Cholinesterase Inhibitors in the Treatment of Dementia

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Dementia associated with probable Alzheimer’s disease (AD) is one of the most common types of dementia. Patients with AD often have cholinergic deficits in association with the disease. The cholinesterase inhibitors donepezil hydrochloride, galantamine hydrobromide, and rivastigmine tartrate are the current mainstays of symptomatic treatment for patients with AD. In clinical trials for all three agents, beneficial effects on standard measures of cognitive and global function have been observed in patients with mild to moderate AD. Although none of the cholinesterase inhibitors has been approved for treatment of patients in advanced stages of AD, all three agents have had beneficial cognitive effects among patients with less severe forms of the disease. The author provides information on recommended dosing for all three medications, noting that cholinesterase inhibitors must be titrated carefully. When administered with caution, galantamine, rivastigmine, and donepezil are generally well-tolerated pharmacologic treatment options. The author notes that, after patients and their caregivers understand that no change in status is considered an “improvement” and a desirable clinical outcome for patients with AD, if no benefits are achieved with the use of one cholinesterase inhibitor, switching to another medication in this class might be beneficial. The author further suggests that the benefits found in cholinesterase inhibitors for patients with AD might also be applicable to patients with other types of dementia such as vascular dementia and dementia with Lewy bodies as cholinergic deficits have been reported in association with these types of dementia as well.

Although symptoms of the disease usually appear after age 60, the incidence of AD increases sharply and steadily after 65 years of age. It has been estimated that nearly half of all people aged 85 years and older have some form of dementia. As the US population ages, the number and percentage of people affected by AD will grow proportionally. The National Institutes of Health predict that, if the current trend continues, there will be 8.5 million Americans with AD by the year 2030.

People in the early stages of AD have impaired cognitive function and tend to be easily confused. In addition, their ability to perform instrumental activities of daily living (ADL)—such as housework, leisure activities, and correspondences—is reduced. Eventually they lose the capacity to function on their own and become completely dependent on other people for their everyday care. Although many family members voluntarily—and gradually—assume the role of primary caregiver, the progressive nature of AD places increasing physical and emotional demands on caregivers, often exerting a negative influence on the caregivers’ lifestyles, family relationships, and health.

In fact, researchers have found that caregivers of cognitively impaired patients have increased physical and psychological morbidity and use a relatively high proportion of healthcare resources. Although the majority of patients with AD have family members who want to provide care for them at home, the burden placed upon family caregivers often becomes intolerable as patients’ independence deteriorates further. Many patients with AD are eventually placed in nursing home facilities.

In terms of direct and indirect costs, AD places a heavy economic burden on society. It is estimated that the total cost of AD to the US economy is $100 billion annually.

Direct costs include physician visits, prescription medications, emergency department visits, acute hospitalizations, and long-term care. In 1996, the annual cost of caring for one patient with mild AD was estimated at $18,408; moderate AD, $30,096; and severe AD, $36,132. Indirect costs associated with caring for patients with AD include lost productivity of patients and caregivers and the costs of stress-associated morbidity in caregivers. Direct and indirect costs increase as the disease progresses.

Increasing costs are mostly driven by the institutionalization of patients with severe cognitive and functional disabilities. Long-term care facilities range from assisted living...
to special AD care units within nursing homes. Costs of AD care have been estimated to be 21% to 30% higher in traditional nursing homes than in assisted living facilities, whereas the costs of specialized AD facilities are higher still.

The second and third most common types of dementia are vascular dementia and dementia with Lewy bodies (LBD), respectively. Executive dysfunction is often seen in patients with vascular dementia, but memory dysfunction may be minimal or nonexistent in patients with a mild form of the disease. Dementia with Lewy bodies can be characterized by symptoms of global cognitive impairment, neuropsychiatric disturbance with visual hallucinations, and parkinsonism.

It can be difficult, however, to diagnose patients with dementia accurately. Although clinical diagnosis usually specifies a single dementia, the elderly are at increased risk for vascular events and AD. In fact, vascular dementia and AD often coexist in a state of mixed dementia. In addition, at autopsy, neuropathologic signs of concomitant AD and cerebrovascular disease have been reported in the brain tissue of 7% to 25% of patients who received a diagnosis of probable AD. Probable AD and LBD also often coexist. It has been estimated that comorbid AD and LBD could account for as many as 20% of patients diagnosed with dementia.

Although there is no cure for dementia of the AD type, several available pharmacologic treatment modalities can reduce the symptoms of cognitive impairment and slow disease progression. Such treatments can increase the number of probable AD cases classified as mild, potentially slowing or preventing the progression of the disease to moderate or severe. It is hoped that these modalities will allow for a shift away from institutional care for these patients and that their use may ease the public health burden of dementia of the AD type, as patients with mild AD exhibit less aberrant behavior and are allowed to function more independently than patients with moderate or severe disease.

The three most commonly prescribed cholinesterase inhibitors—donepezil hydrochloride, galantamine hydrobromide, and rivastigmine tartrate—are the current mainstays of symptomatic treatment for patients with probable AD. The goal of treatment with a cholinesterase inhibitor is to stabilize or reduce aberrant behavior patterns and the declines in cognition and ADLs that are observed in untreated patients.

This review will therefore cover the pathogenesis of dementia and the effects of the cholinesterase inhibitors on disease progression and patient behavior vis-à-vis cognitive and global measures of function.

**Pathogenic Process of Dementia**

The symptoms of all types of dementia are presumed to be related to impaired neurotransmission and degeneration of neuronal circuits in the brain areas affected. Cognitive deterioration occurring in patients with probable AD is associated with a progressive loss of cholinergic neurons and a consequent decline in levels of acetylcholine (ACh) in the brain, particularly in the temporal and parietal neocortex and hippocampus. Cholinergic deficits occur in the brains of patients with AD, vascular dementia, and LBD. These observations suggest that impairment of cholinergic function contributes to the symptoms of all three forms of dementia and that all patients with dementia could potentially benefit from cholinergic replacement therapy, regardless of the final diagnosis at autopsy.

Acetylcholine is hydrolytically destroyed in the brain by two cholinesterases, acetylcholinesterase (AChE) and butryrylcholinesterase (BuChE). Although AChE is found in higher concentrations than BuChE in the brain tissue of patients with AD, there is evidence that BuChE is active in all hippocampal and cortical areas known to receive cholinergic innervation. Studies have also shown that as AD progresses, AChE activity can be reduced by up to 67% of normal levels in the temporal lobe and hippocampus, whereas BuChE activity can increase to up to 165% of the normal level. In addition, preliminary reports have shown that low levels of BuChE activity in the medial temporal cortex of patients with LBD are associated with relatively slow rates of cognitive decline.

