PRACTICE GUIDELINE FOR THE
Treatment of Patients With Alzheimer's Disease and Other Dementias

Second Edition

WORK GROUP ON ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

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STATEMENT OF INTENT

The APA Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA Practice Guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document entitled "APA Guideline Development Process," which is available from the APA Department of Quality Improvement and Psychiatric Services.

This practice guideline was approved in July 2007 and published in October 2007.

OVERVIEW OF GUIDELINE DEVELOPMENT PROCESS

This practice guideline was developed under the auspices of the APA Steering Committee on Practice Guidelines. The development process is detailed in a document entitled "APA Guideline Development Process," which is available from the APA Department of Quality Improvement and Psychiatric Services. Key features of this process include the following:

- A comprehensive literature review
- Development of evidence tables
- Initial drafting of the guideline by a work group that included psychiatrists with clinical and research expertise in dementia
- Production of multiple revised drafts with widespread review; 22 organizations and 64 individuals submitted significant comments.
- Approval by the APA Assembly and Board of Trustees
- Planned revisions at regular intervals

Relevant literature was identified through a computerized search of MEDLINE, using PubMed, for the period from 1994 to 2004. By using the key words "dementia," "dementias," "Alzheimer," "Alzheimer's," "Pick disease," or "mild cognitive impairment," a total of 79,510 citations were found. Limiting the search to clinical trials, practice guidelines, and meta-analyses published in English that included abstracts yielded 2,679 articles, which were screened by using title and abstract information. To locate citations relevant to Part B of the guideline, the above search terms were also used to identify review articles having medical subject heading (MeSH) subheadings of classification, diagnosis, epidemiology, etiology, genetics, or mortality. This search yielded 9,840 citations, of which 4,816 were published in English with abstracts and were screened as described above. To locate other systematic reviews, a search of the Cochrane database was also conducted using the search term "dementia." Additional, less formal literature searches were conducted by APA staff and individual members of the Work Group on Alzheimer's Disease and Other Dementias to identify references on related topics as well as articles published during the guideline development process. Sources of funding were considered when the work group reviewed the literature but are not identified in this document. When reading source articles referenced in this guideline, readers are advised to consider the sources of funding for the studies.

This document represents a synthesis of current scientific knowledge and accepted clinical practice regarding the treat-

ment of patients with Alzheimer's disease and other dementias. It strives to be as free as possible of bias toward any theoretical approach to treatment. In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation, the summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. Each rating of clinical confidence considers the strength of the available evidence and is based on the best available data. When evidence is limited, the level of confidence also incorporates clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

GUIDE TO USING THIS PRACTICE GUIDELINE

The *Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias* consists of three parts (Parts A, B, and C) and many sections, not all of which will be equally useful for all readers. The following guide is designed to help readers find the sections that will be most useful to them.

Part A, "Treatment Recommendations for Patients With Alzheimer's Disease and Other Dementias," is published as a supplement to the *American Journal of Psychiatry* and contains general and specific treatment recommendations. Section I summarizes the key recommendations of the guideline and codes each recommendation according to the degree of clinical confidence with which the recommendation is made. Section II is a guide to the formulation and implementation of a treatment plan for the individual patient. Section III discusses a range of clinical considerations that could alter the general recommendations discussed in Section II.

Part B, "Background Information and Review of Available Evidence," and Part C, "Future Research Directions," are not included in the *American Journal of Psychiatry* supplement but are provided with Part A in the complete guideline, which is available online through the American Psychiatric Association (http://www.psych.org) and in print format in compendiums of APA practice guidelines published by American Psychiatric Publishing, Inc. Part B provides an overview of Alzheimer's disease and other dementias, including general information on natural history, course, and epidemiology. It also provides a structured review and synthesis of the evidence that underlies the recommendations made in Part A. Part C draws from the previous sections and summarizes areas for which more research data are needed to guide clinical decisions.

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INTRODUCTION

The purpose of this guideline is to assist the psychiatrist in caring for a patient with dementia. In particular, it seeks to summarize data to inform the care of patients with dementia of the Alzheimer's type (referred to here as Alzheimer's disease) and other dementias, including vascular dementia, Parkinson's disease, dementia with Lewy bodies, and the frontotemporal dementia spectrum disorders. The guideline does not purport to review research or provide recommendations for every dementia associated with general medical conditions, such as human immunodeficiency virus (HIV) infection, Huntington's disease, head trauma, structural lesions, or endocrine and metabolic disturbances. Nonetheless, many of the recommendations regarding the management of cognitive and functional changes and neuropsychiatric complications apply to dementia in general.

Psychiatrists care for patients with dementia in many different settings and serve a variety of functions. For some patients a psychiatrist will be the primary evaluating or treating physician, for some the psychiatrist will serve as a consultant to another physician or other treating clinician regarding the care of psychiatric symptoms, and for other patients the psychiatrist will function as part of a multidisciplinary team. In all settings, however, the care of every patient with dementia must be individualized to meet the unique needs of that patient and his or her caregivers.

The guideline begins at the point where the psychiatrist or other medical professional has diagnosed a patient with a dementing disorder according to the criteria in DSM-IV-TR (see Table 1 for the criteria for dementia of the Alzheimer's type) and has evaluated the patient for coexisting mental disorders, such as delirium, major depression, and substance use disorders. Making the initial diagnosis of dementia can be challenging, particularly when the initial symptoms are not deficits in memory but are neuropsychiatric symptoms, personality changes, or deficits in executive function. This guideline also assumes that the psychiatrist, neurologist, or primary care physician has evaluated the patient for treatable factors that may be causing or exacerbating the dementia and for general medical or other conditions that may affect its treatment and course.

TABLE 1.   DSM-IV-TR Diagnostic Criteria for 294.1x Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both

   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)

   (2) one (or more) of the following cognitive disturbances:

       (a) aphasia (language disturbance)

       (b) apraxia (impaired ability to carry out motor activities despite intact motor function)

       (c) agnosia (failure to recognize or identify objects despite intact sensory function)

       (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)

   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)

   (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Code based on presence or absence of a clinically significant behavioral disturbance:

   294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

   294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., wandering, agitation).

Specify subtype:

   With Early Onset: if onset is at age 65 years or below

   With Late Onset: if onset is after age 65 years

Coding note: Also code 331.0 Alzheimer's disease on Axis III. Indicate other prominent clinical features related to the Alzheimer's disease on Axis I (e.g., 293.83 Mood Disorder Due to Alzheimer's Disease, With Depressive Features, and 310.1 Personality Change Due to Alzheimer's Disease, Aggressive Type).

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This guideline is intended to be inclusive and to cover the range of necessary treatments that might be used by a psychiatrist who provides or coordinates the overall care of the patient with dementia. Much of the emphasis of this practice guideline is on symptoms that are often referred to as "neuropsychiatric" or "psychiatric and behavioral" symptoms, terms that will be used interchangeably throughout this guideline. These symptoms are highly prevalent, cause significant morbidity, and can often be effectively treated; their evaluation and treatment usually rest upon knowledge acquired in general psychiatry training programs. Many patients also have co-occurring psychiat-ric symptoms that cannot be completely subsumed by one DSM-IV-TR diagnostic category; distinct treatment of these symptoms or disorders may also be needed. In terms of the treatment of dementia, interventions to reduce or correct cognitive and functional deficits are expected to gain importance over time as new approaches are developed. Thus, the psychiatrist caring for a patient with dementia should consider, but need not be limited to, the treatments recommended in this practice guideline. Finally, other key tasks include providing critical support for family members and other caregivers and making referrals to social, legal, and other community resources.

Part A

TREATMENT RECOMMENDATIONS

I. EXECUTIVE SUMMARY

A. CODING SYSTEM

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence:

[I]   Recommended with substantial clinical confidence
[II]   Recommended with moderate clinical confidence
[III] May be recommended on the basis of individual circumstances

B. GENERAL TREATMENT PRINCIPLES AND ALTERNATIVES

Patients with dementia display a broad range of cognitive impairments and neuropsychiatric symptoms that can cause significant distress to themselves and caregivers. As a result, individualized and multimodal treatment plans are required [I]. Dementia is usually progressive, and treatment must evolve with time in order to address newly emerging issues [I]. At each stage the psychiatrist should be vigilant for symptoms likely to be present, should identify and treat co-occurring psychiatric and medical conditions, and should help patients and families anticipate future symptoms and the care likely to be required [I].

1. Psychiatric Management

The treatment of patients with dementia should be based on a thorough psychiatric, neurological, and general medical evaluation of the nature and cause of the cognitive deficits and associated noncognitive symptoms, in the context of a solid alliance with the patient and family [I]. It is particularly critical to identify and treat general medical conditions, most notably delirium, that may be responsible for or contribute to the dementia or associated neuropsychiatric symptoms [I].

Ongoing assessment includes periodic monitoring of the development and evolution of cognitive and noncognitive psychiatric symptoms and their response to intervention [I]. In order to offer prompt treatment, enhance safety, and provide timely advice to the patient and family, it is generally necessary to see patients in routine follow-up at least every 3–6 months [II]. More frequent visits (e.g., up to once or twice a week) or even psychiatric hospitalization may be required for patients with acute, complex, or potentially dangerous symptoms or for the administration of specific therapies [I]. Recommended assessments include evaluation of suicidality, dangerousness to self and others, and the potential for aggression, as well as evaluation of living conditions, safety of the environment, adequacy of supervision, and evidence of neglect or abuse [I].

All patients and families should be informed that even mild dementia increases the risk of vehicular accidents [I]. Mildly impaired patients should be advised to limit their driving to safer situations or to stop driving [I], and moderately impaired patients should be instructed not to drive [I]. Advice about driving cessation should also be communicated to family members, as the implementation of the recommendation often falls on them [I]. Relevant state laws regarding notification should be followed [I].

Important aspects of psychiatric management include educating patients and families about the illness, its treatment, and sources of additional care and support (e.g., support groups, respite care, nursing homes, and other long-term-care facilities) and advising patients and their families of the need for financial and legal planning due to the patient's eventual incapacity (e.g., power of attorney for medical and financial decisions, an up-to-date will, and the cost of long-term care) [I].

2. Specific Psychotherapies and Other Psychosocial Treatments

In addition to the general psychosocial interventions subsumed under psychiatric management, a number of specific interventions are appropriate for some patients. Few of these treatments have been subjected to double-blind

randomized evaluation, but some research, along with clinical practice, supports their effectiveness. Behavior-oriented treatments are used to identify the antecedents and consequences of problem behaviors and attempt to reduce the frequency of behaviors by directing changes in the environment that alter these antecedents and consequences. Behavioral approaches have not been subjected to large randomized clinical trials but are supported by small trials and case studies and are in widespread clinical use [II]. Stimulation-oriented treatments, such as recreational activity, art therapy, music therapy, and pet therapy, along with other formal and informal means of maximizing pleasurable activities for patients, have modest support from clinical trials for improving behavior, mood, and, to a lesser extent, function, and common sense supports their use as part of the humane care of patients [II]. Among the emotion-oriented treatments, supportive psychotherapy can be employed to address issues of loss in the early stages of dementia [II]. Reminiscence therapy has some modest research support for improvement of mood and behavior [III]; validation therapy and sensory integration have less research support [III]; none of these modalities has been subjected to rigorous testing. Cognition-oriented treatments, such as reality orientation, cognitive retraining, and skills training focused on specific cognitive deficits, are unlikely to have a persistent benefit and have been associated with frustration in some patients [III].

3. Special Concerns Regarding Somatic Treatments for Elderly Patients and Patients With Dementia

Medications are effective in the management of some symptoms associated with dementia, but they must be used with caution in this patient population [I]. Because age may alter the absorption, distribution, metabolism, and elimination of many medications, elderly individuals may be more sensitive to their effects. General medical conditions and use of more than one medication may further affect the pharmacokinetics of many medications. In addition, patients with dementia may be more likely to experience certain medication adverse effects, including anticholinergic effects, orthostasis, sedation, and parkinsonism. Finally, symptoms of dementia may alter medication adherence in ways that are unsafe. Consequently, when using pharmacotherapy in patients with dementia, low starting doses, small increases in dose, and long intervals between dose increments may be needed, in addition to ensuring that a system is in place that can enhance proper medication adherence [I].

4. Treatment of Cognitive Symptoms

Three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—are approved by the U.S. Food and Drug Administration (FDA) for treatment of mild to moderate Alzheimer's disease, and donepezil has been approved by the FDA for severe Alzheimer's disease. These medications have similar rates of adverse effects and have been shown to lead to modest benefits in a substantial minority of patients (i.e., 30%–40% in clinical trials). These medications should be offered to patients with mild to moderate Alzheimer's disease after a thorough discussion of their potential risks and benefits [I], and they may be helpful for patients with severe Alzheimer's disease [II].

Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease [I]. Only rivastigmine has been approved by the FDA for this indication, but there is no reason to believe the benefit is specific to this cholinesterase inhibitor.

Cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies [II].

The constructs of mild cognitive impairment and vascular dementia are evolving and have ambiguous boundaries with Alzheimer's disease. The efficacy and safety of cholinesterase inhibitors for patients with these disorders are uncertain; therefore, no specific recommendation can be made at this time, although individual patients may benefit from these agents [II].

Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist, which has been approved by the FDA for use in patients with moderate and severe Alzheimer's disease, may provide modest benefits and has few adverse effects; thus, it may be considered for such patients [I]. There is some evidence of its benefit in mild Alzheimer's disease [III] and very limited evidence of its benefit in vascular dementia [I].

