ABSTRACT

We currently use 4 drugs approved by the US Food and Drug Administration to treat Alzheimer’s disease (AD; donepezil, galantamine, rivastigmine, and memantine), and many other drugs are in clinical and preclinical trials. The currently available drugs act by treating the symptoms of AD (namely memory loss and cognitive functioning), but they do not appear to affect the disease process, thus they can only slow the course of the disease—not reverse it—and only while they are being taken. Newer drugs not only target other aspects of AD pathology but also may prevent AD. This article provides an overview of the 4 currently used drugs with regard to dosing, drug-drug interactions, adverse events, and expected outcomes. Other uses for these drugs (eg, in other stages and forms of dementia) and ongoing clinical studies with new agents are also discussed. Despite their limitations, donepezil, galantamine, rivastigmine, and memantine are important components of standard care for patients with AD. For the pharmacist, the key is to use these drugs optimally (ie, minimizing adverse events, avoiding drug-drug interactions, and educating caregivers on realistic expectations).

**Table 1. Drugs Approved for the Treatment of Alzheimer’s Disease**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Doses</th>
<th>Major AEs</th>
<th>Major Drug-Drug Interactions*</th>
<th>Usual Dosing</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Donepezil</td>
<td>Film-coated tablets or orally dissolving tablets (ODT): 5 mg, 10 mg</td>
<td>Nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue, and anorexia</td>
<td>Inducers of CYP 2D6 and CYP 3A4 (eg, phenytoin, carbamazepine, dexamethasone, rifampin, ketoconazole, quinidine, and phenobarbital) could increase the rate of elimination of donepezil. Monitor for occult or active GI bleeding when coadministered with NSAIDs.</td>
<td>5 mg for 4–6 weeks, then increase to 10 mg if appropriate. Min: 5 mg/day. Max: 10 mg/day</td>
<td>Should be taken in the evening, just prior to retiring. Can be taken with or without food. Allow ODT to dissolve on the tongue and follow with water.</td>
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<tr>
<td>Rivastigmine</td>
<td>Capsules: 1.5, 3, 4.5, 6 mg Oral solution: 2 mg/mL</td>
<td>Nausea, vomiting, loss of appetite, dyspepsia, asthenia, and weight loss</td>
<td>None observed</td>
<td>1.5 mg twice daily (3 mg/day), increase to 3, 4.5, and 6 mg twice daily at 2- to 4-week intervals. Min: 3 mg twice daily (6 mg/day). Max: 6 mg twice daily (12 mg/day).</td>
<td>Twice daily; take with food AM and PM.</td>
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<tr>
<td>Galantamine</td>
<td>Tablets: 4, 8, 12 mg Oral solution: 4 mg/mL ER capsules: 8, 16, and 24 mg</td>
<td>Nausea, vomiting, and weight decrease</td>
<td>Clearance is approximately 20% lower in females versus males. Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine (eg, ketoconazole and erythromycin). Inducers of CYP3A4 or CYP2D6 (eg, carbamazepine and oxcarbazepine) could reduce the effectiveness of galantamine.</td>
<td>Galantamine: Use twice-daily dosing. Galantamine ER: Use every day dosing. Begin at 8 mg/day; increasing at 4-week intervals to 16 and then 24 mg/day. Min: 16 mg/day Max: 24 mg/day. Maximum dose of 16 mg/day for patients with significant hepatic and renal disease.</td>
<td>Galantamine: Twice daily; take with food AM or PM with adequate fluid intake. Galantamine ER: Take with food, AM, once daily.</td>
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<tr>
<td>Memantine</td>
<td>Tablets: 5 and 10 mg Oral solution: 2 mg/mL.</td>
<td>Confusion, dizziness, headache, and constipation</td>
<td>Drugs/diet that alkalize the urine (eg, carbonic anhydride inhibitors and sodium bicarbonate) would be expected to reduce renal elimination of memantine. Drugs eliminated by tubular secretion (eg, HCTZ, cimetidine, and ranitidine) can affect plasma levels of both agents. Aminopyrine, Demerol, and dextromethorphan should be used with caution.</td>
<td>5 mg/day Increase to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), 20 mg/day (10 mg twice daily). Minimum recommended interval between dose increases is 1 week. Min: unknown Max: 20 mg/day. Maximum dose of 5 mg twice daily for patients with renal clearance of &lt;30 mL/min.</td>
<td>Can be taken with or without food.</td>
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</table>

