# Chapter 9
# Cognitive Enhancers


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## Cognitive Enhancers in Mild Neurocognitive Disorders

### *Case Vignette Part 1*

Mr. Jones is a 72-year-old man who was referred to a neurologist by his primary care physician for further evaluation of memory loss. His wife and children report that Mr. Jones has had some difficulty with his memory for the past year. He reports some problems remembering specific details about prior conversations and frequently misplaces his car keys and reading glasses. He admits that he once became lost while driving in a familiar neighborhood. He still manages his finances without any significant errors, although he says these tasks now require more effort. He has no difficulties with activities of daily living (ADLs), such as feeding, dressing, and toileting. His past medical history is significant only for hypertension, for which he takes amlodipine. Physical examination is unremarkable. His score on the Mini-Mental State Examination (MMSE) is 26/30, where he lost two points for only recalling one of three objects and lost two points for errors when performing serial sevens.

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## *Therapeutic Options*

Based on his symptoms, Mr. Jones would meet diagnostic criteria for a mild neurocognitive disorder provided that reversible causes of cognitive decline are ruled out, such as another mental disorder (major depressive disorder, schizophrenia), delirium, medications, infections, and metabolic causes. Mr. Jones demonstrates evidence of modest cognitive decline in several cognitive domains (particularly complex attention and memory) based on feedback from the patient and family members as well as modest impairment in cognitive performance on the MMSE. The key feature that differentiates a mild neurocognitive disorder from a major neurocognitive disorder in this patient is that the cognitive deficits do not appear to significantly interfere with independence in everyday activities. He is still able to perform all his ADLs and instrumental ADLs, even though they now require more effort.

Once the diagnosis is established, many patients will ask what they can potentially do to enhance their cognition and prevent the progression to a major neurocognitive disorder. While some patients with mild cognitive impairment (MCI) will revert back to a cognitively normal status, the estimated annual conversion rate to a major neurocognitive disorder is likely between 3% and 15% per year [1, 2]. With regard to modifiable risk factors that increase the risk of dementia, the Alzheimer's Association concluded that there was strong evidence for traumatic brain injury; moderate evidence for midlife obesity, midlife hypertension, current smoking, and diabetes; and unclear evidence for history of depression, sleep disturbances, and hyperlipidemia [3]. For risk factors that decrease the risk of dementia, there was strong evidence for years of formal education, moderate evidence for physical activity, lower evidence for Mediterranean diet and cognitive training, and unclear evidence for moderate alcohol consumption and social engagement.

Table 9.1 presents select examples of clinical trials examining pharmacologic and non-pharmacologic interventions for the management of MCI [4–16]. The cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine have been approved by the Food and Drug Administration (FDA) for the symptomatic treatment of Alzheimer's disease (AD). These medications inhibit the enzyme acetylcholinesterase, which normally functions to degrade the neurotransmitter acetylcholine. This ameliorates the cholinergic deficit seen in patients with AD. Several clinical trials of ChEIs, ranging from 6 to 48 months, have been performed in patients with MCI. These trials have mostly failed to either demonstrate significant benefits on cognition and functioning or to decrease the time to conversion to AD.

One of these trials, the Investigation into Delay to Diagnosis of Alzheimer's Disease with Exelon (InDDEx) study, involved 1018 patients with MCI randomly assigned to rivastigmine or placebo for up to 48 months [13]. Over the study's duration, 17.3% ($n = 88$) of patients on rivastigmine and 21.4% ($n = 109$) of patients on placebo progressed to AD (hazard ratio (HR) = 0.85; 95% confidence interval (CI) = 0.64, 1.12; $p = 0.225$). Mean time to AD progression was 1318 days in the rivastigmine group and 1289 days in the placebo group. No significant benefits with regard to cognitive, global, functional, or neuropsychiatric outcomes were seen with rivastigmine therapy compared to placebo. Another study evaluating 10 mg of donepezil daily for 3 years reported lower rates of progression to AD during the first 12 months

**Table 9.1** Select examples of interventions tested in patients with mild cognitive impairment

| | Intervention studied | Duration | Results on primary end point | Other notable results |
|---|---|---|---|---|
| Nutrition | Vitamin E (2000 IU daily) [4] | 36 months | No significant difference in probability of progression from MCI to AD at 36 months (HR = 1.02; 95% CI = 0.74, 1.41; $p = 0.91$) | No significant difference at 36 months on ADLs, CDR-SB, GDS, or ADAS-cog |
| | B vitamins (B6, B9, B12) [5] | 24 months | Significantly slower rate of brain atrophy per year by 29.6% with active treatment (0.76%; 95% CI = 0.63, 0.90) compared to placebo (1.08%; 95% CI = 0.94, 1.22; $p = 0.001$) | |
| | DHA (2 g/day) [6] | 12 months | Significant difference in full-scale intelligence quotient at 12 months ($p = 0.039$) | Significant differences in volumes of hippocampus and global cerebrum |
| | Cocoa flavanol [7] | 8 weeks | Significant changes on cognitive z score (from 4 cognitive tests) at 8 weeks ($p < 0.0001$) with high and intermediate flavanol | Effects possibly mediated by improvement in insulin sensitivity |
| Cognition/ exercise | Multicomponent exercise [8] | 6 months | No (group × time) interaction on cognitive tests (MMSE, ADAS-cog) and brain atrophy in MCI patients | Significant (group × time) interaction on MMSE ($p = 0.04$) and reduction in cortical atrophy ($p < 0.05$) in a MCI subgroup |
| | Cognitive activity training [9] | 5 weeks | No significant difference in CAMCOG-R scores at 2-year follow-up | Mostly negative results on secondary outcomes |
| Pharmacological | Antihypertensives (lisinopril, candesartan, or HCTZ) [10] | 12 months | Significant improvement on TMT-B with candesartan ($p = 0.008$) | |

