



# The art of managing dementia in the elderly

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## ■ ABSTRACT

Dementia presents unique challenges for physicians, patients, and families, but it also offers a singular opportunity to practice the essence of the art of medicine. Elderly patients' complaints about cognition require evaluation and should never be written off as a "normal" part of aging. Dementia should be distinguished from conditions such as delirium and depression, and the type of dementia should be identified, since this will determine treatment. Treatments seek to alter the fundamental course of the disorder, to ameliorate symptoms, or to manage concomitant psychiatric and behavioral problems. Even when treatments prove ineffective, providing information and support is of great value to patients and their families and caregivers.

## ■ KEY POINTS

Dementia in the elderly is underdiagnosed, so even though the US Preventive Services Task Force does not recommend formal dementia screening in asymptomatic elderly patients, it is nevertheless worth asking about cognitive complaints during routine office visits.

Despite misconceptions that there is a "normal," aging-associated kind of dementia, any cognitive changes that result in frank disorientation or significant impairment in daily function should never be considered normal.

Reversible, treatable cognitive impairment needs to be ruled out early, often with laboratory studies. Causative conditions may include normal-pressure hydrocephalus, hypothyroidism, vitamin deficiencies, vasculitis, and neurosyphilis.

Studies suggest that cognitive stimulation helps preserve cognition. Intellectual stimulation and mental exercise also may improve quality of life in patients with preexisting dementia.

Treatments include attempts to alter the fundamental course of the condition, to temporarily improve cognitive function, or to manage behavioral problems and functional deficiencies associated with dementia.

**D**ementia presents unique challenges for physicians, patients, and families. Yet for physicians it also offers a unique opportunity to practice the true art of medicine. Although dementia may evoke feelings of helplessness, its more common forms can be readily diagnosed, and many of its symptoms respond to treatment, as do associated psychiatric syndromes and behavioral disturbances. The main goal for clinicians is to remain hopeful and to communicate that hopefulness to patients and their families, keeping in mind that sometimes dementia is curable and that "incurable" does not mean untreatable. Even when treatments are ineffective, patients and their families greatly appreciate the physician's support.

This article reviews key aspects of dementia management from a primary care perspective, including the evaluation and differential diagnosis of dementia, the various types of dementia, and available therapies and management strategies.

## ■ THE SCOPE OF THE PROBLEM

Dementia may be defined as a global decline in cognitive function, including impairment of memory, that is due to an abnormal change in the structure or function of the brain and is sufficient to interfere with day-to-day function.

Dementia, including Alzheimer disease or Alzheimer dementia (AD), is one of the most common neurologic disorders of the elderly, affecting approximately 8% to 10% of people older than 65 years and perhaps as many as 40% of those older than

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**TABLE 1**  
Conditions resembling dementia in the elderly

Condition	Description	Ways to distinguish from dementia	Potential course of action
Age-related cognitive changes	Decline in cognitive performance in the elderly (typically memory lapses) that is normal for age and education	Within norms for age and education No impairment of day-to-day function	Reassure patient that changes are normal
Mild cognitive impairment	Cognitive decline with performance below normal for age and education, not causing significant functional impairment	Not severe enough to impair day-to-day function	Follow closely, consider presumptive treatment
Delirium	Reversible impairment of attention and consciousness caused by intervening medical condition	Acute onset Condition fluctuates from one exam to another Impaired consciousness	Identify and address underlying medical cause
Depression	Mood disorder that may present with cognitive complaints, paucity of speech, or functional difficulties	Depressive symptoms Subacute onset Prior history	Antidepressants and/or psychotherapy

85 years.<sup>1</sup> It has enormous associated costs of as much as \$80 to \$100 billion per year,<sup>2</sup> leads to psychiatric symptoms of “burnout” in caregivers,<sup>3</sup> and is a common cause of institutionalization of elderly persons.<sup>4,5</sup>

The prevalence of dementia in nursing home populations has been estimated at 25% to 74%.<sup>6,7</sup> The Maryland Assisted Living Study, the first large-scale study to perform comprehensive evaluations for dementia on a population sample in this setting, indicated a rate of 68%, with another 7% suffering from other forms of cognitive impairment.<sup>8</sup> This finding suggests that lower estimates may have been, in part, due to cursory examination or the use of proxies to estimate the prevalence of dementia.