*Note that coadministration with anticholinergic agents will decrease the effect of cholinesterase inhibitors. AEs = adverse events; AUC = area under the curve; ER = extended release; GI = gastrointestinal; HCTZ = hydrochlorothiazide; NSAID = nonsteroidal anti-inflammatory drug.
the other hand, in clinical trials had an adverse event profile similar to or even better than placebo.1

Drug-drug interactions are another important consideration, especially because patients with AD are elderly and thus much more likely to be taking several other medications. In AD, antipsychotics may be used to treat some of the behavioral symptoms of AD (e.g., hallucinations, delusions, depression, euphoria, agitation, aggression, abnormal vocalizations, wandering, overactivity, sexual disinhibition, sleep disturbances, and apathy).2,5 Concomitant use of atypical antipsychotics and ChEIs has been linked to parkinsonian symptoms.2,4,5 Galantamine drug interactions have been noted with drugs that affect CYP2D6 and CYP3A4 metabolism, notably erythromycin, ketoconazole, and paroxetine, with observed increases in galantamine bioavailability of 10%, 30%, and 40%, respectively.2,6 CYP interactions appear to be less of a concern with donepezil, even though it is metabolized by the same CYP enzyme isoenzymes. Drug interactions with rivastigmine and memantine are not common, as the former is not metabolized by the CYP enzymes and the latter remains unchanged by metabolic processes.2

Despite a relatively strong track record since their approval, there remain several issues surrounding the use of these 4 drugs, including efficacy, cost effectiveness, use in other forms of dementia, use in other stages of AD, and use in addressing the behavioral symptoms of AD. To address some of these issues, an expert panel (in which I participated) devised recommendations for the treatment and management of dementia based on both published scientific evidence and the panel’s informed expert opinion. Our panel constructed 20 recommendations, outlined in Table 2. Some of those recommendations are discussed here, although the reader is encouraged to read the full set of recommendations.

TREATMENT CHOICE BY DISEASE STAGE

The 4 approved drugs for AD are indicated for specific stages of the disease, yet these stages are somewhat arbitrarily defined, usually by a score on the Mini-Mental State Examination (MMSE), which can be affected by numerous factors, including the patient’s educational level. Furthermore, as AD progresses, there are no clear milestones marking the move from one stage to the next, so physician judgment on the severity of AD in each individual patient is critical. These discussions become important not only regarding off-label use but also in formulary decisions. The decision on which ChEI to use is often based primarily on dosing issues, but also on safety, as their efficacy and tolerability are considered to be clinically equivalent. Donepezil is the only ChEI that does not require dose titration. The other safety consideration is drug-drug interactions. Also, as reviewed by Manju T. Beier, PharmD, FASCP, in this monograph, vascular dementia is a prominent component of mixed dementia and controlled clinical trials have shown benefit with galantamine and memantine in vascular dementia.8-10

EXPECTED CLINICAL BENEFIT

One of the other challenges is defining the expected clinical benefit with our currently available drugs, especially when the drugs only slow or defer disease progression. Clinical researchers have gone to great lengths to quantify the cognitive changes in AD and with AD drugs through many validated assessment tools.

Our panel acknowledged the challenges of determining clinical response outside of a clinical trial, and suggested that “an ‘effective’ response to antidementia therapy occurs when symptoms improve or remain the same for 6 months on a maximum dose, in the clinical judgment of the physician and/or caregiver; a ‘good’ response...occurs when the patient’s symptoms progress more slowly than expected without therapy; and ‘poor’ response occurs when the patient’s symptoms are progressing at a rate that is consistent with no therapy.” On average, when left untreated, dementia patients lose approximately 2 to 4 points per year on the MMSE and experience some decline in functional ability.11

One of the criticisms of the value of AD drugs (especially the ChEIs) has been that the benefits seen in clinical trials are modest.12 Indeed, the United Kingdom has been grappling with the issue of covering these drugs in their national healthcare system. Tariot has provided a discussion on the tangible benefits with these drugs.2 Several studies have shown that use of these drugs can reduce the amount of time caregivers must spend with patients with AD by 32 to 104 min/day.13-15