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**Table 9.1** (continued)

| | Intervention studied | Duration | Results on primary end point | Other notable results |
|---|---|---|---|---|
| | NSAID (rofecoxib) [11] | 4 years | Significantly higher annual AD diagnosis rate with rofecoxib (14.8%) compared to placebo (11.2%, HR = 1.46; $p = 0.011$) | No significant difference on ADAS-cog and CDR |
| | NSAID (triflusal) [12] | 13 months | No significant difference on ADAS-cog (mean difference = 0.89; 95% CI = −0.3, 2.1; $p = 0.139$). Prematurely stopped due to slow recruitment | Significantly lower risk of progression to AD with triflusal (HR = 2.10; 95% CI = 1.10, 4.01; $p = 0.024$) |
| | Donepezil [4] | 36 months | No significant difference in progression from MCI to AD at 36 months (HR = 0.80; 95% CI = 0.57, 1.13; $p = 0.42$) | Lower risk of AD progression for first 12 months ($p = 0.04$). Benefits on secondary measures (CDR-SB, GDS, ADAS-cog) confined to first 18 months |
| | Rivastigmine [13] | 48 months | No significant difference on progression to AD in rivastigmine group (17.3%) compared with placebo group (21.4%; HR = 0.85; 95% CI = 0.64, 1.12; $p = 0.225$) | No significant difference on co-primary outcome of z score for cognitive test battery (−0.10; 95% CI = −0.63, 0.44; $p = 0.726$) |
| | Galantamine [14] | 24 months | No significant difference between galantamine and placebo in conversion rate to AD at 24 months (study 1, 22.9% for galantamine vs. 22.6% for placebo, $p = 0.146$; study 2, 25.4% for galantamine vs. 31.2% for placebo, $p = 0.619$) | Mean decline in CDR-SB was significantly less with galantamine compared with placebo at 24 months in study 1 ($p = 0.028$) but not in study 2 ($p = 0.056$) |

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**Table 9.1** (continued)

| | Intervention studied | Duration | Results on primary end point | Other notable results |
|---|---|---|---|---|
| | Galantamine and memantine [15] | 52 weeks | No significant difference on ADAS-cog score at 6 months. Stopped early due to safety concerns with galantamine in MCI | Significant difference on ADAS-cog in subgroup of MCI with presumed AD etiology |
| | Metformin [16] | 12 months | Nonsignificant advantage with placebo on ADAS-cog at 12 months; nonsignificant advantage with metformin on SRT | Significant advantage with metformin on SRT after adjusting for baseline ADAS-cog ($p = 0.02$) |

*Abbreviations*: *AD* Alzheimer's disease, *ADAS-cog* Alzheimer's Disease Assessment Scale-Cognitive subscale, *ADLs* activities of daily living, *aMCI* amnestic mild cognitive impairment, *CAMCOG* cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly, *CDR-SB* Clinical Dementia Rating Scale Sum of Boxes, *CI* confidence interval, *DHA* docosahexaenoic acid, *GDS* Global Deterioration Scale, *HCTZ* hydrochlorothiazide, *HR* hazard ratio, *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination, *NSAID* nonsteroidal anti-inflammatory drug, *SRT* Selective Reminding Test, *TMT* Trail Making Test

of treatment compared to placebo, most prominently among APOEε4 carriers [4]. However, this benefit was not significant at the 36-month time point, which was the primary end point. Differences on cognitive, global, and functional measures with donepezil compared with placebo were also not significant at 36 months. A Cochrane meta-analysis involving nine studies from eight published reports concluded that there was little evidence that ChEIs affect progression to dementia or scores on measures of cognition (Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog)), global impression (Clinical Dementia Rating (CDR)), or functioning (Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL)) [17]. There were significantly more adverse events (AEs) in patients receiving ChEIs, predominantly diarrhea, nausea, and vomiting.

Other pharmacologic agents that have been tested in clinical trials include antihypertensives, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and *Ginkgo biloba*. Antihypertensives may play a protective role through their blood pressure lowering effects or by altering angiotensin II-mediated processes in the central nervous system [18]. The results from both epidemiologic studies and clinical trials suggest some benefit in patients with hypertension, and the ongoing Systolic Blood Pressure Intervention Trial-MIND (SPRINT-MIND) study will provide more definitive data [10, 19].

While epidemiologic evidence suggests that NSAIDs may protect against the development of AD, clinical trials have failed to replicate these findings. The largest of these trials in patients with MCI was a randomized, double-blind study in 1457 patients randomized to rofecoxib or placebo treatment for up to 4 years [11]. At the

trial's end point, rofecoxib was associated with a significantly higher estimated annual AD diagnosis rate compared to placebo. No significant difference was seen on secondary measures of cognition and global functioning. The authors felt the higher risk of AD progression with rofecoxib was likely not a true effect given the lack of significant difference on secondary measures and may have been due to differential discontinuation rates in the two groups. The AD Anti-inflammatory Prevention Trial (ADAPT) study compared naproxen or celecoxib to placebo in 2528 cognitively normal volunteers over the age of 70 with at least one first-degree relative with AD [20–22]. This trial was stopped early due to safety concerns with celecoxib, and the overall results suggested that neither naproxen nor celecoxib reduced the risk of AD or attenuated decline in cognitive functioning. While NSAIDs cannot be recommended specifically for the purpose of preventing AD, the data from epidemiologic studies is reassuring in that patients requiring NSAIDs for other purposes likely do not have an increased risk of dementia and may derive some benefit.

*Ginkgo biloba* is a dietary supplement that may prevent cognitive decline via reduction of oxygen free radicals and cerebral vasorelaxation [23]. Results from three prominent randomized controlled trials (RCTs) have been negative in demonstrating a benefit in preventing dementia [24]. One RCT involving 3069 community volunteers aged 75 years or older with either normal cognition ($n = 2587$) or MCI ($n = 482$) studied a twice-daily dose of 120 mg extract of *Ginkgo biloba* compared with placebo [25]. Over a median follow-up of 6.1 years, the overall dementia rate was 3.3 per 100 person-years in the *Ginkgo biloba* group compared to 2.9 per 100 person-years in the placebo group (HR = 1.12; 95% CI = 0.94, 1.33; $p = 0.21$). No significant effect was seen in the subgroup of participants with MCI. Another RCT failed to show a reduction in the risk of progression to AD in participants with spontaneously reported memory complaints [26]. A Cochrane meta-analysis found inconsistent evidence for any benefit in patients with MCI [27]. No excess side effects were seen with *Ginkgo biloba* treatment compared with placebo.

