Alzheimer's Disease: Clinical Treatment Options

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Presentation Summary

Comprehensive treatment of Alzheimer's disease (AD) requires thorough caregiver support and a thoughtful and informed use of medications for cognition enhancement, neuroprotection, and the treatment of disturbed behavior. Current treatments such as the cholinesterase inhibitors donepezil and rivastigmine can slow the progression of cognitive and functional deficits in AD over the short term. Sustained improvement and possible disease modification that result from the use of these medications are being evaluated in long-term studies. Treatment with alpha-tocopherol (vitamin E) has been shown to delay the progression of nursing home admission in patients with mild-to-moderate AD. Although antioxidant, anti-inflammatory, and other treatment strategies are promising, recent studies of the treatment of AD with estrogen or prednisone have produced disappointing results. For managing the behavioral symptoms that commonly accompany AD (eg, delusions, aggression, depression, anxiety, irritability), various antipsychotics, antidepressants, and anticonvulsants have been effective in carefully selected patients.

Alzheimer's disease (AD) is incurable but treatable. Unfamiliarity with the available range of clinical treatment options has led to a certain amount of therapeutic nihilism in the professional and lay communities. In this review, the limited but nonetheless valuable goals of the treatment of patients with AD will be reviewed in addition to evidence supporting the use of specific pharmacologic interventions.

Although the use of medications to treat patients with AD is increasing, clinicians and healthcare organizations must realize that supportive care extends beyond the prescription. The basis of comprehensive care for patients with AD rests on substantial and ongoing caregiver support that includes providing caregivers with practical advice on a variety of issues, such as where to obtain financial planning and how to access respite care. If health plans expect caregivers

to assist the patient in maintaining the highest possible level of function, then caregiver education and emotional support must be essential elements of the entire treatment package.

In many cases, the careful and informed use of medications can be combined with behavioral and environmental interventions. Today's pharmacotherapeutic options include agents that enhance cognition and may afford neuroprotection as well as those that treat dementia-associated disturbed behavior.

Understanding treatment goals will help clinicians as well as patients and caregivers set realistic expectations for the outcome of care. Usually, most current treatments that enhance cognition and improve behavior lead to a period of modest symptomatic improvement. After that initial improvement, however, many patients eventually continue their decline, the rate of which (especially in the area of cognitive impairment) varies from patient to patient. Thus patients and their family members can expect some symptomatic improvement and perhaps some slowing of the rate of progression, but they should not anticipate an arrest of the disease process.

In many cases, a stabilization of the disease—a temporary delay in progression—is the most notable outcome of treatment. Is this meaningful or even noticed by family members? How can the clinician measure or explain this benefit? These are important issues that affect the design of each patient's treatment plan and his or her compliance with that plan. Having a thorough understanding of the latest clinical literature on pharmacologic treatment options will assist practitioners in planning protocols for their health plan members.

Cognition Enhancers

The brain of a patient having suffered from AD exhibits damaged neurons and reduced levels of the neurotransmitter acetylcholine (Ach) as well as the enzyme that synthesizes Ach. This finding is essential to the "cholinergic hypothesis," which states that cognitive function may be preserved if levels of Ach are maintained.[1,2] Increasing the level of Ach is not yet possible, but several pharmacologic agents can inhibit the function of the Ach esterase enzyme that normally breaks down Ach that has crossed the synapse. By blocking this enzyme, such agents help maintain Ach levels and thereby sustain cognitive performance.

The cholinesterase inhibitors donepezil and rivastigmine, which have been approved for use in patients with AD, are the mainstays of cognitive enhancement therapy today. Those medications and new cholinesterase inhibitors, such as galantamine, are the most thoroughly studied medications used to treat this devastating disease. Tacrine, an older, less selective agent in that class, is now rarely used. As demonstrated in the studies of the agents reviewed below, the cholinesterase inhibitors have a consistent but modest cross-class efficacy in stabilizing cognitive function in those with mild-to-moderate AD.

