Recommendations for Best Practices in the Treatment of Alzheimer’s Disease in Managed Care

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ABSTRACT

Background: Alzheimer’s disease and related dementias (ADRDs) are increasingly recognized as important causes of impaired cognition, function, and quality of life, as well as excess medical care utilization and costs in the elderly Medicare managed care population. Evidence-based clinical practice guidelines for ADRDs were published in 2001. More recent studies have resulted in the approval of new agents and demonstrated an expanded role for antidementia therapy in various types of dementia, settings of care, stages of disease, and the use of combination therapy. However, these clinical guidelines have not been updated in the past few years.

Objective: The goal of this article was to provide practical recommendations developed by a panel of experts that address issues of early diagnosis, treatment, and care management of ADRDs. The panel also addressed the societal and managed care implications.

Methods: A panel of leading experts was convened to develop consensus recommendations for the treatment and management of dementia based on currently available evidence and the panel’s informed expert opinion. The panel comprised 12 leading experts, including clinical investigators and practitioners in geriatric medicine, neurology, psychiatry, and psychology; managed care medical and pharmacy directors; a health systems medical director; and a health policy expert. In addition, articles were collected based on PubMed searches (2000–2005) that were relevant to the key issues identified. Search terms included Alzheimer’s disease, dementia, clinical practice guidelines, clinical trials, screening and assessment, and managed care.

Results: ADRDs represent a significant clinical and economic burden to individuals and society, including Medicare managed care organizations (MCOs). Appropriate utilization of antidementia therapy and care management is vitally important to achieving quality of life and care for dementia patients and their caregivers, and for managing the excess costs of Alzheimer’s disease. The recommendations address relevant, practical, and timely concerns that are faced on a daily basis by practitioners and by Medicare MCO medical management programs in the care of dementia patients. These consensus recommendations attempt to describe a reasonable current standard for the provision of quality care for patients with dementia. The panel recommendations support the use of screening for cognitive impairment and the use of antidementia therapy for ADRDs in different stages of disease and types of dementia in all clinical settings. The panel members evaluated the use of the 3 marketed cholinesterase inhibitors—donepezil, galantamine, and rivastigmine—as well as the N-methyl-D-aspartate antagonist memantine. Recommendations for using these medications are made with an appreciation of the difficulties in translating the results from investigational clinical trials into clinical practice.

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Conclusions: The recommendations of the expert panel represent a clear consensus that nihilism in the diagnosis, treatment, and management of ADRDs is unwarranted, impairs quality of care, and is ultimately not cost-effective. (Am J Geriatr Pharmacother. 2006;4(Suppl A):S9–S24) Copyright © 2006 Excerpta Medica, Inc.

Key words: Alzheimer’s disease, dementia, managed care, cholinesterase inhibitors, memantine.

INTRODUCTION

Our knowledge of Alzheimer’s disease has expanded rapidly in the past 2 decades. Four antidementia therapies, approved by the US Food and Drug Administration (FDA), are currently on the market in the United States to treat the symptoms of this disease. These include 3 cholinesterase inhibitors (CHEIs)—donepezil,* galantamine,† and rivastigmine ‡ —and memantine,§ an N-methyl-D-aspartate (NMDA) antagonist approved in early 2003.‡ Current evidence-based clinical practice guidelines for the treatment of Alzheimer’s disease were written before the introduction of memantine in 2001. § Since then, several studies have demonstrated an expanded role for antidementia therapy in various types of dementia, settings of care, stages of disease, and the use of combination therapy.1,4 As a result, updated recommendations for clinicians regarding the use of antidementia therapy are needed. With >5.8 million individuals now enrolled in Medicare Advantage managed plans, >5.8 million participants in the Medicare Part D Prescription Drug Plan program, and a total of >30 million Medicare beneficiaries having some type of drug coverage,5 the appropriate use of therapies for the treatment of Alzheimer’s disease and related dementias (ADRDs) also has important implications for managed care in the United States.

To address these issues, we convened a panel of leading experts in this field. The participants discussed and agreed on consensus recommendations for the treatment of dementia based on currently available evidence and their informed expert opinion. These recommendations were developed for use by practicing physicians and other providers, as well as medical directors and pharmacy directors in the managed care setting.

PREVALENCE AND BURDEN OF DISEASE

Alzheimer’s disease is a chronic, debilitating, and fatal disease that directly affects the lives of 4.5 million Americans6 and the millions more who care for them. Due to the cognitive, behavioral, and functional deterioration that occurs, patients and their caregivers require appropriate treatment and care management to treat symptoms, maintain functional abilities, and prevent complications of the disease.7

Considerable research has demonstrated that antidementia therapy can treat cognitive impairment, functional decline, and behavioral symptoms associated with ADRDs.8 An important practical effect of mitigating patient deterioration for as long as possible is that the patient’s health care needs may be more easily managed if dementia symptoms are improved. Indeed, care management can play a considerable role in managing care and costs.10,11 Furthermore, certain medical comorbidities and lifestyle factors have been associated with cognitive decline and dementia, including Alzheimer’s disease and vascular dementia. These factors include hypertension, diabetes mellitus (DM), hyperlipidemia, and other cardiovascular risk factors (eg, elevated homocysteine levels, atrial fibrillation, coronary artery disease), as well as lifestyle factors such as social isolation, lack of exercise, smoking, alcohol abuse, and head trauma caused by not wearing a seatbelt or helmets.12,13 It is possible that managing these risk factors in patients with mild dementia may also influence the rate of progression, particularly for those individuals with vascular dementia. Thus, early diagnosis, use of antidementia treatment, and active medical and care management can substantially benefit patients with dementia and their caregivers.