Dietary supplements, such as vitamin B12 (cobalamin), vitamin B9 (folic acid), vitamin B6 (pyridoxine), vitamin E (alpha tocopherol), selenium, and omega-3 fatty acids, have also been studied in various clinical trials. Elevated plasma homocysteine may be a risk factor for the development of dementia, and supplementation with B vitamins appears to lower plasma homocysteine levels [28, 29]. The VITACOG trial demonstrated that supplementation with B vitamins (vitamins B6, B9, and B12) may slow the mean rate of brain atrophy per year in patients with MCI, particularly those with elevated levels of homocysteine at baseline [5]. However, a meta-analysis of 11 trials involving B vitamins did not demonstrate any significant effect on cognitive domains or global cognitive functioning [30].

Vitamin E and selenium have been proposed to protect against the development of AD primarily through their antioxidant effects. One 3-year trial of 2000 IU/day of vitamin E failed to show any significant effect on progression to AD in patients with MCI [4]. The Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) trial enrolled patients between 60 and 90 years of age to one of four

groups: vitamin E and selenium, vitamin E and placebo, selenium and placebo, or placebo [31, 32]. The study failed to show a difference among the four study arms in dementia incidence, although it was underpowered due to limited recruitment.

Due to an epidemiologic link between increased dietary omega-3 fatty acids and reduction in the risk of AD, supplementation with omega-3 fatty acids, such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid, has been proposed to improve memory function [33]. In a study involving healthy older adults with age-related cognitive decline, supplementation with DHA improved learning and memory [34]. However, these results were not replicated in two other studies [35, 36]. Similarly, a Cochrane review failed to show any benefit of omega-3 supplementation on cognitive function in cognitively healthy older people [37]. Other dietary interventions, such as a Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts, have been shown to improve cognition in patients at high vascular risk [38].

Some exercise interventions have demonstrated modest cognitive improvements in patients with MCI [39–41]. However, the trials are generally small and have low statistical power [42]. The majority (92%) of outcomes in these studies were not statistically significant. Interventions such as home-based and center-based tai chi training sessions have also improved cognitive functioning in patients with MCI [43].

A variety of multimodal approaches have shown benefit in either patients with MCI or cognitively normal patients at higher risk of cognitive decline [44, 45]. Three of the largest studies include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the French Multi-Domain Alzheimer's Prevention Trial (MAPT), and the Prevention of Dementia by Intensive Vascular care (preDIVA) study.

FINGER enrolled 1260 individuals aged 60–77 years who had a higher risk of dementia based on the Cardiovascular risk factors, Aging, and Incidence of Dementia (CAIDE) risk score [46]. The intervention group participated in nutritional education sessions, a physical exercise training program guided by physiotherapists involving aerobic activities and strength training, cognitive training involving group sessions led by psychologists and individual computer-based training sessions, and management of metabolic and vascular risk factors. At the 2-year end point, a significant difference favoring the intervention group was seen on the primary outcome (change in cognitive performance on a neuropsychological test battery (NTB) composed of 14 tests). The control group also experienced an increased risk of cognitive decline, defined as any decline on the NTB total score, compared to the intervention group (odds ratio (OR) = 1.31; 95% CI = 1.01, 1.71; $p = 0.04$).

MAPT was a 36-month study involving patients aged 70 years or older with frailty, defined as either a subjective memory complaint, inability to perform one of instrumental ADLs, or a slow walking speed. Patients were divided into four groups: omega-3 supplementation (800 mg/day of DHA), omega-3 supplementation and multi-domain intervention, placebo and multi-domain intervention, and placebo without any intervention. The multi-domain intervention involved training sessions focused on nutrition, physical activity, and cognition and individualized preventive outpatient visits exploring risk factors for cognitive decline such as hypertension,

diabetes, and hypercholesterolemia [47]. At the 36-month end point, no significant group differences were observed for the primary outcome, defined as change in cognitive function at 36 months based on a composite z score which combined four cognitive tests [48].

preDIVA was a 6-year nurse-led study involving 3526 community-dwelling individuals aged 70–78 without dementia randomized to an intervention or control group [49]. The intervention consisted of visits to a nurse every 4 months in which cardiovascular risk factors such as smoking habits, diet, and physical activity were assessed. Drug treatment was initiated or optimized if indicated, and lifestyle advice was given in accordance with guidelines on cardiovascular risk management. No significant differences were seen on either primary outcome: cumulative incidence of dementia or disability score based on the Academic Medical Center Linear Disability Score at the 6-year follow-up. Dementia developed in 121 (7%) of 1853 participants in the intervention group and in 112 (7%) of 1601 participants in the control group (HR = 0.92; 95% CI = 0.71, 1.19; $p = 0.54$). Among participants with untreated hypertension who were adherent to the intervention, the intervention did significantly reduce the risk of dementia (HR = 0.54; 95% CI = 0.32, 0.92; $p = 0.02$), suggesting that interventions should be focused on those with significant risk factors [50].

## Cognitive Enhancement in Mild Alzheimer's Disease

### *Case Vignette Part 2*

Two years after his initial diagnosis, Mr. Jones and his wife return to the neurologist reporting worsening symptoms. His wife reports that he often repeats the same question, and she no longer feels that he is safe to drive. He has made several mistakes when handling their finances, frequently forgets to take his blood pressure medication, and is beginning to forget certain appointments. His children report that he is more impulsive. His MMSE score is now 22/30.

### *Therapeutic Options*

This patient's continued decline in multiple cognitive domains and difficulty with independence in daily activities suggest a diagnosis of a major neurocognitive disorder, likely due to AD. The only pharmacologic agents FDA approved and available for the treatment of mild AD are the ChEIs donepezil, galantamine, and rivastigmine. Table 9.2 summarizes the formulations, dosages, and titration schemes for the ChEIs. These agents are generally considered equivalent in efficacy and demonstrate modest benefits (Cohen's d effect sizes in the range of 0.2–0.3) across cognitive, functional, and neuropsychiatric domains. For example, one meta-analysis found a difference of −2.37 points (95% CI = −2.73, −2.02) on the

