Medical treatments of Alzheimer disease

CHOLINESTERASE INHIBITORS

Patients with AD have reduced cerebral content of choline acetyltransferase, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function

Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft and provide modest symptomatic benefit in patients with AD

The majority of patients with newly diagnosed AD should be offered a trial of a cholinesterase inhibitor for symptomatic treatment of cognition and global functioning.

the degree of expected benefit is modest, and therapy should not be continued indefinitely in patients who do not appear to be benefiting or who have significant side effects.

There is no convincing evidence that cholinesterase inhibitors are neuroprotective or have the ability to alter the underlying disease trajectory.

CHOICE OF DRUG — Three cholinesterase inhibitors are available for use in a variety of formulations:

●Donepezil, available as a once-daily tablet and a once-daily disintegrating sublingual tablet

●Galantamine, available as a twice-daily tablet or solution and an extended-release once-daily capsule

●Rivastigmine, available as a twice-daily capsule, a twice-daily solution (in some regions), and a 24-hour transdermal patch

All have demonstrated efficacy compared with placebo, and a limited number of direct comparisons do not suggest major differences in efficacy or tolerability among the three drugs . Selection of an agent is therefore based largely upon ease of use, individual patient tolerability, cost, and clinician and patient preference

Dose and administration

Cholinesterase inhibitors used for treatment of dementia: Dose and administration

Drug	Formulations	Starting dose	Maintenance dose	Comments
Donepezil	Tablet or oral disintegrating tablet	5 mg orally, once daily	10 mg daily (increased after 4 to 6 weeks)*	
Galantamine	Immediate-release tablet or solution	4 mg orally, twice daily	12 mg twice daily (increased in monthly intervals by 4 mg twice-daily increments)	Give with meals. Maximum 8 mg twice daily with moderate renal or liver impairment. Do not use with severe renal or liver impairment.
	Extended-release capsule	8 mg orally, once daily	24 mg once daily (increased in monthly intervals by 8 mg once-daily increments)	Maximum 12 mg once daily with moderate renal or liver impairment. Do not use with severe renal or liver impairment.
Rivastigmine	Capsule	1.5 mg orally, twice daily	6 mg twice daily (increased in 2- to 4-week intervals by 1.5 mg twice-daily increments)	Give with meals. Slow and cautious titration with renal or liver impairment or low body weight.
	Transdermal patch	4.6 mg/24 hours	9.5 to 13.3 mg/24 hours (increased in monthly intervals by 4.6 mg increments)	Can cause rash; rotate sites. Fewer side effects than capsule. Maximum dose 4.6 mg/24 hours with mild to moderate liver impairment or low body weight. Do not use with severe liver impairment.

*A 23 mg noncrushable tablet of donepezil is available, but evidence does not support a clinically important advantage to the higher dose and it is associated with increased side effects.

In a pragmatic, open-label trial of 196 older adults with possible or probable AD who were initiating treatment with a cholinesterase inhibitor at one of four memory care practices in the United States, patients were randomly assigned to donepezil, galantamine, or rivastigmine using dosing and formulations at the discretion of the treating clinician . At 18 weeks, rates of discontinuation for any reason (including study withdrawal/loss to follow-up) were similar for the three drugs (39, 53, and 59 percent, respectively; p = 0.06). The most common reasons for discontinuation were adverse events (56 percent) and cost (29 percent). Among the three drugs, donepezil was the most likely to be titrated to the maximum dose (53, 5, and 29 percent) and the least likely to be discontinued for cost-related reasons (0, 26, and 30 percent). Side-effect rates and profiles were largely similar among groups.

Other studies have also found higher discontinuation rates for rivastigmine and similar rates for donepezil and galantamine

Contraindications and precautions

Cholinesterase inhibitors enhance vagal tone and are contraindicated in patients with baseline bradycardia or known cardiac conduction system disease (eg, sick sinus syndrome, incomplete heart block) due to risk of syncope, falls, and fractures.

Caution should be used when any of the three drugs are used in combination with drugs that induce bradycardia or alter atrioventricular (AV) nodal conduction (eg, beta blockers, calcium channel blockers, lacosamide).

