Position Statement of the American Association for Geriatric Psychiatry Regarding Principles of Care for Patients With Dementia Resulting From Alzheimer Disease

Constantine G. Lyketsos, M.D., M.H.S., Christopher C. Colenda, M.D., M.P.H., Cornelia Beck, Ph.D., R.N., F.A.A.N., Karen Blank, M.D., Murali P. Doraiswamy, M.D., Douglas A. Kalunian, M.D., Kristine Yaffe, M.D.

POSITION

There exists currently an effective, systematic care/treatment model for patients with dementia resulting from Alzheimer disease (AD). This consists of a series of therapeutic interventions—pharmacologic and nonpharmacologic—targeted at patients with AD and their caregivers. Although these interventions do not produce a cure of the underlying disease and do not appear to stop its progression, they have been shown to produce benefits for patients and their caregivers. The aims of this care model, often referred to as "Dementia Care," are to delay disease progression, delay functional decline, improve quality of life, support dignity, control symptoms, and provide comfort at all stages of AD. This evolving model is based on scientific evidence of beneficial outcomes, with acceptable risks, and is increasingly targeted at an improving pathophysiological understanding of the biology of AD. Although the evidence is limited, the existing evidence, coupled with clinical experience and common sense, is adequate to produce a minimal set of care principles. In this context, the American Association for Geriatric Psychiatry (AAGP) affirms that there now exists a minimal set of care principles for patients with AD and their caregivers. Consequently, the detection and treatment of AD must now be considered part of the typical care practices for any physician and other licensed clinicians who interact with patients with this disease. This document articulates these principles of care.

DEFINITIONS

Cognitive Impairment No Dementia (CIND)

A clinical syndrome consisting of measurable or evident decline in memory or other cognitive abilities with little effect on day-to-day functioning that does not meet criteria for dementia as defined by *DSM–IV–TR*.[1]

This statement was prepared by a Task Force authorized by the AAGP Board of Directors and was then adopted by the AAGP Board at its September 14, 2005, meeting. The Task Force consisted of Constantine Lyketsos (Chair), Christopher Colenda, Cornelia Beck, Karen Blank, Murali Doriaswamy, Douglas Kalunian, and Kristine Yaffe. Christine deVries, AAGP Executive Director, was instrumental in its development.

Mild Cognitive Impairment (MCI)

A clinical syndrome that is a subgroup of CIND with prominent amnestic symptoms that is in all likelihood a prodrome of AD.

Dementia

A clinical syndrome, that is not entirely the result of delirium, consisting of global cognitive decline with memory plus one other area of cognition affected with significant effects on day-to-day functioning and meets *DSM–IV–TR* criteria.

Dementia Resulting From Alzheimer Disease

The most common type of dementia characterized by decline primarily in cortical aspects of cognition and following a characteristic time course of gradual onset and progression.

Alzheimer Disease

A specific degenerative brain disease characterized by senile plaques, neuritic tangles, and progressive neuronal loss; also, the presumptive cause of AD.

CONTEXT OF THIS POSITION STATEMENT

The aim of this statement is to assert the position of the AAGP regarding the existence of specific principles of care for patients with AD for the purpose of improving care, and access to care, for patients with AD and their caregivers. This statement also aims to provide clinicians with guidance about the key elements of these care principles and about the reasons for which this care should be made available to patients with AD and caregivers. Because this is a position statement about treatment, it is assumed that appropriate diagnostic confirmation of AD has been carried out before the application of this model of care.

Being a position statement, not a practice guideline or parameter, this statement reflects the beliefs and opinions of the members of a professional association with special expertise in the care of patients with AD. As much as possible, this statement is based on the available evidence and is an effort to articulate best principles of care by synthesizing the available evidence with clinical judgments and practices. However, it is recognized that available evidence is not conclusive in most cases and that there are differing views and opinions about how to implement dementia care. Nevertheless, it is important from time to time to produce statements such as this as a guide to clinical practice.

The statement is targeted at AAGP members, other physicians, and other licensed clinicians who care for people with dementia. Although there are similarities in the care of patients with all types of dementia, this document is intentionally targeted at AD, not other forms of dementia, so as to retain focus, because most of the evidence supporting the effectiveness of dementia care is derived from studies of patients with AD and because AD is the most common form of dementia. The reader is referred to other documents regarding the care of patients with non-Alzheimer dementia. Furthermore, this document is not targeted at "mild cognitive impairment" (MCI), considered by many to be the earliest clinical manifestation of AD, because the evidence base regarding the treatment of the latter is limited and in evolution.

This position statement is intended to encompass clinical care for patients with AD in typical clinical settings (e.g., primary care, specialist care, and long-term care, including assisted living environments). Given its scope and purpose, this document intentionally does *not* address nonclinical aspects of dementia care as related to diagnostic tests, research, policy, or reimbursement for care. The reader is referred to other AAGP position statements involving the latter.