Vitamin E (α-tocopherol) is no longer recommended for the treatment of cognitive symptoms of dementia because of limited evidence for its efficacy as well as safety concerns [II].

Nonsteroidal anti-inflammatory agents (NSAIDs), statin medications, and estrogen supplementation (with conjugated equine estrogens) have shown a lack of efficacy and safety in placebo-controlled trials in patients with Alzheimer's disease and therefore are not recommended [I].

5. Treatment of Psychosis and Agitation

Psychosis, aggression, and agitation are common in patients with dementia and may respond to similar therapies. When deciding if treatment is indicated, it is critical to consider the safety of the patient and those around him or her [I]. A careful evaluation for general medical, psychiatric, environmental, or psychosocial problems that may underlie the disturbance should be undertaken [I]. If

possible and safe, such underlying causes should be treated first [I]. If this does not resolve the symptoms, and if they do not cause significant danger or distress to the patient or others, such symptoms are best treated with environmental measures, including reassurance and redirection [I]. For agitation, some of the behavioral measures discussed in Section I.B.2 may also be helpful [II]. If these measures are unsuccessful or the behaviors are particularly dangerous or distressing, then the symptoms may be treated judiciously with one of the agents discussed in the following paragraphs [II]. The use of such agents should be reevaluated and their benefit documented on an ongoing basis [I].

On the basis of good evidence, antipsychotic medications are recommended for the treatment of psychosis in patients with dementia [II] and for the treatment of agitation [II]. These medications have also been shown to provide modest improvement in behavioral symptoms in general [I]. Evidence for the efficacy of these agents is based mostly on 6–12-week trials in nursing home residents and outpatients. There is limited research on their use beyond 12 weeks, but considerable clinical experience supports this practice [II]. Evidence for a difference in efficacy and safety among antipsychotic medications is limited. Antipsychotic medications as a group are associated with a number of severe adverse events, including increased risks for death, cerebrovascular accidents, tardive dyskinesia, neuroleptic malignant syndrome, hyperlipidemia, weight gain, diabetes mellitus, sedation, parkinsonism, and worsening of cognition. Thus, they must be used with caution and at the lowest effective dosage [I], after considering the risks of not treating the psychiatric symptoms [I]. Patients and families should be advised about potential benefits and risks of antipsychotic agents, particularly the risk of mortality [I]. Second-generation (atypical) antipsychotics currently have a black box warning for increased risk of mortality in elderly patients; recent data suggest that first-generation (typical) agents carry at least a similar risk. High-potency agents tend to cause akathisia and parkinsonian symptoms; low-potency agents tend to cause sedation, confusion, delirium, postural hypotension, and peripheral anticholinergic effects. The decision of which antipsychotic to use is based on the relationship between the side-effect profile and the characteristics of the individual patient [I].

Data demonstrating benefit from benzodiazepines are modest, but benzodiazepines occasionally have a role in treating patients with prominent anxiety [III] or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure such as a tooth extraction or a diagnostic examination [II]. Adverse effects of benzodiazepines include sedation, worsening cognition, delirium, increased risk of falls, and worsening of breathing disorders. Lorazepam and oxazepam, which have no active metabolites, are preferable to agents with a longer half-life such as diazepam or clonazepam [III].

There is minimal evidence for the efficacy of anticonvulsants, lithium, and beta-blockers for the treatment of psychosis or agitation in dementia, and these medications have significant adverse effects; therefore, they are generally not recommended except for patients for whom other treatments have failed [III]. The antidepressant trazodone and the selective serotonin reuptake inhibitors (SSRIs) are also not well studied for symptoms other than depression but may be appropriate for nonpsychotic patients with agitation, especially for patients with mild agitation or prior sensitivity to antipsychotic medications [III].

6. Treatment of Depression

Depression is common in patients with dementia. Patients with depression should be evaluated for suicide risk [I]. Depressed mood may respond to improvements in the patient's living situation or to stimulation-oriented treatments [II]. Although evidence for antidepressant efficacy in patients with dementia and depression is mixed, clinical consensus supports a trial of an antidepressant to treat clinically significant, persistent depressed mood [II]. The choice among agents is based on the side-effect profile of specific medications and the characteristics of the individual patient [I]. SSRIs may be preferred because they appear to be better tolerated than other antidepressants [II]. Bupropion, venlafaxine, and mirtazapine may also be effective [II]. Agents with substantial anticholinergic effects (e.g., amitriptyline, imipramine) should be avoided [I]. Despite the lack of research data, clinical experience suggests that unilateral electroconvulsive therapy (ECT) may be effective for patients who do not respond to pharmacological agents [II].

Treatments for apathy are not well supported, but psychostimulants, bupropion, bromocriptine, and amantadine may be helpful [III]. Psychostimulants are also sometimes useful in the treatment of depression in patients with significant general medical illness [III].

7. Treatment of Sleep Disturbances

Sleep disturbances are common in patients with dementia. Interventions include maintaining daytime activities and giving careful attention to sleep hygiene [II]. Pharmacological intervention could be considered when other approaches have failed [II]. If a patient also requires medication for another psychiatric condition, an agent with sedating properties, given at bedtime, could be selected [I]. For primarily treating the sleep disturbance, medica-

tions with possible effectiveness include trazodone, zolpidem, or zaleplon [III], but there are few data on the efficacy of specific agents. Benzodiazepines are not recommended for other than brief use because of risks of daytime sedation, tolerance, rebound insomnia, worsening cognition, falls, disinhibition, and delirium [II]. Diphenhydramine is not recommended because of its anticholinergic properties [II]. Antipsychotic medications should not be used solely for the purpose of treating sleep disturbances [I].

8. Special Issues for Long-Term Care

Many patients eventually require long-term-care placement; approximately two-thirds of nursing home patients have dementia. Care should be organized to meet the needs of patients, including those with behavioral problems [I]. Employing staff with knowledge and experience concerning dementia and the management of difficult behavior is important [II]. Special care units may offer more optimal care, although there is limited evidence that they achieve better outcomes than traditional units [III].

A particular concern is the use of physical restraints and medications to control disruptive behavior. Appropri-

ate use of antipsychotic medications can relieve symptoms and reduce distress and can increase safety for patients, other residents, and staff [I]. However, their use may be associated with worsening cognitive impairment, oversedation, falls, tardive dyskinesia, and neuroleptic malignant syndrome, as well as with hyperlipidemia, weight gain, diabetes mellitus, cerebrovascular accidents, and death [I]. Thus, good clinical practice requires careful consideration and documentation of the indications and available alternatives, both initially and on a regular ongoing basis [I]. A dose decrease or discontinuation should be considered periodically for all patients who receive antipsychotic medications [I]. A structured education program for staff may help to both manage patients' behavior and decrease the use of these medications in nursing homes [II]. Physical restraints are rarely indicated and should be used only for patients who pose an imminent risk of physical harm to themselves or others [I]. Reasons for the use of physical restraints should be carefully documented [I]. The need for restraints can be decreased by environmental changes that decrease the risk of falls or wandering and by careful assessment and treatment of possible causes of agitation [II].

II. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

The treatment of Alzheimer's disease and related dementias is inherently multidisciplinary and multimodal. It is guided by the stage of illness and is focused on the specific symptoms manifested by the patient. This discussion begins with general principles of psychiatric management, essential to the treatment of the patient with dementia, and then reviews specific treatments. These treatments include the broad range of psychosocial interventions used in dementia as well as the pharmacological options, which are organized in the discussion by target symptom.

A. DETERMINING THE SITE OF TREATMENT AND FREQUENCY OF VISITS

Choice of specific treatments for a patient with dementia begins with the establishment of a specific diagnosis and an assessment of the symptoms being experienced by that patient. A multimodal approach is often used, combining, for instance, behavioral and psychopharmacological interventions as available and appropriate. When multiple

agents or approaches are being used and problems persist (or new problems develop), it is advisable, if possible, to make one change at a time so that the effect of each change can be assessed. The continuing utility of all interventions must be regularly reevaluated.

The site of treatment for an individual with dementia is determined by the need to provide safe and effective treatment in the least restrictive setting. Approximately two-thirds of patients with dementia live at home and receive care on an outpatient basis. The frequency of office or facility visits is determined by a number of factors, including the patient's clinical status, the likely rate of change, and the need for specific monitoring of treatment effects. Another factor is the reliability and skill of the patient's caregivers, particularly regarding the likelihood of their notifying the clinician if a clinically important change occurs. Most dementias are progressive, and symptoms change over time. Therefore, in order to offer prompt treatment, enhance safety, and provide timely advice to the patient and family, it is generally necessary to see pa-

tients, usually together with their caregivers, at regular follow-up visits. Patients who are clinically stable or are taking stable doses of medications should generally be seen at a minimum of every 3–6 months. Patients who require active treatment of psychiatric complications should be seen regularly to adjust doses and monitor for changes in target symptoms and side effects. Similarly, attempts to taper or discontinue psychotropic medications require more frequent assessments than are required for routine care. Weekly or monthly visits are likely to be required for patients with complex, distressing, or potentially dangerous symptoms or during the administration of specific therapies. For example, outpatients with acute exacerbations of depressive, psychotic, or behavioral symptoms may need to be seen as frequently as once or twice a week, sometimes in collaboration with other treating clinicians, or be referred to intensive outpatient treatment or a partial hospitalization program.

Individuals with dementia may need to be admitted to an inpatient facility for the treatment of psychotic, affective, or behavioral symptoms. In addition, they may need to be admitted for treatment of general medical conditions co-occurring with psychiatric conditions. For patients who are very frail or who have significant general medical illnesses, a geriatric psychiatry or medical psychiatric unit may be helpful when available (1). Indications for hospitalization include symptom severity (e.g., significant threats of harm to self or others, violent or uncontrollable behavior, inability to care for self or be cared for by others) and intensity and availability of services needed (e.g., the need for continuous skilled observation, electroconvulsive therapy, or a medication or diagnostic test that cannot be performed on an outpatient basis) (2, 3). The length of stay is similarly determined by the ability of the patient to safely receive the appropriate care in a less restrictive setting.

Decisions regarding the need for temporary or permanent placement in a long-term-care facility often depend on the degree to which the patient's needs can be met in the community, either by relatives or other caregivers, either in an assisted living facility or at home. The decision to remain at home should be reassessed regularly, with consideration of the patient's clinical status and the continued ability of the patient's caregivers to care for the patient, manage the burden of care, and utilize available support services. The appropriate level of care may change over time, and patients often move from one level of care to another during the course of dementia. If available, consultation with a social worker or geriatric case manager may be beneficial to assess the current support system and facilitate referrals to additional services. At the end of life, many patients with dementia are cared for in a hospice program.

B. PSYCHIATRIC MANAGEMENT

Successful management of patients with dementia requires the concurrent implementation of a broad range of tasks, which are grouped under the term "psychiatric management." These tasks help to maximize the patient's level of function and enhance the safety and comfort of patients and their families in the context of living with a difficult disease. In some settings, psychiatrists perform all or most of these tasks themselves. In others, they are part of multidisciplinary or interdisciplinary teams. In either case, they must be aware of the full range of available treatments and take steps to ensure that any necessary treatments are administered. Good communication between the patient's psychiatrist and primary care physician ensures maximum coordination of care, may minimize polypharmacy, and may improve patient outcomes (4).

1. Establish and Maintain an Alliance With the Patient and the Family

As with any psychiatric care, a solid therapeutic alliance is critical to the treatment of a patient with dementia. The care of a patient with dementia requires an alliance with the patient, as well as with the family and other caregivers. Family members and other caregivers are a critical source of information, as the patient is frequently unable to give a reliable history, particularly as the disease progresses. Because family members are often responsible for implementing and monitoring treatment plans, their own attitudes and behaviors can have a profound effect on the patient, and they often need the treating physician's compassion and concern. For these reasons, treatment is directed to the patient-caregiver system. The needs of caregivers will vary based on factors such as their relationship to the patient, their long-standing role in the family, and their current customs. Clinical judgment is needed to determine the circumstances in which it is appropriate or necessary to speak with caregivers without the patient present, as well as how to proceed with clinical care when there are disputes among family members. A clear process for medical decision making should be delineated for each patient, and a capacity assessment of the patient should be performed when necessary.

2. Perform a Diagnostic Evaluation and Refer the Patient for Any Needed General Medical Care

a. General Principles

Patients with dementia should undergo a thorough diagnostic evaluation aimed at identifying the specific etiology of the dementia syndrome, because knowledge of the etiology may guide specific treatment decisions. In addition, the

evaluation should determine if any treatable psychiatric or general medical conditions (e.g., major depression, thyroid disease, vitamin B_{12} deficiency, hydrocephalus, structural brain lesion) might be causing or exacerbating the dementia. The details of this evaluation are beyond the scope of this guideline; the reader is referred to the American Academy of Neurology practice parameter on the diagnosis of dementia (5), the American Academy of Neurology practice parameter on early detection of dementia and mild cognitive impairment (6), and the Agency for Health Care Policy and Research clinical practice guideline *Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias* (7) for more complete descriptions of the evaluation of patients with dementia. A brief summary follows.