Acetylcholinesterase is present in three isoforms: G1, which is present in the brain; G4, in the brain and the neuromuscular endplate; and G2, in skeletal muscle and blood-forming cells. Rivastigmine preferentially inhibits the G1 molecular form of AChE and is the only cholinesterase inhibitor to have exhibited preferential selectivity for any of the three isoforms of AChE.

Probable AD is characterized by the presence of neuritic amyloid plaques and neurofibrillary tangles in the brain, pathologic changes associated with cholinergic derangement. Acetylcholinesterase and BuChE are both associated with amyloid plaques. Although it unknown whether AChE plays a role in accelerating the neurotoxicity of amyloid plaques, there is some evidence that BuChE may accelerate maturation of benign plaques into plaques associated with neuronal degeneration and AD.

Alternatively, cognitive impairment associated with vascular dementia is pathologically characterized by ischemic, hypoperfusive, or hemorrhagic brain lesions from cerebrovascular disease or cardiovascular pathology.

Finally, Lewy bodies, which are composed of abnormally ubiquinated neurofilament proteins, occur in the limbic cortex and neocortex of patients with LBD and are surrogate markers for neuronal loss.

When conducting postmortem analysis of brain tissue samples from patients previously diagnosed with dementia, pathologists encounter a substantial proportion that have characteristics of AD mixed with LBD and various manifestations.

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of cerebrovascular disease; they less commonly encounter samples with evidence of LBD exclusively or cerebrovascular disease exclusively.21

Cholinesterase Inhibition and Pharmacologic Profiles of Cholinesterase Inhibitors

Blocking cholinesterase-induced hydrolysis of ACh—and the subsequent increase in ACh concentration in central synapses and the enhancement of cholinergic function—provides the symptomatic improvements observed in patients with probable AD who are treated with cholinesterase inhibitors. Although a number of therapeutic approaches have been tested in the hope of enhancing cholinergic function and cognition in patients with AD, cholinesterase inhibition is the only strategy that has thus far proven to have beneficial effects in patients.

Although the pharmacologic and pharmacokinetic profiles of the most widely used cholinesterase inhibitors have notable differences that may affect efficacy, the clinical significance of these differences remains hypothetical in the absence of large, randomized trials that directly compare the cholinesterase inhibitors with each other.

Acetylcholinesterase is the main enzyme involved in the breakdown of ACh in the normal brain, but as AD progresses, BuChE may become increasingly involved in coregulation of ACh in certain areas of the brain.39 It has been proposed that an intervention that inhibits both AChE and BuChE may decrease patient symptoms.38 The US Department of Health and Human Service’s National Institute on Aging has initiated a research program to develop specific BuChE inhibitors for the treatment of patients with probable AD (see http://www.alzheimers.org/).39,40 Because AChE and BuChE are associated with amyloid plaques, there is a possibility that inhibitors of these enzymes may also have an effect on the underlying pathophysiology of AD.23,39

Selective inhibition of AChE occurs with galantamine and donepezil, whereas rivastigmine inhibits both AChE and BuChE.39 A growing body of evidence indicates that both AChE and BuChE play important roles in cholinergic transmission.41,42 For this reason, both cholinesterases are considered legitimate targets when managing AD.

Donepezil and galantamine are rapidly reversible AChE inhibitors, whereas rivastigmine is a slowly reversible inhibitor. Uprogulation of the production of AChE in the cerebrospinal fluid of patients with AD was reported during 6 months of treatment with rapidly reversible agents, which could eventually lead to diminished response to the agents.23,43 In contrast, rivastigmine produced sustained inhibition of AChE and BuChE activity in the cerebrospinal fluid of patients with AD during 12 months of treatment.44

A dual mechanism of action has also been proposed for galantamine, which inhibits AChE and acts as an allosterically potentiating ligand on nicotinic ACh receptors. Galan-tamine can increase the probability of ACh-induced nicotinic channel opening, which could improve nicotinic cholinergic neurotransmission.45 Whether central activation of the nicotinic ACh receptor translates into cognitive benefits in vivo has yet to be definitively determined.23

Evaluating Clinical Effectiveness of Cholinesterase Inhibitors in Clinical Trials

For regulatory purposes, the US Food and Drug Administration requires that clinical trials of medications intended for use in patients with probable AD demonstrate a beneficial effect on a performance-based cognitive instrument and a global measure of function. On the basis of evidence accumulated in several 3- to 6-month, randomized, double-blind, placebo-controlled trials, the American Academy of Neurology recommends use of cholinesterase inhibitors as standard therapy for patients with mild to moderate AD.5 Table 1 summarizes the cognitive, global, functional, and neuropsychiatric assessment scales most commonly used in these studies.

A primary goal of pivotal trials of cholinesterase inhibitors has been to assess subjects’ responses to treatment in the domain of cognitive decline, most often using the Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog).46 The ADAS-Cog is a sensitive psychometric research tool that assesses multiple cognitive outcomes and is an accepted standard for measuring cognitive abilities in clinical trials. Scores on this scale range from 0 to 70. Untreated patients with mild to moderate AD typically have increased impairment signified by a 3- to 4-point increase in ADAS-Cog points over 6 months; patients with moderate to severe disease have an increase of 4 to 6 points during the same amount of time.47 The scale is more extensive, more sensitive, and less variable than Folstein’s Mini–Mental State Exam (MMSE).48,49 the clinical staging tool regularly used by general physicians. The ADAS-Cog takes approximately 30 to 45 minutes to administer, however (versus 15 minutes for the MMSE), and is therefore not practical for everyday clinical practice.

Another primary goal of pivotal trials of cholinesterase inhibitors has been to assess clinical changes in subjects’ functional abilities. Researchers use a global assessment tool such as the Clinician’s Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus).50 Patient function is assessed in four general areas through a subjective interview by a clinician with a patient and caregiver. If a clinician can detect a drug’s effect during an interview with a patient and caregiver, it is assumed that the effect is likely to be clinically relevant. The CIBIC-plus simply asks whether a patient has improved, stayed the same, or deteriorated overall, and it is suitable for use in clinical practice.

Another measure of global function that has been used as a primary outcome parameter is the Gottfries-Bräne-Steen (GBS) scale.51 Like the CIBIC-plus, the GBS scale assesses patient function in four general areas using a semistructured
interview by a clinician with a patient and caregiver. The scale is intended for use by a variety of healthcare professionals. It can measure changes in the symptoms of dementia over a specified amount of time and can be used to evaluate the effectiveness of treatment.