■ **DETECTING DEMENTIA IN THE ELDERLY**

Dementia is underdiagnosed in clinical settings.<sup>9,10</sup> The US Preventive Services Task Force did not find sufficient evidence to recommend formal dementia screening in asymptomatic elderly persons,<sup>11</sup> but clinicians should ask about cognitive complaints during routine visits. Suspicion of dementia is warranted whenever an elderly patient presents with a memory complaint, difficulties with activities of daily living, personality change, or a new behavioral problem. Obtaining a baseline cognitive score may assist with diagnosis if a patient develops a progressive decline or becomes acutely delirious, much as baseline electrocardiography

may help in the assessment of chest pain.

In addition to the Mini-Mental State Examination (MMSE),<sup>12</sup> tests that have been advocated for screening of dementia include the General Practitioner Assessment of Cognition (GPCOG),<sup>13</sup> the Abbreviated Mental Test (AMT),<sup>14</sup> the clock-drawing test,<sup>15</sup> and the Mini-cog, a clock-drawing test in combination with a three-word recall.<sup>16</sup> The MMSE has the advantages of being widely known and easy to score and of assessing various cognitive domains. Truncating the MMSE to its orientation questions, or describing a patient as “alert and oriented ×3,” is insensitive, is not comparable to the findings of other clinicians, and will tend to miss non-Alzheimer dementias.

■ **EVALUATING FOR DEMENTIA**

The first task of the clinician evaluating a patient with a cognitive complaint is to decide whether an objective problem exists at all.

**Age-related cognitive changes**

The patient may be complaining of normal age-related cognitive changes (Table 1), particularly in the area of memory.<sup>17</sup> The instruments used for cognitive assessment, such as the MMSE, have norms based on age and educational level,<sup>18</sup> but the distinction can be difficult in mild cases and in the very old, in whom dementia is common and norms have not

been well established.

A widely held misconception about dementia is that there is a “normal” kind of dementia, associated with the aging process, that is different from AD and other named conditions. Age-related cognitive changes should not result in frank disorientation or significant impairment in daily function. It is common for families to bring a loved one to the clinic hoping to hear that the changes are simply due to “old age.” The clinician must explain that, while common in the elderly, dementia is a disease process amenable to assessment and treatment and no more “normal” than other diseases of the elderly, such as macular degeneration or osteoporosis.

### Mild cognitive impairment

Another condition to consider is mild cognitive impairment (MCI) (Table 1). Defined relatively recently, MCI is a decline in cognitive function that becomes a focus of clinical attention but is not severe enough to merit the diagnosis of dementia. Recent studies indicate a 10% to 15% annual progression to AD.<sup>19</sup>

Some very educated or intelligent patients may report a decline in their previously very high level of cognitive functioning but, in the absence of baseline testing or because of ceiling effects, may show test performance within norms for their age and educational level. Other explanations of the cognitive complaint, such as depression, should be ruled out, and such patients should be reevaluated periodically to determine whether a dementia has manifested itself and to look for evidence of progression.

There is recent evidence that progression of MCI to dementia may be delayed by some of the medications indicated for the treatment of AD,<sup>20</sup> but there is as yet no professional consensus on the treatment of MCI. Clinicians may consider empiric pharmacotherapy, particularly if there is a family history of dementia.

### Cognitive changes that are not dementia

When a patient with a definitive cognitive change has been identified, various nondementia conditions must also be considered (Table 1). Chief among these are delirium and depression.

**Delirium** may be distinguished from dementia by its more acute onset, a disturbed or fluctuating level of consciousness, and the presence of an acute or chronic medical problem commonly associated with delirium, such as hypoxia, sepsis, renal failure, or polypharmacy. Studies suggest that delirium occurs in 14% to 56% of hospitalized elderly patients, among whom it is associated with death rates of 10% to 65%.<sup>21</sup> The condition is also frequently observed in ambulatory patients.