The general principles of a complete psychiatric evaluation are outlined in APA's *Practice Guideline for the Psychiatric Evaluation of Adults* (8). The evaluation of a patient with dementia frequently involves coordination with a number of medical professionals, including the patient's primary care physician (4). The physician with overall responsibility for the care of the patient oversees the evaluation, which should at a minimum include a clear history of the onset and progression of symptoms; a review of the patient's medical problems and medications (including over-the-counter and herbal medications); assessment of functional abilities; a complete physical examination and a focused neurological examination; and a psychiatric examination, including a cognitive assessment that should include at least a brief assessment of the cognitive domains of attention, memory, language, and visuospatial skills, ideally used with age- and education-adjusted norms (9, 10). An assessment for past or current psychiatric illnesses that might mimic or exacerbate dementia, such as schizophrenia or major depression, is also critical, as are laboratory studies, including a complete blood count (CBC), blood chemistry battery (including glucose, electrolytes, calcium, and kidney and liver function tests), measurement of vitamin B_{12} level, and thyroid function tests. For some patients, toxicology studies, syphilis serology, erythrocyte sedimentation rate, HIV testing, serum homocysteine, a lumbar puncture, or an electroencephalogram may also be indicated. In general, many elements of the history will need to be obtained from the caregiver or the documented medical record as well as from the patient. Often, it may be necessary to conduct a portion of the interview with the caregiver without the patient present, in order to allow for full disclosure of sensitive information.

b.   Neuropsychological Testing

Neuropsychological testing may be helpful in a number of ways. It may help in deciding whether a patient with sub-tle or atypical symptoms actually has dementia as well as in more thoroughly characterizing an unusual symptom picture. It is particularly useful in the evaluation of individuals who present with mild cognitive impairment (see Section IV.F.2), which requires evidence of memory and/or other cognitive difficulties in the presence of intact functioning, and in the evaluation of individuals with the onset of dementia early in life. Testing may help to characterize the extent of cognitive impairment, to distinguish among the types of dementias, and to establish baseline cognitive function. Neuropsychological testing may also help identify strengths and weaknesses that could guide expectations for the patient, direct interventions to improve overall function, assist with communication, and inform capacity determinations.

c.   Neuroimaging

The use of a structural neuroimaging study, such as computerized tomography or magnetic resonance imaging (MRI) scan, is generally recommended as part of an initial evaluation, although clinical practice varies. Imaging is particularly important for those with a subacute onset (less than 1 year), symptom onset before age 65, vascular risk factors suggesting a higher likelihood of cerebrovascular involvement in their dementia, or a history or neurological examination findings suggesting a possible focal lesion. Nonetheless, clinically important lesions may be found on neuroimaging in the absence of these indications (11). The value of imaging in patients with late-stage disease who have not been previously evaluated has not been established. Functional neuroimaging using brain positron emission tomography (PET) scans may contribute to diagnostic specificity in certain instances and has been recently approved by Medicare for the indication of differentiating between Alzheimer's disease and frontotemporal dementia.

The development of additional imaging tools for improved diagnosis, early recognition, and more precise assessment of disease progression is a focus of current study. These additional tools include quantitative MRI, functional MRI, use of investigational PET compounds, and other methods aimed at imaging senile plaques in the brain (12, 13).

d.   Biomarkers

A wide variety of biomarkers are also under investigation with the goal of enhancing diagnostic and prognostic knowledge (14). Biomarkers of current interest include proteins such as tau and amyloid beta protein in the cerebrospinal fluid (CSF) and plasma. Except in rare circumstances (notably the use of CSF-14-3-3 protein when Creutzfeldt-

Jakob disease is suspected and recent stroke or viral encephalitis can be excluded) (5, 15), these techniques remain investigational, and there is insufficient evidence for their utility in routine clinical practice. However, this area is evolving rapidly, so recommendations may change with new discoveries and the development of new markers and/or therapies.

e. Genetic Testing

Although genes involved in a variety of dementia syndromes have been identified (16), and family members of patients with dementia are often concerned about their risk of developing dementia, genetic testing is generally not part of the evaluation of patients with dementia except in very specific instances (5). In particular, testing for apolipoprotein E4 (*APOE4*) is not recommended for use in diagnosis. Apolipoprotein E4 is one form of a gene on chromosome 19 that is more common in individuals with Alzheimer's disease than in elderly individuals without dementia and is associated with late-onset Alzheimer's disease occurring with or without a family history (17–19). However, it is also found in many elderly patients who do not have dementia and is not found in many patients who do have Alzheimer's disease. Thus, the presence of an *APOE4* allele does not change the need for a thorough workup and does not add substantially to diagnostic confidence (5, 20–22).

First-degree relatives of patients with Alzheimer's disease have a risk of developing the disease that is two to four times that of the general population. Three genes associated with the disease have been identified in families with apparent autosomal dominant inheritance of early-onset Alzheimer's disease. These genes include the amyloid precursor protein (*APP*) gene on chromosome 21 (23), presenilin 1 (*PSEN1*) on chromosome 14 (24), and presenilin 2 (*PSEN2*) on chromosome 1 (25). Genetic testing is commercially available for *PSEN1*, which is likely to be found in families with apparent autosomal dominant inheritance and dementia developing before age 50 years. Testing for the other two genes is not commercially available but can sometimes be performed in the context of clinical genetics research. However, the role of such testing in clinical practice has not yet been established. Because no preventive treatments are currently available, testing should only be offered in the setting of thorough pre- and posttest counseling (26). In addition, genetic testing is best done in conjunction with experts familiar with Alzheimer's disease genetics, as test results require careful interpretation. A referral to a local Alzheimer's Disease Research Center or the local chapter of the Alzheimer's Association may be helpful in locating someone who can provide the appropriate counseling and testing. If spe-

cific Alzheimer's genetics resources are not available locally, a referral to a professional genetic counselor or clinical geneticist may help such families characterize their risk and find appropriate resources (27, 28).

Genetic counseling and sometimes genetic testing may also be appropriate for some patients with other dementias and a family history of similar syndromes. In particular, individuals with a clinical picture suggestive of frontotemporal dementia and a family history suggesting autosomal dominant inheritance can be tested for certain mutations (29, 30). Likewise, individuals with a clinical picture suggestive of Huntington's disease can be tested for the gene defect (31), and those suspected of having CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) can be tested for associated *Notch 3* gene polymorphisms (32).

3. Assess and Monitor Psychiatric Status

Ninety percent of patients with dementia develop a neuropsychiatric or behavioral symptom during the course of the disease (33). It is therefore important for the psychiatrist to periodically assess the patient for the presence of noncognitive psychiatric symptoms as well as for the progression of cognitive symptoms.

Both cognitive and noncognitive neuropsychiatric and behavioral symptoms of dementia tend to evolve over time, so regular monitoring allows detection of new symptoms and adaptation of treatment strategies to current needs. For example, among the neuropsychiatric disturbances common in Alzheimer's disease, depression is reported more commonly early in the illness, whereas delusions and hallucinations are more common in the middle and later stages, although any of these symptoms may occur at any stage of the disease (33, 34). It is particularly important to look for the emergence of such symptoms after a medication dose has been lowered or discontinued. Among the cognitive deficits, memory loss is commonly the earliest symptom, whereas language and spatial dysfunction become more overt somewhat later.

Among the neuropsychiatric symptoms that require ongoing assessment are depression (including major depression and other depressive syndromes), suicidal ideation or behavior, hallucinations, delusions, agitation, aggressive behavior, disinhibition, sexually inappropriate behavior, anxiety, apathy, and disturbances of appetite and sleep. Cognitive symptoms that almost always require assessment include impairments in memory, executive function, language, judgment, and spatial abilities. It is often helpful to track cognitive status with a structured simple examination. If the same instrument is used repeatedly, the clinician should watch for practice effects. A detailed

assessment of functional status may also aid the clinician in documenting and tracking changes over time as well as providing guidance to the patient and caregivers. Functional status is typically described in terms of the patient's ability to perform instrumental activities of daily living such as shopping, writing checks, basic housework, and activities of daily living such as dressing, bathing, feeding, transferring, and maintaining continence. These regular assessments of recent cognitive and functional status provide a baseline for assessing the effect of any intervention, and they improve the recognition and treatment of acute problems, such as delirium.

Whenever there is an acute worsening of cognition, functioning, behavior, mood, or psychosis, the clinician should bear in mind that elderly persons in general and patients with dementia in particular are at high risk for delirium associated with medications, general medical problems, and surgery. Newly developing or acutely worsening agitation in particular can be a sign of an occult general medical condition (e.g., urinary tract infection, dehydration), untreated or undertreated pain, or physical or emotional discomfort. Elderly patients may not manifest certain typical signs or symptoms such as fever in the face of infection or pain during a myocardial infarction. Thus, a thoughtful assessment of the patient's overall status and a general medical evaluation must precede any intervention with psychotropic medications or physical restraint, except in an emergency. Assessments should also include examination of the patient's sensory function, since sensory deficits can precipitate or worsen psychiatric and cognitive symptoms and increase the risk that patients will make medication errors.

Before undertaking an intervention, the psychiatrist should enlist the help of caregivers in carefully characterizing the target symptoms. Their nature, intensity, frequency, precipitants, and consequences should be reviewed and documented. This process is critical to revealing the cause of the symptoms, as well as monitoring the impact of any intervention. This approach also assists caregivers in beginning to achieve some mastery over the problematic symptom. Before embarking on any intervention, it is also helpful if clinicians explicitly review their own, the patient's, and the caregivers' expectations.

4. Monitor and Enhance the Safety of the Patient and Others

It is important for the psychiatrist treating a patient with dementia to regularly assess cognitive deficits or behavioral difficulties that potentially pose a danger to the patient or others. The psychiatrist should 1) assess suicidality, 2) assess the potential for aggression and agitation, 3) make

recommendations regarding adequate supervision, for example of medication administration, 4) make recommendations regarding the prevention of falls and choking, 5) address nutritional and hygiene issues, and 6) be vigilant regarding neglect or abuse. Patients who live alone require careful attention. Events that indicate that the patient can no longer live alone include several falls, repeated hospitalization, dehydration, malnutrition, repeated errors in taking prescribed medications, dilapidated living conditions, or other signs of self-neglect. Other important safety issues in the management of patients with dementia include interventions to decrease the hazards of wandering and recommendations concerning activities such as cooking, driving, hunting, and the operation of hazardous equipment (see Section II.B.5). Caregivers should be referred to available books that provide advice and guidance about maximizing the safety of the environment for patients with dementia (35).

a. Suicidal Ideation

All patients (and their caregivers) should be asked about the presence of wishes for death, suicidal ideation, suicide plans, as well as a history of previous self-injurious behavior. If suicidal ideation occurs in patients with dementia, it tends to be earlier in the disease, when insight is more likely to be preserved. It is a particular concern in patients who are clinically depressed but can also occur in the absence of major depression. Elderly persons in general and elderly men in particular are at increased risk for suicide, although the diagnosis of dementia is not known to confer added risk. Interventions to address suicidal ideation are similar to those for patients without dementia and include psychotherapy; pharmacotherapy; removal of potentially dangerous items such as medications, guns, or vehicles; increased supervision; and hospitalization. Factors affecting the choice of intervention include the nature and intensity of the suicidal ideation or behavior and the capacity and support system of the patient (36).

b. Agitation and Aggression

"Agitation" is an umbrella term that refers to a range of behavioral disturbances, including physical aggression, combativeness, threatening behavior, persistent or intermittent psychomotor hyperactivity, and disinhibition. These behaviors pose a particular problem for patients cared for at home, especially by frail spouses. Agitation is more likely to occur later in the course of dementia and often has multiple causes. New or worsened agitation can result from an occult general medical problem, medication side effects, untreated or undertreated pain, constipation, depression, psychotic symptoms, or delirium. Thus, the first priority is a careful medical evaluation, because the agitation will of-

ten resolve with treatment of an underlying condition. The next step is an assessment of other features of the patient's overall situation. Hunger or sleep deprivation can provoke agitation, as can interpersonal or emotional stressors such as undergoing a change in living situation, caregiver, or roommate or experiencing frustration, boredom, loneliness, or overstimulation. Consequently, attending to unmet needs, providing reassurance, redirecting activities, or matching the level of stimulation to the patient's current level of activation may resolve the problem (37).

In designing an intervention to treat a problematic behavior, a structured approach should be taken to facilitate selecting the optimal treatment and monitoring the effect of that treatment (38–40). The first step is to carefully describe the target behavior, including where, when, and how often it occurs. The next step is to assess the specific antecedents and consequences of each problem behavior, which will often suggest specific strategies for intervention. Activities that consistently precede the problem behavior may be acting as precipitants and should be avoided whenever possible. If the activity is a necessary one, for example, bathing, it may be helpful to decrease its frequency or to alter the environment so that the negative consequences are minimized (e.g., switch bath time to allow a home health aid to supervise, or change the location of baths to decrease the impact of aggressive outbursts on family members or other patients). When multistep activities such as dressing and eating precipitate problem behaviors such as aggression, it often helps to simplify the activities (e.g., using clothing with Velcro closures, serving several simple nutritious snacks instead of a large meal). Whatever the intervention, it is critical to match the level of demand on the patient with his or her current capacity, avoiding both infantilization and frustration. Likewise, behavior may also improve by modifying the environment insofar as possible to compensate for the patient's deficits and to capitalize on his or her strengths (41). In assessing the effectiveness of interventions for problematic behaviors, clinicians can recommend that caregivers maintain a log of specific behaviors as well as their intensity, frequency, precipitants, and consequences.

If the agitation is deemed dangerous to the patient or others, it is important to undertake further measures to enhance safety. Such additional measures may include providing one-on-one care, instituting the behavioral measures discussed in Section II.C.4, or initiating pharmacological treatment as discussed in Section II.C.5. If agitation and aggressive behavior cannot be brought under control, hospitalization and/or nursing home placement must be considered.