Despite numerous clinical trials demonstrating the efficacy of antidementia therapy and the value of care management,10,14–16 nihilism still exists among some physicians and other providers regarding the treatment of dementia. These negative attitudes toward therapy may be due to anecdotal individual experiences that reflect the failure of physicians to make an early diagnosis, delayed initiation of treatments,17 suboptimal dosing, inconsistent utilization of antidementia therapy and care management, and—perhaps most importantly—inSENSITIVE OR UNAVAILABLE TOOLS (SUCH AS COGNITIVE ASSESSMENTS) THAT CAN ROUTINELY BE USED IN CLINICAL PRACTICE TO ACCURATELY ASSESS CLINICAL BENEFIT OR STABILIZATION.17,18 THE PRACTICAL RECOMMENDATIONS PROVIDED HERE ADDRESS THESE ISSUES OF EARLY DIAGNOSIS, TREATMENT, AND CARE MANAGEMENT.

The panel considered the societal and managed care implications of ADRDs. ADRDs affect 10% of individ-
uals aged >65 years, up to 25% of individuals aged >75 years, and >40% of individuals aged >80 years.19 With new risk-adjusted payments to Medicare managed care organizations (MCOs), incentives for recognizing and managing Alzheimer’s disease are now aligned.18,20 Because individuals aged >75 years account for the majority of costs in Medicare managed care,21 managing Alzheimer’s disease should be a key component of medical management in this group, as it is the third most costly illness to US society, exceeded only by cardiovascular disease and cancer.22 The total direct and indirect costs of Alzheimer’s disease are estimated to be more than US $100 billion.23,24 The total direct and indirect costs of this disease to US businesses is estimated to be in excess of $61 billion annually,23 including costs related to lost caregiver productivity.

Previous studies have demonstrated a relationship between dementia and increased medical costs in managed care.22 These excess costs are increased further by the complications of the disease, such as impaired function,25 which lead to the need for caregiver support. Excess and avoidable hospitalizations may occur, in part, as a result of medication noncompliance caused by cognitive impairment, which interferes with the management of common medical illnesses suffered by elderly patients (including congestive heart failure and DM).26 Several studies have demonstrated that telephonic care management and disease management approaches to the care of patients with dementia can be effective in delaying hospitalization and preventing nursing home placement.10,11,15,16 In recognition of this relationship, the recent Medicare Health Support27 program for disease management of congestive heart failure and DM sought to incorporate a mechanism for the identification of cognitive impairment and its management into the demonstration programs.

Studies have also demonstrated the pharmacoeconomic value of antidementia therapy.22,28–30 A retrospective case-control analysis of health care costs from a large Medicare managed care database, for example, found that total health care costs for donepezil-treated patients compared with untreated patients over a 12-month period were significantly lower (P = 0.016).29,31 After controlling for age, sex, comorbid conditions, and complications of Alzheimer’s disease as a proxy for stage of disease, the mean annual costs were $3891 (or 30%) lower for donepezil-treated patients versus the untreated patients. Lower inpatient hospitalization accounted for almost 75% of this cost savings. More recent research has confirmed these findings.32 Randomized clinical trials are also needed to support the finding that antidementia therapy has pharmacoeconomic benefit.

Considering these data, the panel concluded that a managed care population-based approach to dementia can have considerable patient, societal, and health economic benefits, and that Medicare MCOs have an important opportunity to improve the quality of care and better manage the costs of this disease.7,8

The goal of this report was to provide practical recommendations developed by a panel of experts that address these issues of early diagnosis, treatment, and care management. The panel also addressed the societal and managed care implications of ADRDs. The recommendations presented here are generally applicable to both primary and specialty care in all care settings. The primary care physician is most often the pivotal point of care for older patients, including patients with dementia.17 The panel concluded that the diagnosis and management of ADRDs should be undertaken by the primary care physician, except in difficult cases. The panel recommendations outlined here were primarily developed to be employed by primary care physicians and managed care medical managers.

MATERIALS AND METHODS
The Alzheimer’s Drug Discovery Foundation (ADDF) convened a panel of 12 leading experts comprising clinical investigators and practitioners in geriatric medicine, neurology, psychiatry, and psychology; managed care medical and pharmacy directors; a health systems medical director; and a health policy expert. The executive director of the ADDF (H.M.F.) selected and invited the panelists to co-author the guidelines based on their area of expertise and experience in the field. The consensus recommendations represent the panel’s expert opinion derived from their accumulated knowledge and experience in clinical trials, clinical practice, and medical management.