It is possible for delirium and dementia to coexist. In fact, demented persons are especially vulnerable to delirium.<sup>22</sup> Sometimes a patient with dementia may present with delirium. In other instances, preexisting dementia may obscure the diagnosis of delirium, with grave consequences if the cause is not addressed.

**Dementia of depression.** Elderly patients with depression may present with cognitive complaints, paucity of speech, or functional difficulties that suggest a dementing process. They may have subjective cognitive complaints<sup>23</sup> or show objective cognitive impairment on the MMSE or on more comprehensive testing.<sup>24</sup> The common term for this condition is “pseudodementia,” although a more accurate term is “the dementia of depression.”<sup>25</sup> The dementia of depression may be compared to other reversible dementias found in conjunction with other severe medical problems such as beriberi or myxedema.

Depression may be distinguished from dementia on the basis of family history, history of depression, subacute onset, presence of overt depressive symptoms, and results of neuropsychological testing, on which it tends to show a more subcortical pattern.<sup>26</sup> Depression can coexist with dementia, leading to a bleaker cognitive picture and making it hard to ascertain the true severity of the dementia. In such cases it is best to withhold prognostic judgment until the depression has been treated.

## ■ DETERMINING THE TYPE OF DEMENTIA

### Evaluation of dementia

Once the clinician is convinced that a patient has dementia, the next step is to identify the type (Table 2). The evaluation of dementia begins with a comprehensive history, often obtained from a family member, paying special attention to whether the onset of the condition was insidious and difficult to pinpoint in time or more subacute, whether the progression (if any) was gradual or stepwise, and specific neurologic and psychiatric symptoms encountered since the onset of the illness.

**The history** is the most informative part of the evaluation, and clinicians will usually have a strong suspicion as to the type of dementia on the basis of the history alone. The diagnosis will then be refined on the basis of the neurologic and mental status examinations, the results of neuropsychological testing, and imaging and laboratory studies. The neurologic examination is useful in detecting focal changes, evidence of extrapyramidal syndromes such as parkinsonism, and frontal release signs.

**Formal neuropsychological testing** is not always

**TABLE 2**  
Dementias of the elderly

Type of dementia	Frequency	Distinguishing features	Supportive tests
Alzheimer dementia	55%–75% of dementia cases	Insidious onset Progressive worsening Clear consciousness Nonfocal exam	CT or MRI Functional imaging <i>ApoE ε4</i> allele
Vascular dementia	13%–16% of cases	Focal neurologic exam Stepwise progression	CT or MRI
Dementia with Lewy bodies	15%–35% of cases	Fluctuating cognition Visual hallucinations Parkinsonism	Functional imaging Neuropsychological testing
Frontotemporal dementia	Uncommon	Insidious onset Gradual progression Impaired personal conduct Emotional blunting Weight loss	Functional imaging Neuropsychological testing

available, but it can help describe the pattern of cognitive deficits. For example, it may help make the distinction between cortical and subcortical dementia. Cortical dementias such as AD are typically characterized by amnesia, disorientation, and relatively preserved personality.<sup>27</sup> Patients with subcortical dementias, such as those associated with HIV infection, Parkinson disease, Huntington disease, and some vascular dementias,<sup>28</sup> tend to show relatively preserved memory but have difficulties in executive function, attention, and concentration. They also generally show a greater degree of personality erosion and psychiatric symptoms such as apathy, irritability, disinhibition, and perseveration.<sup>29</sup> Finally, testing may also be important therapeutically by helping to delineate the patient's strengths and weaknesses and thus to identify likely areas of trouble, to suggest compensation strategies, and to aid in behavioral management.