Within hospital or nursing home settings, physical restraints (e.g., Posey restraints, geri-chairs) are sometimes used to treat agitation or combativeness that puts the patient or others at risk. Nonetheless, principles of humane care as well as federal regulations support minimizing restraint use as much as possible. In addition, some evidence suggests that restraints may increase the risk of falls and contribute to cognitive decline (42, 43) and that reducing restraint use can decrease the rate of serious injuries among nursing home residents (44).

c. Supervision

Decisions regarding supervision of the patient should take into consideration the patient's cognitive deficits, the home environment, and the consequent risk of dangerous activities. For instance, a patient with significant cognitive impairment may not be safe alone at home because he or she might improperly administer medications, be unable to cope with a household emergency, or use the stove, power tools, or other equipment in a dangerous manner. Home occupational therapy functional and safety assessments, as well as other community-based services, may be helpful in determining whether increased supervision is needed.

d. Falls

Psychiatrists caring for patients with dementia should be aware that falls are a common and potentially serious problem for all elderly individuals, especially those with dementia. Falls can lead to hip fracture, head trauma, and a variety of other injuries, including subdural hematomas, which may further worsen cognitive function. A number of interventions to prevent falls in elderly people have been shown to be effective (45). One of the most efficacious is withdrawing medications that are associated with falls, central nervous system sedation, or cardiovascular side effects (especially orthostatic hypotension), when appropriate. If gait disturbances are present, canes, walkers, or other supports may be helpful unless they are otherwise contraindicated (e.g., if their use poses a hazard to others). Patients at high risk for falling may need to be closely supervised while walking.

Environmental modifications can also help reduce the risk of falls. The removal of loose rugs, low tables, and other obstacles can diminish risk. The use of lower beds, night-lights, bedside commodes, and/or frequent toileting may help prevent falls at night. Although bed rails are thought to prevent patients from rolling out of bed, they may actually increase the risk of falls. Therefore, other environmental modifications such as lowering the bed or placing a mattress on the floor are typically recommended. Bed and chair monitors have also been suggested as a way to alert caregivers or nursing staff when patients may be getting out of bed or leaving a chair. In addition, programs for muscle strengthening and balance retraining

have been shown to be helpful in reducing falls in elderly people (45). A physical therapy evaluation may be appropriate for certain patients. For patients in acute inpatient or nursing home settings, restraints are occasionally used on a temporary basis to reduce the likelihood of falling. Under such circumstances, documentation should reflect the rationale for the temporary use of restraints and should include a discussion of the other measures that were tried and failed to bring the behavior under control.

e.   Abuse and Neglect

The psychiatrist should be alert to the possibility of elder abuse, financial exploitation, and neglect. Individuals with dementia are at particular risk for abuse because of their limited ability to protest, their lack of comprehension, and the significant demands and emotional strain on caregivers. Patients whose caregivers appear angry or frustrated may be at even higher risk. Any concern, especially one raised by the patient, must be thoroughly evaluated. Corroborating evidence (e.g., from physical examination) should be sought in order to distinguish delusions, hallucinations, and misinterpretations from actual abuse. In many states, when neglect or abuse is suspected, the psychiatrist is required to make a report to the appropriate local or state agency responsible for investigating elder abuse.

f.   Wandering

Families should be advised that patients with dementia may wander away from home and that wandering may be dangerous to patients. Some patients are unable to find their way back, whereas others lack the judgment to recognize and deal with dangerous situations. Wandering has been associated with more severe dementia and dementia of longer duration. It has also been associated with depression, delusions, hallucinations, sleep disorders, neuroleptic medication use, and male gender (46). Provision of adequate supervision is important to prevent patients from wandering. However, since walking may be beneficial, both as stimulation and exercise, it should not be limited unnecessarily. Providing access to a large, safe area for walking or opportunities for supervised walks is ideal. Environmental changes may also be necessary to prevent unsupervised departures. At home, the addition of a more complex or less accessible door latch may be helpful. Electronic devices to reduce the risk of in-home wandering are under development. If wandering occurs at night when caregivers are asleep, pharmacological intervention may be indicated. In institutional settings, electronic locks or electronic devices that trigger an alarm when the patient tries to leave may be used.

Although a number of interventions of visual and other selective barriers such as mirrors, camouflage, and grids/stripes of tape have been tried, there is no evidence that these subjective barriers prevent wandering in cognitively impaired people (47). If patients are prevented from leaving on their own, adequate supervision must be provided to ensure emergency egress. Pharmacotherapy is rarely effective in the treatment of wandering unless the wandering is due to an associated condition such as mania.

In addition, provision should be made for locating patients should wandering occur. Such measures include sewing or pinning identifying information onto clothes, placing medical-alert bracelets on patients, and filing photographs with local police departments. Referrals to the Safe Return Program of the Alzheimer's Association (1-888-572-8566; http://www.alz.org/safereturn) or similar programs provided by local police departments or other organizations should be considered for patients at risk of wandering.

5.   Advise the Patient and Family Concerning Driving (and Other Activities That Put Other People at Risk)

Most of the available evidence suggests that dementia, even when mild, impairs driving performance to some extent and that the risk of accidents increases with increasing severity of dementia (48). For example, compared to age-matched controls, individuals with probable Alzheimer's disease had more difficulties comprehending and operating a driving simulator, drove off the road more often, spent more time driving considerably slower than the posted speed limit, applied less brake pressure in stop zones, spent more time negotiating left turns, and drove more poorly overall (49). Nonetheless, it is well documented that many individuals with dementia, even some with fairly serious impairment, continue to drive, raising significant public health concerns (50–54).

In an office or hospital setting, accurate assessment of functional abilities such as driving is not possible (55). Furthermore, the influence of neuropsychiatric impairments or behavioral symptoms on driving performance is neither clear-cut nor predictive (56, 57). However, risks of driving should be discussed with all patients with dementia and their families, and these discussions should be carefully documented. Discussions should include an exploration of the patient's current driving patterns, transportation needs, and potential alternatives. The psychiatrist should also ask the family about any history of getting lost, traffic accidents, or near accidents. For patients with dementia who continue to drive, the issue should be raised repeatedly and reassessed over time. This is especially true for patients with Alzheimer's disease or other progressive dementias in which driving risk will predictably worsen over time (58).

At this time, there is no clear consensus regarding the threshold level of dementia at which driving should be curtailed or discontinued (48, 58–61). In mild dementia, the driving risk is greater than for age-matched individuals without dementia, although it is less than that for cognitively intact young drivers (e.g., younger than age 25 years) (48). Thus, some clinicians argue that in mild dementia the benefits to the patient of continued independence and access to needed services outweigh the risk of an accident. Other clinicians argue that no patient with a diagnosis of dementia should drive, because the risk of an accident is elevated even in patients with mild dementia, and it is impossible to say at what point this risk becomes unacceptable. In an evidence-based review of driving and Alzheimer's disease from the American Academy of Neurology, it was found that driving was only mildly impaired in drivers with a Clinical Dementia Rating (CDR) of 0.5 (mild cognitive impairment), but those with a CDR of 1 (mild or early stage dementia) were found to pose significant risks from increased vehicular accidents and poorer driving performance (48) (see Section I.V.E for information on the staging of dementia).

Additional increases in risk may also be associated with a diagnosis of dementia with Lewy bodies. Concomitant neurological symptoms such as motor deficits (e.g., due to stroke or a parkinsonian syndrome, impairments in praxis), sensory deficits (e.g., spatial neglect, visual loss, deafness), or deficits in judgment, coordination, processing speed, and reaction time are also thought to increase risk, although this view has not been confirmed by research (56, 62–64). Finally, general medical problems (e.g., symptomatic cardiac arrhythmia, syncope, seizures, poorly controlled diabetes) or the use of sedating medications may also impair driving ability. A history of at-fault traffic incidents may also signal increased risk (65). Thus, in individuals with mild dementia and one or more of these additional factors, driving cessation may be particularly indicated.

Patients with milder impairment may also need to consider giving up driving. For those who are unwilling to do so, it may be helpful to advise them to limit their driving to conditions likely to be less risky (e.g., familiar locations, modest speeds, good visibility, clear roads) (66). The patient's spouse or other individual may act as a navigator or assessor of driving skill, but the utility of this strategy is unproven, and passengers may be injured in the event of an accident (60, 61). Mildly impaired patients who wish to have an independent assessment of their driving skills may be referred to an occupational therapist, rehabilitation center, driving school, or local department of motor vehicles, but the predictive value of these assessments for actual driving performance has not been established.

In individuals with moderate impairment (e.g., those who cannot perform moderately complex tasks, such as preparing simple meals, household chores, yard work, or simple home repairs), there is some evidence and strong clinical consensus that driving poses an unacceptable risk and patients should be instructed not to drive (48, 59–61). Those with severe impairment are generally unable to drive and certainly should not do so.

Advice about driving cessation should be communicated to family members, as well as to the patient, because the burden of implementing the decision often falls on families. The psychiatrist can also lend moral authority and support to family members who wish to restrict driving but are reluctant to take responsibility for the decision (e.g., writing on a prescription pad, "DO NOT DRIVE"). Eventually, when the point is reached where the danger of continued driving is undeniable, the psychiatrist can provide concrete advice regarding how best to accomplish cessation of driving (e.g., confrontation regarding risks to grandchildren, discussion of the impact on insurance coverage and rates, removing the car from view, hiding the keys, or removing ignition wires). The American Medical Association publication, "Physician's Guide to Counseling and Assessing Older Drivers" (http://www.ama-assn.org/ama/pub/category/10791.html) may be helpful to some clinicians (67). When making recommendations to limit or stop driving, clinicians should be sensitive to the significant psychological meaning of giving up driving. In addition, patients and their families will need to make plans for alternative modes of transportation (60, 61, 68). A social service referral may be helpful for some families to help with transportation arrangements and costs.

Psychiatrists should familiarize themselves with state motor vehicle regulations for reporting individuals with dementia. In some states, disclosure is forbidden. In others, a diagnosis of dementia or Alzheimer's disease must be reported to the state department of motor vehicles, and the patient and family should be so informed. In many states, the physician may breach confidentiality to inform the state motor vehicle department of a patient who is judged to be a dangerous driver. This option is appropriate for patients with significant dementia who refuse to stop driving and whose families are unwilling or unable to stop them.

Although the data and recommendations just described refer to the operation of motor vehicles, similar principles apply to the operation of other equipment that puts the patient and others at risk. Thus, patients whose leisure or work activities involve firearms, use of heavy machinery, aircraft, lawn mowers, or other dangerous equipment or material will need to have these activities limited and discontinued as the disease progresses.

6. Provide Education and Support to Patients and Families

a. Educate the Patient and Family About the Illness and Available Treatments

An important task of the psychiatrist who cares for an individual with dementia is providing or coordinating the education of the patient and family regarding the illness and its natural history. Often the first step is to communicate and explain the diagnosis of dementia, including the specific dementia etiology, if known. Terms should be clarified at the outset to facilitate communication. Patients vary in their ability and desire to understand and discuss their diagnosis. Most mildly and some moderately impaired individuals are able to discuss the matter at some level, but the discussion must be adapted to the specific concerns and abilities of the patient; it may be helpful to seek the family's input regarding the nature and timing of any discussion with the patient (69). The issue of disclosure of the diagnosis to the patient is complex because many patients cannot recognize their deficits. Decisions about how to disclose should take into account factors such as cultural issues that might modify the patient's desire to receive such information (70). In most cases, the psychiatrist will have an explicit discussion with family members regarding the diagnosis, prognosis, and treatment options, adapted to the unique concerns of the patient and family. This discussion will likely span a number of office visits. Certain specific symptoms (e.g., psychosis, extrapyramidal symptoms) are predictive of more rapid decline and thus may be used in tandem with other features to assess prognosis (71).

It is important to educate the patient and family about the range of symptoms that could develop in the current stage of dementia or that may develop in the future. This education allows them to plan for the future and to recognize emergent symptoms that should be brought to medical attention. Family members and other caregivers may be particularly concerned about behavioral and neuropsychiatric symptoms, which they often associate with a loss of dignity, social stigma, and an increased caregiving burden. It may be helpful to reassure patients and their families that these symptoms are part of the illness and are direct consequences of the damage to the brain. Moreover, they may be relieved to know that although cognitive losses are generally not reversible, neuropsychiatric symptoms, especially the more disruptive ones, can often be improved or even eliminated with treatment, resulting in an overall increase in functional status and comfort. By treating these symptoms, educating family caregivers, and providing them with alternative strategies to deal with the patient's disruptive behaviors, the psychiatrist can help to minimize the caregivers' negative reactions to the pa-

tient's behavior (72). Section II.B.6.b includes suggestions for reading materials that may be helpful in providing education to families and caregivers.

The family should be educated regarding basic principles of care, including 1) recognizing declines in capacity and adjusting expectations appropriately, 2) bringing sudden declines in function and the emergence of new symptoms to professional attention, 3) keeping requests and demands relatively simple, 4) deferring requests if the patient becomes overly upset or angered, 5) avoiding overly complex tasks that may lead to frustration, 6) not confronting patients about their deficits, 7) remaining calm, firm, and supportive and providing redirection if the patient becomes upset, 8) being consistent and avoiding unnecessary change, and 9) providing frequent reminders, explanations, and orientation cues. For example, when arriving with visitors, families should say, "This is your nephew, your sister's son" rather than repeatedly testing a patient's memory by saying "Do you remember who this is?" It is also important to individualize the approach to the patient's needs, and, in this regard, psychiatrists and other mental health care professionals can offer more specific behavioral interventions that caregivers can use to avoid or deal with difficult behaviors. For additional details on such interventions, see Sections II.B.4.b and II.C.4.

b. Refer the Family to Appropriate Sources of Care and Support

Family members often feel overwhelmed by the combination of hard work and personal loss associated with caring for an individual with dementia. The caring and pragmatic attitude of the psychiatrist may provide critical support. This attitude may be expressed through thoughtful inquiries about current needs and how they are being met, advice about available sources of emotional and practical support, referrals to appropriate community resources, and supportive psychotherapy.