Emerging data indicate the cognitive stabilization resulting from treatment with cholinesterase inhibitors may persist for up to 1 year in a significant number of patients. The strongest evidence supporting such disease stabilization applies to improved cognition: Placebo-controlled trials[3-6] have indicated consistent improvement in language, memory, and attention as a result of treatment. Positive results have also been reported in functional outcomes such as relating to others, conversation, self-care, finances, and travel. Positive effects on behavioral outcomes have also been noted as a result of treatment with cholinesterase inhibitors.

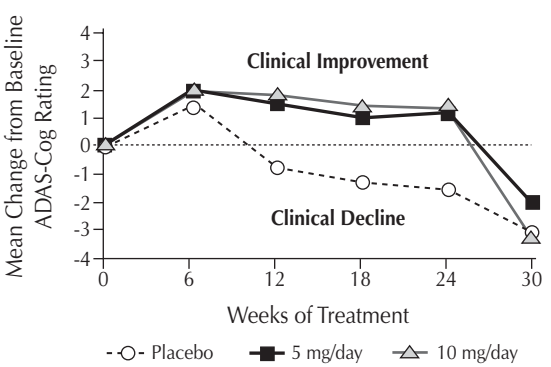
Donepezil. First marketed in January 1997, donepezil is the preeminent drug in its class. To date, more than 1 million patients with AD have been treated with that agent. Long-term clinical experience indicates that donepezil is well tolerated. As with all agents in this class, the degree of efficacy appears to be dose dependent.

The clinical improvement in patients with AD demonstrated in the pivotal clinical trial by Rogers et al[7] of the effectiveness of donepezil is characteristic of cholinesterase inhibitors. That 6-month, multicenter, double-blind trial included more than 150 patients in each of 3 treatment groups randomized to receive either 5 or 10 mg/day of donepezil, or placebo. As shown in Figure 1, the administration of 5 or 10 mg/day of donepezil led to scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) that were superior to those of the patients treated with placebo.[7] Overall, more than 4 of every 5 patients receiving active treatment showed either improvement or no decline in cognitive function during the half-year trial. Results of that trial also showed consistent and statistically significant improvements related to the use of donepezil as measured by broad clinical impressions as measured by the Clinician's Interview-Based Assessment of Change-Plus. In that test, an independent clinician interviews each patient and his or her caregiver to evaluate the changing level of cognitive and behavioral function.

Treatment with donepezil also produced measurable improvements in secondary outcomes such as scores on the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Scale-Sum of the Boxes. The ability of cholinesterase inhibitors to sustain this level of clinical improvement over the entire natural course of AD until the patient's death is unknown. Most trials have evaluated only the results of short-term treatment. Interim open-label results[3] indicate that long-term use of donepezil may be beneficial, but larger double-blind studies are required to demonstrate the effect of cholinesterase inhibitors as a class on long-term disease progression.

In clinical practice, the cognitive improvement produced by donepezil is usually noticed sooner than the first assessment in the study cited, which was 6 weeks after the initiation of treatment.[7] When treatment with donepezil was terminated at week 24 of that study, the cognitive level of the treated patients rapidly deteriorated to that of the group treated with placebo. The side effects of treatment were transient and generally mild in severity, and cholinergic adverse events (primarily diarrhea, nausea, and vomiting) were reported more frequently in the group that received the higher dose of 10 mg/day of donepezil.

Figure 1. Cognitive Improvement After Donepezil Therapy

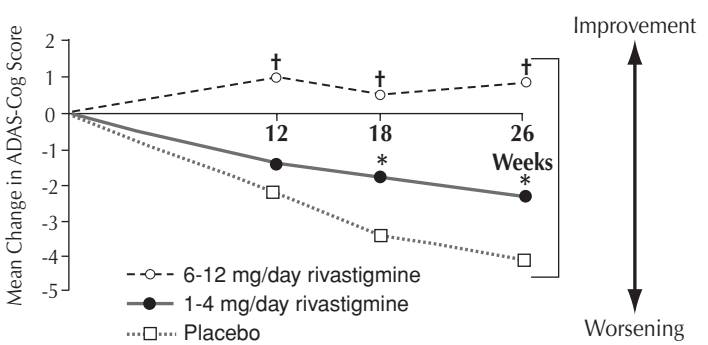


ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale.
Source: Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136-145. Reprinted with permission.