Deterioration of a patient’s ability to perform ADL has a major impact on the quality of life with AD and their caregivers, often influencing physician and caregiver decisions to institutionalize patients. Behavioral symptoms of dementia are another major source of caregiver stress that contributes to the decision to institutionalize. Some trials of cholinesterase inhibitors have assessed the effects of treatment on these parameters using a variety of scales.

In clinical trials, the Progressive Deterioration Scale (PDS) and the Disability Assessment for Dementia (DAD) scale have been used to evaluate the effects of cholinesterase inhibitors on ADL.

A simpler and more personalized method of monitoring the functional performance of patients in the clinical setting is Goal Attainment Scaling. With Goal Attainment Scaling, patients and/or caregivers are interviewed at diagnosis to identify a number of goals that are important to them from a personal perspective. The success of treatment is determined by the extent to which these goals are met.

The Behavior Pathology in AD Rating Scale (BEHAVE-AD) was developed specifically to assess AD-related behavioral disturbances. It focuses on the presence or absence of the following symptoms of dementia: activity disturbances,

### Table 1
Rating Scales Used in Clinical Trials to Evaluate the Efficacy of Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Domains Assessed</th>
<th>Source of Information</th>
<th>Scale Range and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease Assessment Scale Cognitive</td>
<td>Cognition</td>
<td>Patient interview</td>
<td>0–70 points:</td>
</tr>
<tr>
<td>Subscale (ADAS-Cog)</td>
<td></td>
<td>Task administration</td>
<td>0 = no impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70 = severe impairment</td>
</tr>
<tr>
<td>Clinician’s Interview-Based Impression of Change</td>
<td>Global</td>
<td>Patient interview</td>
<td>1–7 points:</td>
</tr>
<tr>
<td>Plus Caregiver Input (CIBIC-plus)</td>
<td></td>
<td>Caregiver interview</td>
<td>1 = marked improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 = moderate improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 = minimal improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 = no change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 = minimal deterioration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 = moderate deterioration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 = marked deterioration</td>
</tr>
<tr>
<td>Disability Assessment for Dementia Scale (DAD)</td>
<td>ADL</td>
<td>Caregiver questionnaire</td>
<td>0–100 points:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 = least impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 = severe impairment</td>
</tr>
<tr>
<td>Gottfries-Bråne-Steen Scale (GBS)</td>
<td>Global</td>
<td>Patient interview</td>
<td>0–162 points:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caregiver interview</td>
<td>0 = no impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>162 = severe impairment</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory (NPI)</td>
<td>Neuropsychiatric Disturbances</td>
<td>Caregiver interview</td>
<td>The higher the score, the more severe the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>disturbance.</td>
</tr>
<tr>
<td>Progressive Deterioration Scale (PDS)</td>
<td>ADL</td>
<td>Caregiver questionnaire</td>
<td>0–100 points:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 = least impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 = severe impairment</td>
</tr>
</tbody>
</table>

*The cholinesterase inhibitors evaluated in the clinical trials noted are donepezil hydrochloride, galantamine hydrobromide, and rivastigmine tartrate.
†Cognition domain includes variables that test memory, language, orientation, reason, and praxis.
‡For CIBIC-plus, global domain includes variables that test ADL, behavior, cognition, and general psychopathology; for the GBS scale, the global domain includes variables that test ADL, behavior, cognition, and emotional reaction or function.
§ADL indicates activities of daily living. For PDS, the ADL domain tests individuals’ abilities to dress, eat, and perform instrumental tasks (eg, financial, housework, and leisure activities or hobbies); for the DAD scale, the ADL domain tests individuals’ abilities to plan, initiate, and perform these activities.
 Armstrong, D. (2017). The 10-item NPI includes variables that test the frequency and severity of patients’ aberrant motor behavior; agitation; anxiety; apathy; delusions; disinhibition; and dysphoria—euphoria, hallucinations, and irritability—as well as resulting caregiver stress. The 12-item NPI includes aberrant eating and sleeping patterns.
affective disturbances, aggressiveness, anxieties, delusions, diurnal rhythm disturbances, hallucinations, and phobias.

The Neuropsychiatric Inventory (NPI)\textsuperscript{52} is also used for assessing behavioral outcomes of patients with dementia, but this tool was developed to assess a slightly wider range of behaviors than the BEHAVE-AD. The NPI, based on a structured interview with a caregiver that allows the physician to focus on at least 10 areas of psychopathology, is sensitive to behavioral improvements following treatment. Screening questions used in the NPI explore a wide range of psychopathology without expending time on unrewarding avenues of inquiry, which is useful when time is at a premium in the clinical setting. The NPI can be completed in 7 to 10 minutes, although longer interviews will be required for caregivers of patients with extensive psychopathology.

**Alzheimer’s Disease**

Inclusion criteria for clinical trials of patients with mild to moderate AD generally specified that subjects meet the guidelines for a diagnosis of probable AD, as described by the National Institute of Neurological Disorders and Stroke (see http://www.ninds.nih.gov/) and the Alzheimer’s Association (see http://www.alz.org/), formerly the Alzheimer’s Disease and Related Disorders Association.\textsuperscript{58} Several trials also specified that patients meet the guidelines for AD-type dementia, as described in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM–III–R) and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM–IV).\textsuperscript{59,60} The guidelines for Dementia of the Alzheimer’s Type are unchanged from DSM–III–R to DSM–IV.

Patients were also generally required to have an MMSE score between 10 and 26 before they were enrolled as subjects in these studies.

**Donepezil Hydrochloride**—In several 12- to 24-week placebo-controlled trials of patients with mild to moderate probable AD (N = 1759), subjects treated with a daily dose of donepezil, 5 mg to 10 mg, demonstrated statistically significant favorable differences on the ADAS-Cog and CIBIC-plus (Table 2).\textsuperscript{61–63} Unlike subjects in the placebo group, whose ADAS-Cog scores showed increased impairment during the study period, subjects in the donepezil group were able to maintain baseline levels of cognitive performance during the treatment period. In addition, when compared with subjects in the placebo group, nearly twice the number of subjects in the donepezil group had improved CIBIC-plus scores.

Although these studies did not routinely report the effects of donepezil on ADLs, some beneficial effects of donepezil treatment were reported when basic activities were not included in the analysis. Such was the case in one study that administered a daily 10-mg dose of donepezil.\textsuperscript{63}

During single-blind, 6-week placebo washout phases, ADAS-Cog and CIBIC-plus scores in the donepezil group during 24 weeks of double-blind therapy reverted to levels similar to those seen in the placebo group.\textsuperscript{62,64} This observation indicates that 6 months of donepezil therapy has a purely symptomatic effect; there is no clinically relevant effect on the progression of the underlying disease.