**Table 9.2** Summary of the formulations, dosages, and titration schemes for the cholinesterase inhibitors and memantine

| Drug | Mechanism | Formulation | Dosages | FDA recommended titration scheme |
|---|---|---|---|---|
| Donepezil | Noncompetitive and reversible ChEI | Tablet | 5, 10, 23 mg | Start at 5 mg/day. Increase to 10 mg/day after 4–6 weeks. Increase to 23 mg/day after at least 3 months on 10 mg/day. The 23 mg/day tablet should not be split, crushed, or chewed. 10 and 23 mg/day dosing FDA approved for moderate-to-severe AD |
| | | Orally disintegrating tablet | 5, 10 mg | |
| Rivastigmine | Pseudo-irreversible ChEI | Capsule | 1.5, 3, 4.5, 6 mg | Start with 1.5 mg BID. Increase to 3 mg BID after 2–4 weeks. Increase to 4.5 mg BID then to 6 mg BID at 2–4 week intervals. Not approved for severe AD |
| | | Oral solution | 2 mg/mL | |
| | | Transdermal patch | 4.6 (5 $cm^2$), 9.5 (10 $cm^2$), 13.3 (15 $cm^2$) mg/24 h | Start with 4.6 mg/24 h patch. Increase to 9.5 mg/24 h patch after 4 weeks. Increase to 13.3 mg/24 h after 4 weeks. 13.3 mg/24 h dose FDA approved for severe AD. Switching from capsules to patch: if total oral dose is <6 mg/day, switch to 4.6 mg/24 h patch; if total oral dose is 6–12 mg/day, switch to 9.5 mg/24 h patch |
| Galantamine | Competitive and reversible ChEI and nAChR modulator | Extended-release capsule | 8, 16, 24 mg | Start at 8 mg/day. Increase to 16 mg/day after 4 weeks. May increase to 24 mg/day after 4 weeks. Not approved for severe AD |
| | | Tablet | 4, 8, 12 mg | Start at 4 mg BID. Increase to 8 mg BID after 4 weeks. May increase to 12 mg BID after 4 weeks. Not approved for severe AD |
| | | Oral solution | 4 mg/mL | |

(continued)

**Table 9.2** (continued)

| Drug | Mechanism | Formulation | Dosages | FDA recommended titration scheme |
|---|---|---|---|---|
| Memantine | NMDA receptor antagonist | Extended-release capsule | 7, 14, 21, 28 mg | Start at 7 mg/day. Increase in 7 mg increments to 28 mg/day in 1 week intervals. FDA approved for moderate-to-severe AD. Can switch directly from 10 mg BID tablets to 28 mg/day ER capsule the day after last dose of tablets |
| | | Tablet | 5, 10 mg | Start at 5 mg once daily. Increase in 5 mg increments to 20 mg/day (10 mg BID) in 1 week intervals. FDA approved for moderate-to-severe AD |
| | | Oral solution | 2 mg/mL | |
| Memantine and donepezil FDC | NMDA receptor antagonist and ChEI | Memantine extended-release and donepezil capsule | 7/10, 14/10, 21/10, 28/10 mg | Patients stabilized on memantine (10 mg BID or 28 mg/day ER) and 10 mg/day donepezil may be switched directly to 28/10 mg. Patients stabilized on 10 mg/day donepezil start at the 7 mg/10 mg tablet and increase weekly in 7 mg increments to maximum dose of 28/10 mg daily. FDA approved for moderate-to-severe AD |

*Abbreviations*: *AD* Alzheimer's disease, *ChEI* cholinesterase inhibitor, *ER* extended release, *FDA* Food and Drug Administration, *FDC* fixed-dose combination, *nAChR* nicotinic acetylcholine receptor, *NMDA* N-methyl-D-aspartate

ADAS-cog at 6 months for ChEIs compared with placebo, which represents a modest improvement on this 70-point scale [51]. The effect size on global clinical scales is similar to that seen with cognition, and there does appear to be a dose response with regard to improved cognition and global impression [52]. ChEIs are symptomatic in nature and do not prevent the progression of disease. Side effects are predominantly cholinergic and related to GI symptoms, such as nausea, vomiting, and diarrhea (Table 9.3) [51, 53–59].

First approved by the FDA in 1996, donepezil is available as oral or orally disintegrating tablets and comes in three dosages (5, 10, and 23 mg/day). In a Cochrane review of donepezil in mild-to-moderate AD, the 5 mg and 10 mg/day dosages showed significant benefits on cognition, global clinical state, ADLs, and behavior [60]. Significant differences from placebo at 24 weeks on the ADAS-cog were slightly smaller with the 5 mg/day dose (−2.01 points, 95% CI = −2.69, −1.34) than the 10 mg/day (−2.80 points, 95% CI = −3.74, −2.12). Significantly more patients

**Table 9.3** Common side effects of cholinesterase inhibitors and memantine in clinical trials and population studies

| | | ChEIs as a group [51] | Donepezil 5 mg [53] | Donepezil 10 mg [53] | Galantamine 24 mg [53] | Rivastigmine 12 mg [53] | Memantine 20 mg [53] |
|---|---|---|---|---|---|---|---|
| Clinical trials (frequency versus placebo) | Withdrawals (any reason) | 29% vs. 18% (OR = 1.76; 95% CI = 1.54, 2.02) | 14.1 vs. 19.9 | 25.9 vs. 19.7[a] | 20.4 vs. 16.4[a] | 21.6 vs. 11.4[a] | 18.0 vs. 21.2 |
| | Withdrawals due to AEs | 18% vs. 8% (OR = 2.32; 95% CI = 1.95, 2.76) | 7.8 vs. 9.1 | 15.3 vs. 8.4[a] | 10.9 vs. 8.3 | 13.4 vs. 6.7[a] | 10.0 vs. 8.4 |
| | Nausea | 31.5% vs. 9.1% (OR = 4.87; 95% CI = 4.13, 5.74) | 5.5 vs. 4.6 | 12.5 vs. 4.2[a] | 18.2 vs. 6.0[a] | 39.1 vs. 9.0[a] | 2.2 vs. 5.9 |
| | Vomiting | 21.4% vs. 5.4% (OR = 4.82; 95% CI = 3.91, 5.94) | 3.8 vs. 3.4 | 11.6 vs. 4.6[a] | 13.0 vs. 4.8[a] | 26.2 vs. 5.0[a] | |
| | Diarrhea | 14.4% vs. 7.9% (OR = 1.91; 95% CI = 1.59, 2.30) | 7.9 vs. 4.5[a] | 13.7 vs. 5.1[a] | 7.3 vs. 8.6 | 12.3 vs. 6.7[a] | 6.1 vs. 7.0 |
| | Anorexia | 12.2% vs. 3.6% (OR = 3.75; 95% CI = 2.89, 4.87) | 2.6 vs. 1.5 | 7.2 vs. 2.5[a] | 7.2 vs. 2.0[a] | 11.5 vs. 1.7[a] | |