Rivastigmine. The second selective cholinesterase inhibitor to emerge has been rivastigmine. This agent, which has a duration of inhibition of 10 hours, is administered twice a day, unlike donepezil, which is administered once daily. However, the dose range of rivastigmine is fairly flexible (from 6 to 12 mg/day).

In a pivotal clinical trial with rivastigmine 699 patients with mild-to-moderate AD were randomized to treatment with a low dose (1 to 4 mg/day) or a high dose (6 to 12 mg/day) of that cholinesterase inhibitor or with placebo.[4] Results are shown in Figure 2. In the high-dose group, ADAS-Cog scores at 12, 18, and 26 weeks of treatment are maintained above baseline and are superior to the scores of those who received placebo, suggesting maintenance of cognitive function. In the low-dose rivastigmine group, cognitive function, as measured by the ADAS-Cog scores, deteriorates below baseline at 12, 18, and 26 weeks but to a lesser degree than in the placebo-treated group. The side-effect profile of rivastigmine is similar to that produced by donepezil, although a conservative dose titration schedule is recommended to avoid significant gastrointestinal intolerance. Rivastigmine is also known to inhibit butyryl cholinesterase, but the theoretical clinical advantage of such activity is unproven.

Figure 2. Cognitive Improvement After Rivastigmine Therapy



†$P < 0.001$ drug versus placebo; *$P < 0.005$ drug versus placebo.
ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale.
Source: Corey-Bloom J, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1998;1:55-65. Reprinted with permission.

Galantamine. Galantamine is an Ach esterase inhibitor that has not yet been approved for use in the United States but which has proven effective in improving cognition, function, and behavior in clinical trials.[5] Data collected 12 months after the initiation of treatment with this agent have also demonstrated a long-term improvement in ADAS-Cog scores compared with placebo.[6] In this pivotal trial, when patients treated with placebo during the first 6 months of the study were changed to galantamine 24 mg/day, the patients' ADAS-Cog scores increased, but not to the level of the group who had received galantamine 24 mg/day continuously since the beginning of the study. Although such results do not necessarily provide evidence for disease modification produced by treatment with this agent, they may indicate that early initiation of treatment is beneficial. Galantamine has been shown to modulate nicotinic cholinergic activity, although how this relates to the efficacy of the drug is unknown.

In summary, the use of cholinesterase inhibitors can provide a significant improvement in the cognitive and functional performance of patients with AD.[8] The drugs are fairly well tolerated, and although they target a secondary degenerative effect of the disease, they provide one of the few pharmacologic tools for delaying the cognitive decline of patients with

AD. There have been no head-to-head clinical trials with agents within this drug class. Without such data and after the variability in patient populations and in the design characteristics of individual studies has been considered, newer cholinesterase inhibitors can be said to be similar in efficacy and safety. Long-term studies on the sustained clinical effects of these agents and their possible role in disease modification are under way.

Antioxidants and Other Therapeutic Strategies

Reduction of oxidative stress within the brain has been another approach to treatment of AD. This popular strategy is based on findings of an age-related vulnerability to excesses of oxygen-based free radicals and decreases in endogenous antioxidant activity.[9] Agents used in various antioxidant neuroprotective strategies for the treatment of AD have included alpha-tocopherol (vitamin E); selegiline, a selective monoamine oxidase inhibitor; ascorbic acid; coenzyme Q; ginkgo biloba; and estrogen.

Vitamin E and Selegiline. Currently, many clinicians and patients use vitamin E as part of their overall AD prevention or treatment strategy. This widespread practice is based partly on the results from a large clinical trial involving selegiline and vitamin E.[10] In that 2-year, multicenter, placebo-controlled trial, 341 patients with moderately severe AD were randomly assigned to receive selegiline, vitamin E, the 2 agents in combination, or placebo. Primary outcomes were determined according to the time from the initiation of treatment to the occurrence of any of the following: death, institutionalization, loss of the ability to perform the basic activities of daily living (ADLs), or a severe decline on a dementia rating scale. The use of survival time and time to nursing home placement (rather than an assessment of cognitive ability) as factors determining outcome was a noteworthy change from the criteria of previous AD studies.