Two double-blind, 12-month placebo-controlled trials of donepezil with a target dose of 10 mg daily have been performed in patients with mild to moderate AD (N = 717).\textsuperscript{64,65} The results suggest that the symptomatic benefits of donepezil can extend to 1 year, though withdrawal rates of 33% were observed in the active treatment groups.

Winblad and colleagues\textsuperscript{65} reported a difference in favor of donepezil over placebo with regard to change on the GBS scale. This difference was borderline statistically significant (P = .05) at week 52 (intent-to-treat data from last observation carried forward). In an analysis of observed cases, the difference was statistically significant (P < .05). Overall, GBS scale scores for subjects in the donepezil group showed a decline only half as large as that reported for subjects in the placebo group.

In addition, PDS scores indicated less deterioration at end point in ADL for subjects in the donepezil group when compared with subjects in the placebo group (P < .05). Specific PDS domains for which there were significant treatment differences include memory, telephone use, and self-care activity or ability. Molts and colleagues\textsuperscript{64} reported that the median amount of time to clinically evident functional decline was delayed by 5 months in subjects taking donepezil compared with those receiving placebo.

None of the cholinesterase inhibitors has thus far been formally approved for the treatment of patients with AD in advanced stages. Some promising results, predominantly for cognition, have been obtained in 6-month placebo-controlled trials of donepezil (target dose: 10 mg daily) in outpatients with moderate to severe probable AD (MMSE score [mean], 11.85; N = 290) and in patients with probable AD in a nursing home setting (MMSE score [mean], 14.4; N = 208).\textsuperscript{66} Overall, the subjects included in these trials had more severe dementia than those in the trials previously described.

At 6 months, 63% of outpatients treated with donepezil and 42% of outpatients receiving placebo showed improvement or demonstrated no change in CIBIC-plus scores (P < .001).\textsuperscript{66} With respect to the DAD scale, outpatients treated with donepezil had a decline in their scores of 0.74 points, compared with an 8.98-point decline for placebo recipients (P < .001). Importantly, caregivers of donepezil-treated outpatients with moderate to severe AD reported spending less time assisting subjects with ADLs than caregivers of placebo recipients.

There was a significant 5.64-point between-group difference in favor of donepezil on the NPI at 6 months in the trial of outpatients with moderate to severe AD (P = .005). The effect of treatment as demonstrated in the NPI was most evident in subjects not using psychoactive drugs at baseline.
Although mean changes on the MMSE favored donepezil in nursing home patients, there were no statistically significant advantages of donepezil over placebo on the primary behavioral outcome measure (i.e., NPI–Nursing Home version [NPI-NH]). Although these data suggest that the benefits of donepezil extend into the moderate to severe stages of AD, it remains unclear as to whether the agent truly benefits patients with severe AD, especially in the nursing home setting, where behavioral issues often transcend cognitive ones.

On the basis of the results of double-blind, randomized, placebo-controlled clinical trials in subjects with mild to moderate probable AD, doses of 5 mg to 10 mg of donepezil are approved for once-daily administration.

**Rivastigmine Tartrate**—In two 26-week trials involving patients with mild to moderate probable AD (N=1424), subjects receiving a daily dose of 6 mg to 12 mg rivastigmine demonstrated favorable and significant differences in ADAS-Cog and CIBIC-plus scores when compared with subjects in the placebo group (Table 2).

Doses of rivastigmine in these two trials consisted of a low daily dose that was between 1 mg and 4 mg (mean 3.5–3.6 mg/d) and a high daily dose between 6 mg and 12 mg (mean 9.7–10.4 mg/d). For subjects in the placebo group, ADAS-Cog scores showed a steady increase in impairment; subjects treated with high-dose rivastigmine, however, maintained their baseline levels of cognitive performance. The 4.9-point difference in overall ADAS-Cog score increases in favor of rivastigmine over placebo in this 26-week trial is the largest observed for any of the cholinesterase inhibitors.

Researchers found that improvements in the cognitive performance of subjects with mild to moderate AD receiving rivastigmine were significantly correlated with central inhibition of both AChE and BuChE. Compared with subjects receiving placebo, approximately twice the number of subjects treated with high-dose rivastigmine had improved CIBIC-plus scores, resulting in overall CIBIC-plus score differences in favor of rivastigmine.

In addition, when compared with subjects in the placebo group, subjects receiving high-dose rivastigmine had reduced deterioration in their abilities to perform ADLs, as assessed by caregivers on the PDS. In fact, PDS scores for subjects receiving high-dose rivastigmine remained near baseline throughout the study, whereas PDS scores for placebo recipients steadily decreased (increased impairment) until, at week 26 in one of

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### Table 2

**Effects of Cholinesterase Inhibitors on Patient Scores from Cognitive Scales in Placebo-Controlled Trials Involving Patients with Mild to Moderate Alzheimer’s Disease**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>End Point (wk)</th>
<th>Analysis Type</th>
<th>Daily Dose (mg)</th>
<th>Mean Drug-Placebo Difference at End Point (Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADAS-Cog Score</td>
<td>CIBIC-plus Score</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Score</td>
<td>Score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Donepezil hydrochloride</td>
<td>Rogers et al62</td>
<td>12</td>
<td>ITT-LOCF</td>
<td>5</td>
<td>-1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>-2.3</td>
</tr>
<tr>
<td></td>
<td>Rogers et al61</td>
<td>24</td>
<td>ITT-LOCF</td>
<td>5</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>-2.9</td>
</tr>
<tr>
<td></td>
<td>Burns et al63.0</td>
<td>24</td>
<td>ITT-LOCF</td>
<td>5</td>
<td>-1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>-2.9</td>
</tr>
<tr>
<td>Galantamine hydrobromide</td>
<td>Tariot et al25</td>
<td>21</td>
<td>OC</td>
<td>8</td>
<td>-1.5</td>
</tr>
<tr>
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<td></td>
<td>16</td>
<td>-3.4</td>
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<td>Raskind et al34</td>
<td>26</td>
<td>OC</td>
<td>24</td>
<td>-3.3</td>
</tr>
<tr>
<td></td>
<td>Wilcock et al76</td>
<td>26</td>
<td>OC</td>
<td>24</td>
<td>-4.1</td>
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<tr>
<td></td>
<td>Core-Blom et al67</td>
<td>26</td>
<td>OC</td>
<td>1-4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>6-12</td>
<td>-2.6</td>
</tr>
<tr>
<td></td>
<td>Rosler et al68</td>
<td>26</td>
<td>OC</td>
<td>1-4</td>
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</tr>
<tr>
<td>Rivastigmine tartrate</td>
<td></td>
<td></td>
<td></td>
<td>6-12</td>
<td>-2.6</td>
</tr>
</tbody>
</table>

* Negative mean values indicate favorable differences for the cholinesterase inhibitor over the placebo.
†ITT indicates intent to treat; LOCF, last observation carried forward; NS, not statistically significant; OC, observed cases.
‡ADAS-Cog indicates Alzheimer’s Disease Assessment Scale—Cognitive Subscale.
§CIBIC-plus indicates Clinician’s Interview-Based Impression of Change plus caregiver input.

