

## Pharmacologic Treatment of Alzheimer's Disease

In this module, learn about:

- Recommended use of Cholinesterase Inhibitors (ChEIs) and memantine for Alzheimer's disease
- Research findings for these treatments agents
- Common side effects
- Comparison of ChEIs
- Other treatment agents, including supplements
- When to discontinue pharmacologic treatment

No pharmacologic treatments currently available for Alzheimer's disease offer a "cure" for the disease. However, early diagnosis and initiation of ChEIs offer the best possible long-term management the disease. Current treatments may slow the rate of decline and stabilize function or behavior. For *some* patients (less than one-third in most studies) treatment may actually improve function over the short-term. In addition, growing evidence suggests that targeted dementia treatment may offer the most effective management as well as prevent the emergence of difficult behavioral problems – the aspect of Alzheimer's that is commonly the most challenging and stressful for caregivers. This module summarizes current knowledge of the therapeutic value of cholinesterase inhibitors, memantine, and other treatment agents that have been studied.

### CHOLINESTERASE INHIBITORS (ChEIs)

ChEIs inhibit degradation of acetylcholinesterase (the enzyme that breaks acetylcholine) within synapses that involve cholinergic neurons thereby augmenting cholinergic function in the brain. Acetylcholine is an important neurotransmitter involved in learning and memory. Four ChEIs are currently available:

- **Donepezil** (Aricept) is started at 5 mg QD. After 4-6 weeks, it may be increased to 10 mg QD. By convention, donepezil is given at HS. Some physicians prefer AM dosing, especially if vivid dreams or nightmares are a problem side effect.
- **Rivastigmine** (Exelon) has a starting dose of 1.5 mg BID. Increased dosage should be tried only after a minimum of two weeks – many

experts recommend four week intervals. It comes in 1.5, 3, 4.5, and 6 mg capsules, so titration can be quite slow when needed. It is recommended that it be taken with food to slow down the rate of absorption to decrease the GI side effects. The lowest effective dose is 3 mg BID, and the maximum dose is 6 mg BID. There is a good possibility that an Exelon patch may be available towards the end of 2007.

- **Galantamine** (Razadyne -- renamed from Reminyl because of confusion with "Amaryl") has a starting dose of 4 mg BID, which can be increased to the minimum effective dose of 8 mg BID after a minimum of 4 weeks. A further increase to 12 mg BID should be attempted after another four weeks, if the patient is tolerating the medication. For renal insufficiency, the maximum dose should be kept at 16 mg/day. Galantamine is also available in an extended release form (Razadyne ER) that can be dosed once a day. It is recommended that Razadyne be taken with food.
- **Tacrine** (Cognex) is rarely used because of its high GI side effects and significant hepatotoxicity. Tacrine is not suitable for use by most primary care physicians, and has very limited use even in the hands of dementia specialists.

### Common Side Effects of ChEIs

It is worth noting that even the "common" side effects of ChEIs are relatively infrequent, but are seen most often during the titration periods. ChEIs are overall well tolerated, especially when a slow approach to dose titration is used. Specialists in dementia report quite low rates of discontinuation of ChEIs because of side effects in clinical practice. Adverse effects may be gastrointestinal, cardiovascular, neuromuscular, or related to the central nervous system:

**Gastrointestinal:** Nausea, vomiting, diarrhea or abdominal pain may result in anorexia and weight loss.

**Cardiovascular:** Bradycardia, tremor or dizziness may result in asthenia and fatigue.

**Neuromuscular:** Muscle cramps and weakness may result in falls.

**Central Nervous System:** Insomnia, nightmares, agitation or a panic-like state.

Adverse event profiles reported in the Physicians' Desk Reference suggest the most frequent side effect is nausea. Vomiting and diarrhea were reported more frequently than anorexia, dizziness or fatigue.

Other side possible side effects are:

- Sleep disturbances, including insomnia and vivid dreams/nightmares
- Muscle cramps, fatigue, syncope
- Worsening of peptic ulcer disease

We should use caution giving any cholinesterase inhibitor to patients with severe asthma or COPD as these drugs can cause bronchoconstriction. Close monitoring of the pulmonary condition will keep serious problems from developing in most patients. These pulmonary problems are NOT absolute contraindications to the use of ChEIs – we need to consider the potential benefits as well as the possible risks. Symptomatic bradycardia is a possible side effect, especially when combined with digoxin or calcium channel blockers that also slow the conduction through the AV node.

⌘ With slow dosage titration, ChEIs are generally well tolerated.

### Comparing the Three Commonly Prescribed ChEIs

A meta analysis (Ritchie 2004) of many of the trials done comparing the three commonly prescribed ChEIs found that all three drugs showed beneficial effects on cognitive tests, as compared with placebo. For donepezil and rivastigmine, larger doses were associated with larger effect. This was not the case with galantamine. The odds of clinical global improvement demonstrated superiority over placebo for each drug, with no dose effects noted. Dropout rates were greater with galantamine and rivastigmine. There was little difference in dropout rate for each drug at each dose-level, except with high-dose donepezil. In summary, all three drugs had similar cognitive efficacy, with donepezil and rivastigmine showing a dose effect across the dosing levels studied. However, both galantamine and rivastigmine were associated with a greater risk of trial dropout than placebo, especially at higher dosing levels.