Galantamine should not be used in patients with end-stage kidney disease or severe hepatic impairment, and the rivastigmine patch requires dose adjustments for hepatic impairment and low body weight

Donepezil

Donepezil is the oldest cholinesterase inhibitor still in use and remains a preferred and widely prescribed drug in this class due to its once-daily dosing and ease of use. The recommended starting dose of donepezil is 5 mg per day, increasing to 10 mg per day after four to six weeks. Donepezil is available in pill form and also as an oral disintegrating tablet for those unable or unwilling to swallow a pill. Because nightly dosing can be associated with vivid dreaming or nightmares, we typically start with morning dosing to avoid sleep disturbances and then switch to nightly dosing if daytime nausea occurs.

A 23 mg noncrushable tablet of donepezil is available, but evidence does not support a clinically important advantage to the higher dose and it is associated with increased side effects

Gastrointestinal symptoms (upset stomach, nausea, diarrhea, anorexia) are the most common side effects with prolonged use of donepezil, occurring in approximately 20 to 30 percent of patients .Symptomatic bradycardia can occur and is also related to cholinergic toxicity . Rare cases of rhabdomyolysis and/or neuroleptic malignant syndrome have been reported in postmarketing surveillance .

No dose adjustments are needed for renal or hepatic impairment

Galantamine

Galantamine is available as a twice-daily tablet or solution and as a once-daily extended-release capsule. The latter is preferred unless patients cannot swallow capsules.

The recommended starting dose is 8 mg once daily (4 mg twice daily for immediate release), increasing to 16 mg once daily (8 mg twice daily for immediate release) after four weeks and then to a target maintenance dose of 24 mg once daily (12 mg twice daily for immediate release) after four more weeks.

Gastrointestinal symptoms (nausea, vomiting, diarrhea, anorexia, weight loss) are the most common adverse effects and may be more likely with galantamine than with donepezil. Galantamine should be given with meals to decrease the risk of nausea.

Galantamine should not be used in patients with end-stage kidney disease or severe hepatic impairment. A maximum dose of 12 mg is advised in patients with moderate renal (creatinine clearance 9 to 59 mL/minute) or hepatic impairment.

The use of galantamine has been associated with increased mortality in patients with mild cognitive impairment .Increased mortality has not been observed in patients treated for AD, mixed dementia, or vascular dementia.

Rivastigmine

Rivastigmine is available in oral and transdermal formulations. The transdermal patch is preferred over the oral formulation because it has better tolerability and similar efficacy

Three dose levels of the transdermal patch are available: 4.6, 9.5, and 13.3 mg/24 hours. The recommended starting dose of 4.6 mg/24 hours can be titrated upwards every four weeks. The patch can cause skin irritation, and application sites should be rotated. Two trials have shown a possible dose effect, with greater cognitive improvement on some but not all outcome measures with higher-dose patches .
The transdermal patch should be used at the lowest dose only (4.6 mg/24 hours) in patients with mild to moderate hepatic impairment, and the patch has not been studied in patients with severe hepatic impairment. The lowest dose should also be used in patients with low body weight (<50 kg).

If used, oral rivastigmine should be given with food and titrated more slowly than the other drugs due to increased risk of nausea, vomiting, anorexia, and headaches. Rivastigmine pill or solution is started at 1.5 mg twice daily, increasing in two- to four-week intervals by 1.5 mg twice-daily increments. If treatment is interrupted for longer than several days, it should be restarted at the lowest daily dose and then titrated again . One trial found that side effects of oral rivastigmine may be ameliorated and higher daily doses achieved when it is given three times a day, rather than twice daily

Approach to common side effects — Because the benefits of cholinesterase inhibitors are modest, clinicians should assess whether the patient is benefiting from the drug before persisting, and use caution to avoid prescribing cascades (ie, prescribing a new drug to treat an unrecognized adverse effect of an existing therapy)

Nausea and diarrhea — The most common side effects of cholinesterase inhibitors are gastrointestinal (primarily diarrhea, nausea, and vomiting). The toxicity is dose related and often resolves with time or dose reduction.