**P**<.05 versus galantamine, 8 mg.

**P**=.01 versus galantamine, 8 mg.
the studies, the difference in PDS scores between the high-dose rivastigmine and placebo groups reached 4.5 points ($P < .001$). Such a difference would confirm the favorable effect of rivastigmine on overall clinical status, as measured on CIBIC-plus.

Sustained benefits of rivastigmine have been reported over a 1-year period in an open-label extension of the placebo-controlled trial by Corey-Bloom and colleagues. After receiving double-blind placebo or rivastigmine at a daily dose of 1 mg to 4 mg or 6 mg to 12 mg for 26 weeks, subjects were eligible to enter the extension phase of the trial, during which they all received individually optimized doses (between 2 mg and 12 mg per day) of open-label rivastigmine.

The withdrawal rate for subjects treated with rivastigmine (6 mg to 12 mg per day with forced dose titration) during the initial double-blind phase of the study was 35%. For subjects enrolled in the extension phase of the trial, dose titration was more flexible and the rate of withdrawal was reduced to 19%.

A large difference (5.7 points) was seen in ADAS-Cog scores between the treatment group and the placebo group even at 52 weeks, especially relative to the projected 8-point increase in scores (increased impairment) for subjects receiving placebo ($P < .001$). As reflected in ADAS-Cog scores, although impairment advanced in both groups, subjects originally receiving placebo for 6 months did not demonstrate the same amount of benefit (increase of 3.7 points, increased impairment) as subjects treated with effective doses of rivastigmine for the entire 52 weeks (increase of 2.3 points, increased impairment). Such observations suggest the benefits of starting rivastigmine therapy as soon as possible, although these results could also be indicative of a disease-modifying—rather than symptomatic—effect.

There are additional data in support of a potential beneficial residual effect of rivastigmine therapy after the withdrawal of treatment. Subjects involved in pivotal 26-week placebo-controlled trials who discontinued rivastigmine therapy before the end of the study demonstrated less deterioration in cognitive function at week 26 than subjects in the same trials who discontinued placebo. At 26 weeks, pooled analysis of trial data showed that subjects who had been receiving rivastigmine and had been off therapy for a mean of 95 days had a 2.5-point increase (increased impairment) in ADAS-Cog scores from baseline, compared with a 5.69-point increase (increased impairment) in subjects who had been receiving placebo and had been off of sham therapy for a mean of 55 days ($P < .01$). This finding indicates that a persistent benefit was seen with rivastigmine therapy even 3 months after the last dose, suggesting that the medication may have a disease-modifying effect.

Although pivotal trials of rivastigmine measured cognitive and functional changes, reported data have shown that rivastigmine can be beneficial in the treatment of patients with behavioral disorders. A total of 173 nursing home patients with moderate to severe probable AD (MMSE, 9.2 [mean]), the majority of whom exhibited behavioral disturbances, were enrolled in a 6-month open-label trial in which they received a daily dose of rivastigmine, 3 mg to 12 mg. Ninety-eight subjects continued to receive rivastigmine in a 6-month extension of this trial. As measured on the NPI-NH, observed case analysis showed that rivastigmine was associated with improvements in behavioral symptoms (less severe disturbance) at both 26 and 52 weeks, with a mean decrease of 1.6 points (decreased impairment) from baseline at 52 weeks.

In addition, at 52 weeks, approximately 50% of subjects with at least one behavioral disturbance at baseline had an improvement (score decrease) in total NPI-NH score of 30% or better. Analysis of the use of neuroleptic medications revealed a 35% reduction in the use of these agents in subjects who required them at baseline. Cognitive function remained stable in the rivastigmine group at 52 weeks, as evidenced by a minimal mean change in total MMSE score (decline of 0.2 points), whereas in an untreated moderate to severe AD population, one would expect an approximate 3-point decline in MMSE scores over 1 year.

Switching between drugs is widely practiced in therapeutic areas for which multiple treatment options exist, but switching medications has not been routine clinical practice in treating patients with probable AD who fail to respond to, or are unable to tolerate, treatment with a particular cholinesterase inhibitor. A 6-month study involving intent-to-treat data from 366 subjects with mild to moderate probable AD who had failed to benefit from treatment with donepezil (eg, lack of efficacy and/or tolerability issues) has shown that a switch to rivastigmine can be beneficial.

In that 6-month study, 56.2% of subjects responded well to therapy with rivastigmine, which was able to stabilize patients’ conditions or demonstrate improvement (ie, decreased score) on the Clinicians’ Global Impression of Change scale, which measures overall disease severity. A previous lack of efficacy with donepezil was unrelated to rivastigmine’s ability to stabilize or reduce the severity of symptoms associated with AD. Likewise, poor tolerability with donepezil did not predict poor tolerability with rivastigmine.

A retrospective analysis recently reported on the efficacy of rivastigmine in patients with moderately severe AD. Data were pooled from three 6-month randomized, placebo-controlled, double-blind trials. Patients with severe cognitive impairment were identified for study inclusion if they had MMSE scores of 10 to 12. Out of 2126 total potential subjects, 117 patients met the specified criteria and received placebo or daily treatment with rivastigmine, 6 mg to 12 mg.

After 6 months, subjects in the rivastigmine group demonstrated a 0.2-point decrease in mean ADAS-Cog scores (decreased impairment) compared with baseline, whereas subjects in the placebo group had an increase of 6.3 points.
(increased impairment) \( P < .001 \). Clinical improvement was also observed with the MMSE, the PDS, and the BEHAVE-AD. These results suggest that rivastigmine may provide clinical benefit to patients with more moderate and more severe AD.

The recommended daily dosage range for rivastigmine is 6 mg to 12 mg in divided doses.

**Galantamine Hydrobromide**—Several large 5- to 6-month placebo-controlled trials for patients with mild to moderate probable AD (N = 2267) found favorable and significant drug-placebo differences in results of the ADAS-Cog and CIBIC-plus scales for subjects who received a daily dose of galantamine, 16 mg to 24 mg (Table 2).74–76

Although other studies have proven that a higher daily dose of galantamine, 32 mg, is also effective, this higher dosage was no more effective than lower doses and was less well tolerated.\(^74\) Therefore, it is not included in the recommended dosage range presented here.