WHY THIS DOCUMENT NOW

Dementia is a major public health problem already that is expected to worsen given the aging of the population. Over 4.5 million Americans have the most common form of dementia, AD; this number will likely triple in the next 40–50 years.[2] Despite the commitment of significant effort and resources to the development of curative therapy for AD, a cure remains many years, possibly decades, away. In the

meantime, it is important that medical professionals care for patients who currently have the disease, and their caregivers, using the most advanced methods available. The public has an increasing awareness of AD and is presenting to the healthcare system for care in ever-increasing numbers. Improvements in the diagnosis and the understanding of the biology of AD and significant evidence to support the effectiveness of therapies for AD all contribute to the timeliness of this position statement. The evidence base supports the effectiveness of the dementia care "package," which has been shown now in a variety of clinical settings to have wide-ranging benefits for patients and caregivers with regard to delay of functional decline, control of many symptoms, maximization of quality of life, and delay of disability and institutionalization. The evidence supporting dementia care has been extensively articulated in a series of Practice Guidelines, Care Parameters, Consensus Statements, Conference Proceedings, scientific papers, and books proposed previously by AAGP, and also by the American Psychiatric Association, the American Academy of Neurology, the Alzheimer Association, the federal Agency for Health Care Policy and Research (now AHRQ), and others. Despite this, detection rates for dementia remain low overall, no better than a decade ago,[3] and the Guidelines are probably not being followed in most settings where dementia patients are seen, in part as a result of failure to detect.[4,5] In the current climate where there is evidence of treatment efficacy, for treatment albeit not cure, it is incumbent on professional organizations such as AAGP to assert minimal care principles for the medical profession in their areas of expertise.

ORGANIZATION OF THIS DOCUMENT

The remainder of this document articulates general principles of dementia care, encompassing the full spectrum of available treatments, both pharmacologic and nonpharmacologic, organized around the following key areas of therapy:

- Disease therapies for AD, targeted specifically at aspects of the current pathophysiological understanding of the disease;
- Symptomatic therapies for cognitive symptoms;
- Symptomatic therapies for other neuropsychiatric symptoms;
- Interventions targeted at, and the provision of, supportive care to patients; and
- Interventions targeted at, and the provision of, supportive care to caregivers.

DISEASE THERAPIES FOR ALZHEIMER DISEASE TARGETED SPECIFICALLY AT ASPECTS OF THE CURRENT PATHOPHYSIOLOGICAL UNDERSTANDING OF THE DISEASE

A detailed discussion of the current understanding of the complex pathophysiology of AD is beyond the scope of this document. Briefly, this understanding implicates the misprocessing of the amyloid precursor protein (APP) as the key initial event. Processing of this protein in brain neurons through the beta secretase pathway leads eventually to the deposition of insoluble deposits referred to as beta amyloid plaques, eventually leading to synaptic failure, neuronal injury, formation of tangles of hyperphosphorylated *tau* protein, and apoptotic neuronal death. The loss of neuronal systems leads to the loss of multiple neurotransmitters, which in turn lead to the emergence of the cognitive, other neuropsychiatric, and functional symptoms of the disease. This process occurs over years, perhaps even decades, before the onset of symptoms. If the amyloid hypothesis is correct, and there are reasons to think that it may not be the whole story, the ideal disease therapy for Alzheimer brain disease would be one that either prevents the deposition of beta amyloid plaques or one that prevents the synaptic and neuronal damage caused by these plaques. Several treatments along these lines are in development, some in early human trial phases. The most promising are medications that diminish the production of the toxic, insoluble forms of beta amyloid, and "immunotherapies," both passive and active, that are intended to remove beta amyloid from the brain.

In addition to directly targeting amyloid deposition or clearance, several factors have been identified as "accelerators" of the AD progression, some of which are being or have been considered as targets of therapy. These include:

- Postmenopausal loss of estrogen in women;
- Inflammatory response;
- Oxidative free radicals;
- Brain vascular disease;
- High cholesterol; and
- Glutamate excitoxicity.

Estrogen replacement, with and without progesterone, has been studied extensively as a treatment or preventive for Alzheimer dementia. Although epidemiologic studies and early clinical trials were promising, several trials have concluded that estrogen replacement does not attenuate dementia progression.[6,7] There is some suggestion from epidemiologic studies that estrogen replacement for a 5–10-year period soon after menopause might delay or prevent the onset of Alzheimer decades later,[8] but this hypothesis will be very difficult to test. *For now, estrogen is not an appropriate therapy for AD.*

The association of brain inflammation with AD has led to several tests of the hypothesis that antiinflammatory treatment may delay the progression of AD dementia.[9] Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and indomethacin have been associated with a lower risk of developing AD in several epidemiologic studies. However, there is a long-term risk of gastrointestinal bleeding and renal disease and now evidence that NSAIDs are associated with rare cardiovascular toxicity. Thus far, trials of prednisone[10] and NSAIDs[11–15] have suggested that antiinflammatory treatments are not effective for AD. *At present, antiinflammatory agents are not recommended for the treatment of AD and should not be used for this purpose.*

The association of oxygen free radicals with AD dementia has raised the question of whether antioxidant therapy in AD is warranted. Epidemiologic evidence supports the concept that vitamin E, perhaps in combination with vitamin C, may prevent AD.[16] In addition, there has been one randomized trial that suggested high-dose vitamin E, 2,000 IU/day, might delay the progression of functional decline in AD.[17] The trial, however, had methodological weaknesses that made its findings less compelling. Nevertheless, the American Psychiatric Association and the American Academy of Neurology treatment guidelines for AD both recommend consideration of high-dose vitamin E as a treatment option. This recommendation is tempered by recent findings that vitamin E therapy did not delay progression of MCI to AD,[18] a putative precursor clinical state to Alzheimer dementia, and by findings from a meta-analysis, that vitamin E in very high doses increased mortality in older people.[19] *Although vitamin E may still be an option to be considered for AD, given concerns about mortality, however small, doses above 400 IU per day should probably be avoided.*