For oral rivastigmine, taking smaller doses more frequently or changing to a patch formulation may help. Both galantamine and oral rivastigmine should be taken with meals .

Donepezil seems to be less likely to cause gastrointestinal upset than the other two drugs, so switching to donepezil may be reasonable in patients who do not tolerate galantamine or rivastigmine.

Anorexia and weight loss

Weight loss occurs more commonly with cholinesterase inhibitors than placebo, but the clinical importance of this effect can be difficult to determine in individual patients, as dementia itself is often associated with weight loss.

In a case-control study that included 1188 patients with dementia who were started on a cholinesterase inhibitor (mostly donepezil and galantamine) and 2189 propensity score-matched controls, the mean weight loss over one year was 3.1 pounds in treated patients and 2.5 pounds in controls (p = 0.02) [33]. The proportion of patients who developed significant weight loss (10 pounds or more over one year) was also significantly higher in treated patients (29 versus 23 percent). In a meta-analysis of nine placebo-controlled randomized trials with a median follow-up of five months, the risk of any weight loss was twofold higher in patients randomized to receive a cholinesterase inhibitor (6 versus 3 percent; odds ratio [OR] 2.18, 95% CI 1.50-3.17) [34].

In patients who are noted to be losing weight while on a cholinesterase inhibitor, we typically pursue nutritional counseling before stopping therapy and monitor the trend in weight over time. AD is often associated with anosmia, which detracts from taste. Enhancing the taste of food with spices, sweet and sour flavoring, or soy sauce can help with appetite. For patients with comorbid depression, mirtazapine is a good choice of antidepressant because it can augment appetite

Bradycardia and hypotension — Bradycardia, heart block, and syncope can arise due to enhanced vagal tone. Cholinergic therapy should be discontinued in patients who develop symptomatic bradycardia and/or hypotension for which no other addressable cause is identified (eg, concomitant antihypertensive therapy).
Cholinesterase inhibitors should be avoided in patients with baseline bradycardia or known cardiac conduction system disease. (In one population-based cohort, the incidence of hospitalization for syncope was 3.2 events per 100 person-years for individuals taking cholinesterase inhibitors (68 percent were taking donepezil) .This event rate was 1.7 times higher than in a control group. Similarly, a meta-analysis of 54 randomized trials found that cholinesterase inhibitors were associated with 1.5-fold greater risk of syncope than placebo

Sleep disturbances — Insomnia, vivid dreams, and other sleep disturbances may be more common with donepezil than the other two drugs. If vivid dreams or nightmares arise on donepezil, switching to morning dosing or to an alternative drug may help

FOLLOW-UP AND MONITORING — Patients who are started on a cholinesterase inhibitor should be seen for follow-up at three and six months to assess drug tolerance and response. A phone call at two weeks can be useful to troubleshoot early side effects. Patients on a stable dose of drug are then seen every 6 to 12 months thereafter. Routine laboratory monitoring is not required for any of the cholinesterase inhibitors.

Assessment of response — Response to cholinesterase inhibitors can be subtle and gradual. We typically counsel patients and families to anticipate a six-month trial before making a decision about whether the medication is helping or not.

The Mini-Mental State Examination (MMSE) is not specific enough for following response; we generally use a combination of naming, recall of a four-word list or story at 30 seconds and five minutes, and semantic fluency (eg, naming as many animals as possible in one minute). The Montreal Cognitive Assessment (MoCA) can be administered at each visit to track change over time. It is a 30-point test that takes approximately 10 minutes to administer.

Caregiver impression of change, behavioral symptoms, sleep, and other neuropsychiatric symptoms should also be assessed at each visit

Patients who do not respond initially — Since cholinesterase inhibitors are a symptomatic treatment and not disease modifying, some clinicians, patients, and families choose to stop treatment after a six-month trial if there has been no subjective or objective improvement. Unless the medication is already at the lowest dose, it should be tapered by 50 percent for two to three weeks before stopping to minimize risk of worsening.