Before the meeting, one of the panel members and health policy expert (G.M.C.) met with the executive director of the ADDF to identify a preliminary set of key issues. Following the initial meeting, this panel member further developed the set of key issues in interviews and discussions with the panelists using a focus group approach. Subsequently, articles were collected based on PubMed searches that were relevant to the key issues identified. Search terms included Alzheimer’s disease, dementia, clinical practice guidelines, clinical trials, screening and assessment, and managed care for the years 2000 to 2005, to identify articles published since previous evidenced-based guidelines.3,33 Selected
articles, including previous clinical guidelines and relevant clinical trial reviews, were provided to the panelists for review and discussion.

A meeting was held with all 12 panelists in October 2005 at which the key issues were refined, recommendations discussed, and consensus developed. After the panel’s meeting, the recommendations were developed over the next several months through an iterative consensus process that involved several rounds of review during which the proposed manuscript was circulated among the group. During these subsequent rounds of edits, additional articles were identified by panelists for review by the group. Much of this information was provided directly by the participants beyond the scope of the original literature search and is referenced herein where applicable.

Each recommendation includes a brief discussion of the rationale behind it. For many important practical clinical treatment issues addressed by the panel, the recommendations could not be based on available evidence because such complete evidence does not exist. As a result, for these issues, the recommendations of the expert panel were based on consideration and review of both relevant clinical trial evidence and clinical experience. The panel recognizes that some recommendations are for non-FDA approved uses allowable in clinical practice. Therefore, in all cases, the panel advises that physicians, patients, and their caregivers must evaluate the potential known risks and benefits of antidementia therapy for each individual patient.

RESULTS

Recommendation 1: Early detection and diagnosis of Alzheimer’s disease and other dementias is critical to achieve optimal quality of care.

The panel recommended that patients with Alzheimer’s disease be diagnosed at the earliest possible stage so that pharmacotherapy and care management can be initiated to achieve optimal quality of care. The panel concluded that early detection and diagnosis can result in effective medical management of dementia and reduce excess and potentially avoidable costs.22,34 Unfortunately, the majority of patients (~76%) in clinical care are not diagnosed until the disease is in a moderate stage,17 often at times of medical and social crises. The mean time from diagnosis to death in some academic studies ranged from 6 to 9 years, but in clinical practice it may be as little as 3 to 5 years because patients in clinical practice generally do not receive an early diagnosis.35,36 It is the consensus panel’s recommendation that best practice would identify patients in the early or mild stage of the disease, when pharmacotherapy and care management could preserve cognition and function in patients for the longest period, in the most independent state.

Recommendation 2: Screening for cognitive impairment should be conducted, especially for individuals aged ≥75 years. To do this, managed care organizations (MCOs) should use brief telephonic screening for cognitive impairment in their medical management programs. Age-dependent, office-based screening for cognitive impairment in community-based care should also be a standard of care. All elderly individuals with a memory complaint, both in clinical practice and in MCO medical management programs, should be screened for cognitive impairment and evaluated for dementia.

In making this recommendation, the panel considered the yield, cost, and practicality of screening for cognitive impairment in MCOs and in the medical practice setting. The panel agreed that screening was critical to promote early detection and diagnosis of dementia and was, therefore, essential to quality of care for dementia. The panel acknowledged that, at this time, there are no conclusive, prospective, randomized studies demonstrating the value of screening for cognitive impairment in the elderly.37 Despite this, the panel determined that the impact of cognitive impairment on quality of care, quality of life, and costs of care, as well as the increasing prevalence of dementia with age, justifies an age-dependent, annual or biannual screening process, especially in people aged ≥75 years (Table I).38 This recommendation is consistent with what others have recently proposed.38,39

The panel recommended that population-based MCO medical management programs, such as case management, disease management, and health risk assessments, should incorporate methods for brief telephonic screening of cognitive impairment. The panel endorsed the use of several brief telephonic instruments for population-based screening of cognitive impairment in MCOs.40-47 Currently available mailed surveys and Internet-based screening were deemed less useful, since patients with cognitive impairment may not be able or willing to comply with these methods. In addition, the panel endorsed incorporating brief telephonic screening for cognitive impairment for new MCO members, particularly in persons aged ≥75 years.

The panel also endorsed brief, office-based screening for cognitive impairment in clinical practice, especially for patients aged ≥75 years. Office-based screening should
also be initiated when a caregiver, patient, medical office employee, case manager, or assisted living facility staff notes the presence of cognitive impairment, such as memory loss or confusion, regardless of the patient’s age. In clinical practice, screening for cognitive impairment should use validated instruments that are brief. Instruments to screen for cognitive impairment due to dementia are presented in Table II, which lists some of the most commonly accepted tools, their levels of accuracy, and the time they require to administer. The panel refrains from recommending any instrument.