(continued)

**Table 9.3** (continued)

| | | ChEIs as a group [51] | Donepezil 5 mg [53] | Donepezil 10 mg [53] | Galantamine 24 mg [53] | Rivastigmine 12 mg [53] | Memantine 20 mg [53] |
|---|---|---|---|---|---|---|---|
| | Dizziness | 14.8% vs. 7.8% (OR = 1.99; 95% CI = 1.64, 2.42) | 6.8 vs. 4.8 | 8.2 vs. 5.0[a] | 14.1 vs. 3.1[a] | 14.3 vs. 5.2[a] | 5.9 vs. 5.8 |
| | Headache | 14.5% vs. 9.7% (OR = 1.56; 95% CI = 1.27, 1.91) | 2.9 vs. 0.8 | 10.8 vs. 7.7 | 5.7 vs. 4.3 | 13.0 vs. 6.0[a] | 5.0 vs. 4.3 |
| Population studies | ChEIs as a group: Increased frequency of hospital visits for syncope, bradycardia, pacemaker insertion, and hip fracture [54]. Increased risk of hospitalization for bradycardia [55]. Increased risk of syncope, but not falls, fracture, or accidental injury [56]. Increased risk of 10 lb weight loss at 1 year [57]. Conflicting data on risk of pneumonia with rivastigmine compared to donepezil [58, 59] | | | | | | |

[a]Indicates $p < 0.05$

*Abbreviations*: *AEs* adverse events, *ChEIs* cholinesterase inhibitors, *CI* confidence interval, *OR* odds ratio

receiving 10 mg/day compared to placebo withdrew before the end of treatment. Donepezil is typically started at the 5 mg/day dose and may be titrated to the 10 mg/day dose after a period of 4–6 weeks. Clinicians should warn patients of a potential increase in cholinergic-related AEs (vomiting, diarrhea) that occur during uptitration.

First approved by the FDA in 2000, rivastigmine is available as a capsule, oral solution, or transdermal patch. A Cochrane review of clinical trials involving rivastigmine reported modest benefits on cognitive function, ADLs, and global functioning, with a weighted mean difference from placebo on the ADAS-cog of −1.79 points (95% CI = −2.21, −1.37) and a standardized mean difference on measures of ADLs of 0.20 (95% CI = 0.13, 0.27) [61]. Rivastigmine is the only ChEI currently available as a transdermal patch, with the 9.5 mg/24 h (10 $cm^2$) patch considered equivalent to the 6 mg BID capsule dosing. The 13.3 mg/24 h (15 $cm^2$ patch) was approved for severe AD in 2013. Potential advantages of the patch compared to oral administration include reduced caregiver burden, improved adherence, and a better tolerability profile possibly related to decreased peak-trough fluctuations and slower rate of drug release [62]. Disadvantages include application site reactions, such as pruritus, erythema, and dermatitis and increased cost. The patch may be beneficial in patients prone to GI side effects of medications as well as those who have difficulty swallowing capsules. In the Investigation of Transdermal Exelon in Alzheimer's disease (IDEAL) study, use of the 10 $cm^2$ patch compared to 6 mg BID capsules was associated with a decreased frequency of nausea (7.2% vs. 23.1%) and vomiting (6.2% vs. 17.0%) [63]. More patients in the 10 $cm^2$ patch group reached the target dose compared with patients in the capsule group (95.9% vs. 64.4%, respectively). Efficacy was similar between the 10 $cm^2$ patch and the capsules. Clinicians should make sure to review with patients and caregivers the proper administration of the patch as some deaths have been reported owing to the administration of multiple patches at once [64]. The patch should be removed after 24 h before placing a new patch, and only one patch should be applied per day [65].

First approved by the FDA in 2001, galantamine is available as once-daily extended-release capsules, twice-daily immediate-release tablets, and an oral solution. Similar to donepezil and rivastigmine, galantamine produces modest benefits on cognition, functioning, and global impression. One unique study involving galantamine was a 2-year RCT of galantamine in patients with mild-to-moderate AD (MMSE 10–26) randomly assigned to galantamine ($n$ = 1024) or placebo ($n$ = 1021) [66]. This study reported a significantly lower mortality rate in patients receiving galantamine compared to placebo (HR = 0.58; 95% CI = 0.37, 0.89) as well as significant benefits on cognition (MMSE scores) and functional impairment (Disability Assessment in Dementia score). While the effective dosage in clinical trials was 16–24 mg/day, the 16 mg/day dosing may be more favorable in a mild AD population given that it displays a similar efficacy to the 24 mg/day dose and was associated with a trend toward fewer discontinuations due to AEs in one post hoc analysis [67]. In a trial involving galantamine extended release and galantamine immediate release, both forms produced statistically significant differences from placebo at week 26 on the ADAS-cog but not the Clinician's

Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus) [68, 69]. AE profiles were similar between the ER and IR forms. In clinical practice, galantamine immediate release is typically initiated at the 8 mg/day dose (4 mg BID) and increased to a maintenance dose of 16 mg/day (8 mg BID) after a period of 4 weeks. Patients who begin to decline on the 16 mg/day dose may be titrated to a 24 mg/day dose (12 mg tablets BID) with the caveat that this dose has not been shown to be significantly better than the 16 mg/day dose.

Despite belonging to the same general class, patients who are unable to tolerate one ChEI or do not demonstrate any treatment response may benefit from a therapeutic trial with an alternative ChEI owing to different pharmacologic properties [70, 71]. Interestingly, one open-label study reported that lack of efficacy or presence of intolerable side effects with donepezil therapy was not predictive of similar problems when switched to rivastigmine [72]. Greater than half (54.5%) of patients who discontinued donepezil due to lack of efficacy responded to rivastigmine by the end of 6 months on a global measure of disease severity. Patients and their families should also be reminded that mild improvement or a lack of significant decline is considered a positive treatment response based on the nature of disease progression. Given that most of the clinical trials involving ChEIs were performed for a period of 6 months, a therapeutic trial of this duration is often necessary to determine if there is a clinical response. When considering a switch of ChEI due to intolerance, clinicians should generally wait until the initial symptoms have fully resolved before initiating and titrating the new ChEI according to the package insert. In the case of lack of benefit (i.e., unsatisfactory response within the first year of treatment), clinicians may safely switch between ChEIs immediately [73].