An alternative cholinesterase inhibitor is not typically used in this setting unless a patient is unable to achieve a target dose on the initial chosen drug due to side effects or formulation. Memantine can be added or substituted in patients with moderate to severe dementia.

Others feel that it is not possible to determine which patients are responders based on initial response to medication and therefore suggest continuing medication as long as the patient agrees to it and tolerates it . Support for this approach is also drawn from a clinical trial of 295 patients with moderate to severe AD who were already taking donepezil, which compared the efficacy of four treatment strategies: no therapy (donepezil discontinued), donepezil continued alone, donepezil continued with memantine added, and memantine therapy alone . After one year, patients assigned to receive donepezil therapy had, on average, a higher score on the MMSE (1.9 points) and a better score on the Bristol Activities of Daily Living Scale (BADLS; 3.0 points) compared with those not receiving donepezil. The average differences in the MMSE score, but not the BADLS, met the prespecified threshold considered by the investigators to be clinically important. The trial was stopped early due to slow recruitment. A post hoc analysis suggested that discontinuation of donepezil might increase the risk of nursing home placement over the next 12 months, but not over the prespecified four-year follow-up period

Other reasons for discontinuation — Aside from lack of perceived benefit, other reasons for discontinuation of cholinesterase inhibitors include:

●Intolerable side effects despite dose reduction. If the main reason for discontinuation of a drug is gastrointestinal side effects, sometimes switching to a different formulation or drug can help. Memantine is also an option in patients with moderate to severe disease and may be better tolerated.

●Rate of cognitive, functional, or behavioral decline is greater on treatment compared with pretreatment baseline. Of note, fluctuations in cognition and behavior are common in patients with dementia and are often multifactorial.

●Comorbidities or nonadherence make continued use of the drug unacceptably risky or futile.

●Progression to an advanced stage of dementia (eg, Functional Assessment Stage 7 ,in which there is little hope for a clinically meaningful benefit to continued therapy

Patients who worsen when drug is stopped — Occasionally patients will worsen after stopping therapy, even when appropriately tapered over a two- to three-week period . It is not clear if this is a sign that they benefited from the medication, but we generally reintroduce it when clinical decline is closely temporally linked with medication withdrawal. While data from clinical trials suggested that treatment gaps (periods in which the patient did not take cholinesterase inhibitor) were associated with worse outcomes, a large observational study of older adult patients prescribed cholinesterase inhibitors found that the risk of institutionalization or death did not appear to be increased among those who experienced treatment gaps

Role of memantine — Memantine is commonly added to cholinesterase inhibitor therapy when patients reach a moderate stage of AD (MMSE ≤18), based on moderate-quality data that the combination therapy leads to modest symptomatic benefits on cognition and behavior. Memantine can also be used as a single agent among patients who do not tolerate cholinesterase inhibitors

- Mild dementia – MMSE 19 to 26; MoCA 12 to 16; CDR 1
- Moderate dementia – MMSE 10 to 18; MoCA 4 to 11; CDR 2
- Severe dementia – MMSE <10; MoCA <4; CDR 3

Mild to moderate dementia — For patients with newly diagnosed mild to moderate AD dementia, we suggest a trial of a cholinesterase inhibitor.

The average benefit of cholinesterase inhibitors in patients with mild to moderate dementia (eg, MMSE 10 to 26; MoCA 4 to 16; CDR 1 or 2) is a small improvement in cognition, neuropsychiatric symptoms, and activities of daily living (ADLs)

The degree of benefit is summarized by a meta-analysis of 13 randomized trials of donepezil, galantamine, or rivastigmine versus placebo in more than 3000 patients with AD (mostly mild to moderate disease severity) .When assessed at 6 to 12 months, cholinesterase inhibitors led to modest improvements on the 70-point Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; mean difference 2.7 points, 95% CI 2.3-3.0) and MMSE (mean difference 1.37 points, 95% CI 1.13-1.61) as well as global impression by caregivers and ADLs. One analysis estimated that these effects would be similar to preventing a two-months-per-year decline in a typical patient with AD ; another concluded that for every 12 patients treated, one would benefit by achieving minimal improvement or better and one would develop a treatment-related adverse effect .