### Alzheimer dementia

AD is the most common type of dementia, accounting for approximately 55% to 75% of cases on the basis of autopsy studies.<sup>30,31</sup>

According to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), the criteria for probable AD include a course characterized by gradual-onset and continuing cognitive decline and the following:

- (1) Dementia established by examination and objective testing
- (2) Deficits in two or more cognitive areas
- (3) Progressive worsening of memory and other cognitive functions
- (4) No disturbance in consciousness
- (5) Onset between 40 and 90 years of age
- (6) Exclusion of systemic disorders and other brain diseases that could account for the cognitive and memory deficits.<sup>32</sup>

AD is often spoken of as a diagnosis of exclusion, but this may lead some clinicians to avoid making an explicit diagnosis even in straightforward cases. Although microscopic examination of the brain is the only way to be 100% certain, the clinical diagnosis of AD is approximately 90% accurate as shown by autopsy confirmation.<sup>33</sup>

**Other tests to confirm the diagnosis of Alzheimer dementia.** In addition to the clinical evaluation, a number of tests may serve to confirm or strengthen the diagnosis in patients with an unusual presentation, in patients who are unusually young, or even when the patient or family are having difficulty accepting the diagnosis. These may include functional neuroimaging such as positron-emission tomography and single-photon-emission computed tomography, and genetic tests such as for the *ApoE ε4* allele, a risk gene that is associated with the common late-onset variety of AD<sup>34</sup> and that may support the diagnosis of AD in a patient with a likely clinical presen-

tation. However, being homozygous for the *ApoE*  $\epsilon$ 4 allele does not guarantee that the dementia is AD, and having no *ApoE*  $\epsilon$ 4 allele does not exclude it.

Commercial testing is also available for presenilin 1<sup>35</sup> and the much less common presenilin 2.<sup>36</sup> These are causative mutations associated with a familial early-onset form of AD, and testing should be reserved for unusual cases.<sup>37</sup> More widespread use of genetic testing for AD is controversial and, because of ethical considerations, should generally be limited to research studies.

#### **Withholding the diagnosis of Alzheimer dementia.**

Reluctance to tell patients and families of the diagnosis of AD may stem more from a lack of comfort in discussing dementia than from genuine uncertainty. At least in the United States, it is no longer considered ethical to deliberately withhold a diagnosis from a patient except in the most extreme circumstances. Clinicians sometimes worry that telling a patient that he or she is suffering from AD will precipitate depression or otherwise reduce the person's quality of life. There is no evidence to support this idea. In fact, explaining the diagnosis and prognosis to patients and families in a supportive way, emphasizing how common the problem is, that progression is slow, that treatments are available, and that it is still possible to enjoy life, will enable the patient to make appropriate plans for the future, abstain from dangerous or especially frustrating activities, and take advantage of available therapies and support services and organizations.

#### **Vascular dementia**

Vascular or multi-infarct dementia is probably the second most common form of dementia and accounts for approximately 13% to 16% of cases.<sup>30,31</sup>

The clinical diagnosis of vascular dementia is not as accurate as that of AD, with AD and mixed pathology often found at autopsy.<sup>38</sup> Published criteria<sup>39</sup> define it as a cognitive disorder resulting from ischemic or hemorrhagic stroke or from ischemic-hypoxic brain lesions as evidenced by the following:

- (1) A diagnosis of dementia
- (2) Cerebrovascular disease defined by the presence of focal signs on neurologic examination and evidence on brain imaging
- (3) A relationship between criteria 1 and 2 implied by onset of dementia within 3 months after a stroke, with abrupt deterioration in cognitive function or fluctuating, stepwise progression of cognitive deficits.

Criterion 2 is particularly important, as vascular dementia should not be diagnosed in the absence of

focal findings, solely on the basis of vascular risk factors such as hypertension or diabetes. To do so might yield the wrong prognosis and would deprive patients of available therapies indicated for AD.

#### **Dementia with Lewy bodies**

Dementia with Lewy bodies (DLB) is a third type of dementia, with its own characteristic neuropathologic findings, ie, the presence of cytoplasmic inclusions, which are found in the substantia nigra of patients with idiopathic Parkinson disease but in DLB are distributed widely throughout the cortex.<sup>40</sup>

Clinically, as in most dementias, the central feature is progressive cognitive decline interfering with normal functioning. However, prominent or persistent memory impairment is not necessarily present in the early stages, whereas deficits on tests of attention and frontal-subcortical skills may be prominent. The core clinical features are fluctuating cognition; recurrent visual hallucinations, typically of a well-formed and detailed sort; and parkinsonism. One of these features is required for a diagnosis of possible DLB and two for probable DLB. Features considered supportive of the diagnosis are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions, and hallucinations in other modalities.<sup>41</sup> Functional neuroimaging may also be helpful in identifying likely cases.