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that is FDA approved for the treatment of moderate-to-severe AD. Clinical trials involving memantine in mild AD have not shown a significant benefit, and its use is not recommended at this stage [74, 75]. Use of vitamin E (alpha tocopherol) supplements in patients with diagnosed AD is controversial. One trial randomized Veterans Affairs (VA) patients (>95% male) with mild-to-moderate AD (MMSE between 12 and 26 inclusive) who were currently taking a ChEI to receive either 2000 IU/day alpha tocopherol (given as 1000 IU twice a day), 20 mg/day memantine, memantine and alpha tocopherol, or placebo [76]. Over a mean follow-up period of 2.27 years, participants receiving alpha tocopherol demonstrated a slower rate of decline compared with placebo as measured by the ADCS-ADL (primary outcome) (mean difference = 3.15; 95% CI = 0.92, 5.39; $p = 0.03$). No significant difference on the primary outcome was seen with the memantine only or the alpha tocopherol plus memantine groups compared with placebo. Secondary outcomes that measured cognition (ADAS-cog, MMSE) and neuropsychiatric symptoms (Neuropsychiatric Inventory) were not significantly different from placebo with any treatment group after adjustment for multiple comparisons. Based on the results of this study and an earlier trial (using a dose of 1000 IU twice a day), vitamin E supplementation may be offered to patients, especially men based on the results of the VA study, looking for other options [77]. While early meta-analyses suggested that high-dosage

vitamin E supplements may increase all-cause mortality, this finding was not replicated in a recent meta-analysis which included mortality data from additional large-scale studies [78, 79]. Since vitamin E may induce vitamin K deficiency, it should be used with caution in patients taking warfarin [80].

NSAIDs, statins, and omega-3 fatty acids have been studied in multiple trials in mild-to-moderate AD populations without much success. Both simvastatin and atorvastatin failed to show any effect on cognition, as measured by ADAS-cog scores, or global functioning, as measured by the ADCS-CGIC [81, 82]. Trials involving *Ginkgo biloba* in the treatment of AD have demonstrated inconsistent effects on cognition and were limited due to small sample size, considerable heterogeneity, and poor methodological quality [83–86]. As a supplement, patients wishing to take *Ginkgo biloba* should be aware of the considerable variability in quality control among companies producing this supplement. Addition of omega-3 fatty acids has generally not demonstrated a statistically significant slowing in the rate of cognitive or functional decline in mild-to-moderate AD [87–89]. Of the few studies that reported adverse events, no significant differences in frequency of all AEs or serious AEs were seen [90]. Huperzine A, a natural cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata*, did not demonstrate any cognitive, global, or functional benefit in an RCT involving patients with mild-to-moderate AD [91].

Non-pharmacologic approaches that have been shown to delay functional decline and improve quality of life in people with dementia include exercise and dyadic interventions [92, 93]. Dyadic interventions are psychosocial programs that involve both the patient with dementia and care partner. These interventions may include support components, with educational tools that focus on communication skills and planning pleasant activities. These interventions have minimal side effects and should be recommended for interested patients.

## Cognitive Enhancement in Moderate-to-Severe Alzheimer's Disease

### *Case Vignette Part 3*

Mr. Jones was started on 5 mg/day donepezil by his neurologist, which was titrated up to 10 mg/day after 4 weeks. He experienced some nausea during the first week, but his symptoms subsided. He and his family noticed some improvement in his cognition during the first several months. However, over the next 2 years, he begins to require more assistance with dressing and personal hygiene. He is no longer oriented to month or year, and his wife reports that he has trouble recognizing his grandchildren. His MMSE is 14/30.

## *Therapeutic Options*

Several different methods can be used to assess the severity of Alzheimer's disease. Clinical trials will typically use various MMSE cutoffs as inclusion criteria that can vary between individual studies. For example, MMSE scores between 21 and 26 may indicate a mild AD population, 10–20 as moderate AD, and less than 10 as severe AD. The Global Deterioration Scale (GDS) and the CDR are additional tools used for staging AD [94, 95]. The GDS is broken into seven stages with characteristics listed that are typical of each stage. The CDR is a five-point scale that encompasses six domains of cognitive and functional performance, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Characteristics typical of moderate dementia include inability to remember names of close family members, disorientation to time and sometimes place, impairment in problem solving and social judgment, restricted interests, and requiring assistance in dressing and hygiene. This patient has now entered the moderate stages of AD given his MMSE score and impairments in cognition and functioning.

If patients continue to deteriorate on the 10 mg/day donepezil dose, one option is to escalate to the 23 mg/day dose which was approved in 2012 for patients with moderate-to-severe AD. The approval of this dose was based on a 24-week RCT involving patients with MMSE scores 0–20 who were stabilized on donepezil 10 mg/day for ≥12 weeks [96]. The 23 mg/day dose demonstrated a statistically significant benefit over the 10 mg/day dose on the SIB (LSMD = 2.2; $p < 0.001$). No significant difference was seen on the co-primary outcome measure, CIBIC-plus, which is a measure of global functioning. No significant difference was seen on the secondary measures (MMSE and ADCS-ADL). While a post hoc analysis suggested a significant benefit on the CIBIC-plus in patients with more impairment at baseline (MMSE 0–16) ($p = 0.028$), the FDA statistical reviewers demonstrated that many subgroups did not reach statistical significance [97]. For example, in a subgroup of patients with MMSE scores of 0–14, there was no statistical significance on the CIBIC-plus ($p = 0.1663$). AEs with the 23 mg/day dose that occurred at >5% and >2× the frequency of the 10 mg/day dose included nausea (11.8% vs. 3.4%), vomiting (9.2% vs. 2.5%), and anorexia (5.3% vs. 1.7%). The mean duration of vomiting was 5.61 days in the 23 mg/day group and 1.25 days in the donepezil 10 mg/day group, with most vomiting classified as moderate in severity [98]. Most withdrawals due to AEs occurred within the first 2 weeks during the uptitration phase. Due to the uncertain clinical benefit and higher incidence of adverse events, the medical and statistical reviewers recommended against approval of the 23 mg/day dose. However, the summary reviewer recommended approval based on the superiority on the cognitive measure and the recognition that the 23 mg/day dose was likely as effective as the 10 mg/day dose on global functioning. Donepezil 23 mg/day may be an option in patients with moderate-to-severe AD who have been stabilized on the 10 mg/day dose for at least 3–6 months. Clinicians should monitor patients for side effects during the first few weeks after the dose increase. Patients

in the clinical trial who were particularly prone to AEs and may not be appropriate candidates for the 23 mg/day dose include those with low body weight (e.g., <55 kg), poor appetite, history of GI bleeding, and bradycardia [99, 100].