Whether these drugs significantly improve long-term outcomes, such as the need for nursing home admission or maintaining critical ADLs, remains in doubt, and the evidence is conflicting .The AD2000 study, one of few nonindustry-sponsored trials of a cholinesterase inhibitor versus placebo with long-term follow-up, found no significant benefit of donepezil compared with placebo for the two primary endpoints: entry to institutional care and progression of disability .

Additional evidence suggests that the response to cholinesterase inhibitors may be quite variable, with as much as 30 to 50 percent of patients showing no observable benefit , while a smaller proportion (up to 20 percent) may show a greater than average response (≥7 point ADAS-Cog improvement) . These findings reinforce the importance of making individualized decisions for each patient based on clinical response and side effects

Advanced disease — The relative effects of cholinesterase inhibitors appear to be similar for patients with more severe dementia (eg, MMSE <10; MoCA <4; CDR 3) at the time of diagnosis, but fewer studies have been performed and the absolute effects may be less clinically important than those seen in patients with mild to moderate dementia.

As in earlier-stage disease, small benefits on some but not all cognitive and functional outcomes have been noted in short-term trials of either donepezil or galantamine in previously untreated community-dwelling adults and nursing home residents with moderate to advanced dementia .

Decisions on long-term use depend on the patient's functional response to treatment and long-term goals of care and should be made in consultation with caregivers and family .

MEMANTINE

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism of action of memantine is distinct from those of the cholinergic agents; it is proposed to be neuroprotective. Glutamate is the principal excitatory amino acid neurotransmitter in cortical and hippocampal neurons . One of the receptors activated by glutamate is the NMDA receptor, which is involved in learning and memory . Excessive NMDA stimulation can be induced by ischemia and lead to excitotoxicity, suggesting that agents that block pathologic stimulation of NMDA receptors may protect against further damage in patients with vascular dementia (VaD) . In addition, the physiologic function of the remaining neurons could be restored, resulting in symptomatic improvement .

Memantine does not appear to have significant side effects. A 2008 systemic review concluded that memantine has been shown to improve cognition and global assessment of dementia, but with small effects that are not of clear clinical significance; improvement in quality of life and other domains are suggested but not proven . As a result, treatment decisions should be individualized and include considerations of drug tolerability and cost

Moderate to severe Alzheimer disease — We suggest the use of memantine in combination with a cholinesterase inhibitor in patients with advanced AD. A combination capsule of donepezil-memantine in two different strengths is available.

Memantine appears to have modest benefits in patients with moderate to severe Alzheimer disease

Mild AD – There is little, if any, evidence that patients with milder AD benefit from memantine. A systematic review reported the results of pooled data from three unpublished studies of memantine in mild to moderate AD .Intention-to-treat analysis indicated a very small but statistically significant beneficial effect for memantine at six months on cognition (<1 point on the 70-point Alzheimer Disease Assessment Scale-Cognitive Subscale [ADAS-Cog]) but no effect on behavior or ADLs. Another study analyzed data on 431 patients with mild AD (MMSE 20 to 23) from three trials and found no substantial benefit with memantine [35]. No benefit was seen in patients assigned to memantine in the Department of Veterans Affairs (VA) Cooperative Studies Program

The combination of memantine and a cholinesterase inhibitor leads to modest improvements in cognition and global outcomes in patients with advanced disease . The largest trials demonstrating the efficacy of combination therapy include the following:

●A 24-week trial studied the effects of either memantine or placebo in addition to donepezil in 322 patients with moderate to severe AD [32]. MMSE scores ranged from 5 to 14 (mean approximately 10) at study entry. Treatment with memantine plus donepezil resulted in significantly better outcomes than placebo plus donepezil on measures of cognition, activities of daily living (ADLs), global outcome, and behavior. Significantly more patients taking placebo than memantine discontinued the trial, and the rate of discontinuation due to adverse events was lower in the memantine-treated group than in the placebo group.

●A second 24-week randomized trial compared memantine with placebo in 433 patients with mild to moderate AD who were on stable doses of a cholinesterase inhibitor (either donepezil, rivastigmine, or galantamine) . There was no difference in outcome measures between the treatment groups.