For subjects treated in a double-blind, placebo-controlled trial comparing three dosing levels of galantamine (8 mg, 16 mg, and 24 mg) against placebo, subjects at the two higher doses showed a difference of less progression of impairment amounting to a 3.9-point difference in the results of ADAS-Cog scores.74–76 In addition, a higher proportion of subjects receiving daily treatment with galantamine, 16 mg or 24 mg, had CIBIC-plus scores that showed “no change” or “minimal deterioration” than did placebo recipients (64% to 70% vs 47% to 55%, respectively).

With respect to changes in subjects’ total DAD scores from baseline, after 6 months, there were no significant differences between subjects receiving galantamine, 24 mg, and those receiving placebo.\(^74\) Tariot and colleagues\(^77\) reported that subjects’ NPI scores showed more severe disturbance relative to baseline at 5 months in placebo recipients \( P < .05 \) vs baseline) but remained close to baseline measures in subjects treated with galantamine at doses of 16 mg or 24 mg per day \( P < .05 \) vs placebo. Results of a 6-month open-label extension of the 6-month placebo-controlled trial by Raskind and colleagues\(^74\) have been briefly described.

After 12 months of therapy, subjects whose dosage of galantamine was set at 24 mg per day had ADAS-Cog scores that remained stable relative to baseline measures. Alternatively, the projected rate of increased impairment, as measured in ADAS-Cog scores, for subjects in the placebo group during this time was an increase of 4 to 5 points. The galantamine group (dosage: 24 mg daily throughout intervention) had better ADAS-Cog outcomes than did subjects who received placebo during the initial 6-month double-blind study period \( P < .05 \). Subjects’ DAD scores were maintained at baseline level in the galantamine group, whereas they declined significantly (increased impairment) over that 12-month period in the group of subjects who initially received placebo \( P < .001 \).

The recommended daily dosage range for galantamine is 16 mg to 24 mg in divided doses.

**Memantine Hydrochloride**—This medication was approved by the US Food and Drug Administration in October 2003 for the treatment of patients with moderate to severe probable AD. A comparison of various characteristics of memantine and the cholinesterase inhibitors is shown in Table 3. Memantine is not a cholinesterase inhibitor; it is an antagonist at the N-methyl-D-aspartate receptor, which is involved in the excitatory glutamatergic neurotransmitter system. Memantine, which is well tolerated, can be used in monotherapy\(^77,78\) or in combination therapy, as an adjunct to a cholinesterase inhibitor.\(^79,80\)

In clinical trials of memantine, subjects’ MMSE scores ranged from 3 to 14 points at baseline. Memantine has proven clinical effectiveness in patients with cognitive impairments. Researchers conducting placebo-controlled trials of memantine have used the Severe Impairment Battery to evaluates subjects’ improved abilities to perform basic cognitive tasks.\(^77,79\)

Memantine has also been shown to reduce deterioration in subjects’ abilities to perform ADLs.\(^77–79,81\)

Finally, in 55% of subjects treated with memantine, evaluations using the CIBIC-plus indicated that their condition showed no change or improved for 6 months, as compared to a rate of 45% for stabilization or improvement for subjects in the placebo group.\(^79\)

The recommended daily dosage range for memantine is 10 mg to 20 mg in divided doses.

**Other Dementias**

None of the cholinesterase inhibitors has been formally approved for patients with any form of dementia other than that associated with AD. It is, however, quite possible that vascular disease and possible LBD contributed to dementia in a high number of patients with probable AD who were involved in pivotal trials of the cholinesterase inhibitors.

Data are now starting to emerge demonstrating that cholinesterase inhibitors have the potential to benefit all patients with dementia, whether they have AD, vascular dementia, LBD, or comorbid pathologies (ie, mixed dementia).\(^82–86\)

In fact, placebo-controlled trials have shown that cholinesterase inhibitors can delay the cognitive decline that would otherwise occur within 6 to 12 months in patients who remain untreated. Because cholinesterase inhibitors can be beneficial in patients with probable AD, vascular dementia, LBD, or comorbid pathologies, and exact diagnosis is frequently uncertain before autopsy, patients may benefit from cholinergic replacement therapy regardless of dementia type. As with cholinesterase inhibitor therapy when used in the treatment of patients with AD, if clinical benefits are not evident after a minimum of 4 to 6 months, physicians may yet find the desired benefits for their patients with vascular dementia, LBD, or comorbid pathologies by prescribing another cholinesterase inhibitor.

**Vascular Dementia**—When patients present with disease characteristics that are more consistent with vascular dementia characteristics that are more consistent with vascular dementia...
dementia, rivastigmine (target dose: 6 mg daily) in a controlled study involving 208 subjects was able to stabilize or lessen other symptoms typical of this disorder, including faltering executive function and behavioral problems.84 During the 12-month study period, deterioration in subjects’ MMSE scores was greater in subjects randomized to aspirin (decline of 3.94 points) than in subjects receiving rivastigmine (decline of 2.54 points). Executive function, as assessed using the Ten-Point Clock Drawing test, deteriorated to a significantly greater extent in subjects receiving aspirin than in those treated with rivastigmine (P < .05). There was a 16.37-point improvement in