The over-the-counter antioxidant ginkgo biloba, and its putative active form EGB in doses of 120 mg/per day or higher, may have some efficacy in treating dementia as some trials suggest.[20] However, the effect is likely to be small, and safety concerns have been raised about the use of over-the-counter substances for long time periods in the absence of extensive testing or careful manufacturing oversight for purity. *Therefore, in general the use of ginkgo is not recommended for AD.*

There is now strong evidence that brain vascular disease plays a role in the progression of Alzheimer dementia in two ways. First, brain vascular disease may add to the cognitive impairment of dementia for a given amount of Alzheimer pathology in the brain.[21] This should be no surprise because two pathologic processes would be expected to worsen the clinical syndrome of dementia. Second, brain vascular disease has been implicated as a factor in the development of the Alzheimer pathology,[22] perhaps by accelerating amyloid deposition and by increasing amyloid toxicity to synapses or neurons. *Therefore, the management of vascular brain disease and its associated risk factors is now part of the care for disease treatment for AD for patients with significant risk factors.* Control of high blood pressure is an important component of this. The level of control is somewhat controversial, but at least one clinical trial has suggested that maintaining systolic below 140 mm Hg is associated with less rapid dementia progression.[23] Treatment of hypercholesterolemia, homocystinemia, and hyperglycemia are other aspects of this approach. Therefore, the treatment of patients with dementia should include monitoring of blood pressure, glucose, cholesterol, and homocysteine and the initiation or modification of appropriate interventions when indicated. *For patients with AD* plus *significant brain vascular disease, initiation of low-dose aspirin therapy or, if appropriate, of other forms of anticoagulation should be seriously considered as a treatment that might prevent the worsening of dementia.*

Evidence is emerging that links high levels of cho-

lesterol, APP metabolism, and the risk for AD. The e-4 allele of apolipoprotein E gene is involved in the central nervous system (CNS) distribution of cholesterol among neurons. Although the exact mechanism by which cholesterol effects Ab1-42 production is not known, several retrospective observational studies have found that the chronic use of 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors (statins) are associated with a decreased risk of developing AD.[24] A randomized, controlled trial using pravastatin over three years, however, did not demonstrate a significant effect on cognitive function in elderly individuals at risk for cardiovascular disease.[25] *Although HMG-CoA reductase inhibitors ("statins") may hold promise for prevention of AD, current data suggest they are not indicated to treat AD other than in the context of their use to reduce plasma cholesterol levels.*

Glutamate is the main excitatory neurotransmitter in the CNS. Glutamate excitotoxicity has been implicated in the etiopathogenesis of AD. Injured or dying glutamate-producing neurons will under certain conditions release large amounts of glutamate in their synaptic clefts leading to toxicity and death in the downstream neurons of their synaptic connections. An increase of extracellular glutamate is believed to increase NMDA-receptor activation that increases intracellular accumulation of Ca++[26]. Increased intracellular Ca++ in turn activates a series of intracellular systems such as the caspase system, leading to cell death. Memantine, an NMDA noncompetitive antagonist, protects cells from glutamate-activated excitotoxicity. Two randomized, controlled trials have reported benefits in advanced stages of dementia on measures of Clinical Global Impressions of Change and behavior scales, although one study found that the intention-to-treat analysis with last observation carried forward revealed no difference between placebo and memantine.[27,28] Memantine–donepezil combination therapy for severe AD was superior to donepezil alone in a recent six-month randomized trial.[29] Safety data so far are very good, also suggesting that memantine can be administered safely with cholinesterase inhibitors such as donepezil. Recent pharmacoeconomic analysis of memantine in moderate-to-severe AD concluded, despite limitations of the data available for analysis, that memantine is a cost-effective treatment at this point in time.[30] Given mechanistic, clinical trial and economic data, memantine is indicated for moderate-to-severe AD, and its use earlier in milder dementia may be justified. *In this light, a discussion with patients of the pros and cons of memantine is now part of the care for patients with AD with moderate to severe dementia.*

SYMPTOMATIC THERAPIES FOR COGNITIVE SYMPTOMS

One of the earliest pathologic findings associated with AD was the loss of neurons in the nucleus basalis, the main origin of cholinergic neurotransmission to the cortex. Although the cholinergic hypothesis of AD has lost favor in light of the amyloid hypothesis, overcoming this cholinergic deficit of AD continues to be a mainstay of treatment for the cognitive symptoms of the disease. Several lines of evidence suggest that acetylcholine (ACh) neurotransmission is important to the normal functioning of memory. Inhibitors of acetylcholine such as atropine or diseases that reduce acetylcholine levels such as AD lead to memory loss.