●A clinical trial of 295 patients with moderate to severe AD who were already taking donepezil compared the efficacy at one year of four treatment strategies: no therapy (donepezil discontinued), donepezil continued alone, donepezil continued with memantine added, and memantine therapy alone as discussed above . No significant benefits of the combination of donepezil-memantine over donepezil alone were noted; however, this study was stopped early due to slow recruitment

Dosing — Memantine is initiated 5 mg once daily; the dose can be increased by 5 mg weekly to a maximum tolerated dose of 20 mg per day, usually in two divided doses. An extended-release form for once-daily administration is available.
When medication is discontinued, a tapering schedule with a similar timeline should be followed.

Adverse effects — Memantine also appears to have fewer side effects than the cholinergic agents . Dizziness is the most common side effect associated with memantine. Confusion and hallucinations are reported to occur at a low frequency, but we have noticed that memantine use seems to increase agitation and delusional behaviors in some patients with AD. Others have reported that worsening of delusions and hallucinations is particularly problematic in patients who have dementia with Lewy bodies (DLB)

ADUCANUMAB

Aducanumab is a recombinant monoclonal antibody directed against amyloid beta. The US Food and Drug Administration (FDA) has approved aducanumab for the treatment of mild AD using the accelerated approval pathway, based on the positive clinical results of one of the two pivotal phase III trials (the results in the other were negative) and aducanumab's effect on a surrogate endpoint of reducing amyloid beta plaques in the brain .

The approval of this medication has led to significant controversy given that the FDA scientific advisory panel had previously recommended against approval of aducanumab, and since the surrogate endpoint of reducing amyloid beta plaques is not yet established as predicting clinical benefit . Postapproval trials are required to verify the clinical benefit. As the first new therapy for AD since 2003, there is a great deal of excitement in the community, but this must be tempered by the lack of clarity in the clinical trials, the risk of adverse effects, and the monitoring requirements.

The use of aducanumab should be limited to the following patients:

- **Mild cognitive impairment or mild dementia** – Cognitive decline should be mild, and testing cutoffs such as Mini-Mental State Examination (MMSE) ≥21, Montreal Cognitive Assessment (MoCA) ≥17, or clinical dementia rating (CDR) 0.5 to 1 can be used. Formal neuropsychological testing can be considered for quantification of deficits and changes over time.

- **Documented amyloid pathology** – Clinicians should limit use of aducanumab to those patients proven to be amyloid positive (by amyloid positron emission tomography [PET] scan or lumbar puncture), as was required in the clinical trials that evaluated the drug.

- **No contraindications** – Patients with cognitive decline attributed to non-AD pathologies (eg, Lewy body disease, vascular dementia [VaD]) should not be offered aducanumab. At present, experts suggest against treating patients with AD in the setting of Down syndrome until more information is available .

Patients should not be offered aducanumab if they have a high risk of hemorrhagic side effects. Risk factors include hemorrhagic findings on brain MRI including >4 microhemorrhages, any areas of superficial siderosis, prior macrohemorrhage, and underlying brain lesion or vascular malformation. Other risk factors contraindicating treatment are anticoagulant or antiplatelet use (other than aspirin 81 mg daily), bleeding disorders, or any other condition leading to increased risk of central nervous system (CNS) hemorrhage.

Aducanumab should also not be offered to patients with unstable medical conditions, patients with unstable psychiatric conditions, or patients who are pregnant or breastfeeding.

Risks

Adverse effects observed with aducanumab include ARIA(Amyloid-related imaging abnormalities) ,which were reported in approximately 40 percent of patients treated with the highest dose of aducanumab in clinical trials, and especially in *APOE* ε4 carriers

Hypersensitivity, including angioedema and urticaria, was reported in one patient in the clinical trials .

Headache, falls, diarrhea, and confusion were also modestly more frequent in aducanumab- versus placebo-treated patients . Except for diarrhea, these may reflect symptoms of ARIA.