Programs have been developed that reduce the burden and lessen the stress and depression associated with long-term caregiving. These interventions include psychoeducational programs for coping with frustration or depression; psychotherapy focused on alleviating depression and anxiety, and improving coping; exercise interventions for caregivers; and workshops in stress management techniques (73–77). In addition, extensive clinical experience and substantial scientific literature demonstrate that support groups, especially those combining education with support, improve caregiver well-being (78–85). Support groups conforming to this general pattern are available in many localities through local chapters of the Alzheimer's Association and/or hospitals, community organizations, and religious groups. Support groups may vary widely in their approaches as well as composition, and caregivers

may elect to try several before finding one that suits them. In addition to providing helpful information about the disease, how to care for someone with the disease, and ways to decrease caregiver burden, these groups may enhance the quality of life of patients and spouses or other caregivers and may delay nursing home placement (79, 86–88). Internet message boards and chat rooms may also be helpful for some caregivers.

In addition to providing families with information on support groups, there are a number of benefits of referral to the local chapter or national office of the Alzheimer's Association (1-800-272-3900; http://www.alz.org), the Alzheimer's Disease Education and Referral Center (ADEAR) (1-800-438-4380; http://www.nia.nih.gov/Alzheimers/), and other support organizations. Services offered by these organizations include providing information about local resources, operating hotlines staffed by well-informed volunteers, offering caregiver support services, and distributing a wide array of educational material written for patients, caregivers, and health professionals.

Many other resources provide logistical support for caregivers who are trying to care for individuals with dementia at home. Respite care allows the caregiver periods of relief from the responsibilities of dementia care. It provides essential physical and emotional support, serving the dual purposes of decreasing the burden of care and allowing caregivers to continue to work, participate in recreational activities, or fulfill other responsibilities. Respite care may last for hours to weeks and may be provided through companions, home health aides, visiting nurses, day care programs, and brief nursing home stays or other temporary overnight care. Depending on the available local resources and individual circumstances, these types of care may be available from local senior services agencies, from the local chapter of the Alzheimer's Association, religious groups, U.S. Department of Veterans Affairs facilities, or other community organizations. Although respite care clearly provides benefit for the caregiver, the evidence is mixed as to whether these programs actually delay institutionalization (89–93). Clinical experience suggests that by decreasing caregiver burden these programs may also improve the quality of life for patients and their families. Other resources that may be helpful include social service agencies, community-based social workers, home health agencies, cleaning services, Meals on Wheels, transportation programs, geriatric law specialists, and financial planners. Useful information for caregivers from the Family Caregiver Alliance is available at http://www.caregiver.org.

Many clinicians also recommend that families read articles or books written specifically for lay readers interested in understanding dementia and its care, such as *The*

Thirty-Six Hour Day: A Family Guide to Caring for Persons With Alzheimer's Disease, *Related Dementing Illness, and Memory Loss in Later Life* (94); Mayo Clinic: *Guide to Alzheimer's Disease: The Essential Resource for Treatment, Coping, and Caregiving* (95); *Practical Dementia Care* (41); or *The Complete Guide to Alzheimer's-Proofing Your Home* (35) or view informational video media that may be available from the local Alzheimer's Association chapter or public library.

c.   Watch for Signs of Caregiver Distress
With or without support, caregivers frequently become frustrated, overwhelmed, or clinically depressed (96). Among the causes of demoralization are the progressive nature of dementia and the patient's lack of awareness of the extent of support being provided. Psychiatrists caring for patients with dementia should be vigilant for these conditions in caregivers, because they increase the risk of substandard care, neglect, or abuse of patients and are a sign that the caregivers themselves are in need of care. Signs of caregiver distress include increased anger, social withdrawal, anxiety, depression, exhaustion, sleeplessness, irritability, poor concentration, increased health problems, and denial. When a caregiver is in significant distress, his or her need for greater psychosocial support should be evaluated. If treatment is indicated, it can be provided (according to the preference of psychiatrist, patient, and caregiver) by the patient's psychiatrist or through a referral to another mental health professional.

d.   Support Families During Decisions About Institutionalization
When family members feel that they are no longer able to care for the patient at home, they may need both logistical and emotional support in placing the patient in a long-term-care facility (i.e., continuing care retirement community, group home, assisted living facility, or nursing home). Often, such transitions occur at times of crisis (e.g., medical hospitalizations or caregiver illness). The psychiatrist can be a valuable resource in informing families about the available options and helping them evaluate and anticipate their needs in the context of their values, priorities, and other responsibilities. The question of referral to a long-term-care facility should be raised well before it becomes an immediate necessity so that families who wish to pursue this option have time to select and apply for a suitable facility, plan for financing long-term care, and make needed emotional adjustments. A referral to a social service agency, social worker, or the local chapter of the Alzheimer's Association may assist with this transition. Some social service agencies provide comprehensive home service assessments that may help families recognize and address their needs.

7.   Advise the Family to Address Financial and Legal Issues

Patients with dementia usually lose the ability to make medical, legal, and financial decisions as the disorder progresses, and consequently these functions must be taken over by others (97). Clinical evaluation, including cognitive testing when needed, can assist in determining whether a patient with Alzheimer's disease has the capacity to make medical decisions (98–100).

If family members act while the patient is still able to participate, they can seek his or her guidance regarding long-term plans. This approach can help in incorporating the patient's own wishes and values into the decision-making process, as well as in avoiding future conflict. Although the specific laws vary from state to state, advance planning regarding health care and finances can help families avoid the difficulty and expense of petitioning the courts for guardianship or conservatorship should such arrangements become necessary later in the illness. Issues that might be raised related to health care in the later stages of the illness include preferences about medical treatment, the use of feeding tubes, the care desired for infections and other potentially life-threatening medical conditions, and artificial life support. Medical decision making can be transferred in advance to a trusted family member (or friend) in the form of a durable power of attorney for health care or designation of a health care agent. For some patients, a living will or advance directive may also be appropriate, but which document is used and its specific features depend on the prevailing state law.

Patients and family members should be offered the opportunity to discuss preferences about participation in research studies early in the course of the illness, while the patient is still able to make his or her wishes known (101). The Alzheimer's Association has developed recommendations for Institutional Review Boards and investigators for obtaining research consent for cognitively impaired adults (102).

An individual's capacity to understand and give consent to a particular intervention (including taking of medications, particularly those with potentially significant side effects) will vary over time and with the nature and complexity of the intervention (99, 100). As individuals with dementia become more impaired, responsible family members are usually brought into the consent discussion. When a patient's capacity is diminished but still sufficient to give consent, consent or at least agreement is usually obtained from both patient and family member. Once a patient no longer has adequate decisional capacity, consent is obtained from either a health care proxy decision maker designated in an advance directive or a guardian, if either has been named. When such a legally designated decision maker does not exist, the closest relative is typically asked to provide consent. Nevertheless, the psychiatrist is encouraged to be familiar with local jurisdictional requirements, because procedures vary by state and some states require judicial review.

Patients may also transfer authority for legal and financial decision making in the form of a durable power of attorney for financial matters. At a minimum, it is recommended to include a family member as a cosigner on any bank accounts so that payment of expenses can proceed smoothly even when the patient is no longer able to complete the task him- or herself. In some instances, it may be a good idea to warn families about the vulnerability of individuals with dementia to unscrupulous individuals seeking "charitable" contributions, selling inappropriate goods, or promoting sweepstakes. If needed, the family can ask the patient to give up charge cards, ATM cards, and checkbooks to prevent the loss of the patient's resources. Clinicians should remain vigilant for evidence of exploitation of patients.

Patients should be advised to complete or update their wills while they are able to make and express decisions (103). Patients and families should also be advised of the importance of financial planning early in the illness. This advice may include a frank discussion regarding the financing of home health care and/or institutional care. Unfortunately, once the diagnosis of dementia is established, it is often too late to purchase long-term-care insurance, but careful planning in the early stages may help to lessen the burden of nursing home care or home health services later in the disease course. A patient with more complex financial issues should be referred to an attorney or financial planner to establish appropriate trusts, plan for transfer of assets, and make other financial arrangements.

C.   DEVELOPMENT AND IMPLEMENTATION OF A STAGE-SPECIFIC TREATMENT PLAN

The treatment of dementia varies through the course of the illness, because symptoms evolve over time. Although many symptoms can and do occur throughout the illness, certain symptoms are typical of the broad stages, as outlined in Section IV.E. This outline of stages conforms most to the typical course of Alzheimer's disease, but it does not apply as well to other types of dementias, particularly the frontotemporal dementia spectrum disorders.

The following sections provide general recommendations for treating patients in three stages of illness (mild, moderate, and severe) and specific recommendations for the implementation of select psychotherapeutic and pharmacological treatments. The evidence supporting the ef-

ficacy of these treatments is reviewed in Section V of this guideline. At each stage of the illness, the psychiatrist should be vigilant for cognitive and noncognitive symptoms likely to be present and should help the patient and family anticipate future symptoms. The family may also benefit from reminders to plan for the care likely to be necessary at later stages.

1. Mildly Impaired Patients

At the early stages of a dementing illness, patients and their families are often dealing with acceptance of the illness and recognition of associated limitations. They may benefit from pragmatic suggestions for how to cope with these limitations (e.g., making lists, using a calendar, avoiding overwhelming situations such as certain child-care responsibilities). Patients may benefit from referral to health promotion activities and recreation clubs (104). It may be helpful to identify specific impairments and highlight remaining abilities. Patients often experience a sense of loss and perceived stigma associated with the illness. Consequently, psychotherapeutic interventions may be helpful for patients who are struggling with the diagnosis and its implications. Features of treatment plan development for mildly impaired patients that have already been outlined in detail include addressing the issue of driving cessation (see Section II.B.5), assigning a durable power of attorney and addressing other legal and financial matters (see Section II.B.7), and addressing caregiver well-being (see Section II.B.6.b). Support groups for patients and families with mild Alzheimer's disease exist in many communities.

Patients with early Alzheimer's disease should be offered a trial of one of the three available cholinesterase inhibitors approved and commonly used for the treatment of cognitive impairment (i.e., donepezil, rivastigmine, galantamine), after a thorough discussion of their potential risks and benefits. Given the possible risks of long-term high-dose vitamin E and selegiline and the minimal evidence for their benefit, they are no longer recommended. Specific recommendations for implementing these treatments are provided in Section II.C.5.a. Mildly impaired patients may also be interested in referrals to local research centers for participation in clinical trials of experimental agents for the treatment of early Alzheimer's disease. Additional information regarding such trials may be obtained from a local or the national chapter of the Alzheimer's Association, from the National Institute on Aging, or at http://www.clinicaltrials.gov.

Mildly impaired patients should be evaluated for neuropsychiatric symptoms, especially depressed mood or major depression, which may require pharmacological or psychotherapeutic intervention, as described in Section II.C.5.c. Patients with moderate to severe major depression who do not respond to or cannot tolerate antidepressant medications should be considered for ECT. Mildly impaired patients should also be carefully assessed for suicidality, even if they are not obviously depressed.

2. Moderately Impaired Patients

As patients become more impaired, they are likely to require more supervision to remain safe, and safety issues should be addressed as part of every evaluation (see Section II.B.4). Families should be advised about the possibility of accidents due to forgetfulness (e.g., fires while cooking), of difficulties coping with household emergencies, and of the possibility of wandering. Family members should also be advised to determine whether the patient is handling finances appropriately and to consider taking over the paying of bills and other responsibilities. At this stage of the disease, nearly all patients should not drive. Families should be counseled to undertake measures to prevent patients from driving, as many patients lack insight into the risk that their continued driving poses to themselves or others (as described in Section II.B.5).

As a patient's dependency increases, caregivers may begin to feel more burdened. A referral for some form of respite care (e.g., home health aid, day care, brief assisted living, or nursing home stay) may be helpful. At this stage, families should begin to consider and plan for additional support at home as well as discuss the patient's possible transfer to a long-term-care facility. Family members may differ in their opinion of the patient's level of functioning and may have different psychological responses to the patient's impairments, generating family conflict. It may be beneficial to meet with family members to openly discuss these issues.

Treatment for cognitive symptoms should also be considered. For patients with Alzheimer's disease, currently available data suggest that the combination of a cholinesterase inhibitor plus memantine is more likely to delay symptom progression than a cholinesterase inhibitor alone during this stage of the illness. Specific implementation of these treatments is described in Section II.C.5.a.

Delusions and hallucinations are prevalent in moderately impaired patients, as are agitation and combativeness. The patient and family may be troubled and fearful about these symptoms, and it may be helpful to reassure them that the symptoms are part of the illness and are often treatable. Therapeutic approaches to these symptoms are described in Section II.C.5.b. For patients in whom wandering is the only symptom, pharmacotherapy will rarely be indicated. Depression often remains part of the

picture at this stage and should be treated vigorously (105). The pharmacotherapy of behavioral and neuropsychiatric symptoms is described in Sections II.C.5.b, II.C.5.c, and II.C.5.d.

3. Severely and Profoundly Impaired Patients

At this stage of the illness, patients are severely incapacitated and are almost completely dependent on others for help with basic functions, such as dressing, bathing, and feeding. Families are often struggling with a combined sense of burden and loss and may benefit from a frank exploration of these feelings and any associated resentment or feelings of guilt. They may also need encouragement to get additional help at home or to consider transient respite or relocation of the patient to a nursing home.