Approaches taken to increase acetylcholine levels in diseased brains include increasing production by providing the chemical precursors, directly stimulating the ACh receptor or delaying breakdown of the ACh that is naturally produced. It is not feasible to give ACh directly because it is very short-lived in the body. Acetylcholine precursors such as choline and lecithin are taken up by brain neurons to make more ACh. They are not effective in the treatment of memory disorder or AD, however. Direct stimulation of cholinergic postsynaptic receptors (through nicotinic and muscarinic agonists) is still under investigation but does not appear too promising both as a result of safety concerns and as a result of limited efficacy. The most successful approach has been to reduce the naturally occurring degradation (breakdown) of acetylcholine. Acetylcholine is normally degraded through an enzyme known as acetylcholine esterase (AChE), which is floating outside neuronal cells in brain tissue. Inhibition of AChE results in increased acetylcholine levels because of reduced degradation.

The U.S. Food and Drug Administration (FDA) has approved four drugs, tacrine, donepezil, rivastigmine, and galanthamine, for the treatment for AD. In addition, Huperzine-A, an over-the-counter "nutriceutical," has been shown to have cholinesterase ac-

tivity and may have efficacy as a treatment of the cognitive symptoms of AD in some clinical trials. However, Huperzine-A has not been adequately tested for this purpose and, given the alternative agents, is not high on the list of possible treatments.

In terms of the four FDA-approved cholinesterase inhibitors (CEIs), tacrine should not be used in light of the alternatives, its complex titration, and associated risk of hepatic toxicity.

Over a dozen controlled, 3–6-month duration trials have reported that CEIs can improve or slow cognitive losses and improve global functioning (relative to placebo) in mild to moderate AD. Regarding the long-term effects of these medications, one 12-month study marginally missed significance on its primary end point and open studies that have been reported are subject to biases, so that there is a need for confirmatory long-term controlled trials. One study of donepezil (known as "AD2000") did not report significant cognitive or functional benefits at 36 months, but these results remain controversial because of the study design and sampling issues. Some preliminary data suggest that CEIs may also delay nursing home placement, reduce caregiver stress, and yield economic benefits.

In very mild or more severe AD, the benefits of CEI are less well proven. One 6-month randomized, controlled trial of donepezil in moderate to severe AD found significant benefits to both cognition and global function. Another 6-month randomized, controlled trial of donepezil in very mild AD reported significant benefits on some cognitive measures but not on a global measure. There are no published trials with rivastigmine or galanthamine in very mild or in moderate to severe AD.

The available direct comparison studies of CEIs (12–48 weeks) have found no consistent differences in efficacy despite some differences in tolerability and dropout rates. To date, there are no published long-term trials directly comparing all three agents, and the conduct of such a study by an independent entity will enhance the field.

Benefits of treatments in individual patients can be difficult to judge but may manifest initially as either improvement or stabilization. Most clinicians and experts in this area agree that at least for some patients, albeit a small number, CEIs make a notable clinical difference. Over longer periods, a slowing of cognitive and functional losses is the expected benefit. Although there is still disagreement on what should be the minimum duration of a therapeutic trial, it is reasonable that patients who are tolerating these agents be tried on them for at least 6 months (which is the duration of the key trials that showed therapeutic benefits).

The evidence regarding combined use of CEI with memantine is better than the evidence regarding switching between agents or combining two CEIs, although there is much need for additional data. Both memantine and CEIs are approved for moderate AD and hence clinicians have a choice of which agent to start therapy based on factors such as ease of use, patient preference, cost, and safety issues. In judging treatment response, clinicians should always seek information from a reliable informant, take into account dementia and general health fluctuations, and evaluate changes in cognition, function, and behavior. It is also important to educate the family on realistic expectations to enhance compliance. Families should also be cautioned that abrupt discontinuation can occasionally lead to worsening cognition or behavior.

The CEIs are the class of drugs with the strongest evidence supporting their efficacy in treating the cognitive symptoms of mild to moderate AD and should be considered as part of the care for all such patients who do not have contraindications as long as they are used after careful education of patients and their caregivers and with careful and ongoing assessment of the benefit–risk after they have been initiated.

SYMPTOMATIC THERAPIES FOR OTHER NEUROPSYCHIATRIC SYMPTOMS

General Approach

Although cognitive deficits are the clinical hallmark of dementing diseases, including AD, noncognitive neuropsychiatric symptoms (NPS) are nearly universal, affecting over 90% of patients with AD, and can influence the presentation and course of the dementia.[31] These NPS of dementia include agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among others. In addition, an affective disturbance, referred to as "depression of Alzheimer disease" or "Alzheimer-asso-

ciated affective disorder" affects as many as 50% of patients with AD at all dementia severities.[32] NPS, especially behavioral disturbances, are more common in later stages and are associated with increased hospital lengths of stay, increased nursing home placement, as well as caregiver stress and depression. Interventions aimed at treating NPS have a tremendous positive impact on patients, caregivers, and society. *The detection, management, or treatment of all forms of the noncognitive neuropsychiatric symptoms is a key part of the care of AD.* Detection can be accomplished reliably in everyday clinical practice with high reliability using systematic interviews of patients and caregivers such as through the use of the Neuropsychiatric Inventory (NPI) or its questionnaire version, the NPQ.[33]

Once a noncognitive NPS have been detected, a series of activities are a critical part of the development of dementia care. These activities include:

- Differentiating which disturbance is present, for example, delirium, apathy, mood or affective disorder ("depression"), psychotic disorder (hallucinations, delusions), isolated sleep disorder, isolated resistiveness with care, or a specific behavior problem in the absence of those mentioned (such as wandering, restlessness, verbal agitation, or physical aggression);
- Considering possible contributing causes and the need for workup. For example, one or more of the following might be contributing causes: medications, medical illness (especially, pain, constipation, dehydration, urinary tract infection, upper respiratory infection, or other medical illness), cognitive symptoms, environmental precipitants, unsophisticated caregiving, unmet physical needs, or unmet psychologic needs; and
- Making sure contributing causes are *all* addressed and that basic needs are met, and then deciding if a specific additional treatment is needed.