Overall, the administration of selegiline or vitamin E delayed progression in all endpoints. However, the most interesting finding of the study was that vitamin E delayed the progression of nursing home placement by approximately 7 months when compared with the effect of placebo. Because vitamin E is also safer and usually less expensive than selegiline, that finding has prompted the widespread clinical use of vitamin E in patients with AD. The dose of the vitamin used in the study cited was rather high (1000 IU twice a day), and there is still no consensus on the best dose for use in routine clinical practice. Patients with bleeding problems or those taking heparin must use vitamin E with caution. The main contraindication to vitamin E therapy is vitamin K deficiency.

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Estrogen. In addition to its potential antioxidant properties, estrogen is thought to possess other properties that might inhibit the progression of AD, such as potentiating reductions in the apolipoprotein E plasma level, inflammation, and beta-amyloid accumulation.[11] Unfortunately, recent results from the following key clinical trials of the effectiveness of estrogen in the treatment of AD have been negative.[12,13]

In the Alzheimer's Disease Cooperative Study[12] conducted

between 1995 and 1999, 120 women whose MMSE scores ranged from 12 to 28 were randomized to 1 of 2 doses of estrogen or to treatment with placebo. Estrogen treatment did not slow disease progression as indicated by scores on the Clinical Global Impression of Change 7-point scale, and it did not improve cognitive or functional outcomes.

In addition, a 16-week placebo-controlled trial of estrogen in 42 women with mild-to-moderate dementia caused by AD also indicated no significant differences in primary outcomes according to the cognitive scale of the ADAS-Cog or to other clinician-rated or caregiver-rated markers.[13] These failures of estrogen in the treatment of AD are striking, but they do not exclude the possibility that estrogen therapy may help to prevent the disease.

Table. Matching Medications to Behavioral Symptom Clusters in Patients with Alzheimer's Disease

Antipsychotics (eg, risperidone, olanzapine, cholinergics)
– Delusions
– Hallucinations
– Aggression
Antidepressants (eg, citalopram, sertraline)
– Depression
– Dysphoric agitation
– Lability of affect
– Anxiety
– Apathy
Anticonvulsants (eg, divalproex sodium)
– Mania
– Impulsivity
– Irritability
– Lability of affect
– Agitation

Source: Reference 17.

Anti-Inflammatory Agents. The use of anti-inflammatory agents in the treatment of AD is based on the wide spectrum of activated inflammatory components (eg, complement, cytokines, acute phase proteins) that have been noted in patients with AD.[14] The unexpectedly low incidence of AD in patients taking nonsteroidal anti-inflammatory agents supports the theory that inflammation is involved in dementia.[15] In this context, prednisone has been of particular interest as a potential agent in the treatment of AD because of its extremely broad anti-inflammatory effect. However, the recently published results of one long-awaited trial involving the use of prednisone in the treatment of AD were also negative.[16]

Thus, despite intriguing experimental evidence and some encouraging preliminary clinical results showing that therapies targeting oxidative or inflammatory mechanisms may halt or reverse the underlying progression of AD, no current therapy has proven effective in doing so.[11] As work on these and other strategies involving even more direct assaults on the characteristic beta-amyloid plaque of AD evolves, available cholinesterase inhibitors will continue to offer patients with early stage AD the best hope for slowing the relentless progression of the disease.

Managing the Behavioral Problems Associated with AD

Cognitive impairments are not the only problems associated with AD progression. Behavioral disabilities are also closely linked to the functional impairments of AD. Those signs of disturbed behavior, such as agitation or combativeness, can be ameliorated to some degree with medications or by educating caregivers.

An essential first step in managing disturbed behavior is to help a patient's caregiver recognize and characterize the psychiatric symptoms of AD as well as what triggers

these symptoms and what can be done to relieve them. Caregivers should be encouraged to use simple, clear terminology when describing the symptoms to the clinician so that the best approach for treatment and resolution can be determined.

