Tailor Dementia Treatment to Each Patient

BY MICHELE G. SULLIVAN
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Cholinesterase inhibitors and memantine are not one-size-fits-all drugs that can be prescribed to every patient with dementia and should only be employed after assessing each drug's risk/benefit profile in light of an individual patient's needs, according to a new set of clinical guidelines.

"The most important thing to keep in mind is that there is no cure for dementia," said Dr. Amir Qaseem, author of the guidelines and a member of the Joint American College of Physicians/American Academy of Family Physicians Panel on Dementia.

"These drugs can only alleviate symptoms and may slightly delay progression. But they should not be prescribed to every dementia patient because the benefits are very modest and some patients may not show benefit at all, and all the drugs carry potential harms."

Although many patients do show statistically significant improvements while taking the drugs, most of those changes are small and not clinically meaningful, according to the guidelines (Ann. Intern. Med. 2008;148:370-8).

The panel also concluded that there is insufficient evidence to recommended one drug over another for the treatment of dementia. Instead, "the choice of therapy should be based on an evaluation of adverse events, tolerability, and cost, because there is no evidence that one treatment is more effective than another," Dr. Qaseem said in an interview.

The recommendations are particularly important for primary care physicians, who care for most patients with dementia, said Dr. William Thies, vice president of medical and scientific affairs for the Alzheimer's Association.

"The bulk of dementia patients are being managed by primary care physicians, and this is only going to increase as we deal with the oncoming tidal wave of Alzheimer's patients over the coming decades," he said in an interview. "As these guidelines point out, the emphasis when treating these patients should be that the physician, patient, and family work together as a unit to decide the best use of a medication and also, the best time to stop."

The guidelines panel mined data from 59 studies that examined any of the five drugs approved for dementia treatment in the United States (donepezil, rivastigmine, galantamine, tacrine, and memantine). Drugs were assessed for their effects on symptoms (cognition, function, and behavior), quality of life, and their adverse event profile. The results of this evidence review accompany the guidelines (Ann. Int. Med. 2008;148:379-97).

The largest body of high-quality evidence was seen for donepezil: Twenty-four studies compared it with either placebo or vitamin E. Most showed statistically significant effects in favor of the drug for at least one measure of cognition. Improvements in function also were reported. Nine studies also showed that these improvements were clinically meaningful. "These findings are important because although the average improvement in cognition … did not reach statistical significance, a subset of patients may have clinical improvement," the panel noted. Up to 57% of patients discontinued their donepezil because of adverse events; the most commonly reported were gastrointestinal upset and muscle cramps.

Ten studies examined the use of galantamine. The drug was associated with statistically significant, but not clinically important, improvements in cognition and behavior. Withdrawal because of adverse events ranged from 8% to 57%, with the most common being gastrointestinal symptoms, eating disorders, weight loss, and dizziness.

Rivastigmine was assessed in nine placebo-controlled studies. Overall, there was significant but very inconsistent cognitive benefit, and no significant benefits on behavior or quality of life. Up to 29% of patients withdrew because of adverse events, including dizziness, nausea and vomiting, diarrhea, weight loss, and headache.

Eight studies examined the use of tacrine; seven were placebo-controlled and one compared tacrine with idebenone. One trial showed a significant cognitive benefit, and three showed significant benefit in function; there were no effects on behavior or quality of life. Up to 55% of patients discontinued the drug, which was associated with serious adverse events, including hepatic abnormalities and abnormal liver enzymes. The panel concluded that there was insufficient evidence to substantiate any benefit of tacrine on cognition or behavior.

Memantine, the only neuropeptide-modifying agent available in the United States, was assessed in five studies, all of which compared the drug with placebo. Three trials showed significant, but not clinically important, improvements in cognition.

One study showed significant improvements in behavior, and three showed significant quality of life benefits. The withdrawal rate varied from 9% to 12%. Adverse events included nausea, dizziness, diarrhea, and agitation. The panel found only three high-quality head-to-head trials. Two pitted donepezil against galantamine. One 52-week study showed no significant difference in the primary outcome of function. The other, an 8-week trial, favored galantamine for cognition.

The third trial compared donepezil with rivastigmine over 2 years. Patients taking rivastigmine fared significantly better in function and some measures of behavior, but experienced more adverse events than did those receiving donepezil.