Nonpharmacologic Interventions

Once NPS have been identified, differentiated, and contributing causes sorted out, specific tailor-made treatments are often needed. The principles of care require that nonpharmacologic interventions be tried first. Such interventions, often delivered through caregivers, might include *cognitive interventions* (reorientation; reminders, cues, task sequencing, or prompts), *environmental modifications* (adjustment of noise level; provision of familiar objects; reduction of clutter or visual distractors; use of pictures to provide cues), *changes in activity demand* (implementation of routines and scheduling, reduction in amount and complexity of activities), or *interpersonal approaches* (simplified language; use or avoidance of touch; focus on patient's wishes, interests, and concerns). The selection of specific nonpharmacologic therapies should be based on the unique characteristics of the patient, the caregiver, the availability of the therapy, the severity of the NPS, and the likelihood that the specific symptoms will respond to the specific therapy.

A recent systematic review of the literature identified several specific nonpharmacologic interventions that appear to be effective based on controlled trials for the NPS of dementia.[34] Cognitive stimulation, improved socialization (perhaps through the use of "adult day care"), or behavioral management techniques centered on either the patient's or the caregiver's behavior is the most effective treatments whose benefits might last for months. Specific education for caregivers about how to manage NPS has similar benefits, but other caregiver interventions do not. Music therapy, use of snoezelen rooms, and possibly sensory stimulation are useful ways of deescalating agitation and can reduce NPS during the treatment session but do not seem to have longer-term effects. Changing the visual environment such as through the provision of cues and visual cues to patients who wander may work for some patients. *Clinicians taking care of patients with dementia are behooved to become familiar with such techniques and either to develop the knowledge allowing them to implement these themselves or to develop referral sources to clinicians who have such expertise.*

Pharmacologic Therapies

Despite nonpharmacologic efforts, the management of noncognitive NPS often requires the introduction of medication therapies specifically targeted at these symptoms. There is no clear standard regarding which medications to use for which types of symptoms. Nevertheless, the principles of care require the use of medications when other approaches

have failed and there continues to be a need to treat or when the clinical situation presents sufficient urgency to require pharmacologic intervention before other approaches can be properly instituted. Generally speaking, a need to treat with medications exists when the NPS constitute a problem such as causing subjective distress to the patient or caregiver, interfering with function or causing disability, impeding the delivery of essential care, or posing a danger to self or others; the specific symptoms are likely to be medication-responsive (especially if they have failed to respond to other treatment modalities); a threshold of symptom severity, distress, disability, interference with care, or danger has been exceeded; and the balance between expected benefits and known risks of medication treatment is acceptable to the patient or surrogate decision-maker.

Medications should be used cautiously with defined targets and under close monitoring. Certain general approaches might be considered following a recently proposed algorithm[35] in which medications are used to treat underlying causes of delirium or distressing physical symptoms such as pain, dyspnea, and constipation. It is also reasonable to initiate therapy with a CEI for milder NPS, if the patient is not already on one, because they are well tolerated and may benefit cognition and function. Trials of CEIs have reported consistent, albeit rather small, positive effects on NPS. However, the data supporting this conclusion are from trials in which NPS were secondary outcomes.

If specific psychotropic medication therapy is to be instituted for the management of NPS, there are two reasonable approaches. One is to identify the target symptom and choose a medication that is known to treat a symptom most closely related to the one the patient is exhibiting. For example, one might use an antipsychotic for psychotic symptoms or an antidepressant for anxiety symptoms such as repetitive vocalizations or pacing. Although this approach is intuitive, randomized clinical trials have not been designed to confirm that this approach is effective.

An alternative approach is more empirically based, guided by the current state of evidence, and expert consensus in combination with the goal of minimizing adverse effects. Although there are multiple classes of drugs in use for treating NPS, including antipsychotics, antidepressants, anxiolytics, mood stabilizers, beta-adrenergic receptor blockers, and many others, there is limited evidence regarding the use of individual medications. Most atypical antipsychotics have moderately convincing evidence of efficacy for treating some NPS of dementia. There have been recent reports that newer atypical antipsychotics have been associated with infrequent but serious adverse events, including a small increased risk of death.[36] Typical antipsychotics such as haloperidol also may have efficacy in this context, but they should be used with caution as a result of concerns about side effects and because they too may be associated with similar small increases in risk of death.[37] Analyses focused on the number needed to harm for these adverse events must be assessed against findings from cost-effectiveness and cost-utility analyses of the effects of these drugs on patient and caregiver quality of life, survival, and costs of care.[38] Data from trials of other classes of drugs for NPS such as selective serotonin reuptake inhibitors (SSRIs) and "mood stabilizer" anticonvulsants are conflicting. At this point, it is clear that none of the medications in use for NPS offer a "magic pill" and the treatment effects have been modest.