After a particular behavior has been recognized by the caregiver and communicated to the clinician, a treatment plan that includes medications, behavioral techniques, and environmental changes can be designed. Only limited clinical data are available in those areas, but several classes of medication have been used in the management of specific symptom clusters in patients with AD (Table).[17] Despite widespread use of psychiatric drugs in those patients, no specific agent has been approved by the Food and Drug Administration (FDA) to treat behavioral symptoms in those with AD.

Risperidone. Despite a lack of formal sanction, compelling evidence now supports the use of risperidone or olanzapine in patients with AD who exhibit significant delusions, hallucinations, or aggressive behavior. One such pivotal multicenter study of the effect of risperidone involved 625 nursing home patients.[18] Most of the patients had been diagnosed as having AD, but in some, the diagnosis was vascular dementia or mixed dementia. All patients studied exhibited significant behavioral symptoms or psychosis. They were randomized to treatment with placebo or with 1 of 3 doses of risperidone: 0.5, 1, or 2 mg/day. At 12 weeks of treatment, about 70% of the patients had completed the study. They represented a typical cross section of behaviorally disturbed patients with AD (mean MMSE score, 6.6; mean age, 83 years). This study population had a very high response rate (52%) to treatment with placebo. Patients who were randomized to 1 or 2 mg/day showed improvement that was superior to the placebo-treated group on the Behavioral Pathology in Alzheimer's Disease rating scale total score, psychosis subscale score, and aggressiveness subscale score. Benefit over placebo was also demonstrated for the 1 or 2 mg/day dose groups over placebo on the Cohen-Mansfield Inventory verbal, physical, and total aggression scales. With neither outcome measure was 0.5 mg/day shown to be of significant benefit over placebo. Because of the significantly higher rates of side effects (including extrapyramidal effects, somnolence, and mild peripheral edema) in the group who received 2 mg/day of risperidone, the target dose for therapy is 1 mg/day.

Olanzapine. A key study evaluating the efficacy of olanzapine for the treatment of psychosis and agitation in patients with AD recently indicated results similar to those of the study on risperidone cited above.[19] The trial on the effect of olanzapine was a 6-week, multicenter, double-blind, placebo-controlled study of 206 patients with dementia. The mean MMSE of those nursing home patients was 7, and the mean age of the patients was 83 years. Patients receiving fixed doses of 5 or 10 mg/day of olanzapine responded better than did those receiving placebo with respect to scores measuring combined agitation, delusions, and hallucinations on the nursing home version of the Neuropsychiatric Inventory. However, the group receiving the highest dose (15 mg/day of olanzapine) showed no advantage when compared with those receiving placebo. The main side effects of treatment with olanzapine were somnolence and a change in gait.

Antidepressants. Antidepressants are of some value in treating patients with AD who have depression, dysphoric agitation, lability of affect, anxiety, and (perhaps) apathy. Several Scandinavian studies, for example, have evaluated the use of the selective

serotonin reuptake inhibitor (SSRI) citalopram in patients with dementia and reported significant efficacy.[20,21] Two studies have indicated positive results after administering the SSRI sertraline to patients with AD who had dysphoric affect and agitation, as well as in those who refused food.[22,23] Although not as well designed as the research just cited, several other studies[24,25] have evaluated the effects of SSRIs, such as fluoxetine and fluvoxamine, on the behavioral symptoms of patients with AD. The results of those studies varied.

Anticonvulsants. Finally, anticonvulsants can be effective in the control of impulsivity, irritability, lability of affect, and agitation. In a multicenter study of the effect of the anticonvulsant divalproex sodium in the treatment of patients with dementia, 172 nursing home residents with behavioral disturbances, including manic behavior, were given the anticonvulsant at 20 mg/kg/day for 10 days.[5] Although the study was suspended because several patients exhibited significant sedation or anorexia, analysis of the data indicated that divalproex sodium produced an antiagitation effect, and a new trial in which a more conservative dose titration is used is under way.