Patients who are on the 10 $cm^2$ (9.6 mg/24 h) rivastigmine patch may benefit from an increase to the 15 $cm^2$ patch (13.3 mg/24 h), which is indicated by the FDA only for severe AD. In a mild-to-moderate (MMSE scores ≥10 and ≤24) AD population, the Optimizing Transdermal Exelon in Mild-to-Moderate Alzheimer's disease (OPTIMA) trial failed to demonstrate a significant difference on the ADAS-cog between the 15 and 10 $cm^2$ patch at 48 weeks ($p = 0.227$) [101]. However, there was a significant difference at week 48 on functioning as measured by the Instrumental Activities of Daily Living domain of the ADCS-ADL scale (co-primary outcome) as well as a significant difference at week 24 on the ADAS-cog ($p = 0.027$). Given that the population was more in the moderate-to-severe AD range (mean MMSE of 14.2), the ADAS-cog might not have been able to detect differences at week 48 due to floor effects seen in more severe AD populations. Notable adverse events that occurred at higher rates with the 15 $cm^2$ patch compared to the 10 $cm^2$ patch included nausea (12.1% vs. 4.9%), vomiting (10.4% vs. 4.6%), weight decrease (6.9% vs. 2.8%), and decreased appetite (6.4% vs. 2.5%).

Approval of the 15 $cm^2$ patch for severe AD was based on the ACTivities of daily living and cognitION (ACTION) study, which compared the 15 $cm^2$ (13.3 mg/24 h) patch to the 5 $cm^2$ (4.6 mg/24 h) patch in patients with severe AD (MMSE scores ≥3 and ≤12) [102]. Treatment with the 15 $cm^2$ patch resulted in significantly less deterioration on both primary outcomes, the Severe Impairment Battery and ADCS-ADL-severe impairment version compared with the 5 $cm^2$ patch at 24-week end point. In clinical practice, the rivastigmine patch is initiated at the 4.6 mg/24 h (5 $cm^2$) dose and titrated up to the 9.5 mg/24 h (10 $cm^2$) dose after a minimum of 4 weeks. Patients with mild-to-moderate AD may be titrated to the 13.3 mg/24 h (15 $cm^2$) dose based on the results of the OPTIMA trial. The rivastigmine patch displays a more linear dose-response curve compared to the capsules which means that there is a potentially greater benefit at higher doses compared to up-titrating the capsules, although this has not been proven in clinical trials. Based on clinical experience, titration is generally better tolerated with the patch than the capsules due to lower GI side effects. However, the OPTIMA trial results still demonstrated higher rates of nausea, vomiting, and decreased appetite in the 15 $cm^2$ patch group which may be of concern in certain patients.

Memantine is FDA approved for moderate-to-severe AD and may be used as monotherapy or in combination with ChEIs. Immediate-release tablets and once-daily extended-release capsules are available. Clinical trials involving memantine have generally shown statistically significant improvements over placebo across broad clinical domains, with one meta-analysis reporting effect sizes of 0.26 for a cognitive domain ($p < 0.001$), 0.22 for a global domain ($p < 0.001$), 0.18 for a functional domain ($p < 0.001$), and 0.12 for a behavioral domain ($p = 0.03$) [103, 104]. Combination therapy involving memantine and a ChEI appears to show significant benefits compared to ChEI monotherapy on some but not all domains [105, 106]. A recent scientific panel concluded that combination therapy provided

modestly significant benefits on behavior, cognitive function, and global assessment compared to monotherapy [107]. No benefit was seen on functioning. This is similar to another analysis, which concluded that combination therapy provides additive benefits that continue to accumulate through 6-month treatment periods compared to monotherapy [108]. Memantine is generally well tolerated, with fewer discontinuations due to AEs compared with placebo in clinical trials (odds ratio = 0.80; 95% CI = 0.59, 1.09) [101]. Potential side effects include dizziness, headache, and somnolence.

Patients with moderate-to-severe AD who were not on any medication previously may be started on combination therapy directly. Typically, one drug is initiated and titrated to the effective dosage before starting the second medication. There is a theoretical advantage to starting memantine before a ChEI because it is a 5-HT3 antagonist, which may decrease the rates of nausea and vomiting during titration with a ChEI [109]. Patients can also be titrated on a fixed-dose combination of memantine extended release and donepezil, which was approved by the FDA in 2014 [110]. Advantages of the combination include a simplified medication regimen and the ability to sprinkle the capsule onto soft foods. While it remains a more expensive option, it may be beneficial in patients with significant dysphagia or a history of poor compliance.

## Treatment Duration and Discontinuation in Alzheimer's Disease

### *Case Vignette Part 4*

The patient was continued on donepezil 10 mg/day and started on memantine, which was gradually titrated to 10 mg BID. Over the next 2 years, Mr. Jones begins to forget the name of his wife and becomes more dependent on her for dressing, bathing, and feeding. He eventually becomes incontinent and is no longer able to walk. He was admitted to a nursing home a few months ago. On physical exam, he exhibits generalized rigidity. His MMSE is 7/30.