The guideline writing panel attempted to address the appropriate duration of therapy; however, the response to pharmacotherapy varies so widely. Generally, the beneficial effect from any of the drugs—disease stabilization or symptom improvement—will be apparent within 3 months of initiating treatment but will be temporary. When slowing decline is no longer a therapeutic goal, "treatment with a cholinesterase inhibitor or memantine is no longer appropriate."

Honest communication at the time of diagnosis is the best way to optimize medical therapy, according to Dr. David A. Smith, professor of family medicine at Texas A&M University, College Station. When families and patients understand up front that the benefit from these drugs will be modest and temporary, they are more likely to stick with the treatment plan, squeezing every possible benefit from it. "A lot of people do get started on these drugs, but the dropout rate is huge, because there is this expectation of large benefit," he said. "But it's important to remember that even small changes in cognition and behavior can roll into bigger changes over time, like in the rate of institutionalization."

Dr. Thies agreed. Despite their limitations, these drugs are the best that we have, and you don't want patients to throw away the only opportunity that we do have, he said. "You want the patient and family to go into therapy with a rational view of what is going to happen. The more they know about what to expect, the better they will do."

Early diagnosis is key to getting everyone on the same page about expectations, Dr. Thies said. "If someone with Alzheimer's is to get into this discussion in a rational fashion, early diagnosis is critical. That way, patients can be involved in determining not only the course of therapy, but [also] can express their opinions on placement and end-of-life care. All these questions become much easier if the patient is involved, rather than having the family guess about his wishes at a later point." ■

One of First Prevalence Studies Finds More MCI in Men

BY MARY JO M. DALES
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CHICAGO — Men have more mild cognitive impairment than women do, yet there is no gender difference in the prevalence of dementia, according to the results of one of the first studies to measure mild cognitive impairment prospectively in a population-based setting.

The findings, reported by Dr. Rosebud O. Roberts at the annual meeting of the American Academy of Neurology, suggest that dementia progresses either faster in women or slower in men.

For the ongoing study, called the Mayo Clinic Study of Aging, mild cognitive impairment was evaluated in a population sample from Olmstead County, Minn. The sampling scheme aimed for equal numbers of individuals in each gender and age group. The 70- to 79-year-old group included 490 women and 596 men and the 80- to 89-year-old group included 512 women and 452 men. For both age groups, there were 1,002 women and 1,048 men.

Either a nurse, physician, or neuropsychologist evaluated each individual using face-to-face measures. Subjects were evaluated in four domains—memory, executive function, language, and visual/spatial skills. Mild cognitive impairment (MCI) was defined as impairment in one or more domains or an overall mild decline across cognitive abilities that is greater than would be expected for an individual's age or education but is insufficient to interfere with social and occupational functioning.

Based on these evaluations, 74% of the group had normal cognition, 16% had mild cognitive impairment, and 10% had dementia. Of the nearly 2,000 study participants without dementia, 51% were male, 47% had less than 12 years of education, 52% were 80-89 years old, and 61% were married.

Subjects were studied prospectively beginning in October 2004 and follow-ups will continue through 2010. This differs from most other studies of MCI, which had the limitations of applying MCI criteria to previously collected data or were conducted in study samples, such as those attending memory clinics, who might not be representative of the general population, said Dr. Roberts, an epidemiologist at the Mayo Clinic, Rochester, Minn.

In men, the prevalence of mild cognitive impairment spiked after age 85 to affect 40%.

DR. ROBERTS

In men, the prevalence of mild cognitive impairment steadily increased from about 10% at age 70 and suddenly spiked after age 85 to affect 40%. In women, the rate rose more slowly and the prevalence was far lower, peaking at less than 20% at age 85.

Even after the data were corrected for age plus education, marital status, and disease burden, women had less cognitive impairment but comparable rates of dementia, compared with men, Dr. Roberts said.

"We found the overall prevalence of mild cognitive impairment is quite high—over 16%," said Dr. Roberts. "But perhaps the more surprising finding is the higher prevalence of MCI in men with the comparable prevalence of dementia for men and women." Several possible explanations for this disparity include a prevalence of risk factors in middle age vs. later life, the progression rate from MCI to dementia, and death among persons with MCI.

Dr. Roberts said that she and her coinvestigators are adding on another 1,000 study participants to continue the follow-up study and are applying for additional funding. The study was supported by grants from the National Institutes of Health and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program. ■

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