Conclusion

Although AD is currently incurable, there is little doubt that the disease is eminently treatable. The clinician and the healthcare organization responsible for the care of the patient with AD can do much to relieve the burden of the disease by providing a strong, consistent, multifaceted level of support for the caregiver. Pharmacotherapy can augment thoughtful and structured care interventions. In particular, treatment with cholinesterase inhibitors and vitamin E may be effective in slowing the rate of disease progression of AD, and newer psychotropic agents have been beneficial in treating the behavioral disturbances that usually emerge in later stages of the disease.

··· DISCUSSION HIGHLIGHTS ···

Initiating the Use of Cholinesterase Inhibitors in Patients with AD

Dr. Fillit: Some physicians still wonder about the clinical significance of the cholinesterase inhibitors measured in various studies. Sometimes those physicians (and perhaps the patient's family members) don't see a dramatic change in the patient who has been treated with 1 of those drugs. How do we respond to those situations?

Dr. Reichman: I would respond in 2 ways. First, it's true that we have not yet measured outcomes in those studies in a way that captures the experience of people dealing with the disease. The early studies, for example, used the ADAS-Cog to assess patients' cognitive status, and that evaluation is not terribly meaningful to families. In more recent studies, more meaningful markers are used, such as changes in performing the ADLs and the time required for caregiving. The second point I would make is that even if the patient does not improve noticeably after 9 or 12 months of treatment, that itself may be significant. This is a progressive disease in all patients, and a delay in that progression by a year in a subset of patients is considered a meaningful and positive outcome.

Dr. Fillit: In clinical practice guidelines for use of these agents, how long should the treatment trial last? How do you decide to continue?

Dr. McCarten: We at the Veterans Administration [VA] published guidelines last year on the treatment of AD. Of course our Pharmacy and Therapeutics [P&T] committees were very concerned about the duration of

therapy in those patients. We decided that if the medication was well tolerated and the disease had stabilized after 6 months of treatment, the patient should continue therapy. If there was no evidence of benefit, then the therapy should be terminated. If the patient's disease became worse after the cessation of treatment, the therapy should be reinitiated.

Dr. Fillit: The VA has taken a very proactive approach. But how do you measure improvement or stabilization in practice? Most doctors are not performing MMSEs or other psychometric tests over time, so improvement or lack of progression is based on the clinician's gestalt perception. Some managed care organizations [MCOs] require an MMSE for approval of the pharmacy benefit. I've often had to fax a medical director evidence that a patient had an MMSE score between 5 and 20 to obtain approval for drug benefits for that patient.

Dr. Parker: Are your requests for drug approval frequently denied? Or is it just a formality that requires test results be kept on file with the third-party payer?

Dr. Fillit: Continuation and initiation requests have been denied, either because the patients are too early in their disease stage or are too advanced, or because they don't meet other requirements. But I'm a specialist, and I'm willing to jump through those hoops. I'm worried about the primary care physician who may doubt the efficacy of the drug, is aware of the high cost of treatment, and then sees that an MMSE is required as part of a utilization decision. I can see that physician saying "Forget it." I am also aware of MCOs that place cholinesterase inhibitors on their first tier of the formulary so that those agents are approved and widely used.

Dr. Rabins: The MMSE is an inappropriate standard for approval because scores vary by education. Patient eligibility should be determined by a clinical diagnosis of possible or probable AD.

> ***"In clinical trials, we are moving beyond the results of neuropsychological testing to measure what caregivers, physicians, and family members can actually observe."***
>
> **—William E. Reichman, MD**

Dr. Reichman: The MMSE is widely used, but I'm concerned about its inherent variability, even when the same person is administering that evaluation over a short period of time. It may not be a reliable measure of change over 6 to 12 months. I'm very reluctant to use it alone to determine whether a patient is benefiting from treatment. In clinical trials, we are moving beyond the results of neuropsychological testing to measure what caregivers, physicians, and family members can actually observe. Perhaps a simple version of a test, such as the Clinical Global Impression of Change, can be applied in the clinical setting to determine whether the patient should continue treatment with a particular drug.