Up to 0.6 percent of patients in the clinical trials developed aducanumab antibodies; no determination was made as to whether such antibodies are neutralizing

Vitamin E — We feel that vitamin E (1000 international units twice daily) is a reasonable intervention in patients with mild to moderate AD. Although the available data allow only limited confidence that vitamin E is an effective therapy for AD, this is balanced by the excellent safety and tolerability profile of supplementation in both studies and the general lack of very effective therapies for patients with AD. The benefits of vitamin E are likely to be modest

High-dose vitamin E supplementation has been inconsistently associated with an increase in all-cause mortality and also with heart failure in patients with cardiovascular disease . Such concerns have not been validated in the AD population, however; in the VA study described above, patients assigned to 2000 international units of vitamin E daily had a trend towards lower annual mortality compared with patients assigned to memantine, the combination, or placebo

In summary, although both of the larger studies have issues limiting confidence in the conclusion that vitamin E is an effective therapy for AD, this is balanced by the excellent safety and tolerability profile of supplementation in both studies and the general lack of effective therapies for patients with AD. We therefore feel that vitamin E (2000 international units daily) is a reasonable intervention in patients with mild to moderate AD. The benefits of vitamin E are likely to be modest, however, and could be offset by combination therapy with memantine.

We do not recommend vitamin E for the routine prevention of AD or for the treatment or prevention of other types of dementia

Selegiline — We do not use selegiline in patients with AD as the evidence of efficacy is quite limited.

The ADCS trial compared vitamin E, selegiline, the combination, and placebo and is discussed above . There was a delayed progression to outcome for patients treated with selegiline compared with placebo (655 versus 670 days) after statistical adjustment because the placebo group had higher MMSE scores at baseline. Performance on cognitive tests (including the MMSE and the ADAS-Cog) was similar between the groups.

In addition to the ADCS trial, a number of smaller studies have also investigated the use of selegiline with varying results. A meta-analysis of 12 trials found that 8 of the studies suggested some beneficial effect of selegiline in the treatment of cognitive benefits and, in three trials, in the treatment of behavior and mood . Analysis of three studies with a longer-than-one-year follow-up reported significant delays in time to the primary outcome (death, institutionalization, loss of ability to perform ADLs, or severe dementia) . However, the magnitude of the benefits in the meta-analysis was small and largely dependent on the ADCS study . Thus, the clinical importance for the population at large is unclear

THERAPIES WITH UNPROVEN BENEFIT

Estrogen replacement — There is no evidence that initiating estrogen replacement is beneficial in the treatment or prevention of dementia.

In summary, we see no current evidence for initiating HRT in patients with established dementia, and, given the data on HRT for primary prevention of dementia, HRT may actually be harmful.

Antiinflammatory drugs

clinical trials do not support this treatment: Except for one small clinical trial of indomethacin , randomized trials of antiinflammatory medications including naproxen, hydroxychloroquine, diclofenac, rofecoxib, and aspirin have not found a benefit for these agents in slowing cognitive decline in patients with AD . In addition, adverse events have been more common in treated patients compared with controls

Ginkgo biloba — A systematic review of ginkgo for cognitive impairment and dementia concluded that ginkgo biloba, while safe, has inconsistent and unconvincing evidence of benefit . There have not been subsequent studies that alter this conclusion. We do not advocate use of ginkgo because of questionable efficacy and lack of regulation, including variability in the dosing and contents of herbal extracts

Dietary supplements

- **Vitamin B** – Supplementation with B vitamins, in particular those that are involved in homocysteine metabolism, have been studied in patients with AD in hopes that they may demonstrate efficacy in preventing or slowing the progression of AD. An 18-month randomized trial of high-dose vitamin B-complex supplementation (folate, B6, B12) in 340 patients with mild to moderate AD found no beneficial effect on cognitive measures .

- **Omega-3 fatty acids** – Observational studies have suggested a possible association between dietary intake of fish and omega-3 fatty acids and a lower risk of dementia.
However, clinical trials have not supported a therapeutic role for omega-3 fatty acid supplementation in the treatment of AD

Alois Alzheimer

German psychiatrist

1906