Of the cholinesterase inhibitors, only donepezil has thus far been approved for use in late-stage disease, and some studies show that other members of this class may also be beneficial (106, 107). Memantine, which has been approved for use in severe dementia, may provide modest benefits and has few adverse effects (108). If the benefit of a medication is unclear, a brief medication-free trial may be used to assess whether continued treatment is worthwhile.

Depression may be less prevalent and more difficult to diagnose at this stage but, if present, should be treated vigorously. Psychotic symptoms and agitation are often present and should be treated pharmacologically if they cause distress to the patient or significant danger or disruption to caregivers or to other residents of long-term-care facilities.

At this stage, it is important to ensure adequate nursing care, including measures to prevent bedsores and contractures. The treatment team should help the family prepare for the patient's death. Ideally, discussions about feeding tube placement, treatment of infection, cardiopulmonary resuscitation, and intubation will have taken place when the patient could participate, but if they have not, it is important to raise these issues with the family before a decision about one of these options is urgently required.

Hospice care is an underused resource for patients with end-stage dementia (109, 110). Hospice provides physical support for the patient (with an emphasis on attentive nursing care and relief of discomfort rather than medical intervention) and emotional support for the family during the last months of life. A physician must certify that the patient meets hospice criteria for admission for hospice benefits to be available (111).

4. Implementation of Psychosocial Treatments

The psychiatric care of patients with dementia involves a broad range of general psychosocial interventions for the patient and his or her family, as introduced in Section II.B.

In addition, some patients may benefit from more specific psychosocial interventions. These more specific psychosocial treatments for dementia can be divided into four broad groups: behavior oriented, emotion oriented, cognition oriented, and stimulation oriented. Although these treatment approaches differ in philosophy, focus, and methods, they share the broadly overlapping goals of improving quality of life and maximizing function in the context of existing deficits (see references 112 and 113 for a comprehensive review). Many of these therapies have the improvement of cognitive skills, mood, or behavior as an additional goal. All of these approaches reflect a person-centered philosophy of care in which an understanding of the individual is emphasized (114). For many individuals, several modalities will be selected at the same time. Because these treatments generally do not provide lasting effects, those that can be offered regularly may be the most practical and beneficial. These treatments are generally delivered daily or weekly. Beyond these considerations, the choice of therapy is generally based on the patient's characteristics and preference, availability of the therapy, and cost. For instance, some approaches are available only in institutional settings, such as nursing homes or day care centers, whereas others can be used at home.

Behavioral techniques and interventions are in wide clinical use with patients who have difficult-to-manage behavioral problems. There is some evidence for modest benefits of such therapies, particularly while the intervention is ongoing (112, 115, 116), but additional well-designed clinical trials are needed. There also is some evidence that behavioral interventions can reduce patients' depressive symptoms (117, 118).

Stimulation-oriented treatments (e.g., recreational activities or therapies, art therapies, exercise) are often included in the care of patients with dementia as well. They provide the kind of environmental stimulation that is recognized as part of humane care, and modest efficacy data exist that support their use for improving mood and reducing behavioral disturbances (117, 119–121).

Emotion-oriented treatments (e.g., reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, simulated presence therapy) are often used in the treatment of patients with dementia to address issues of loss and to improve mood and behavior. Although there is modest research support for the effectiveness of reminiscence therapy for improvement of mood and behavior (122–124), none of these modalities has been subjected to rigorous scientific testing. Cognition-oriented treatments (e.g., reality orientation, cognitive retraining, skills training) may provide mild short-term improvements in selected domains of cognition, but such improvements, when achieved, are not lasting (125, 126).

Short-term adverse emotional consequences have sometimes been reported with psychosocial treatments. This is especially true of the cognitively oriented treatments, during which frustration, catastrophic reactions, agitation, and depression have been reported (86, 127). Thus, treatment regimens must be tailored to the cognitive abilities and frustration tolerance of each patient.

5. Implementation of Pharmacological Treatments

The following summarizes principles that underlie the pharmacological treatment of elderly patients and those with dementia (128). First, elderly individuals have decreased renal clearance and slowed hepatic metabolism, which alter the pharmacokinetics of many medications. Moreover, because elderly individuals may have multiple coexisting medical conditions and therefore may take multiple medications, it is important to consider how these general medical conditions and associated medications may interact to further alter the absorption, serum protein binding, metabolism, and excretion of the medication (129). Therefore, low starting doses, small dose increases, and long intervals between dose increases are necessary. This is true even in the inpatient setting, where utilization review pressures may encourage physicians to employ rapid titration schedules. However, some patients may ultimately need doses as high as would be appropriate for younger patients.

Pharmacodynamics may also be altered in elderly patients and those with dementia. As a result, certain medication side effects pose particular problems for elderly patients and those with dementia; medications with these side effects must therefore be used judiciously. Anticholinergic side effects may be more burdensome for elderly patients owing to coexisting cardiovascular disease, prostate or bladder disease, or other general medical conditions. These medications may also lead to worsening cognitive impairment, confusion, or even delirium (130). Orthostasis is common in elderly patients because of decreased vascular tone and medication side effects. As a result, elderly patients, especially those with dementia, are more prone to falls and associated injuries. Medications associated with central nervous system sedation may worsen cognition, increase the risk of falls, and put patients with sleep apnea at risk for additional respiratory depression. Finally, elderly patients, especially those with Alzheimer's disease, Parkinson's disease, or dementia with Lewy bodies, are especially susceptible to extrapyramidal side effects.

For all these reasons, medications should be used with considerable care, and polypharmacy should be avoided whenever possible. In nonemergency situations or when neuropsychiatric symptoms are not severe, nonpharma-cological approaches should be attempted first to avoid the very significant morbidities associated with psychotropic medication use in elderly patients. Nonetheless, many elderly individuals with dementia manifest neuropsychiatric symptoms that do not respond to psychosocial or environmental interventions but may respond to psychotropic medications individually or in combination.

The sections that follow describe somatic therapies used to treat the cognitive symptoms and functional losses associated with dementia, as well as the prevalent neuropsychiatric symptoms of psychosis, anxiety, agitation, depression, apathy, and sleep disturbances. Although the sections are organized by these specific target symptoms, many medications have broader impact in actual practice.

a. Treatments for Cognitive and Functional Losses

Because there is no cure for most cases of dementia, the primary goal of medication treatment for cognitive symptoms in dementia is to delay the progression of symptoms, with the hope that this delay will translate into a preservation of functional ability, maintaining the patient for as long as possible at a particular level of symptom severity. However, no medication treatment has been shown to delay the progression of neurodegeneration.

A number of psychoactive medications are used to achieve these goals. The only FDA-approved medications for dementia or cognitive impairment are the cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine), memantine, and the combination of ergoloid mesylates (approved for nonspecific cognitive decline). In addition, other drugs, including vitamin E, ginkgo biloba, and selegiline (approved by the FDA for treatment of Parkinson's disease and in patch form for the treatment of depression), are occasionally used for this purpose in selected patients, although they are not generally recommended, because their efficacy and safety are uncertain.

Several other medications that had been proposed for the treatment or prevention of cognitive decline, including NSAIDs, statin medications, and estrogen supplementation (with conjugated equine estrogens), have shown a lack of efficacy and safety in placebo-controlled trials in patients with Alzheimer's disease and therefore are not recommended. Many additional agents are currently being tested. Participation in clinical trials is another option available to patients with dementia.

Certain interventions for specific medical conditions such as the use of antihypertensive medications to control blood pressure, use of aspirin to prevent further strokes, and prescription of levodopa as a general treatment of Parkinson's disease may also lead to positive effects on

cognition but are beyond the purview of this practice guideline.

1. Cholinesterase inhibitors

a. Alzheimer's disease and general considerations

In 1993 tacrine became the first agent approved specifically for the treatment of cognitive symptoms in Alzheimer's disease. Tacrine is a reversible cholinesterase inhibitor with evidence for efficacy from multiple double-blind placebo-controlled trials (131–135) that is thought to work by increasing the availability of intrasynaptic acetylcholine in the brains of patients with Alzheimer's disease. The FDA approved other cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—in 1997, 2000, and 2001, respectively, for treatment of cognitive decline in mild to moderate Alzheimer's disease. These agents are now preferred over tacrine because of tacrine's reversible hepatic toxicity and the requirement that it be given 4 times per day. Evidence for the efficacy of these medications in mild to moderate Alzheimer's disease also comes from a substantial number of randomized, double-blind, placebo-controlled trials of donepezil (136–146), rivastigmine (147–152), and galantamine (153–159). Results of a smaller number of clinical trials (106, 107) suggested that cholinesterase inhibitors might have some limited benefits in severe Alzheimer's disease. In 2006, donepezil was approved by the FDA for this indication.

Given the evidence from randomized controlled trials for modest improvement in some patients treated with cholinesterase inhibitors and the lack of established alternatives, it is appropriate to offer a trial of one of these agents for patients with mild or moderate Alzheimer's disease for whom the medication is not contraindicated. Many clinicians in fact prescribe cholinesterase inhibitors for patients with the entire range of Mini-Mental State Examination (MMSE) scores, with moderate medical or psychiatric comorbidity, or with possible Alzheimer's disease, even though these patients would not have been eligible for most clinical trials completed to date. Whenever cholinesterase inhibitors are prescribed, patients and their families should be apprised of the limited potential benefits as well as the potential costs.

Results of the numerous large placebo-controlled trials of individual cholinesterase inhibitors have suggested similar degrees of efficacy, although tolerability may differ among the medications. Nonetheless, currently available data do not allow a fair, unbiased direct comparison among the cholinesterase inhibitors. Four clinical trials have compared cholinesterase inhibitors (two compared donepezil and galantamine, and two compared donepezil and rivastigmine) (160–163), but a number of these studies have significant methodological problems and none resolves the question of superiority (164). There are also no data on whether or how to switch from one cholinesterase inhibitor to another.

As would be expected with cholinesterase inhibitors, common side effects in clinical trials are associated with cholinergic excess, particularly nausea and vomiting, but these symptoms tend to be mild to moderate in severity for all agents. In the randomized clinical trials noted earlier, these side effects were observed in approximately 10%–20% of patients (136–159). Additional cholinergic side effects include muscle cramps; bradycardia, which can be dangerous in individuals with cardiac conduction problems; decreased appetite and weight; and increased gastrointestinal acid, a particular concern in those with a history of ulcers. These side effects occur infrequently with these agents, but bradycardia should be considered a relative contraindication to their use. In general, cholinergic side effects tend to wane within 2–4 days, so if patients can tolerate unpleasant effects in the early days of treatment, they may be more comfortable later on. Finally, cholinesterase inhibitors may induce or exacerbate urinary obstruction, worsen asthma and chronic obstructive pulmonary disease, cause seizures, induce or worsen sleep disturbance, and exaggerate the effects of some muscle relaxants during anesthesia.

Reversible, direct medication-induced hepatotoxicity with hepatocellular injury is a unique property of tacrine, occurring in approximately 30% of those taking it 6–8 weeks after initiating the medication (165). Because of this hepatotoxicity, tacrine is very uncommonly used. Hepatotoxicity has not been associated with donepezil, rivastigmine, or galantamine.

The main contraindication to use of cholinesterase inhibitors is hypersensitivity to the individual drugs. Some considerations in limiting treatment include the existence of gastrointestinal disorders such as gastritis, ulcerative disease, or undiagnosed nausea and vomiting, because cholinesterase inhibitors will increase gastric acid secretions. Cholinesterase inhibitors should also be used with care in patients with sick sinus syndrome or conduction defects, cerebrovascular disease, or seizures, as well as in patients with asthma or chronic obstructive pulmonary disease.

With respect to dosing and dosage, donepezil is given once per day, usually starting at 5 mg/day. This dosage can be increased to 10 mg/day, if tolerated. Some clinicians start treatment with 2.5 mg/day for patients who are frail or very sensitive to medication side effects and increase the dose by 2.5-mg increments. Galantamine is started at 8 mg/day in divided doses and increased gradually to a target range of 16–24 mg/day in divided doses, although certain patients may benefit from dosages up to 32 mg/day. A

once-daily formulation of galantamine has recently been released. Rivastigmine is started at 3 mg/day in divided doses and increased gradually to a target range of 6–12 mg/day in divided doses. Doses may be titrated upward every 4 weeks. Slower titration can be helpful in managing side effects, if these occur. Higher dosages may be effective in some patients when lower dosages are not; therefore, patients who have not shown clear benefit while taking a lower dosage should receive an increased dose, if tolerated, before the conclusion is made that the medication is ineffective. Minimal effective dosages are 5 mg/day for donepezil, 16 mg/day for galantamine, and 6 mg/day for rivastigmine.

It is uncertain how long patients should be treated with cholinesterase inhibitors. Data from placebo-controlled clinical trials have demonstrated benefits over placebo for 6 months to 2 years with donepezil (136, 137, 139), for up to 1 year with rivastigmine (150), and for up to 6 months with galantamine (156). A number of open-label extension clinical trials have been conducted examining the efficacy of these agents beyond the time in which placebo controls were actually used. Subjects who continued to take the study drug were compared to a "historical" control group, namely a projection of the decline of a placebo control group. The authors of these studies claimed to demonstrate ongoing efficacy beyond the conclusion of the actual placebo-controlled trials, but comparisons using projected outcomes of a placebo group are methodologically problematic and do not establish efficacy.