Dr. Moak: This is a challenging area for the MCO that wants to balance demand management with member satisfaction. In New England, the HMOs usually use rigidly defined MMSE guidelines to determine coverage for donepezil. But I recently persuaded a pharmacy benefit manager [PBM] to accept a Physical Self-Maintenance Examination as a measure for monitoring. This seemed relatively open-minded. But

what happens when a family using more subjective criteria, such as global impressions of response, believes that the drug is helping the patient although that patient's MMSE score remains very low? If the patient is in a nursing home and is fairly debilitated, the MCO may want to terminate treatment with the drug. But denial of coverage may trigger an angry response from the patient's family.

Dr. Relkin: I agree that the instruments used to test the efficacy of those drugs in clinical trials should not be applied to individuals to track their progress over time. It doesn't work. One reason for this is the lack of inter-rater reliability of these instruments for individual patients over even short periods of time. There are no proven measures of efficacy for these agents in individual patients. To make policies based on misinterpreted test results makes subscribers angry.

Dr. Relkin: The whole current approach to treatment for AD is actually counterintuitive in the context of therapy for most chronic diseases. Imagine a patient with arthritis who, 3 or 5 years after treatment initiation, experiences disease progression and worsening of symptoms. Do you withdraw the nonsteroidal anti-inflammatory drug and deny treatment because the disease has progressed?

Dr. Fillit: That analogy is good, because nonsteroidal anti-inflammatory drugs have never been shown to affect the progression of arthritis. They just relieve pain. Similarly, the cholinesterase inhibitors don't affect the progression of AD as far as we know, but they may improve cognition at all stages of the disease.

Cost Issues

Dr. Fillit: Without good data, it's no wonder that MCOs and P&T committees have difficulty generating good evidence-based prescribing guidelines. But those committee members still make decisions every day, so what can we tell them about costs and utilization? Who should receive those drugs?

Dr. Reichman: One way to help a healthcare organization decide who should receive those drugs is to present subgroup analyses. We tend to report aggregate data that tend to wash out the very robust responses of subgroups. So, for example, if I showed an MCO that 25% of patients treated with cholinesterase inhibitors exhibited a strong response with respect to cognitive measures and performing the ADLs, would that drug be listed on the formulary? I think it would, and I think this demonstrates that a higher standard has been set for the treatment of patients with AD as opposed to other chronic diseases.

Dr. Fillit: I'm not sure that the standard is set higher, but it's different. I think that AD has definitely been put in a special classification, partly as a result of ignorance and partly because it's a cognitive disease that is often treated in a primary care setting. Although we might all agree that the clinical diagnosis (rather than other instruments with questionable validity) can provide the criteria for treatment approval, the state of the art in primary care practice is not where we would like it to be for the treatment of AD.

Dr. Rabins: Demonstrating improvements in quality of life may be another outcome measurement that will help people make judgments about the benefit of drug therapy in those with AD. If those improve-

ments can be added to economic outcomes such as decreased time for care, reductions in the incidence of costly comorbid conditions, prevention of hospitalization, and health benefits, those decisions will become easier.

Dr. Reichman: It would be helpful if ongoing long-term studies verified short-term results indicating that increased morbidity is associated with the termination of treatment with donepezil.

Dr. Relkin: With respect to the discontinuation of cholinesterase inhibitors, I often advise against setting a time limit or using the results of an MMSE evaluation or another instrument to trigger a change in treatment protocol. Instead, if some sort of decision tree is required, I sometimes advocate a drug holiday after a certain period of time has elapsed. It's an imperfect idea, because some patients return to their "preholiday status" when treatment is resumed. However, a P&T committee or a pharmacy director may be better able to monitor response to a brief discontinuation than to judge efficacy by other means.

Dr. Fillit: Over the past few years, emerging data about the cholinesterase inhibitors have indicated that function is maintained at 1 year of therapy. At that time, treated patients remain above their baseline function; those treated with placebo decline. These data should influence P&T committees with respect to the length of time allotted for treatment.

Dr. McCarten: In the VA guidelines, we tried to put decision making into the hands of the clinician. The MMSE did not have a cutoff at the higher end of the scale because we know that those with more education do better on that test. The guidelines suggest that patients score higher than 10, but there was no restriction on the use of a cholinesterase inhibitor. These guidelines were written to encourage the use of cognitive enhancers by primary care providers, and yet we have had very little demand for cholinesterase inhibitors apart from those from our clinic for the treatment of dementia. I've had almost no calls from primary care providers asking for the authority to prescribe donepezil.