**Recommendation 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.

Dementia is a syndrome of chronic, progressive cognitive impairment, involving multiple domains of cognition, significant enough to cause functional impairment, and not due to a medically reversible cause. The most common cause of dementia is Alzheimer’s disease, followed by vascular dementia or dementia with Lewy bodies (DLB). A diagnosis of dementia, according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, distinguishes these patients from those with normal cognitive aging and mild cognitive impairment.

To aid in differential diagnosis, assessment of patients with cognitive impairment in the primary care setting should include questions that, in addition to cognition, also examine function and behavior. Brief assessment instruments for evaluating daily function have been extensively validated.

Behavior problems and mood disorders are common in patients with dementia (~40% have depression) and often result in difficulties in care management as well as excess costs. Clinicians can obtain information from caregivers about behavioral issues, such as anxiety, apathy, hallucinations, depression, sleep disturbance, and other problems. For the structured evaluation of behavior, assessment instruments have primarily been used in clinical trials.

The diagnostic algorithm should include a medical evaluation to assess the presence of potentially reversible causes of dementia, such as polypharmacy, depression, B12 deficiency, or thyroid dysfunction. Neuroimaging should be used to determine the presence of structural abnormalities such as strokes causing vascular dementia, tumor, or hydrocephalus (see Recommendation 4). Once these factors that cause or contribute to dementia have been eliminated, a diagnosis of Alzheimer’s disease can be made with good reliability.

Patients should be referred to a specialist if they have rapid deterioration; abnormal neurologic signs, such as focal neurologic signs, prominent early aphasia, asymmetrical use of the limbs, parkinsonism, or gait disorder; an atypical or complicated diagnosis; complex management issues; or very early onset (defined as <60 years of age). The panel determined that appropriate specialists for referral include neurologists, geriatricians, or geriatric psychiatrists, depending on the nature of the complex problem. With the exception of these cases, the primary care practitioner should remain as the primary provider of diagnosis and care for patients with dementia.

**Recommendation 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 (eg, a Mini–Mental State Examination score <10).
The panel recommended that structural imaging should be part of the diagnostic process. The only exception is a patient who presents in a severe or profound stage of the disease after a typical presentation and long duration of illness, where imaging would still be appropriate but is not required.

The panel recommended a noncontrast computed tomography (CT) scan or noncontrast magnetic resonance imaging (MRI). The panel relied on the recommendation of the American Academy of Neurology, which determined that structural imaging was needed to rule out strokes, tumors, subdural hematomas, and normal-pressure hydrocephalus. Despite the relatively low yield of these tests, the opportunity to improve care in some patients is considerable. Although a CT scan is less expensive in most health care markets, it is also less sensitive to vascular lesions and does not evaluate the posterior regions of the brain as effectively as an MRI.

The panel leaves the decision to individual health plans whether to endorse functional neuroimaging scans such as positron emission tomography (PET) and single-photon emission CT, which are not required for diagnosis but can provide helpful information. At present, metabolic fluorodeoxyglucose-PET scanning of the brain is approved for payment by the Centers for Medicare and Medicaid Services only to diagnose frontotemporal dementia (FTD). FTD is often characterized by early problems with executive function and changes in personality with relatively preserved memory, in contrast to Alzheimer’s disease where memory loss is often the first and most prominent symptom. However, disease presentations can overlap in these disorders, making the differential diagnosis difficult.

Recommendation 5: Treatment of Alzheimer’s disease should be determined by the stage at the time of diagnosis.

The panel determined that the stages of Alzheimer’s disease are arbitrarily defined and that it is often difficult to distinguish stages of Alzheimer’s disease in individual patients in clinical practice. The panel acknowledged the importance of physician judgment on a case-by-case basis in selecting, maintaining, and discontinuing therapies.

Alzheimer’s disease is usually described in clinical trials and clinical practice in 3 stages: mild, moderate, and severe. However, in clinical practice, the disease progresses as a continuum from point of diagnosis to end-stage without clear milestones as patients transition...
from one stage to the next. Some clinicians describe additional fourth and fifth stages as “profound” and “end-stage” disease. There is also considerable heterogeneity in the presentation of dementia symptoms and cognitive dysfunctions.

However, the detailed assessment instruments used in clinical trials and in academic research to stage dementia cannot be practically used in clinical practice. There is also a general underutilization or routine use of neuropsychometric assessments in clinical practice due to a lack of expertise on the part of clinicians, as well as time and payment barriers. Nevertheless, the FDA label indications for the use of approved Alzheimer’s medications divide the disease into “mild to moderate” and “moderate to severe” stages. Thus, FDA recommendations regarding the use of antidementia therapy, which are based on clinical trial research data that clearly define disease stage, may often be difficult to translate into clinical practice.

The panel recommended the following general guidelines for identification of patients at various stages of the disease in clinical practice, using the Mini–Mental State Examination (MMSE) scores: mild disease, 24–20; moderate disease, 19–10; severe disease, <10; and profound disease, 0 or a score cannot be obtained. Some high-functioning people with MMSE scores >24 may also suffer mild dementia. These scores require an adjustment according to the patient’s level of education.