In practice, the decision whether to continue treatment with cholinesterase inhibitors is a highly individualized one. Reasons that patients choose to stop taking these medications include side effects, adverse events, lack of motivation, lack of perceived efficacy, and cost. Individual patients may be observed to have some stabilization of symptoms or slowing of their decline. Under these circumstances, a physician might consider continuing the medication. Conversely, a patient who is declining rapidly despite taking cholinesterase inhibitors may be considered a medication nonresponder, and the medication can be discontinued. Discontinuation of cholinesterase inhibitor medication during placebo-controlled trials after 12–24 weeks has been associated with a regression of cognitive improvement to the level of the associated placebo group. Whether resumption of the cholinesterase inhibitor reverses this symptomatic worsening is unclear. Some patients have shown pronounced deterioration within several weeks of discontinuing cholinesterase inhibitors and improvement when the medication has been restarted. In contrast, the results of one study suggested that donepezil-treated patients who had treatment interrupted for 6 weeks and then restarted treatment never regained cognition back to the level achieved before medication discontinuation (166).

b. *Vascular dementia and mixed dementia (Alzheimer's disease and vascular dementia)*

Trials of cholinesterase inhibitors in patients with vascular dementia and mixed dementia have produced inconclusive results. In addition, serious concerns about safety and potential increases in mortality have arisen with the use of these medications in this patient population (167). As a result of these factors, as well as the lack of FDA approval for this indication (see Sections III.B.4 and V.B.1.a.2), no specific recommendation can be made in favor of the routine use of cholinesterase inhibitors in patients with vascular dementia at this time, although individual patients may benefit from their use.

c. *Dementia with Lewy bodies*

Cholinesterase inhibitors could be considered for patients with dementia with Lewy bodies. Dosing and titration are similar to those for patients with Alzheimer's disease (168, 169).

d. *Dementia of Parkinson's disease*

Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease. Only rivastigmine has been studied in a randomized, double-blind, placebo-controlled trial (170) with an open-label extension (171) and approved by the FDA for this indication. Nevertheless, there is no reason to believe the benefit is specific to this cholinesterase inhibitor. Dosing and titration are similar to those for patients with Alzheimer's disease.

e. *Mild cognitive impairment*

The term "mild cognitive impairment" describes a heterogeneous group of individuals, with some patients in the earliest stages of Alzheimer's disease and others suffering from other conditions. There are no FDA-approved medications for the treatment of mild cognitive impairment at this time. Clinical trials of cholinesterase inhibitors for mild cognitive impairment have enrolled a narrower and better defined population of patients with mild cognitive impairment than most clinicians actually treat in practice, but even with these well-defined patients the evidence from clinical trials supporting use of cholinesterase inhibitors is weak (172, 173). Given the inconclusive data, the potential safety concerns that exist with this class of medications in this patient population, and the lack of FDA approval for this indication (reviewed in Sections V.B.1.a.4 and II.C.5.a.1.a), no specific recommendation can be made in favor of routine use of cholinesterase inhibitors in patients with mild cognitive

impairment at this time. Nonetheless, individual patients may benefit from their use.

2. Memantine

Memantine is a noncompetitive NMDA receptor antagonist approved by the FDA for the treatment of moderate to severe Alzheimer's disease.

Given the evidence for its efficacy in randomized controlled trials (174, 175), memantine should be considered for treatment of patients with moderate to severe Alzheimer's disease. Memantine can be prescribed for people either currently taking or not taking a cholinesterase inhibitor. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone (175), but there is no evidence that this combination is better than memantine alone. There are not yet data to argue for or against the use of memantine beyond 6 months (108, 176).

In patients with mild Alzheimer's disease, the evidence is suggestive of a small clinical benefit of memantine over placebo (108, 177), although this result is not conclusive and additional trials should be performed. Given that there are few safety concerns with the use of memantine in mild Alzheimer's disease, clinicians may consider using it for individual patients.

For vascular dementia, the evidence does not support the use of memantine (178, 179), although further trials are necessary.

Reported adverse events with memantine are infrequent, appear to be mild, and include confusion, dizziness, headache, sedation, agitation, falls, and constipation (174, 175, 177). Dropout rates during clinical trials have generally been the same for memantine as for placebo.

Memantine treatment begins at 5 mg once daily, and this dosage is increased by 5 mg/day every week until a target dosage of 10 mg b.i.d. is reached. A therapeutic dosage range for memantine has not been conclusively established. One study demonstrated efficacy at a dosage of 10 mg/day (180), and the effects of dosages above 20 mg/day have not been studied. Because memantine is cleared primarily by the kidneys, lower dosages (e.g., 10 mg/day) should be considered in patients with compromised renal function.

3. Vitamin E

Vitamin E is no longer recommended for the treatment of cognitive symptoms of dementia. Previous recommendations for its use had balanced the weakness of the evidence for its efficacy with the perceived lack of risk with use of vitamin E. However, new safety concerns, namely the unexpected findings of increased dose-dependent mortality in a meta-analysis of vitamin E clinical trials (181) and an increased rate of heart failure with vitamin E treatment in

a large randomized trial of cancer and heart disease prevention in individuals with diabetes mellitus and/or vascular disease (182), make the case for its use much less compelling. The evidence from the one placebo-controlled, double-blind, multicenter trial of vitamin E for the treatment of moderate Alzheimer's disease is limited (183). Furthermore, vitamin E failed to show efficacy in one study of individuals with mild cognitive impairment (173). In this trial nearly one-half of the subjects later received a diagnosis of Alzheimer's disease during the 3 years of observation and hence had early Alzheimer's disease at the beginning of the trial. Nevertheless, after considering the potential risks and benefits of vitamin E, some physicians and their patients may elect to use it, particularly at doses at or below 400 IU daily. Because vitamin E has been associated with worsening of coagulation defects in patients with vitamin K deficiency (184), it should be avoided in this population.

4. Other agents

A number of medications marketed for other indications have been proposed for the treatment of dementia on the basis of epidemiological data or pilot studies (185–189), but they are not recommended for routine use at this time because of lack of efficacy in subsequent studies (190–200) and potential for adverse effects. These other agents include aspirin and other NSAIDs, hormone replacement therapy, the hormone melatonin, the botanical agent ginkgo biloba, the chelating agent desferrioxamine, the irreversible monoamine oxidase B (MAO-B) selective inhibitor selegiline, and a mixture of ergoloid mesylates currently marketed under the trade name Hydergine. Because some of these agents are popular, psychiatrists should routinely inquire about their use and should advise patients and their families that some of these agents are marketed with limited quality control and have not been subjected to adequate efficacy evaluations.

b. Treatments for Psychosis and Agitation

As discussed in Section II.B.3, psychosis and agitation occur commonly in patients with dementia and are important targets of psychiatric intervention. In DSM-IV-TR Alzheimer's disease and other dementias with delusions and hallucinations and Alzheimer's disease with behavioral disturbances are classified separately, and provisional criteria for psychosis of Alzheimer's disease have been published (201). In clinical practice, however, these symptoms frequently co-occur.

Treatments that decrease psychotic symptoms (delusions and hallucinations) and associated or independent behavioral disturbances such as aggression, combativeness, and agitation are often essential to increasing the

comfort and safety of patients and easing the burden of provision of care by families and other caregivers.

Clinicians facing the challenge of treating patients with significant psychosis or behavioral disturbances must weigh the risk of not treating these complications of dementia against the risks of active treatment described below in Sections II.C.5.b.1, II.C.5.b.2, II.C.5.b.3, and II.C.5.b.4. This weighing of risks also includes consideration of the evidence supporting the efficacy of the agent in question, the patient's overall medical condition, and the evidence of risk and benefit of any potential treatment alternatives, followed by documentation of the reasons for using the medication and the fact that a discussion has taken place with the patient or caregiver.

As outlined in Section II.C.4, there are a number of nonpharmacological interventions that can be used before a trial of an antipsychotic or other medication is begun. Consideration and use of behavioral, psychosocial, and psychotherapeutic treatments is particularly critical, given the large number and potential severity of side effects associated with pharmacotherapy. Interventions for psychosis should be guided by the patient's level of distress and the risk to the patient, caregivers, or other patients. If psychotic symptoms cause minimal distress to the patient and are unaccompanied by agitation or combativeness, they are best treated with environmental measures, including reassurance and redirection. If the symptoms do cause significant distress or are associated with behavior that may place the patient or others at risk, treatment with low doses of antipsychotic medication is indicated in addition to nonpharmacological interventions. Treatment with an antipsychotic medication is also indicated if a patient is agitated or combative in the absence of psychosis, as this indication for antipsychotic use has significant support in the literature. The use of these agents should be reevaluated and their benefit documented on an ongoing basis. When antipsychotics are ineffective, carbamazepine, valproate, or an SSRI may be used in a careful therapeutic trial. If behavioral symptoms are limited to specific times or settings (e.g., a diagnostic study), or if other approaches fail, a low-dose benzodiazepine may prove useful, although side effects in elderly patients can be problematic (see Section II.C.5.b.2). Although mood stabilizers and SSRIs are commonly used in clinical practice to treat agitation, delusions, and aggression, they have not been consistently shown to be effective in treating these symptoms, nor is there substantial evidence for their safety. Thus, in making decisions about treatment, these agents should not be seen as having improved safety or comparable efficacy, compared to antipsychotic medications.

As a dementing illness evolves, psychosis and agitation may wax and wane or may change in character. As a result, the continued use of any intervention for behavioral disturbances or psychosis must be evaluated and justified on an ongoing basis. In the nursing home setting, this clinical recommendation is also a requirement under regulations of the Federal Nursing Home Reform Act of the Omnibus Budget Reconciliation Act of 1987 (see Section III.C.3). In addition, periodic reevaluation and revision of the treatment plan, including a change in dose, a change in medication, or medication discontinuation, may be indicated. Patients whose symptom severity was relatively low at the time of medication initiation may be more easily withdrawn from psychotropic medications than those with more severe symptoms at the time of treatment initiation (202).

1. Antipsychotics

Antipsychotics are the primary pharmacological treatment available for psychotic symptoms in dementia. They are also the most commonly used and best-studied pharmacological treatment for agitation. There is considerable evidence from randomized, double-blind, placebo-controlled trials and meta-analyses for the efficacy of both first-generation (203–217) and second-generation agents (201, 212, 218–227), although this benefit is often modest. Findings from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE-AD) study, funded by the National Institute of Mental Health (NIMH), failed to demonstrate conclusive benefits of second-generation antipsychotics over placebo in patients with Alzheimer's disease and psychosis or aggression, although there were advantages to the medications on certain outcome variables and the discontinuation rate due to lack of efficacy was lower with olanzapine and risperidone than it was for placebo or quetiapine (228).

Given the side effects and potential toxicity of antipsychotic agents (225, 228), the risks and benefits of these medications must be reassessed on an ongoing basis. The lowest effective dose should be sought, and emergent side effects should first be treated by dose reduction. Because of the risks involved with the use of antipsychotics, indications for their use should be generally limited to psychosis or behavioral disturbances, and they should not be used primarily for sleep disorders or anxiety. In addition, periodic attempts (e.g., every several months) to reduce or withdraw antipsychotic medications should be considered for all patients, while weighing the probability of a relapse and the dangerousness of the target behavior(s) (229). In general, agents with significant anticholinergic properties should be avoided in patients with dementia, although they may be considered under specific circumstances.

Mild to moderate adverse effects of antipsychotics include akathisia, parkinsonism, sedation, peripheral and

central anticholinergic effects, delirium, postural hypotension, cardiac conduction defects, urinary tract infections, urinary incontinence, and falls. Antipsychotic agents are also associated with a risk of more serious complications that must be considered in weighing the risks and benefits of antipsychotic treatment (see Section V.B.2.a.2 for additional details). Serious complications include tardive dyskinesia (the incidence of which increases with dose and duration of treatment and which occurs more commonly in women, in individuals with dementia or brain injury, and in elderly patients in general), neuroleptic malignant syndrome (a rare but potentially lethal adverse effect of antipsychotic medications that occurs less frequently with second-generation antipsychotic agents), agranulocytosis (with clozapine), hyperlipidemia, weight gain, diabetes mellitus, cerebrovascular accidents, and death. An increased risk of cerebrovascular accidents has recently been found with the second-generation antipsychotics aripiprazole, olanzapine, and risperidone, although not with quetiapine. Meta-analyses of clinical trials of the second-generation antipsychotics aripiprazole, olanzapine, quetiapine, and risperidone (225), as well as of first-generation antipsychotics (230), have found an increased mortality when used in elderly patients with dementia. These concerns have led to "black box" warnings on the second-generation antipsychotics (231).

Accepted clinical practice is to prescribe antipsychotic agents at standing doses rather than as needed, although as-needed doses may be appropriate for symptoms that occur infrequently. Oral administration is generally preferred, although an intramuscular injection may sometimes be used in an emergency or when a patient is unable to take medications by mouth (e.g., for a surgical procedure). Low starting dosages are recommended, e.g., 0.25–0.5 mg/day of haloperidol, 0.25–1.0 mg/day of risperidone, 12.5 mg/day of clozapine, 1.25–5.0 mg/day of olanzapine, 12.5–50 mg/day of quetiapine. The best starting dosages for aripiprazole and ziprasidone are not known, although the available evidence suggests that 5 mg/day of aripiprazole may be safe for most patients. The dose can be increased on the basis of the response of the target symptom(s). The usual maximum dosages of these agents for patients with dementia are 2 mg/day of haloperidol, 1.5–2 mg/day of risperidone, 75–100 mg/day of clozapine, 200–300 mg/day of quetiapine, 10 mg/day of olanzapine, and 15 mg/day of aripiprazole. In addition, risperidone causes fewer extrapyramidal symptoms when used at dosages of 1 mg/day than when used at higher doses (218). Clinicians should keep in mind that these medications take time to work and that increasing doses too rapidly may lead to the development of side effects rather than more rapid efficacy. Although most patients with dementia do best with dosages below these

maxima, younger and less frail individuals may tolerate and respond to somewhat higher doses, and very severely agitated patients may also need higher dosages. In contrast, antipsychotic agents must be used with extreme caution in patients with dementia with Lewy bodies or Parkinson's disease, who can be exquisitely sensitive to the extrapyramidal effects of these agents (232).