When considering the tangible benefits of these drugs, it is also important to consider their effect on daily functioning. All 4 drugs have shown significant benefit in primary outcome measures of function (basic activities of daily living [ADLs], instrumental ADLs, leisure activities, and initiation/planning/organization), in addition to secondary outcome measures.16-24 This also holds true for the recent study of combination therapy with memantine and donepezil, with statistically significant
benefits in grooming, toileting, conversing, watching television, and being left alone, when the individual outcome items were analyzed.\textsuperscript{25}

In short, the use of antidementia drugs, as recommended by our expert panel should be continued unless there is a rapid and unexpected deterioration not due to reversible causes or discontinuation is required briefly due to hospitalization. Otherwise, patients and caregivers should be counseled with regard to realistic expectations of antidementia pharmacologic treatment. Extra time for the caregiver, or the retention of basic ADLs by the patient, not only eases caregiver burden but also allows the patient the dignity of maintaining as much of their independence for as long as possible.

\begin{table}
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\caption{Summary of Recommendations for Best Practices in the Treatment of Alzheimer’s Disease in Managed Care}
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1. Early detection and diagnosis of Alzheimer’s disease (AD) and other dementias is critical to achieve optimal quality of care  
2. Screening for cognitive impairment should be conducted, especially for individuals 75 years or older  
   - Managed care organizations (MCOs) should use brief telephonic screening in medical management programs  
   - Age-dependent, office-based screening for cognitive impairment  
   - All elderly individuals with a memory complaint (clinical practice and MCO management programs) should be screened for cognitive impairment and evaluated for dementia  
3. When cognitive impairment is detected, a structured approach to diagnosis should be employed. The assessment of individuals with dementia should include an evaluation of cognition, function, and behavior  
4. Neuroimaging should be conducted as part of a complete diagnostic assessment except when the initial presentation indicates a typical course of progression and an advanced stage of disease  
5. Treatment of AD should be determined by the stage at the time of diagnosis  
   - First diagnosis, mild AD: treat with a cholinesterase inhibitor (ChEI)  
   - First diagnosis, moderate AD: treat with a combination of a ChEI and memantine. For those who progress from mild to moderate AD, memantine should be added to ChEI therapy  
   - First diagnosis, severe AD: treat with memantine. Combination with a ChEI can be added  
6. Monotherapy with memantine may be used at the mild stage of AD when a ChEI is not tolerated or in combination with a ChEI when the disease is progressing rapidly  
7. All patients should receive the same course of treatment, regardless of the care setting  
8. Patients with mixed dementia (AD + vascular dementia), pure vascular dementia, dementia with Lewy bodies, and Parkinson’s dementia may be treated according to these AD guidelines  
9. Patients with frontotemporal dementia should be referred to a specialist  
10. The use of other medications to treat dementia (eg, hormones, nutraceuticals, and vitamins) is not recommended  
11. Newly diagnosed patients should be re-evaluated within 2 months, and then monitored every 6 months thereafter to ensure appropriate treatment and care management  
12. Patients and caregivers should be counseled with regard to “realistic” expectations of antidementia pharmacologic treatment  
13. If a patient deteriorates on antidementia therapy at an unexpectedly rapid rate, potentially reversible causes of cognitive and/or functional impairment (eg, medical comorbidities, effects of other drugs, behavioral disturbances, and delirium) should be considered  
14. ChEI and memantine may be discontinued in patients who advance to “profound” disease and who have lost all cognitive and functional abilities  
15. Antidementia therapy should be continued during acute illness and hospitalizations, unless contraindicated. If stopped, it should be resumed as quickly as possible  
16. Antidementia drugs are well tolerated in patients with medical comorbidities. However, appropriate adjustments must be made for patients with renal or hepatic failure  
17. Geriatric care management and counseling should be provided to all patients with a diagnosis of AD and to their caregivers  
18. ChEI and memantine should be distinguished as 2 separate classes of drugs under Medicare Part D formulary guidelines, as patients need access to both  
19. Antidementia therapy should be accessible as a preferred formulary product to reduce the out-of-pocket cost to patients and encourage appropriate use  
20. Medicare MCOs should not discriminate against use of antidementia therapy through administrative burdens, such as preauthorization and appeals \\
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\textsuperscript{Shaded recommendations refer to drug therapy for AD and are discussed in this article.}
\textsuperscript{Data from Fillit et al.}
**ONGOING CLINICAL TRIALS OF APPROVED DRUGS**