The panel members evaluated the use of the 3 marketed CHEIs—donepezil, galantamine, and rivastigmine—as well as the NMDA antagonist memantine. The recommendations are based on their FDA label indications as well as their application in practice. In making its recommendations, the panel noted the formulary policies of other major organizations, such as the US Department of Veterans Affairs, which includes all 4 antidementia therapies on formulary, although utilization strategies may vary regionally. The panel also noted the recent, controversial, and unique recommendation of the United Kingdom’s National Institute for Health and Clinical Excellence, which recommended the use of CHEIs in moderate Alzheimer’s disease only and against the use of memantine for Alzheimer’s disease; these recommendations, however, have not yet been adopted by the United Kingdom’s National Health Service. In contrast, the USP formulary, a model formulary for the US Medicare Part D Prescription Drug Plan program, includes both CHEIs and NMDA antagonists as antidementia agents, without reference to stage of disease.

The panel also considered the clinical utility of antidementia therapies. The panel concluded that CHEIs as a class have relatively similar efficacy. CHEIs do differ based on their need for titration, tolerability, and safety profiles. Donepezil is the only CHEI that does not require dose titration, as the first dose is a clinically effective dose. However, published data indicate greater average efficacy for the 10 mg dose versus the 5 mg dose. Galantamine and rivastigmine require dose titration. Donepezil and galantamine are dosed QD. Generally, the CHEIs have similar safety profiles. The most common side effects include nausea, vomiting, diarrhea, upset stomach, and sleep disturbances. Some research suggests rivastigmine has a higher incidence of adverse gastrointestinal events. Memantine also requires dose titration and is taken BID. Dizziness, confusion, headache, and constipation were the most common side effects of memantine reported in clinical trials in patients with moderate to severe Alzheimer’s disease. The overall incidence of adverse events reported with memantine has been found to be similar to that of placebo.

**Recommendation 5a: Patients first diagnosed with mild Alzheimer’s disease should be treated with a cholinesterase inhibitor.**

A CHEI should be initiated on diagnosis of mild Alzheimer’s disease as a standard of care. The panel determined that there is little evidence suggesting that available CHEI agents differ in efficacy. The panel did not recommend any one CHEI but did propose that physicians make the decision based on need for titration as well as tolerability and safety issues for the individual patient. Memantine is currently not FDA approved for mild dementia.

**Recommendation 5b: Patients first diagnosed with moderate Alzheimer’s disease should be treated using combination therapy with a cholinesterase inhibitor and memantine.** For patients who progress from mild to moderate Alzheimer’s disease, memantine should be added to therapy with a cholinesterase inhibitor.

The panel recognized studies demonstrating that, in clinical practice, ~50% of patients are diagnosed at the moderate stage of Alzheimer’s disease. At this stage, the panel endorsed the use of combination therapy with a CHEI and memantine. Although the panel recognized that only one 6-month trial (comprising 198 patients receiving donepezil + memantine and 197 receiving donepezil or placebo) found that

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adding memantine to a CHEI (donepezil) improved cognition and global functioning, the panel’s clinical experience supported the view that combination therapy conferred added benefits over the use of a single agent.

The panel recommended starting a CHEI and then adding memantine at least 2 months after the CHEI reaches an optimal dose and adverse effects have been minimized. When adding memantine, the CHEI dose does not need to be reduced. The panel also recommended that monotherapy with memantine be reserved for those patients with moderate to severe disease who have demonstrated that they do not tolerate a CHEI.

Recommendation 5c: Patients first diagnosed with severe Alzheimer’s disease should be treated with memantine. Combination therapy with a cholinesterase inhibitor can be added.

When a patient presents with severe Alzheimer’s disease, memantine should be prescribed as initial therapy. At the time of this writing, memantine is the only medication FDA approved for severe Alzheimer’s disease, although clinical trials have demonstrated efficacy of a CHEI (donepezil) in patients with severe dementia. (Prior to publication, donepezil received FDA approval for moderate to severe dementia on October 13, 2006.) The panel therefore recommended that, in patients who progress to the severe stage of the disease while taking a CHEI, the CHEI should be continued and memantine should be added if not previously instituted. If a patient is started on memantine when diagnosed with severe Alzheimer’s disease, a CHEI can be added later.

The panel recommended continuation of antidementia therapy into profound stages of dementia only if there is evidence of continued benefit. The panel recognized that patients with profound or end-stage disease with little or no function are unlikely to benefit from antidementia therapy.

Recommendation 6: Monotherapy with memantine may be used at the mild stage of the disease when a cholinesterase inhibitor is not tolerated or in combination with a cholinesterase inhibitor when the disease is progressing rapidly.

The panel recommended that memantine should be used as monotherapy at mild stages of the disease only in patients who do not tolerate a CHEI. The panel also recommended that a rapidly progressing patient with mild disease in the absence of reversible causes (see Recommendation 13) may benefit from the addition of memantine to therapy with a CHEI.