In the absence of specific evidence for efficacy of individual medications, if nonpharmacologic interventions or ChIs have failed, the NPS of dementia are best treated with a range of other psychotropic medications following an empiric approach as recommended by a recent Consensus panel of experts[39] or established treatment guidelines.[40]

In light of a recent FDA "black box warning," physicians considering the prescription of atypical antipsychotics to treat the NPS of patients with AD should discuss the potential risks and benefits of such treatment with patients and their surrogate decision-makers, especially for patients with risk factors for cerebrovascular disease. It is important to emphasize that no psychoactive medication prescribed to treat NPS of dementia should be continued indefinitely and attempts at drug withdrawal should be made regularly. The reader is referred to a recent AAGP commentary on the matter.[41]

Given the complexities and risks involved in the pharmacologic management of NPS in AD, the principles of care require giving serious consideration to the involvement of a specialist such as a geriatric psychiatrist, geriatrician, or neurologist with specific expertise in the pharmacologic treatment of the NPS of AD.

INTERVENTIONS TARGETED AT AND THE PROVISION OF SUPPORTIVE CARE TO PATIENTS

General Approach

A key component of the principles of care involves the provision of proper supportive care to patients with AD. The specific interventions that individual patients require should be tailor-made to their condition and their circumstances and typically change with the progression of cognitive and functional decline associated with AD. Clinicians caring for patients with AD should become familiar with and or develop checklists (e.g., the checklists offered by Rabins et al.[42]) that will help them address systematically the elements of supportive care that the principles require. At a minimum, clinicians should be prepared to review such checklists and deliver appropriate supportive care interventions, or refer the patient to clinicians who are able to do so, as the circumstances may require.

Critical Intervention Areas

The following is a minimal checklist of issues to be addressed. The details involved in the specific approach to individual issues can be obtained from multiple sources, including books, practice guidelines, and the Alzheimer's Association web site (www.alz.org).

1. Safety Matters Should Be Addressed, Especially With Regard to Driving, Living Alone, Medication Administration, Environmental Hazards, Wandering, and Falls. Many books exist that can be provided to caregivers about how to safety-proof the home of a person with AD. An in-home occupational therapy assessment, using a functional assessment method such as the Assessment of Motor and Process Skills (AMPS), can provide information about level of care needs and medication administration and also about home safety. Patients with AD, especially those at risk for wandering, should be referred for enrollment in the Alzheimer's Association *Safe Return* or a similar program. In more severe dementia, fall risk should be assessed on an ongoing basis and walking aides or physical therapy intervention should be considered to prevent falls. Regarding driving,[43] rational recommendations can be made by clinicians provided the physician understands the substantial limits of current information and also the applicable local reporting laws. Department of motor vehicle reporting requirements vary by state. Research suggests that discontinuation of driving should be strongly considered for all patients with AD, even in mild dementia. Patients whose illness has progressed beyond the early stage of dementia should be advised to terminate driving, whereas those with very earliest manifestations should be referred for driving performance evaluation by a qualified examiner while noting the limitations in on road testing. Because of the expectation of progression, clinicians should reassess dementia severity and appropriateness of continued driving every six months.

2. The Day-to-Day Living of Patients Should Be Structured to Maximize Their Remaining Abilities and Function. This preserves their dignity, makes life easier for caregivers, and possibly encourages abilities to persist for longer periods of time. Clinicians should work with caregivers to find settings and environments in which limitations are minimized and remaining abilities maximized such as making sure that patients are well nourished and hydrated, are properly socialized, receive a minimal level of activity, have support for the performance of activities of daily living, and have good sleep hygiene. Setting up the environment is one specific approach that might be used to address this aspect of care. According to this, the environment is manipulated to achieve a balance between objective environmental demands and a patient's cognitive and physical competencies, in the following layers: 1) physical: manipulation to daily objects, structural elements or sensory aspects of environment; 2) task: manipulation to daily routines including communication, cueing techniques, and ways in which persons interact with objects; 3) social: manipulation to organization, composition and interactions of social groups; and 4) combination: manipulation to one or more of these.

3. General Medical Health Should Be Closely Monitored. Medical comorbidity is a major source of functional and cognitive impairment for patients with AD[44] and has been associated with accelerated cognitive and functional decline. Relatively minor medical illness can have a major impact on patients with AD. The prevention of delirium and the adverse

effects of medical illness is a major aspect of dementia care. The clinician should encourage general health maintenance, including exercise, annual influenza immunization, dental hygiene, necessary sensory aids, and good bowel routines, and in later phases of the disease, attend to basic requirements such as nutrition, hydration, and skin care. This is best accomplished by ensuring that the patient has a good primary care physician who is mindful of the special issues that arise in the care of patients with AD.

4. Advanced Care Planning and Advanced Directives. Because loss of decisional capacity can be anticipated, estate wills, advance directives, and durable powers of attorney for health care are necessary to extend the patient's autonomous decision-making. More evidence-based studies are needed to help determine the benefits of various assessments for determining capacity of patients with dementia to consent to clinical care and research participation. All patients retaining capacity should be strongly encouraged to complete advance directives for medical care and institutional placement, and be educated about the potential adverse consequences of not doing so. During the later stages, decisions about life-extending measures such as gastrostomy and intravenous hydration should respect advance directives by patients and incorporate participation from surrogate decision-makers.