<table>
<thead>
<tr>
<th>Medication</th>
<th>Doses Available</th>
<th>Dosing Recommendations</th>
<th>Titration</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil hydrochloride</td>
<td>Tablets, mg:</td>
<td>Once daily at night,</td>
<td>Starting dosage of 5 mg daily for 4 to 6 weeks before increasing dose to 10 mg daily.</td>
<td>Anorexia, Diarrhea, Dreams (vivid), Fatigue, Insomnia, Muscle cramps, Nausea, Vomiting, Weight loss</td>
</tr>
<tr>
<td>(Aricept)</td>
<td>5, 10</td>
<td>before bed. Can be taken with or without food.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine hydrobromide (Reminyl)</td>
<td>Tablets, mg:</td>
<td>Twice daily in morning and evening with full meals.</td>
<td>Starting dose is 4 mg twice daily. Increase dose to 8 mg or 12 mg twice daily, as tolerated, after a minimum of 4 weeks of treatment at the lower dose.</td>
<td>Anorexia, Diarrhea, Nausea, Vomiting, Weight loss</td>
</tr>
<tr>
<td>(4, 8, 12)</td>
<td>Oral solution:</td>
<td>4 mg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivastigmine tartrate</td>
<td>Capsules, mg:</td>
<td>Twice daily in divided doses* in morning and evening with full meals.†</td>
<td>Starting dose is 1.5 mg daily. Most researchers agree that the dose may be increased to 3 mg twice daily after 4 weeks of treatment. Thereafter, at 4-week intervals, the dose may be increased to 4.5 mg and 6 mg twice daily.</td>
<td>Anorexia, Nausea, Vomiting, Weight loss</td>
</tr>
<tr>
<td>(Exelon)</td>
<td>1.5, 3, 4.5, 6</td>
<td>Oral solution: 2 mg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine hydrochloride</td>
<td>Tablets, mg:</td>
<td>Twice daily in divided doses.* Can be taken with or without food.</td>
<td>Starting dose is 5 mg four times daily. Dose increases should be in 5-mg increments after a minimum of 1 week of treatment.</td>
<td>Agitation, Constipation, Dizziness, Hallucinations, Headache, Insomnia</td>
</tr>
<tr>
<td>(Namenda)‡</td>
<td>5, 10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Divided doses indicates that, for example, a daily dose of 10 mg can be divided into two daily doses of 5 mg each. Similarly, a daily dose of 15 mg can be divided into three daily doses of 5 mg each.
† Patient tolerance of rivastigmine is improved if it is taken with full meal (eg, breakfast and dinner).
‡ Memantine is not a cholinesterase inhibitor as are the other agents listed in this table. Memantine is an antagonist at the N-methyl-D-aspartate receptor, which is involved in the excitatory glutamatergic neurotransmitter system. Memantine can be used as an adjunct to cholinesterase inhibitors or alone.
BEHAVE-AD total scores in the rivastigmine group \((P<.01\) vs. baseline), as opposed to a 1.44-point deterioration in the aspirin treatment group \((P<.01\), between-group difference). Apart from the continued presence of one symptom, delusions, all individual BEHAVE-AD items were significantly improved from baseline measures in subjects treated with rivastigmine.

- **Dementia with Lewy Bodies**—The results of a randomized, double-blind, placebo-controlled trial of rivastigmine (target dose: 6 mg to 12 mg daily) in 120 subjects with a prospective diagnosis of probable LBD have suggested that cholinesterase inhibitors could be a rational treatment choice for amelioration of behavioral manifestations of disease in such patients.\(^{85}\)

  The main Lewy body behavior cluster in the patient sample predictably consisted of apathy, delusions, depression, and hallucinations. Over the 20-week study period, rivastigmine had a significant beneficial impact on subjects’ behavior (less severe disturbance), as evidenced by a 6.4-point difference between groups on the 10-item NPI score favoring rivastigmine over placebo in an analysis of observed cases \((P=.005)\).

  Specifically, patients treated with rivastigmine were less anxious and apathetic, had fewer delusions and hallucinations, and had less aberrant motor behavior than those receiving placebo. Change in subjects’ MMSE scores favored rivastigmine, with a 1.5-point improvement in rivastigmine recipients contrasting with a 0.1-point decline in placebo recipients \((0.05 < P < .1)\). There are no published data from equivalent large, randomized, placebo-controlled studies of galantamine or donepezil in patients with LBD.

- **Mixed Dementia**—Subgroup analyses of results from the 6-month trial by Corey-Bloom and colleagues\(^ {67}\) indicate that high-dose rivastigmine has beneficial effects in patients with AD, regardless of the presence of vascular risk factors.\(^ {67}\) In fact, the effect size was largest in patients with vascular risk factors when subjects in the treatment group were compared with subjects in the placebo group; there was a 6.15-point treatment difference on ADAS-Cog scores for subjects with vascular risk factors and a 4.03-point treatment difference for subjects without vascular risk factors.

  Significant beneficial effects of galantamine (target dose: 24 mg daily) on ADL, behavior, cognition, and global function were observed in a 6-month randomized, double-blind, placebo-controlled trial involving 592 patients with a prospective diagnosis of probable vascular dementia or possible AD with concurrent cerebrovascular disease.\(^ {68}\) Compared with subjects in the placebo group, subjects treated with galantamine demonstrated a 2.7-point beneficial treatment effect (decrease) on the ADAS-Cog scale \((P<.001)\), a 4.6-point benefit on the DAD scale \((P<.005)\), and a 2.2-point benefit on the NPI \((P<.05)\). A high proportion of galantamine recipients showed no change or showed improvement on the CIBIC-plus scale \((74\%\ vs 59\%\ of placebo recipients; \(P=.001)\).

## Adverse Effects of Cholinesterase Inhibitors

Although clinical trials have shown that all commonly used cholinesterase inhibitors are safe and are generally well tolerated, cholinesterase inhibitors can also increase ACh levels throughout the body, putting patients at risk of cholinergic adverse effects.

The most severe adverse effects occur when patients are administered higher doses of cholinesterase inhibitors, when patients have low body weight, and during upward dose titration. Forced weekly titration schedules were generally used in placebo-controlled trials of cholinesterase inhibitors in patients with mild to moderate AD, but practical experience has shown that slow-dose titration can minimize the impact of adverse effects.\(^ {89}\)

Although adverse effects often resolve after 1 to 3 weeks, it is important that clinicians prescribing cholinesterase inhibitors take the following specific precautions to ensure that patients will be well monitored and that any adverse effects they experience will be minimal:

- **Donepezil**—Daily treatment with 10 mg should not be initiated until patients have been on 5 mg dosing for 4 to 6 weeks.

- **Rivastigmine**—Therapy should begin at 3 mg per day for 4 weeks, and then increase stepwise to 6 mg daily. Higher doses of 9 mg or 12 mg per day are recommended after at least 4 weeks of well-tolerated treatment at the previous dosing levels. Not all patients need to achieve the maximum recommended dosing of 12 mg daily.

- **Galantamine**—Therapy should be increased to the initial 16 mg daily maintenance level only after 4 weeks of well-tolerated therapy at the 8 mg per day starting dose. A further increase to 24 mg per day should only be attempted after at least 4 weeks of well-tolerated treatment at the 16 mg per day dosing level.

  In general, if treatment with rivastigmine or galantamine is interrupted for several days or longer, dosing should be reinitiated with the lowest daily dose and the titration process repeated. Rivastigmine and galantamine should be taken in the morning and the evening with meals. Donepezil can be administered in the morning or evening with or without food. Provision of meals to patients at regular times should be part of a holistic AD treatment regimen. Routine administration of cholinesterase inhibitors in conjunction with meals should help ensure patient compliance and tolerability.