Recommendation 7: All patients should receive the same course of treatment, regardless of the setting of care.

The panel recommended that all patients with newly diagnosed mild to moderate Alzheimer’s disease should be started on a CHEI and that the setting of care should not determine the course of treatment. These recommendations include patients in community settings as well as in assisted living or long-term care facilities.

Recommendation 8: Patients with mixed dementia (Alzheimer’s disease and vascular dementia), pure vascular dementia, dementia with Lewy bodies, and Parkinson’s dementia may be treated according to these Alzheimer’s disease guidelines.

The panel recommended the use of antidementia therapy, particularly CHEIs, in patients with DLB and Parkinson’s dementia. The panel noted evidence for cholinergic deficits in these syndromes, and also noted one placebo-controlled trial showing behavioral improvement with a CHEI in DLB and another demonstrating cognitive and functional benefit in patients with Parkinson’s dementia. Based in part on the results of the Exelon in Parkinson’s Disease Dementia Study, the European Union approved the use of rivastigmine and an FDA advisory committee gave a favorable opinion on the use of rivastigmine in mild to moderate Parkinson’s dementia. Systemic data assessing memantine for these indications are lacking, but most panelists would also use memantine for these conditions as a second agent in addition to a CHEI.

Patients suspected of having vascular dementia frequently have Alzheimer’s disease as well, and pure vascular dementia is probably uncommon in geriatric patients. Vascular dementia accounts for 15% to 20% of all cases of dementia. Controlled clinical trials have suggested cognitive benefits of using CHEIs and memantine in vascular dementia. Preclinical studies indicate a rational basis for use of these agents with mixed and vascular dementia. Therefore, the panel recommended that clinicians consider employing antidementia therapy in patients suspected of having mixed dementia or pure vascular dementia.

Recommendation 9: Patients with frontotemporal dementia should be referred to a specialist.

Patients with FTD should be referred to a neurologist for further evaluation and treatment. The panel concluded that there is no evidence that the available antidementia pharmacologic therapies are effective in FTD.
Recommendation 10: The use of other medications to treat dementia—such as hormones, nutraceuticals, and vitamins—is not recommended.

Estrogens, dehydroepiandrosterone, ginkgo biloba, vitamins E and C, and other medications and nutraceuticals without demonstrated efficacy in Alzheimer’s disease are not recommended. A single study suggested that high-dose vitamin E (1000 IU BID) may have value in the treatment of Alzheimer’s disease. However, since recent studies indicate that high-dose vitamin E (400 IU/d) may lead to a slightly statistically significant increase in mortality, especially in patients with heart disease, the panel recommended against the routine use of high-dose vitamin E.

Recommendation 11: Newly diagnosed patients should be re-evaluated within 2 months, and then monitored at least every 6 months thereafter, to ensure appropriate treatment and care management.

The panel recognized that patients have continuing care management needs and may improve, remain stable, or decline while receiving pharmacotherapy. Patients should be re-evaluated within 2 months after therapy is initiated to determine tolerability, and then again at a minimum of 6-month intervals to assess for efficacy. Follow-up should determine whether there are any beneficial cognitive, functional, or behavioral effects (including stabilization or slowed progression) and/or adverse events, and evaluate the quality of care management. The methods used to evaluate cognitive, functional, and behavioral ability at the time of diagnosis should be repeated at subsequent visits. Rapid declines in function (as discussed in Recommendation 13) may indicate a need to re-evaluate the diagnosis, search for other medical causes of decline, maximize antidementia therapy drug dosages, or institute the use of combination therapy.

Recommendation 12: Patients and caregivers should be counseled with regard to “realistic” expectations of antidementia pharmacologic treatment.

Counseling caregivers with regard to expectations of antidementia therapy based on the results of clinical trials is critical to appropriate therapy in clinical practice. Given that dementia is a chronic progressive disease, 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 to antidementia therapy occurs when the patient’s symptoms progress more slowly than expected without therapy. Determining this in clinical practice may be difficult and subjective, but on average, untreated patients with dementia lose ~2 to 4 points per year on the MMSE and experience some decline in functional ability. A “poor” response occurs when the patient’s symptoms are progressing at a rate that is consistent with no therapy. The panel recognized that this definition of a poor response in clinical practice is subjective and based on clinical judgement when performed outside the context of a clinical trial.

Although patients receiving antidementia therapy are still expected to have symptomatic decline over time, clinical trials suggest that this decline is delayed with the use of such therapy. The panel recognized the difficulty in objectively demonstrating differences in rate of decline outside of a clinical trial setting. Thus, based on the extensive results from clinical trials and the difficulties of monitoring progression in clinical practice, the panel recommended that, unless contraindicated, antidementia therapy should be empirically continued unless there is clear evidence that such therapy is no longer effective.

Recommendation 13: If a patient deteriorates on antidementia therapy at an unexpectedly rapid rate, potentially reversible causes of cognitive and/or functional impairment—such as cognitive impairment due to medical comorbidities, the effects of other drugs, behavioral disturbances, or delirium—should be considered.