INTERVENTIONS TARGETED AT AND THE PROVISION OF SUPPORTIVE CARE TO FAMILY CAREGIVERS

General Approach

A key component of the principles of care involves the provision of proper support to the family and other informal caregivers of patients with AD. Such interventions have been shown in controlled trials to enhance life quality for patients and caregivers, and to delay institutionalization for home residing caregivers. The specific interventions that individual caregivers require should be tailor-made to their condition and their circumstances, and typically change with the progression of cognitive and functional decline of the patient for whom they care. *Clinicians caring for patients with AD should become familiar with and or develop checklists that will help them address systematically the elements of supportive care for caregivers that the principles require. At a minimum, clinicians should be prepared to review such checklists and deliver appropriate supportive care interventions, or refer the patient to clinicians who are able to do so, as the circumstances may require.*

Critical Intervention Areas

The following is a minimal checklist of issues to be addressed. The details involved in the specific approach to individual issues can be obtained from multiple sources, including books, practice guidelines, and the Alzheimer's Association web site (www.alz.org).

1. Educating Caregivers. Critical areas for education include dementia, AD, cognitive impairment, noncognitive functional, and NPS, how diagnosis is made, prognosis, treatment options, and supportive care. A very important topic is the approach to the patient and the changing role of the caregiver from their previous role as a specific family member to being a caregiver. Another important area for education involves teaching caregivers how to avoid arguing with patients and how to involve them only in decisions appropriate to their current level of cognitive ability. Helping caregivers identify which of the patient's symptoms arise from the brain injury and which likely have other causes is also an important goal of the education process. Well-informed caregivers are best equipped to address the problems that AD presents. How much education caregivers need depends on their role in the caregiving situation, their ability to learn about a very complex situation, and their interest. Educational needs also vary over time because most dementias are progressive. Furthermore, the caregiver's ability to comprehend, learn, and accept information may change over time. Most can absorb only so much information in one hearing, and their ability to learn may be affected by their emotional state. Caregivers learn by different methods. Some learn best by listening, others by reading, and most by repetition. Written material is helpful for many people, and several organizations, including the Alzheimer's Association (www.alz.org), provide excellent pamphlets on specific topics.

2. Teaching Problem-Solving Skills. Patients with dementia develop many problems that neither they nor their caregivers have faced previously. Common sense problem-solving is frequently effective. Even when solutions are only partially successful in resolving a problem, they can provide tremendous support to the patient and the caregiver. One of the benefits of focusing on common sense problem-solving is that most individuals are able to learn the principles and use them to address new problems when they arise. Despite this, caregivers are often either not adept at problem-solving or have trouble applying it when faced with a specific situation. Teaching caregivers how to problem-solve by role playing or detailed face-to-face instruction is a critical and very effective aspect of providing care to caregivers.

3. Accessing Resources Assisting caregivers in accessing resources is a critical part of dementia care. Helping them find alternative caregivers in the family is an important first step. Referral to the local Alzheimer's Association chapter or to support groups, if needed and appropriate, may be necessary. Access to the patient's primary clinician on a 24-hour basis to address any crisis arising in the patient's condition is a critical aspect of good dementia care. Other important resources may be elder care attorneys, rehabilitation therapists (occupational therapist, physical therapist, speech), social workers, elder "care managers," and others.

4. Long-Range Planning Caregivers must be encouraged to conduct long-range planning as much as possible with regard to financial matters, planning for assisted living or institutionalization, advanced directives, and dealing with late-stage dementia care. This is important both from the planning point of view and also so that decisions that are difficult might be made in the most deliberate way possible.

5. Emotional Support Caregivers should be encouraged to attend to their personal health and mental health needs and be provided with assistance in resolving family conflicts, referrals for counseling and mental health or physical health assessment, and emotional support to "ventilate" and express their frustrations, as appropriate.

6. Respite Almost all caregivers eventually need a break from caregiving. Clinicians should carefully monitor for signs of caregiving strain and consider respite as early as possible. This should be encouraged as much as possible and strongly recommended when it is evident that the caregiver is becoming overwhelmed. Setting the stage early after diagnosis to prepare caregivers for the potential need of respite in the future is also very important. With more severe dementia AD, patients often become very dependent on and may "shadow" their caregiver. This can be very overwhelming and may well be preventable by the careful introduction of other caregivers through respite earlier in the disease. Many options for respite exist, including use of other family or informal caregivers, adult day care, professional caregivers, weekend (or longer) admission to an assisted living facility, and others. The clinician should be prepared to offer advice and appropriate referral.

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Please visit their website at www.AAGPonline.org.