### *Therapeutic Options*

A common question in managing patients with AD revolves around the duration of pharmacotherapy. Because most RCTs are only performed for 6 months to a year, long-term observational controlled studies (LTOCs) provide complementary data to RCTs regarding long-term therapy [111]. These trials are performed in a real-world setting and involve patients who often have multiple comorbidities, take multiple medications, and may not always be adherent with treatment regimens. One important finding from these studies was that greater treatment persistence, defined

as total years of drug use divided by the total years of disease symptoms, was associated with significantly slower rates of decline on the MMSE, instrumental ADL scale, Physical Self-Maintenance Scale (PSMS), and CDR-SB [112]. Compared with untreated patients, maximally treated patients would have less decline in the range of 1 point per year on the MMSE and 0.6 points per year on the CDR-SB. After 5 years, maximally treated patients would retain 4 more points on the MMSE and 1.6 fewer points on the CDR-SB. In another study, combination therapy significantly slowed cognitive and functional decline compared to ChEI monotherapy, with effect sizes that increased with treatment duration [113]. A third study found that use of ChEIs delayed admission to nursing homes compared to patients never receiving a ChEI (relative HR = 0.37; 95% CI = 0.27, 0.49) [114]. In addition, patients receiving memantine and a ChEI were significantly less likely to be admitted to a nursing home versus those receiving only ChEI therapy (relative HR = 0.29; 95% CI = 0.11, 0.72). Combined data from these studies suggests that greater persistence with therapy can slow cognitive and functional decline and may delay admission to nursing homes.

Decisions regarding discontinuing AD pharmacotherapy are difficult and must be individualized based on careful assessment of risks versus benefits [115]. AD can be broken into four major stages: mild, moderate, severe, and terminal. The terminal stage occurs when patients become hospice eligible and is characterized by a loss of all verbal abilities, incontinence, inability of walk, and assistance with most ADLs. It is our opinion that AD pharmacotherapy should be discontinued when patients enter this stage. Only medications indicated for comfort should be continued. Other potential indications for treatment discontinuation include intolerable side effects and comorbidities that make continued use of these agents futile. Discontinuation may lead to worsening of cognition and neuropsychiatric symptoms and increased risk of admission to a nursing home in community-dwelling patients [116–118]. However, at least one study demonstrated that ChEI discontinuation was safe and well tolerated in the majority of patients with moderate-to-severe AD in an institutionalized setting [119]. Particular caution should be given to discontinuing these medications in patients with baseline hallucinations and delusions, as discontinuation might lead to worsening of symptoms. Ultimately, the choice of whether or not to discontinue these medications should be made on a case by case basis, weighing the potential for worsening of cognition and increased neuropsychiatric symptoms with the risk of side effects and drug costs. The dose should be tapered over a period of 2–4 weeks, and the patient should be monitored over the next few months.

## Cognitive Enhancers in Other Disorders

Table 9.4 presents a survey of other disorders that are associated with cognitive decline. Treatment of cognitive symptoms in these disorders is often limited, and many clinical trials have been performed demonstrating little benefit.

**Table 9.4** Examples of cognitive enhancers tested in other neurologic and psychiatric disorders

| Disorder | Intervention |
|---|---|
| Vascular dementia | Inconclusive evidence for ChEIs and memantine based on several randomized trials with considerable heterogeneity. Small, positive effect on cognition; limited effect on function, behavior, and global impression; increase in adverse events [120, 121] |
| | Benefit with galantamine in mixed population of vascular dementia or AD [122] |
| Frontotemporal dementia | No benefit of rivastigmine on cognition, but some benefit on behavior [123] |
| | No benefit of memantine on cognition based on 2 RCTs, but small benefit on global impression [124] |
| Lewy body dementia | Benefit with rivastigmine on neuropsychiatric inventory (NPI-4) [125] |
| | Benefit with donepezil and rivastigmine on cognitive and global measures [126] |
| | Possible benefit with memantine on global impression [127] |
| Parkinson's disease dementia (PDD) | Rivastigmine FDA approved for mild-to-moderate PDD [128] |
| | Questionable benefit with memantine [129, 130] |
| HIV-associated neurocognitive disorders (HAND) | Antiretroviral treatment is mainstay of therapy [131]. For patients with symptoms of HAND, neuroimaging and CSF analysis may be warranted. Patients can be switched to a regimen with higher CNS penetration effectiveness rank based on CSF viral load |
| | Negative studies with memantine, [132] minocycline, [133] and selegiline [134] |
| Huntington's disease | No significant effects on cognition with donepezil or rivastigmine in small RCTs [135, 136] |
| Multiple sclerosis | Treatment with disease-modifying therapies may improve cognition [137] |
| | ChEIs, memantine, and *Ginkgo biloba* generally show no significant benefits on cognition [138] |
| | Small benefits with neuropsychological rehabilitation and cognitive training [139] |
| Depression | SSRIs, SNRIs, and vortioxetine associated with improvements on cognitive measures [140, 141] |
| | No apparent benefit of galantamine augmentation [142] |
| Schizophrenia | Mostly negative studies involving ChEIs (donepezil, rivastigmine, galantamine) and glutamatergic agents (glycine, D-cycloserine) [143–145]. Mixed evidence with memantine [146] |

*Abbreviations*: *AD* Alzheimer's disease, *ChEIs* cholinesterase inhibitors, *CNS* central nervous system, *CSF* cerebrospinal fluid, *RCTs* randomized controlled trials, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

## Clinical Pearls

Patients with MCI should be advised that the best way to prevent or delay the conversion to a major neurocognitive disorder is through a multi-domain approach. An emphasis is placed on lifestyle modification, exercise (both physical and mental), dietary modification such as the Mediterranean diet, mindfulness and stress reduction, and control of cardiovascular risk factors (e.g., hypertension, hyperlipidemia, and smoking). A B complex multivitamin may also be added, although the evidence is mixed. Once a diagnosis of Alzheimer's disease is made, patients should be initiated on a ChEI, with the recognition that most patients will experience either slight improvement or clinical stability. Patients unable to tolerate one ChEI or demonstrate continued cognitive decline at a period of 6 months on a therapeutic dose may be switched to another ChEI. Any attempt to titrate ChEIs to higher doses may result in AEs such as nausea, vomiting, or diarrhea particularly within the first few weeks. In the moderate-to-severe stages of AD, patients can be initiated on combination therapy with a ChEI and memantine. In these stages, patients and their families should be counseled that the goals of care will gradually shift from improving cognition to maintaining function, delaying institutionalization, and managing the behavioral and psychological symptoms of dementia. Evidence from LTOCs suggest that greater persistence with AD pharmacotherapy may slow the rate of cognitive and functional decline and delay admission to a nursing home. When patients become hospice eligible, AD pharmacotherapy may be safely discontinued due to the limited benefits and side effects.

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