Dr. Fillit: But if the clinical practice guidelines recommend that people begin or try drug treatment then it becomes an issue of underutilization, which is a quality issue that can be measured. The average time of compliance for patients taking drugs like donepezil and rivastigmine is between 3 and 6 months, and yet data indicate that patients maintain function and benefit at 52 weeks of therapy. Clearly, not all patients receive treatment for a sufficient length of time. This is a utilization issue for pharmacy.

Dr. McCarten: More people might benefit from treatment with medication if those drugs weren't restricted to patients with the diagnosis of AD.

Dr. Fillit: The FDA indicates the use of cholinesterase inhibitors for the treatment of mild-to-moderate AD, although physicians in practice can use medicines for any indication.

Dr. Relkin: Many patients now receiving donepezil do not have the diagnosis of AD. Those drugs clearly benefit patients with other forms of dementia. Studies are under way, and in a few years we may see indications for the use of cholinesterase inhibitors in the treatment of vascular dementia or dementia with Lewy bodies.

Vitamin E

Dr. Relkin: The effect of FDA approval on the use of antidementia drugs in the managed care environment extends beyond the cholinesterase inhibitors. For example, vitamin E does not produce measurable cognitive benefits, yet it is relatively inexpensive and only some bleeding morbidity results from its use. But it's not approved by the FDA for the treatment of dementia. And what about ginkgo biloba and other agents that demonstrate some efficacy but not enough for FDA approval? Do we uniformly deprive patients of access, or do we find some way of "wrapping" these agents into the management of the disease so that patients who might benefit from therapy are not denied treatment?

Dr. Fillit: Remember, most PBMs and managed care pharmacy benefit packages don't include vitamins and alternative medicines. Certainly, many of us are quick to use vitamin E. But there has been only 1 study on the use of vitamin E in AD and that study has been criticized for its methodology and data interpretation. Giving 2000 IU of vitamin E to a frail elderly patient already taking 10 other medications will not be an irrelevant cost. Are the benefits really worth it?

Dr. Rabins: If that cost of vitamin E is prohibitive to a managed care member, shouldn't the MCO consider paying for it? The data on vitamin E from Sano et al[10] that show a 200-plus day prolongation of time to nursing home admission will have a considerable cost impact.

Dr. Fillit: But are the data really there? I'm not sure we are right to be recommending vitamin E to everyone at this point.

Dr. Reichman: My patients are already taking vitamin E when I evaluate them, and so is everyone else in their family.

Dr. Rabins: The National Institute on Aging-sponsored vitamin E study results by Sano et al[10] are limited by failed randomization. The results are only significant if you control for the fact that MMSE scores were different at baseline in the treatment groups. The underlying question is how much evidence we need to make a decision on who receives vitamin E therapy.

Dr. Rabins: The American Psychiatric Association treatment committee did recommend the use of vitamin E and recommended against the use of selegiline, primarily because of safety issues.

Dr. Fillit: These are the difficult decisions that medical managers must make when they are filling in the boxes of their treatment algorithms. Should everyone be screened? Who should undergo magnetic resonance imaging? Who should receive treatment with vitamin E? Academics can study those issues for 10 years, but those writing practice guidelines in managed care settings must make those decisions even when datasets are incomplete.

Behavioral Drugs

Dr. Fillit: Is there evidence that antipsychotic drugs delay the progression of AD?

Dr. Reichman: Not that I'm aware of. Patients may actually deteriorate cognitively and functionally with the use of some conventional neuroleptics. But in the cited trial of olanzapine, there was a suggestion of cognitive improvement in some patients who were using the drug to treat behavioral changes associated with AD.

Dr. Rabins: The same may be true of antidepressant medications. Sometimes, significant cognitive and functional improvements are observed in depressed patients with AD who receive treatment with antidepressants.

Dr. Fillit: Is there a real difference between the effect of olanzapine and that of risperidone in terms of extrapyramidal symptoms?

Dr. Reichman: Yes, especially when risperidone 2 mg/day is given.

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