Acetylcholinesterase enhances gastrointestinal motility, which may lead to diarrhea. Central cholinesterase inhibition can lead to nausea and vomiting. Such adverse events are common to all of the cholinesterase inhibitors, however. Clinical trials have consistently shown higher rates of gastrointestinal adverse effects in subjects treated with rivastigmine, donepezil, and galantamine than in subjects receiving placebo.\(^ {61–63,67,74–76}\) Package inserts for galantamine, rivastigmine, and donepezil all warn that cholinesterase inhibitors are associated with gastrointestinal events; however, these
events typically resolve with continued use of the agents. Although gastrointestinal events were generally of mild to moderate severity in patients receiving 6 mg to 12 mg of rivastigmine daily in placebo-controlled trials, such events occurred relatively frequently, particularly during forced weekly dose titration.\textsuperscript{67,68} Although similar patterns were observed with forced titration schedules for galantamine and donepezil, it has been proposed that slow-dose escalation (ie, at 4-week intervals) and delayed absorption by administration with food may be particularly important with rivastigmine, as its pharmacologic properties may lead to relatively potent and fast elevation of ACh levels.\textsuperscript{90}

Cardiovascular adverse effects, such as a bradycardia, can occur in association with cholinesterase inhibitors. This can be particularly problematic for patients with underlying supraventricular cardiac conduction disorders such as sick sinus syndrome. In support of this hypothesis, selective central cholinesterase inhibition may be associated with reduced probability of peripheral cholinergic adverse events.\textsuperscript{91}

For example, a pooled analysis of placebo-controlled trial data showed that rivastigmine, 6 mg to 12 mg per day, was not associated with a significantly increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or any abnormalities in the results of electrocardiograms, including vagal effects.\textsuperscript{92} Neither bradycardia nor syncopal episodes were reported as adverse events in placebo-controlled trials of rivastigmine or galantamine in patients with AD.\textsuperscript{67,68,74-76} Prescribing information acknowledges that, in placebo-controlled trials, syncopal episodes have been reported in 1% to 2% of placebo recipients and in 2% to 3% of subjects receiving rivastigmine, 6 mg to 12 mg per day, or galantamine, 24 mg per day. Placebo-controlled trials with donepezil have reported bradycardia or syncpe as adverse events in association with 1% to 3% of subjects receiving donepezil and up to 2% of placebo recipients. Prescribing information warns that syncopal episodes have been reported in association with the use of donepezil.

Neuromuscular adverse events, such as muscle cramps, can occur as a result of excessive stimulation of nicotinic receptors at the motor endplate. It has been suggested that selective inhibition of the G1 form of AChE, which is not prevalent in skeletal muscle, may decrease the risk of muscle cramps or weakness.\textsuperscript{32} In pivotal trials, the incidence of muscle cramps was reported as rare in association with high-dose rivastigmine or galantamine and no different from that reported for placebo.\textsuperscript{67,68,74-76} In their pivotal placebo-controlled trial, Rogers and colleagues\textsuperscript{61} reported muscle cramps in significantly more subjects treated with donepezil, 10 mg per day, than in placebo recipients (8% vs 1% of subjects, respectively; \(P<.05\)).

Insomnia has been reported in association with donepezil in placebo-controlled trials.\textsuperscript{89} If donepezil is administered before retiring, peak plasma concentrations will occur during sleeping hours.\textsuperscript{52} Therefore, morning administration may eliminate sleep disturbances.\textsuperscript{32}

The potential risk of adverse events occurring as a result of pharmacokinetic drug interactions is relevant to a high proportion of elderly patients with dementia who are likely to require multiple medications for comorbid conditions. Galantamine and donepezil are metabolized by hepatic cytochrome P450 isoenzymes whereas rivastigmine is primarily hydrolyzed by brain esterases.\textsuperscript{93} Therefore, there is a theoretical risk of clinically significant interactions between donepezil or galantamine and other drugs known to inhibit P450 isoenzymes CYP2D6 and CYP3A4.

In particular, donepezil is highly protein bound, which may lead to complications if it is administered in conjunction with other drugs that are also highly protein bound (eg, digoxin, theophylline, warfarin sodium). Such interactions may not be recognized in generalized placebo-controlled trials, however.

It is relatively unlikely that clinically significant drug interactions involving rivastigmine will be found. In fact, in one study, when rivastigmine was administered to patients receiving concomitant medications (22 therapeutic classes in the overall study population) for common comorbidities, there was no evidence of drug interactions.\textsuperscript{94}

**Comment**

Large placebo-controlled trials studying the effectiveness of cholinesterase inhibitors have shown that patients with mild to moderate AD can have an improvement in cognitive and global function—or a stabilization or reduction in the rate of decline of those functions—with this treatment modality, prolonging patients’ abilities to perform ADLs. Placebo-controlled trials have shown that cholinesterase inhibitors can delay by approximately 6 to 12 months the cognitive decline that would otherwise occur in patients with AD that are untreated.

Another benefit of this treatment modality for patients with AD may include reduced demands on caregiver time and delayed nursing home placement.\textsuperscript{95}

The decision of whether to titrate cholinesterase inhibitors to the highest recommended dosage is a matter of clinician preference, patient response to therapy, and tolerability. As long as dosage is titrated carefully, maintenance therapy with rivastigmine, donepezil, or galantamine is generally well tolerated. Although cholinesterase inhibitors are formally approved for use only in patients with mild to moderate probable AD, evidence is emerging that this drug class may also prove beneficial in later stages of the disease, as well as in patients with signs of vascular dementia or LBD. There is also some evidence that cholinesterase inhibitors can have a stabilizing effect on neuropsychiatric symptoms associated with dementia.

On a practical level, the advent of cholinesterase inhibitors means that the symptoms of AD are now treatable. Furthermore, it is recommended that treatment with galantamine, rivastigmine, or donepezil be offered and initiated as early as
possible for all patients with probable AD. If treatment is well tolerated, it should be continued for as long as there is no clear evidence of unchecked progression of dementia—as indicated by physician global assessment and caregiver reports at 2- to 6-month intervals.

It is important, however, that caregivers understand that patients are unlikely to regain lost functions, that “no change” is a positive outcome when treating patients for AD, and that discontinuation of some cholinesterase inhibitor therapies may be associated with irreversible cognitive decline.

Differences in the pharmacologic profiles of rivastigmine, donepezil, and galantamine suggest that, when treatment with a particular cholinesterase inhibitor is perceived to be ineffective or poorly tolerated, a patient may benefit from another drug in this class. In particular, rivastigmine (which inhibits both AChe and BuChE) represents an attractive treatment option for patients with dementia who have failed to receive sustained benefit from an AChe-specific inhibitor. Cholinesterase inhibitor therapy should not, therefore, be forsaken when an initial treatment choice fails, as switching therapy can lead to longer treatment duration and extended symptomatic benefits. Only long-term, head-to-head comparative trials will establish whether pharmacologic differences between donepezil, galantamine, and rivastigmine have clinically relevant differences in efficacy. Such studies have been initiated and results are forthcoming.96

References


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