When a patient exhibits significant and rapid deterioration in cognition or function during the use of CHEIs and/or memantine, the physician should evaluate the patient for potentially reversible causes. These include the effects of other drugs the patient may be taking; infections or other metabolic disturbances causing delirium; poorly controlled medical comorbidities such as cerebral vascular hypoperfusion due to congestive heart failure; ischemia or stroke due to hypertension, DM, hyperlipidemia, or atrial fibrillation; or the presence of poorly controlled behavioral disturbances or mood disorders. Similarly, drugs with anticholinergic activity commonly employed in geriatric patients occasionally have cognitive side effects, and their use should be assessed. Examples of these anticholinergic drugs include those used to treat urinary incontinence such as cimetidine, prednisolone, theophylline, digoxin, nifedipine, furosemide, ranitidine, isosorbide dinitrate, warfarin, diprydamole, codeine, triamterene with hydrochlorothiazide, and captopril.
Recommendation 14: Cholinesterase inhibitors and memantine may be discontinued in patients who advance to “profound” disease and who have lost all cognitive and functional abilities.

Although the panel recommended ongoing pharmacology throughout the course of the disease, it also believed a patient who is in the profound stage of the disease may be discontinued from therapy. The panel defined profound disease as a stage when there is no preserved cognition or function.

Recommendation 15: Antidementia therapy should be continued during acute illness and hospitalizations, unless contraindicated. If stopped, it should be resumed as quickly as possible.

The continuation of antidementia therapy is critical to its ongoing efficacy. Experience and some published data have shown that a period of interruption can result in significant loss of cognition and function that may not be recoverable, or may result in the development of behavioral problems. The panel determined that there may be adverse consequences of discontinuing a CHEI for even a few weeks. Therefore, antidementia therapy should be continued during periods of acute illness and hospitalizations, except in cases where the patient can take nothing by mouth or if the medications must be stopped during a hospital evaluation. Should any of these cases occur, therapy should be resumed as soon as possible.

Antidementia therapy should also be maintained during transitions from one care setting to another, such as from subacute or long-term care. The panel noted that transitions due to functional decline may afford a chance for re-examination of current treatment patterns and present the possibility of adjustment or discontinuation of antidementia therapy if the patient has progressed to a profound dementia status.

Recommendation 16: Antidementia drugs are well tolerated in patients with medical comorbidities. However, appropriate adjustments must be made for patients with hepatic and renal failure.

The panel concluded that antidementia drugs are generally well tolerated in most patients, even in those with multiple medical comorbidities. However, appropriate adjustments must be made for patients with renal and hepatic failure.

Drug–drug interactions may also be problematic in geriatric patients taking multiple medications, particularly drugs with anticholinergic effects (see Recommendation 13). Many drugs with high anticholinergic activity may affect cognition. Previous studies have documented that dementia patients are more likely to use anticholinergic agents, including the concomitant use of CHEI and anticholinergic agents. Patients with conditions that could be exacerbated by CHEI drugs should be evaluated on a case-by-case basis for potential drug–disease interactions. These may include cardiac conditions such as angina, cardiac conduction disease, and congestive heart failure; orthostatic hypotension and/or falling due to gait problems other than parkinsonism; chronic obstructive pulmonary disease; liver disease; renal failure; prostatic hypertrophy; and gastrointestinal disease, including peptic ulcers. Memantine dosing should also be adjusted in patients with renal impairment.

Recommendation 17: Geriatric care management and counseling should be provided to all patients with a diagnosis of Alzheimer’s disease and to their caregivers.

Due to the complex medical and care management issues of dementia, the panel recommended that counseling and geriatric care management should be provided to all patients who have been diagnosed with ADRDs and to their caregivers. Evidence supports the view that counseling for dementia has value. Physicians (particularly primary care physicians), other provider MCO medical management programs, and public service organizations, such as the Alzheimer’s Association, can provide such counseling.

Case managers in managed care plans should be trained in the specific elements of Alzheimer’s disease care management, including early detection, nonpharmacologic behavior management, referral coordination, caregiver and family support, placement assistance, and social supports, including home care and adult day care as appropriate. Alzheimer’s disease care management should also include referrals for discussions of advanced directives, proxy assignment, and durable power of attorney, as well as financial planning for long-term care and medical assistance, as needed.

Other important issues in the management of patients with ADRDs are behavior problems and depression, and their treatment. A full discussion of these issues is beyond the scope of these guidelines. However, reviews of these subjects are available elsewhere.

Recommendation 18: Cholinesterase inhibitors and N-methyl-D-aspartate antagonists should be distinguished as 2 separate classes of drugs under
Medicare Part D formulary guidelines, as patients need access to both classes.

Due to the value of antidementia therapy in reducing the overall clinical and financial burden associated with Alzheimer's disease, as well as the panel's recommendation for combination therapy in clinical practice, the panel concluded that CHEIs and NMDA receptor antagonists be included in Medicare Advantage and prescription drug plan formularies as distinct classes to ensure that both classes of agents will be available to members.

