national health insurance based on a 2016 analysis that concluded that the clinical effect was at best modest and that the side effects were of concern, particular in an older population with multiple comorbidities and frequent polypharmacy.[124] Likewise, the American Geriatrics Society (AGS) advised a cautious approach to acetylcholinesterase inhibitors in the Choosing Wisely campaign, noting modest clinical benefits and adverse effects, and recommended discontinuation if "goals of treatment are not attained after a reasonable trial," such as 12 weeks.[125]

The discrepancy in these recommendations seem to arise from differences of opinion whether the observed effects are clinically meaningful and whether these benefits outweigh the impact of adverse effects. A 3 point improvement has been proposed as the minimal clinically relevant change on the ADAS-Cog scale,[126] which is commonly used as the cognitive endpoint in AD clinical trials, and is the approximate effect size seen in meta-analyses of acetylcholinesterase inhibitors. However, this threshold is debated, with some authors finding the use of change scores unreliable,[127] while others have found that even smaller changes can represent improvement in goal attainment scaling (GAS), a patient-oriented outcome.[128] Thus clinicians should take into account the modest benefit while considering adverse effects and individual patient and caregiver preferences. In particular, given the clinical effect of acetylcholinesterase inhibitors is primarily in symptom stabilization or slowing of functional decline, a short term trial as suggested by AGS may not be sufficient to fully appreciate their clinical benefit.

Conclusion

For newly diagnosed patients with AD, offering a prescription of an acetylcholinesterase inhibitor is generally an appropriate first step given the evidence and acceptable safety profile (fig 1). As AD pathology is often co-existent with vascular and Lewy body pathology, use of acetylcholinesterase inhibitors should be considered in these overlapping groups. No factors consistently predict a good, or poor, clinical response, so a trial is appropriate for all patients without medical contraindications. Pharmacogenomic testing may some day provide insight into medication selection (such as testing for variants in BCHE enzyme and the CYP450 system)

	MCI	MILD DEMENTIA	MODERATE DEMENTIA	SEVERE DEMENTIA
Cognitive enhancers	Consider AChEI in select patients	Start oral AChEI unless contraindications If gastrointestinal distress, trial of rivastigmine patch	Continue AChEI; consider dose increase in select patients Start memantine	Continue cognitive enhancers unless concern for adverse effects until goals of care shift towards palliation
	Assess for interest in research participation and clinical trials			—
Nutrition and supplements	—	Consider vitamin E supplementation in select patients Consider medical foods in select patients	Consider vitamin E until initiation of memantine	—
Exercise	Encourage exercise for brain and cardiovascular health; evidence for effect in Alzheimer's disease is limited	Encourage exercise for general health and possible mild benefit on executive function and activities of daily living; no clear benefit for memory		

MCI = mild cognitive impairment
AChEI = acetylcholinesterase inhibitor

Fig 1 | Treatment algorithm for Alzheimer's disease

QUESTIONS FOR FUTURE RESEARCH

- How does the risk/benefit profile of cognitive enhancers change in subpopulations such as the oldest people (>85 years old) or medically frail?
- Do lifestyle interventions' effects on cognition result from changes in underlying AD pathology or from other mechanisms?
- Do lifestyle approaches to slow cognitive decline work additively or synergistically?

but currently it does not provide additional benefit on top of a "try and see" approach.

To set appropriate expectations and improve medication adherence, patients and families should be counseled that the expected goal of these agents is to stabilize the patient's cognitive symptoms rather than achieve noticeable improvement. Acetylcholinesterase inhibitors seem to provide continuing, though modest, benefit throughout all stages of the disease, so our approach is to continue them in the absence of side effects until there is a shift in the goals of care toward a palliative approach. For patients with mild cognitive impairment that is thought to be due to prodromal AD, acetylcholinesterase inhibitors seem to be less effective.

Memantine, although frequently prescribed in the US for mild AD, has no consistent measurable benefit until the disease reaches the moderate stages. At that point, the modest benefit on cognition seems to be additive to that provided by acetylcholinesterase inhibitors, and, given the lack of significant adverse effects, combination therapy is appropriate for most patients. Evidence for the efficacy of vitamin E supplementation and medical foods is weak but might be considered in the context of cost, availability, and safety in individual patients.

The lack of disease modifying treatment continues to frustrate patients with AD as well as their caregivers and health professionals. One limiting factor in drug development is the need for sufficient numbers of patients for clinical trials. With most trials recruiting patients in the early stages of the disease, timely referral of eligible patients is needed. Finally, even if a disease modifying treatment is ultimately successful in slowing cognitive decline, there is a continued need for therapeutic options in the later stages that preserve functional abilities and allow patients to live at home longer.

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