As of this writing, there are 140 studies on www.clinicaltrials.gov regarding AD, including studies of neuroimaging, caregiver interventions, patient and caregiver education, and treatment of depression in dementia patients. Donepezil is also being studied regarding psychotic symptoms of dementia patients, hippocampus structure, regional brain volume, and functional brain imaging in mild AD, in addition to adjunctive therapy with vitamin E and memantine in mild to moderate AD, and as add-on therapy to PRX-03140 in mild AD and to antidepressant medication. Donepezil is also being studied in patients with APOE gene polymorphisms. It should be noted that donepezil has shown benefit in a 6-month, randomized, controlled trial when given in conjunction with memantine in patients with moderate to severe AD. Galantamine is being studied for attention and frontal lobe function in AD, use in severe AD, functional brain imaging in mild AD, and executive function in Parkinson’s dementia. Rivastigmine is under evaluation as a transdermal patch in mild to moderate AD and as add-on therapy to memantine in those with probable AD. Finally, memantine is being studied for treatment of agitation and aggression in severe AD, volumetric changes measured by magnetic resonance imaging and cognition in moderate AD, as add-on therapy to rivastigmine, in women at risk for cognitive decline, in frontotemporal dementia, Parkinson’s disease and dementia, and for measures of brain structure and chemistry.

**NEW DRUGS FOR ALZHEIMER’S DISEASE**

As outlined in Table 3, there are more than 20 different therapeutic targets for AD, but only a few of these are currently in phase III clinical trials. For example, Neurochem is studying an agent that inhibits Aβ aggregation by binding Aβ monomers to a small molecule, thought to be a proteoglycan mimic. The phase III study expects a total enrollment of 930 patients in Europe and compares 2 different doses of the drug to placebo. The agent is known as tramiprosate (Alzhemed, Neurochem, Inc., Laval, Quebec, Canada), or 3-amino-1-propanesulfonic acid.

Myriad Pharmaceuticals is conducting a global efficacy study of its compound, MPC-7869 (R-flurbiprofen), one component of the racemic mixture of flurbiprofen, currently used as a nonsteroidal anti-inflammatory drug. R-flurbiprofen appears to modulate the activity of γ-secretase in in vitro studies, and a phase II study in patients with mild AD showed decreased rate of decline in cognitive function but no notable improvement in those with moderate AD. In the current phase III study, expected total enrollment is 800 and the primary outcomes will measure cognition and ADLs, with secondary outcome measures of global function and cognition. There is also an open-label study for those who previously participated in a MPC-7869 protocol, in which the primary outcome was safety.

Sanofi-aventis is evaluating AVE1625, a selective antagonist of cannabinoid receptors, in phase I and II studies (expected total enrollment of 150). The primary outcomes are safety and tolerability in addition to measures of change in cognition, global functioning, and behavior at week 12.

**VACCINES**

The first studies of immunization with an Aβ peptide were stopped early because some of the study patients suffered brain inflammation. However, 2 new vaccines are showing some promise. First, Elan is testing passive immunization using antibodies specific for diff-
fferent Aβ species (Aβ40, Aβ42, and truncated Aβ) and preliminary results from 3 patients show evidence of clearance of these species. Studies of a DNA vaccine in mice, which uses DNA encoding for Aβ, also show good results in a mouse model of AD.

**CONCLUSIONS**

Donepezil, galantamine, rivastigmine, and memantine are important components of standard care for patients with AD. They improve cognition and function for patients with AD and reduce caregiver burden. Moreover, we are gaining a greater understanding of how they can be used in different stages of AD and in other forms of dementia. For the pharmacist, the key is to use these drugs optimally (ie, minimizing adverse events, avoiding drug-drug interactions, and educating caregivers on realistic expectations).

**REFERENCES**