Prices are comparable for all three agents. Donepezil is slightly cheaper by AWP pricing and slightly higher by Red Book data. As with all drug choices, we need to consider individual formulary requirements in our selection.

Donepezil has some perceived advantages over rivastigmine and galantamine: as the agent longest on the market, it has the most data available. It has the simplest titration schedule and the lowest GI side effects according to data presented in the PI.

The percentages of adverse events from monotherapy titration reported in the 2006 Physicians' Desk Reference were highest in every category (diarrhea, nausea, vomiting, anorexia, dizziness, and fatigue) for rivastigmine (6-12 mg). Galantamine (16-24) percentages were higher than donepezil (5-10 mg), except for diarrhea, but the differences between galantamine and donepezil were less substantial than the difference between rivastigmine and the other two. The data do not represent a head-to-head comparison.

Although some experts have suggested switching from one ChEI to another if the expected benefit is not realized, this practice is not supported by either clinical trials or expert consensus. Switching is sometimes done when one CHEI is not tolerated over the other, so in essence it may be done for safety purposes.

### Other ChEI Considerations

Keep in mind that many drugs have anticholinergic effects (drugs for overactive bladder, antihistamines, antidepressants, etc.) that can not only decrease the efficacy of cholinesterase inhibitors but also independently worsen dementia, cause delirium and other CNS side effects. Studies suggest that serum anticholinergic activity (SAA) can be detected in most older persons in the community and that even low SAA is associated with cognitive impairment (Mulsant 2003). Many patients with dementia are also using many other medications for comorbidities. The risks of prescribing cholinesterase inhibitors along with anticholinergic drugs needs to be diligently evaluated and monitored. It is important to consider medications with mild anticholinergic effects along with those with stronger effects since the anticholinergic burden is cumulative. The cumulative anticholinergic burden is associated with higher incidence of delirium and cognitive impairment.

### Summary

ChEIs have been shown in prospective, randomized, double-blind, and placebo-controlled trials to:

- Reduce the rate of cognitive decline for 6-12 months
- Reduce the rate of functional decline for 6-12 months
- Stabilize or improve the clinician global impression of change after 6-12 months

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Rev. 08.14.07

- Improve or delay the onset of neuropsychiatric and behavioral symptoms

Many trials, however, have excluded patients with comorbid illnesses, making the results less representative of the general population of patients with Alzheimer's.

There have been no prospective, double-blind, placebo-controlled trials lasting longer than 12 months, although long-term, open label data for as long as four years exists for some of these agents. There is now an ethical argument against the design of a placebo-controlled trial with any of these agents since we now know that they have symptomatic benefits over and above placebo. Some other important variables, including effects on health care costs and caregiver burden, have also been assessed.

Trials of donepezil (Feldman 2003) and galantamine (Salo 2003) have demonstrated a reduction in caregiver time required for patients receiving treatment. Both studies were of 28 week duration. The donepezil trial was conducted with moderate to severe dementia patients while the galantamine trial was with mild to moderate dementia patients. The donepezil trial yielded a reduction of 52.4 minutes per day caregiving time and the galantamine trial yielded 32 minutes per day reduction.

In summary, the benefits of ChEIs are, at best, modest. Nevertheless, delay of symptom progression is an important goal, especially for caregivers. The American Academy of Neurology recommends the use of ChEIs, while noting that average benefit is small. Currently, this is the best FDA approved treatment we have to offer for mild to moderate stage dementia.

⌘ ChEI therapy is endorsed as standard first-line therapy for patients with mild to moderate Alzheimer's disease.
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## **MEMANTINE (NAMENDA)**

Memantine is an NMDA (N-methyl-D-aspartate) receptor blocker, currently approved for moderate to severe Alzheimer's disease. It is indicated for use as a single agent and also indicated in combination with ChEIs for this purpose. There are now trials with donepezil and rivastigmine published and the PI does not mention only donepezil. Modest effects have been demonstrated in slowing cognitive decline and functional decline its use as compared to placebo. A trial of memantine (Wimo 2003) of 28 week duration with moderate to severe dementia

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patients yielded a 92 minutes per day reduction in caregiver time (compared to the 52.4 and 32 minutes for donepezil and galantamine respectively). There is also data to support the use of the two-drug combination (donepezil and memantine) as being superior to donepezil alone for some domains of the Neuropsychiatric Inventory (NPI) for behavior.

Some experts are using memantine for the mild stage of disease, both alone and in combination with a ChEI. However, its use for the mild stage is off label since the FDA has not approved its use for mild disease and is unlikely to do so in the future. One U.S.-based trial has suggested it is valuable earlier in the dementia process, but European studies have been negative.