References

1. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition with Text Revision. Washington, DC, American Psychiatric Association, 2003
2. Hebert LE, Scherr PA, Bienias JL, et al: Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003; 60:1119–1122
3. Black BS, Kasper J, Brandt J, et al: Identifying dementia in high-risk community samples: the memory and medical care study. Alzheimer Dis Assoc Disord 2003; 17:9–18
4. Barton C, Miller B, Yaffe K: Evaluation of the diagnosis and management of cognitive impairment in long-term care. Alzheimer Dis Assoc Disord 2003; 17:72–76
5. Rosenblatt A, Samus Q, Steele C, et al: The Maryland Assisted Living Study: prevalence, recognition and treatment of dementia and other psychiatric disorders in the assisted living population of central Maryland. J Am Geriatr Soc 2004; 52:1618–1625
6. Mulnard R, Cotman C, Kawas C, et al: Estrogen replacement therapy for treatment of mild to moderate Alzheimer's disease: a randomized, controlled trial. JAMA 2000; 283:1007–1015
7. Henderson V, Paganini-Hill A, Miller V, et al: Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 2000; 54:395–401
8. Zandi PP, Carlson MC, Plassman BL, et al: Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA 2002; 288:2123–2129
9. Yip AG, Green RC, Huyck M: Nonsteroidal anti-inflammatory drug use and Alzheimer's disease risk: the MIRAGE study. BMC Geriatr 2005; 5:2
10. Aisen PS, Davis KL, Berg JD, et al: A randomized controlled trial of prednisone in Alzheimer's disease. Neurology 2000; 54:588–593
11. Aisen PS, Schmeidler J, Pasinetti GM, et al: Randomized pilot study of numesulide treatment in Alzheimer's disease. Neurology 2002; 58:1050–1054
12. Aisen PS, Schafer K, Grundman M, et al: Effects of rofecoxib and naproxen vs. placebo on Alzheimer's disease progression. A randomized controlled trial. JAMA 2003; 289:2865–2867
13. Sainati SM, Ingram DN, Talwaker S, et al: Results of a double blind, randomized, placebo-controlled study of celecoxib in the treatment of progression of Alzheimer's disease. Proceedings of the 6th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy, Stockholm, Sweden, 2000: 180
14. Van Gool WA, Weinstein HC, Scheltens PK, et al: Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomized, double-blind, placebo-controlled study. Lancet 2001; 358:455–460
15. Thal LJ, Ferris SH, Kirby L, et al: A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 2005; Mar 2 [Epub ahead of print]
16. Zandi PP, Anthony JC, Khachaturian AS, et al: Cache County Study Group. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004; 61:82–88
17. Sano M, Ernesto C, Thomas RG, et al: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336:1216–1222
18. Petersen RC, Thomas RG, Grundman M, et al: Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; April 13 [Epub ahead of print]
19. Miller 3rd, ER Pastor-Barriuso R, Dalal D, et al: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005; 142:37–46. Epub 2004 Nov 10. Summary for patients in: Ann Intern Med 2005; 142:I40
20. van Dongen M, van Rossum E, Kessels A, et al: Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. J Clin Epidemiol 2003; 56:367–376
21. Snowdon DA, Greiner LH, Mortimer JA, et al: Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. JAMA 1997; 277:813–817
22. Adecola C, Gorelick PB: Converging pathogenic mechanisms in vascular and neurodegenerative dementia. Stroke 2003; 34:335–337
23. Papademetriou V: Hypertension and cognitive function. Blood pressure regulation and cognitive function: a review of the literature. Geriatrics 2005; 60:20–22, 24
24. Jick H: Statins and the risk of dementia. Lancet 2000; 356:1627–1631
25. Shepherd J, Blauw G, Murphy M, et al: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet 2002; 360:1623–1630
26. Scarpini E, Scheltens P, Feldman H: Treatment of Alzheimer's disease: current status and new perspectives. Lancet Neurol 2003; 2:539–547
27. Winblad B, Poritis N: Memantine in severe dementia: results of the M-Best Study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999; 14:135–146
28. Reisberg B, Doody R, Stoffer A, et al: Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348:1333–1341
29. Tariot PN, Farlow MR, Grossberg GT, et al: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291:317–324
30. Plosker GL, Lyseng-Williamson KA: Memantine: a pharmacoeconomic review of its use in moderate-to-severe Alzheimer's disease. Pharmacoeconomics 2005; 23:193–206
31. Rabins PV, Lyketsos CG, Steele CD: Practical Dementia Care, 2nd Ed. Oxford, Oxford University Press, 2005
32. Lyketsos CG, Lee HB: Depression and treatment of depression in Alzheimer's disease: a practical update for the clinician. Dement Geriatr Cogn Disord 2004; 17:55–64
33. Kaufer DI, Cummings JL, Ketchel P, et al: Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000; 12:233–239
34. Livingston G, Johnston K, Katona C, et al: Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry 2005; 162:1996–2021
35. Sink KM, Holden KF, Yaffe K: Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005; 293:596–608
36. Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005; 294:1934–1943
37. Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005; 353:2335–2341
38. Murman DL, Colenda CC: The economic impact of neuropsychiatric symptoms in Alzheimer's disease: can drugs ease the burden? Pharmacoeconomics 2005; 23:227–242

39. Alexopoulos GS, Jeste DV, Chung H, et al: Treatment of dementia and its behavioral disturbances: consensus panel. Postgrad Med 2005
40. American Psychiatric Association: Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. Am J Psychiatry 1997; 154(suppl): 1–39
41. AAGP Atypical Position Statement. Available at: http://www.aagponline.org/prof/antipsychstat_0705.asp
42. Rabins PV, Lyketsos CG, Steele CD: Practical Dementia Care, 2nd Ed. Oxford, Oxford University Press, 2006
43. Dubinsky RM, Stein AC, Lyons K: Practice parameter: risk of driving and Alzheimer's Disease (an evidence based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000; 54:2205–2211
44. Lyketsos CG, Toone L, Tschanz JT, et al: A population-based study of medical co-morbidity in early dementia and cognitive impairment no dementia (CIND): association with functional and cognitive impairment. The Cache County Study. Am J Geriatr Psychiatry 2005; 13:656–664