Estimates of the prevalence of DLB are somewhat controversial. Autopsy studies have demonstrated the presence of Lewy bodies in approximately 15% to 35% of demented autopsy subjects, which would make DLB the second most common type of dementia.<sup>42</sup> However, many of these subjects never manifested the expected syndrome while living.

The precise relationship of DLB to both AD and Parkinson disease is not fully understood. As with vascular dementia, the diagnosis of DLB should not be made in patients who do not meet any of the core criteria, ie, only on the basis of supportive findings such as psychosis or adverse response to a neuroleptic drug.

#### **Frontotemporal dementia**

Finally, there are several subtypes of frontotemporal dementia.<sup>43</sup> The consensus criteria include insidious onset and gradual progression, with early decline in social conduct, impaired regulation of personal conduct, emotional blunting, and loss of weight. Supportive features include a behavior disorder characterized by decline in personal hygiene, mental rigidity, distractibility, hyperorality and dietary changes, perseveration and stereotyped behavior, and utilization behavior (ie, unrestrained exploration of objects

**TABLE 3**  
Commonly prescribed agents for Alzheimer dementia (AD)

Drug	Indication	Starting dose	Effective dose	Maximum dose	Side effects
Donepezil	Mild-moderate AD	5 mg once daily	5 mg once daily	10 mg once daily	Nausea, vomiting, diarrhea
Rivastigmine	Mild-moderate AD	1.5 mg twice daily	3 mg twice daily	6 mg twice daily	Nausea, vomiting, anorexia, dizziness
Galantamine (extended-release)	Mild-moderate AD	8 mg once daily	16 mg once daily	24 mg once daily	Nausea, vomiting, anorexia, dizziness, syncope
Memantine	Moderate-severe AD	5 mg once daily	10 mg twice daily	10 mg twice daily	Dizziness, headache, confusion, constipation

in the environment). Speech and language abnormalities are often present, characterized by altered speech output, stereotypy, echolalia, perseveration, and mutism. Physical signs can include primitive reflexes, incontinence, akinesia, rigidity and tremor, and low or labile blood pressure.<sup>44</sup> Dementias due to other neurologic disorders such as Parkinson disease, Huntington disease, or hydrocephalus can presumably be recognized by the features of these conditions.

**Conditions to rule out**

A number of reversible, or at least treatable, forms of cognitive impairment need to be ruled out early in the process, often by means of laboratory studies. These include conditions such as normal-pressure hydrocephalus, hypothyroidism, vitamin deficiencies, vasculitis, and neurosyphilis. The usual panel of tests consists of an interview to rule out depression, an imaging study, if not previously performed, vitamin B<sub>12</sub>, and thyroid-function screening. Rapid plasma reagin, erythrocyte sedimentation rate, and other tests such as HIV antibody or toxicology screening may be dictated by specific elements of the history or presentation.<sup>45</sup> Although these conditions rarely account for the entire presentation, they are easily ruled out by simple tests and may result in permanent or fatal complications if left untreated.

■ **TREATMENT OF DEMENTIA**

Treatment of dementia has many different meanings. It can refer to treatments that seek to alter the fundamental course of the condition, symptomatic treatments that temporarily improve cognitive function, or strategies that help to manage some of the comorbidities of dementia, such as behavioral problems and functional deficiencies.

No treatments have been definitively shown to alter the histopathologic progression of AD. In the case of vascular dementia, plausible treatments include an attempt to mitigate the progressive course through aggressive management of vascular risk factors, such as hypertension, hypercholesterolemia, or diabetes. Aspirin and other anticoagulants are commonly used for secondary prevention of further cerebrovascular accidents but have not been definitively established as useful for vascular dementia. Vascular dementia may respond symptomatically to some of the medications used for AD.<sup>46</sup>

**Cognitive stimulation**

Patients' families often ask whether some form of mental exercise will help maintain cognitive function in persons suffering from dementia. Some studies suggest a protective effect of cognitive stimulation.<sup>47</sup> Intellectual stimulation and mental exercise may also improve quality of life in persons who already have dementia—for example, by helping them maintain an appropriate sleep-wake cycle. This is a particular focus of 2005 Alzheimer's Association chapter educational programs. The practice, however, should not be taken to extremes, putting patients at odds with their families or doctors over exercises and challenges that are beyond their desire and capabilities.