Memantine seems to be even better tolerated than the cholinesterase inhibitors, both as a single agent and in combination with donepezil. In some patients, memantine causes dizziness, headache, or constipation. Less common adverse events may include fatigue, pain, hypertension, vomiting, confusion or somnolence, hallucinations, coughing, and dyspnea.

Start patients on 5 mg QD and slowly increase by 5 mg each week until a dose of 10 mg BID is reached. It may be taken with or without food. Dose reductions (total dose of 5 mg/BID) for patients with moderate renal dysfunction (est CrCl 5-29 ml/min) should be considered, and it is not recommended for patients with severe renal dysfunction. When starting therapy with both memantine and a ChEI, consider starting the memantine first to reduce the likelihood of adverse GI effects from the ChEI.

Use of memantine with other NMDA receptor antagonists (amantadine, dextromethorphan, ketamine, etc.) has not been evaluated in clinical trials, but could be assumed to be problematic on theoretical grounds after prolonged or high-dose use.

## **OTHER AGENTS**

Other potential treatment agents or supplements have been suggested, and patients or family members may ask about them.

**Vitamin E:** A single trial showed controversial benefit with 2,000 IU/day vs. placebo and selegiline. (Sano) The researchers concluded that Vitamin E was shown to delay nursing home placement and functional disability, but not cognitive decline. Critics of the study have noted that the study population did not reflect the general Alzheimer's population:

subjects were younger, had more severe dementia, and were not taking *any* psychoactive medications.

A Cochrane review reported that there was insufficient evidence to recommend Vitamin E, and the AAN says that its use “should be considered.” A recent meta-analysis of the risk of Vitamin E supplementation (in all users, not just those with dementia) concluded that supplements higher than 400 mg per day were associated with a significant increase in all-cause mortality (Miller ER, *Annals of Internal Medicine* 2005; 142: 37-46). Subsequently, another large study showed no difference in cardiovascular events or cancer and related mortality, but a possible increase in heart failure (Lonn 2005).

If you decide to use Vitamin E treatment, exercise caution in patients already taking antiplatelet or anticoagulant drugs because of the possible increase in the risk of bleeding.

**Estrogen:** Despite several descriptive studies that had shown postmenopausal women taking estrogen supplements to have a lower rate of dementia, a large prospective trial has now shown that use of estrogen combined with progestin may actually increase the rate of dementia and stroke (Shumaker 2003). And in a related large prospective trial, therapy with estrogen alone showed an adverse effect on cognition that was greater among women with lower cognitive function at treatment outset (Espeland 2004).

**Anti-inflammatories:** Inflammation around the beta amyloid plaques and subsequent neuronal destruction has been thought to be a key factor in the pathogenesis of Alzheimer’s disease, and several observational studies have demonstrated that people who regularly use NSAIDs have a decreased incidence of Alzheimer’s. However, neither NSAIDs nor prednisone have been shown to have any benefit in the treatment of those identified with Alzheimer’s in prospective, randomized, placebo-controlled trials.

**Statins:** Observational studies have shown a decrease in Alzheimer’s disease as well as slowing of its progression with the use of statins. A large cooperative randomized controlled trial of simvastatin is underway, but results may be delayed. Researchers have found that so many patients are now already on statins or have strong indications for their use, that recruitment of subjects eligible for randomization has been slower than anticipated.

**Complementary/alternative therapies:** There is insufficient evidence to support the use of any other treatments for dementia. A large NIA trial with huperzine (an acetylcholinesterase inhibitor found in Chinese Club Moss) is underway.

## **STOPPING PHARMACOLOGIC TREATMENT**

There is no clear consensus regarding how or when to stop any of the pharmacologic agents for dementia. As with most clinical decision-making, this must be evaluated on an individual basis. We need to assess and weigh the benefits and burdens (including cost and side effects) of treatment in light of the patient's earlier expressed wishes and with the caregiver or decision-maker.

Some experts recommend that pharmacologic therapy should be continued "until there are no meaningful social interactions and quality of life has irreversibly deteriorated" (Farlow & Cummings). This recommendation assumes that the patient's cognitive and functional status are monitored at six-month intervals.

When considering withdrawal of treatments aimed at altering the course of dementia, we need to consider what function the patient still has that is worth preserving. The answers, of course, vary according to individual values and situations.

- Most experts do agree that ChEIs and memantine should be stopped at the point that the patient no longer has meaningful function and/or when the patient is enrolled in hospice services. Is this patient doing anything that we want to preserve?
- Do NOT perform a "trial" off medication. Prior level of benefit is unlikely to be regained and there may be a precipitous decline after stopping.
- After a patient has been hospitalized and needs to be re-initiated on the ChEI, the drug should be re-titrated from the starting dose. This is especially true for rivastigmine and galantamine; even a 2-week stopping interval necessitates restarting therapy at the lowest dose.

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Rev. 08.14.07

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