Recommendation 19: Antidementia therapy should be accessible as a preferred formulary product to reduce the out-of-pocket cost to patients and encourage appropriate utilization.

Patients—particularly the frail and indigent elderly—may either not fill prescriptions, or refill prescriptions and then skip or cut doses of necessary medication because of financial concerns.

Therefore, the panel recommended that antidementia therapy be provided to patients in a preferred formulary position to ensure appropriate utilization, compliance, and persistence.

Recommendation 20: Medicare managed care organizations should not discriminate against use of antidementia therapy through administrative burdens such as preauthorization and appeals.

Loss of cognitive and daily function due to dementia substantially impacts a patient's quality of life. Ease of access is essential to providing antidementia therapy to this particularly frail and frequently indigent elderly population. Financial and administrative burdens on physicians, patients, and caregivers are barriers to providing adequate and appropriate care. Medicare MCOs should not discriminate against antidementia therapy by implementing formulary design strategies imposed to create hurdles to appropriate utilization, such as preauthorization requirements and medical necessity appeals for ongoing utilization across stages of the disease.

DISCUSSION AND CONCLUSIONS

ADRDs represent a significant clinical and economic burden to individuals and society, including Medicare MCOs. Appropriate utilization of antidementia therapy and care management is vitally important to achieving quality of life and care for dementia patients and their caregivers, and for managing the excess costs of Alzheimer's disease. The recommendations presented here represent the consensus opinion of an expert panel comprising an interdisciplinary group of experts from academia, medical practice, managed care, and public policy. The recommendations attempt to translate the most recent investigational data into clinical practice and managed care medical management. Although the recommendations for many of the issues addressed here are not—and in many cases cannot be—strictly based on evidence at this time, they are, in fact, based on available literature as well as clinical experience. The issues addressed include relevant, practical, and timely concerns that are faced on a daily basis by practitioners and by Medicare MCO medical management programs in the care of dementia patients. In both clinical practice and in Medicare MCOs, medical management issues often arise that cannot be clearly and conclusively resolved by available research data. In these cases, decision makers—such as practicing physicians and Medicare MCO medical and pharmacy directors—must make critical decisions about utilization of therapies for individual patients. In this “practice of medicine” setting, expert opinion can guide decision making until conclusive data are available.

Cognition and function are key drivers of quality of life and costs for dementia patients, their caregivers, and society. Nevertheless, the value of antidementia therapy continues to engender ongoing debate. Most elderly persons with dementia suffer multiple medical comorbidities. In comparing the relative value of therapy for these medical illnesses, a number-needed-to-treat (NNT) analysis based on clinical trial data may be useful. As seen in Table III, the NNT approach indicates that antidementia therapies have clinical value compared with therapies for other conditions, especially for geriatric patients for whom cognition is a key outcome. Effect sizes for dementia therapy have also been calculated and are comparable to effect sizes for other conditions.

These consensus recommendations attempt to describe a reasonable current standard for the provision of quality care for patients with dementia. The panel recommendations support the use of screening for cognitive impairment and the use of antidementia therapy for ADRDs in different stages of disease and types of dementia in all clinical settings. Recommendations for using these medications are made with an appreciation of the difficulties in translating the results from investigational clinical trials into clinical practice.

The recommendations of the expert panel represent a clear consensus that nihilism in the diagnosis, treatment, and management of ADRDs is unwarranted, impairs quality of care, and is ultimately not cost-effective.
Table III. Comparison of number-needed-to-treat (NNT) analysis for dementia outcomes versus outcomes in other common conditions in the elderly.28,30,101,102

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Outcome Prevented</th>
<th>Treatment Duration, y</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Hip fracture</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Statins</td>
<td>Myocardial infarction</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Death in congestive heart failure</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Antihypertensives (meta-analysis)</td>
<td>Major event (myocardial infarction, stroke, or death)</td>
<td>5</td>
<td>29–86</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Improved cognition</td>
<td>0.25</td>
<td>6–12</td>
</tr>
<tr>
<td>Cholinesterase inhibitor (meta-analysis)</td>
<td>Global decline</td>
<td>≤1</td>
<td>12</td>
</tr>
<tr>
<td>Cholinesterase inhibitor (donepezil)</td>
<td>Loss in activities of daily living</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Cholinesterase inhibitor (donepezil)</td>
<td>Nursing home placement</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Memantine</td>
<td>Global decline</td>
<td>&lt;0.5</td>
<td>3–9</td>
</tr>
<tr>
<td>Memantine</td>
<td>Cognition</td>
<td>&lt;0.5</td>
<td>7–10</td>
</tr>
<tr>
<td>Memantine</td>
<td>Function</td>
<td>&lt;0.5</td>
<td>8–10</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme.
*All drugs listed are used in mild to moderate dementia with the exception of memantine, which is used in moderate to severe dementia.

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