**Drugs approved for Alzheimer dementia**

Five drugs have been approved by the US Food and Drug Administration for the treatment of AD, and four are commonly prescribed (Table 3). All are intended to target symptoms, although there have been suggestions<sup>48</sup> that they could also affect underlying pathologic changes.

The life expectancy of the typical AD patient is

approximately 4 to 6 years.<sup>49</sup> The use of these agents is therefore justified by the fact that they can provide symptomatic improvement for most of that time, as controlled and uncontrolled studies suggest.<sup>50,51</sup>

**The acetylcholinesterase inhibitors (ACIs)** tacrine, donepezil, rivastigmine, and galantamine have all been shown in controlled studies to improve measures of cognitive function such as the MMSE or AD Assessment Scale cognitive subscale (ADAS-cog), measures of functional abilities,<sup>52,53</sup> and measures of behavioral disturbance such as the Neuropsychiatric Inventory (NPI).<sup>54-56</sup> Tacrine is rarely used any more because of its hepatic side effects and complicated dosing regimen. Despite pharmacologic speculations to the contrary, the remaining three agents appear to be about equally efficacious.<sup>57,58</sup> Donepezil is the most widely used and seems to be the most easily tolerated.<sup>59</sup> Patients can be switched from one agent to another in the case of inefficacy or intolerability but should first receive an adequate trial.

The effects of the ACIs can be subtle and must be observed against a background of expected cognitive decline. A reasonably sensitive quantitative instrument such as the MMSE is important for detecting initial improvement, demonstrating treatment effects to the patient and family, and following the patient longitudinally.

Educating patients and families is also paramount. Patients and families should understand that improvements will usually be mild and that the patient's condition will continue to decline but, it is hoped, not to the same point as would be reached without treatment. Families tend to lose heart when the patient who showed a response to an ACI crosses the initial baseline, and they sometimes conclude that the drug has "stopped working." However, sudden discontinuation at this point deprives the patient of ongoing benefit from the drug and sometimes leads to a sharp decline in function.

How long to continue these agents is currently a matter of individual clinical judgment, but an ACI need not be discontinued at some arbitrary point if it is well tolerated and the patient clearly showed an initial response.

The ACIs are approved only for the treatment of patients with mild to moderate AD, which might correspond to an MMSE score of 10 or above. Recent studies suggest a possible role for these medications in patients with moderate to severe AD<sup>60</sup> and vascular dementia.<sup>61</sup>

**Memantine** is an N-methyl-D-aspartate receptor antagonist approved in the United States for the

treatment of moderate to severe AD. Controlled studies have shown that it improves cognition and function<sup>62</sup> compared with placebo, with an effect size similar to that of the ACIs. The role of memantine in vascular dementia is unclear, with some data to suggest an improvement in cognition but not in global function.<sup>63</sup>

Memantine is the only agent approved for use in patients with severe AD (MMSE  $\leq$  10, approximately), but is not currently approved for mild cases (MMSE  $>$  17, approximately), but the range of indications for all these agents will probably expand.

Since memantine belongs to a different class than the ACIs, combination therapy may be possible. There is already evidence that the addition of memantine can further improve the cognitive function of responders to donepezil.<sup>64</sup>

#### Do current drugs improve long-term outcomes?

A controversial topic is whether the ACIs produce long-term benefits that might improve mortality or institutionalization rates. Some observational studies seem to demonstrate better long-term outcomes for AD patients who continue to take ACIs.<sup>65</sup> Unpublished data from the Maryland Assisted Living Study suggest that ACI use has a significant effect on retention of AD patients in assisted living centers, at least until the 6-month mark. On the other hand, in a recently published controlled study of community-dwelling AD patients in the United Kingdom, donepezil produced improvements in cognition and function compared with placebo but did not improve institutionalization rates.<sup>66</sup> The study population was much smaller than intended because of recruitment problems. On the basis of these findings the authors concluded that ACIs are "not cost-efficient."

Based on controlled clinical trials, ACIs improve the cognition, function, and quality of life of AD patients, and these effects are detectable and clinically significant. These studies support the routine use of such medications in patients with mild to moderately severe AD. Issues of cost and long-term outcomes are still unresolved but should not prevent clinicians from attempting to provide symptom relief. Even small gains in function can be very important to patients and their families when the baseline is already so impaired.

#### Proposed therapies with little supportive evidence

**Vitamin E.** In AD, retrospective studies have seemed to show prophylactic effects for vitamins E and C.<sup>67</sup> These results have led to trials in the symptomatic population. A randomized clinical trial compared

vitamin E and the antiparkinson drug selegiline, alone and in combination, with placebo in 341 patients with AD.<sup>68</sup> In the first analysis, there were no significant differences between any of the groups in the primary outcome measure, time to death or institutionalization. When a statistical correction was performed to account for the MMSE score at baseline, a significant effect emerged for both agents. This led some physicians to treat AD patients with 1,000 units of vitamin E twice a day. However, recent concerns about all-cause mortality in relation to vitamin E doses of 400 units or higher has caused most clinicians to stop recommending the use of vitamin E.<sup>69</sup> There has been no similar trend toward the use of selegiline.

A recent trial of vitamin E in MCI has thus far yielded negative results.<sup>20</sup>

To date there is no direct evidence that vitamin supplements prevent AD.

**Hormone therapy and NSAIDs.** Like vitamin therapy, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has appeared to show a protective effect against AD in retrospective studies.<sup>70,71</sup> Additionally, hormone replacement therapy in women has been associated with a lower risk of developing AD in a prospective study,<sup>72</sup> although estrogen-progestin combination therapy actually appeared to increase the risk of AD in another prospective trial.<sup>73</sup> Among patients already symptomatic for AD, estrogen replacement proved ineffective against AD in one study,<sup>74</sup> as did NSAIDs in another.<sup>75</sup> The Alzheimer Disease Anti-inflammatory Prevention Trial, a large-scale study of the prophylactic effect of the NSAIDs naproxen and celecoxib vs placebo in subjects at risk for AD by virtue of age and family history, has been suspended because of safety concerns.<sup>76</sup>

#### Treatment of behavioral problems in dementia

Behavioral symptoms are extremely common in persons with dementia,<sup>77</sup> are frequently serious,<sup>78</sup> and can lead to caregiver burnout, institutionalization, and higher costs.<sup>79</sup> Even if the dementia does not respond to treatment of cognitive dysfunction, successful treatment of psychiatric and behavioral problems may produce a substantial difference in outcome.

**Depression.** The reported prevalence of major depression in patients with dementia is high—approximately 20%.<sup>80,81</sup> Depression should not be dismissed as simply the patient's reaction to having dementia. It may have an atypical presentation in this population because of impaired communication. The patient may present with such problems as anorexia, social withdrawal, insomnia, or increased agitation.

Purely symptomatic treatments such as benzodiazepines may make matters worse. In ambiguous cases, presumptive treatment for depression may be considered.

Depressed persons with dementia are not amenable to most forms of psychotherapy but can be supported and reassured. A wide range of antidepressant drugs may be useful, although there are few published efficacy trials such as the Depression in Alzheimer's Disease Study (DIADS).<sup>82,83</sup> This population is very sensitive to side effects and delirium, so clinicians should be cognizant of polypharmacy issues, including the half-lives, potential interactions, and anticholinergic properties of the drugs in question. Selective serotonin reuptake inhibitors (SSRIs) are probably the most common first choice. The drug selected must be given in an appropriate geriatric dose for an appropriate duration (generally 8 to 12 weeks) in the initial trial, and the patient must be evaluated at intervals to see if the treatment is helping.

**Psychosis.** Psychosis, the presence of delusions and hallucinations, is not uncommon in demented patients.<sup>77</sup> It can be a primary feature of the dementia itself or an aspect of other conditions such as delirium or, in the case of visual hallucinations, eye disease.<sup>84</sup> Apparent psychosis in patients with dementia does not always require drug treatment—or any intervention, for that matter. For example, demented patients frequently confabulate, but this is unlikely to respond to neuroleptics and differs from delusions in that the erroneous beliefs are not fixed. When confabulating patients report impossible events such as visits by deceased relatives, families often tell the clinician, incorrectly, that the patient is hallucinating.

Visual agnosias and misinterpretations such as being unable to recognize one's own reflection may also be misinterpreted as hallucinations. When the presence of delusions or hallucinations is confirmed, the clinician must rule out reversible causes and consider how much harm the symptom is actually producing and whether the benefits of drug therapy are likely to outweigh the risks. A delusion that a caregiver is actually the patient's daughter, for example, might be handled with humor and gentle reminders or may not need to be confronted at all. Families should be instructed to "pick their battles" and not to argue unnecessarily in an attempt to counter false beliefs.

When pharmacotherapy is attempted, the newer antipsychotic agents such as risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are generally better tolerated by elderly patients. Among the older drugs, high-potency agents such as haloperidol have



fewer anticholinergic effects. It is also possible that ACIs alone may mitigate psychosis.<sup>54-56</sup>

**Executive dysfunction.** Patients with every sort of dementia, but particularly the so-called subcortical varieties such as the dementia of Parkinson disease, Huntington disease, or HIV infection, may show a constellation of symptoms described by the pseudo-anatomical term “frontal.” This may be described more accurately as the executive dysfunction syndrome.<sup>85</sup> Typical symptoms include apathy, disinhibition, perseveration, and irritability. Common problem behaviors include wandering, calling out, rooting, and explosive outbursts. Some of these behaviors may be managed by close observation and control of the environment. Very scant treatment data are available, and there are no established or approved therapies, but medications that have been tried include ACIs, SSRIs, amphetamines, and dopaminergic agents such as amantadine.<sup>86</sup>

**Agitation.** Agitation is a term that conveys little useful information. It is not a diagnosis, and there are no specific treatments for it. Caregivers and staff members should be trained by the clinician to describe the actual problem behavior, whether it is calling out, hitting, wandering, being uncooperative with personal care, or some other issue. The clinician’s task is to determine the nature and pattern of the problem behavior, to uncover precipitants and mitigating factors, and to make specific diagnoses where possible. For example, an elderly patient with dementia may be constantly irritable and combative, as in a condition such as mania; may be combative only during short, predictable intervals, such as during personal hygiene; or may display a truly random pattern. The first problem would require a specific treatment. The second might be managed environmentally with extra supervision, a gentle manner, and possibly very time-limited use of physical restraints. Only the final scenario

might require “something for agitation.”

In cases of explosive, violent, or obnoxious behavior that seems to arise directly out of the dementia and is not amenable to behavioral treatment or environmental interventions, the possible range of medications includes antidepressants, neuroleptics, anticonvulsants, benzodiazepines, beta-blockers,<sup>87</sup> amphetamines, and dopaminergic agents.<sup>86</sup> Deliberate sedation is a last resort, since the goal is to treat the behavioral syndrome while preserving the patient’s ability to participate in activities that contribute to quality of life.

## ■ SUMMARY AND SYNTHESIS

Dementia is a common, serious, yet treatable condition in the elderly. Although many clinicians do not have a high level of comfort in screening for, diagnosing, and treating dementia, the most common forms of dementia can be readily diagnosed, largely on the basis of the history. Many symptomatic treatments exist, and the outlook is even more favorable for treatment of associated psychiatric syndromes and behavioral disturbances.

Clinicians can offer the best care by striving to remain hopeful and to communicate hopefulness to patients and their families, keeping in mind that sometimes dementia is curable, necessitating a comprehensive initial evaluation and a search for reversible causes; that “incurable” does not mean untreatable; and that even when dementia does not respond to direct treatment, it may have treatable consequences, such as depression.

The management of the patient with dementia, including the provision of diagnosis, prognosis, and support, even when other treatments prove ineffective, is greatly appreciated by patients and their families. The clinician need not feel helpless and should take comfort in knowing that the services he or she is providing represent the very essence of the physician’s art.

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