There are few relative efficacy data to guide the choice among second-generation antipsychotic agents. The CATIE-AD trial did not find significant differences in efficacy or tolerability among olanzapine, quetiapine, and risperidone, although the time to discontinuation due to lack of efficacy was longer for olanzapine and risperidone than for quetiapine (228). Instead, the choice is based most often on the side effect profile. As the overall side-effect burden appears to be lower with second-generation agents, drugs in this class are usually selected first. Widespread clinical practice is to select the agent whose most common side effects are least likely to cause problems for a given patient. For instance, clozapine might be avoided if the patient is likely to be sensitive to anticholinergic effects, or an agent lacking significant motor side effects such as aripiprazole, clozapine, or quetiapine might be chosen if the patient has Parkinson's disease, dementia with Lewy bodies, or other sensitivity to extrapyramidal side effects. Aripiprazole and quetiapine may be better first choices because their overall side effect profile is more benign than that of clozapine (233–237).

The side effects of some medications might actually be beneficial for certain patients. For example, a more sedating medication could be given at bedtime for a patient who has difficulty falling asleep in addition to agitation or psychosis. Antipsychotics are most commonly administered in the evening, so that maximum blood levels occur when they will help foster sleep and treat behavioral problems that peak in the evening hours (sometimes called "sundowning"). Most of these medications have long half-lives, and once-a-day dosing is generally sufficient. The one exception may be quetiapine, which is usually administered twice daily. However, morning doses or twice-a-day doses of the other agents may be helpful for patients with different symptom patterns.

The availability of a specific formulation of an antipsychotic may also contribute to the choice of a particular agent. Some antipsychotics are available in liquid form (e.g., aripiprazole, risperidone, ziprasidone, fluphenazine, haloperidol), and some (e.g., clozapine, olanzapine, risperidone, aripiprazole) are available as rapidly dissolving wafers. Olanzapine, ziprasidone, aripiprazole, fluphenazine, and haloperidol are available in a rapid-onset injectable form, whereas risperidone, haloperidol, and fluphenazine are available in long-acting injectable forms.

With the exception of olanzapine (223), these formulations have not been studied in patients with dementia.

2. Benzodiazepines

Benzodiazepines may have a higher likelihood of side effects and a lower likelihood of benefit than antipsychotics (223, 238–243); nonetheless, they are occasionally useful in treating agitation in certain patients with dementia, particularly those in whom anxiety is prominent. Their long-term use is generally to be avoided, but they may be particularly useful on an occasional as-needed basis for patients who have only rare episodes of agitation or those who need to be sedated for a particular procedure, such as a tooth extraction or a diagnostic study. Given the risk of disinhibition and consequent worsening of target behaviors, oversedation, falls, and delirium, their use should be kept to a minimum, with a maximum of 1–3 mg of lorazepam (or equivalent doses of other benzodiazepines) in 24 hours.

Among the benzodiazepines, many clinicians favor agents such as oxazepam and lorazepam that do not require oxidative metabolism in the liver and have no active metabolites. Temazepam shares these characteristics but is more problematic because of its long half-life. Oral lorazepam (or intramuscular in the event of an emergency) may be given on an as-needed basis in doses from 0.5 to 1.0 mg every 4–6 hours. Standing oral doses of 0.5–1.0 mg may be given from 1 to 4 times per day. Oxazepam is absorbed more slowly, so it is less useful on an as-needed basis. Standing doses of 7.5–15.0 mg may be given 1 to 4 times per day. Some clinicians prefer long-acting agents, such as clonazepam (starting at 0.5 mg/day with increases up to 2 mg/day) (244). However, such agents must be used with caution as described in the next paragraph.

The most commonly reported side effects with benzodiazepines are sedation, ataxia, amnesia, confusion (even delirium), and possibly paradoxical anxiety. These can lead to worsening cognition and behavior and increase the risk of falls (245). Benzodiazepines also carry a risk of respiratory suppression in patients with sleep-related breathing disorders. Because all of these effects are dose related, the minimum effective dose should be used. Agents with long half-lives (e.g., clonazepam) and long-lived metabolites (e.g., diazepam, chlordiazepoxide, clorazepate, flurazepam) can take weeks to reach steady-state levels, especially in elderly patients, so they generally are not used in this patient population. Under unusual circumstances when they have to be used, it must be with particular caution, with very low starting doses and very gradual dosage increases. Elderly patients taking long-acting benzodiazepines are more likely to fall, and to suffer hip fractures, than those taking short-acting agents (246), although it is possible that the total dose, not the duration

of action, is responsible for the increased fall risk (247). Clinical experience suggests that like alcohol, benzodiazepines may lead to disinhibition, although there are few data to support this association. The risk of benzodiazepine dependence is also a concern. If benzodiazepines are prescribed for an extended period (e.g., 1 month), they should be tapered rather than stopped abruptly because of the risk of withdrawal.

3. Anticonvulsants

There is some evidence to suggest that carbamazepine may have modest benefit for agitation when used in low doses in patients with dementia (248–252). However, given the relatively small body of clinical trials evidence, the high risk of drug-drug interactions, and the known tolerability problems expected with long-term use, carbamazepine is not recommended for the routine treatment of agitation in patients with dementia.

Routine use of valproate to treat behavioral symptoms in dementia is not recommended based on the current evidence. Most (253–255), but not all (256), randomized placebo-controlled trials showed no benefit of valproate, compared with placebo. In addition, a 2004 Cochrane review (257) concluded that the various formulations of valproate had not yet been shown to be effective.

Nonetheless, a therapeutic trial of carbamazepine or valproate may be considered in individual cases (258), for example, in patients who are sensitive or unresponsive to antipsychotics, who have significant vascular risk factors, or who do not have psychosis but are mildly agitated. Given the potential toxicity of both of these anticonvulsant agents, it is important to identify and monitor target symptoms and to discontinue the medication if no improvement is observed.

If used, carbamazepine may be given in two to four doses per day, started at a total dosage of 50–100 mg/day, and increased gradually as warranted by behavioral response and side effects or until blood levels reach 8–12 ng/ml. Divalproex sodium may be given in two or three doses per day and should be started at 125–250 mg/day, with gradual increases based on behavioral response and side effects or until blood levels reach 50–60 ng/ml (or, rarely, 100 ng/ml).

The principal side effects of carbamazepine include ataxia, falls, sedation, and confusion, all of which are of particular concern for elderly patients and those with dementia. Carbamazepine can cause drug interactions through its effect on the cytochrome P450 system. In rare instances, carbamazepine can lead to bone marrow suppression or hyponatremia through the syndrome of inappropriate antidiuretic hormone secretion. Valproate's principal side effects are sedation, gastrointestinal disturbances, confu-

sion, ataxia, and falls. Bone marrow suppression, hepatic toxicity, thrombocytopenia, and hyperammonemia can occur. Many clinicians monitor the CBC and electrolyte levels in patients taking carbamazepine and monitor the CBC and liver function values in patients taking valproate, owing to the possibility of bone marrow suppression, hyponatremia, and liver toxicity. However, these practices are not followed by all clinicians. A particularly cautious approach is warranted when treating elderly patients and those with dementia, who may be more vulnerable to adverse effects, particularly central nervous system effects, and yet less likely to be able to report warning symptoms.

For additional details concerning the assessment and monitoring necessary during use of these agents, along with their side effects and potential toxicities, the reader is referred to APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder*, 2nd edition (259).

4. Other agents

Support for the use of trazodone or buspirone is limited to data from case series and small clinical trials (214, 260–269). Therefore, neither agent can be recommended for the routine treatment of agitation and psychosis in patients with dementia. Although the evidence suggesting efficacy of SSRIs for agitation is somewhat stronger (262, 270, 271), further study is needed before they can be recommended for routine use. Nonetheless, a therapeutic trial of trazodone, buspirone, or an SSRI may be appropriate for some nonpsychotic but agitated patients, especially those with relatively mild symptoms or those who are intolerant of or unresponsive to antipsychotics.

When patients are taking SSRIs, clinicians need to keep in mind the serotonin syndrome, caused by excessive serotonergic activity, usually as a result of serotonergic medications being combined (including buspirone and SSRIs). Symptoms include delirium, autonomic instability, and increased neuromuscular activity, such as myoclonus.

When trazodone is used, the principal side effects are postural hypotension, sedation, and dry mouth. Priapism can occur but is uncommon. Trazodone is generally given before bedtime but can be given in two or three divided doses per day. It can be started at 25–50 mg/day and gradually increased to a maximum dosage of 150–250 mg/day.

When male patients display inappropriate sexual behavior, a particular problem in patients with frontal lobe dementias, medroxyprogesterone and related hormonal agents are sometimes recommended (272–274), a recommendation supported only by case series at present. Because SSRIs may reduce libido and are probably safer, they may be tried before hormonal agents (275).

Lithium carbonate has also been suggested as a treatment for agitation because of its occasional utility for ag-

itated patients with mental retardation, but support for it is quite limited, and side effects and toxicity are common, including delirium (210). Therefore, routine use of lithium to treat agitation in patients with dementia is not recommended.

Beta-blockers, notably propranolol, metoprolol, and pindolol, have also been reported to be helpful for some agitated patients with dementia (276). However, most of the patients included in the case reports had somewhat atypical clinical features, raising questions about the generalizability of these reports. In addition, large dosages (e.g., 200–300 mg/day of propranolol) were used, and such dosages create a considerable risk of bradycardia, hypotension, and delirium for elderly patients. One small randomized, double-blind, placebo-controlled trial of propranolol in patients with Alzheimer's disease and behavioral disturbance did show benefit over placebo for certain symptoms although it was noted that beta-blocker use was contraindicated for many subjects who would otherwise have been eligible for the study (277). Therefore, routine use of beta-blockers to treat agitation in patients with dementia is not recommended.

c. Treatments for Depression and Related Symptoms

Recognition and treatment of depression is crucial in individuals with dementia, because the presence of depression has been associated with higher rates of disability, impaired quality of life, and greater mortality (278). The best approach to diagnosing depression in the context of dementia is not yet clear. Provisional criteria for depression of Alzheimer's disease have been proposed but not yet validated (279). The Depression and Bipolar Support Alliance Consensus Statement Panel reported that the diagnostic criteria for depression in individuals with dementing disorders must be revised (105). They recommended that the criteria take into account the instability and fluctuation of symptoms over time, the reduction in positive affect or pleasure, and the inclusion of irritability, social withdrawal, and isolation as indicators of depression. Until criteria for depression in dementia are established, patients should be carefully evaluated for any of the symptoms of depression outlined in DSM-IV-TR. Even those patients with depressive symptoms who do not meet the diagnostic criteria for major depression should be considered as candidates for depression treatment. The presence of neurovegetative symptoms, suicidal ideation, and mood-congruent delusions or hallucinations may indicate a need for more vigorous and aggressive therapies (such as higher medication dosages, multiple medication trials, or ECT).

Depression may worsen cognitive impairment associated with dementia. Therefore, one goal of treating depression in dementia is to maximize cognitive functioning.

Sometimes cognitive deficits partially or even fully resolve with successful treatment of the depression. Nonetheless, because as many as one-half of such persons do develop dementia within 5 years (280, 281), caution is urged in ruling out an underlying early dementia in patients with both affective and cognitive symptoms, particularly when the first episode of depression is in old age. Treatment of depression may also reduce other neuropsychiatric symptoms associated with depression such as aggression, anxiety, apathy, and psychosis (282, 283).

When treatment for depression is being considered, patients should be evaluated for conditions that may be causing or contributing to the depression. Among these conditions are other psychiatric disorders (e.g., alcohol or sedative-hypnotic dependence), other neurological problems (e.g., stroke, Parkinson's disease), general medical problems (e.g., thyroid disease, cardiac disease, or cancer), and the use of certain medications (e.g., corticosteroids, benzodiazepines).

1. Antidepressants

As described in APA's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*, 2nd edition (284), many well-designed clinical trials support the efficacy of antidepressants in depressed elderly patients without dementia (285–288). However, these data may not extrapolate to patients with co-occurring dementia. Placebo-controlled trials of antidepressants in patients with dementia have shown mixed results (289–296). Despite this mixed evidence, clinical consensus supports a trial of an antidepressant to treat clinically significant, persistent depressed mood in patients with dementia. SSRIs may be preferred because they appear to be better tolerated than other antidepressants (297–299). Some patients with dementia and depression do not tolerate the dosages needed to achieve full remission. When a rapid response is not critical, a very gradual dosage increase may increase the likelihood that a therapeutic dosage will be reached and tolerated. After prolonged use, medications should be withdrawn gradually whenever possible, in order to avoid withdrawal symptoms.

The reader is referred to APA's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*, 2nd edition (284) for a detailed discussion of the side effects of antidepressant agents. Side effects, divided by medication class, are briefly summarized here.

Compared to cyclic antidepressants and monoamine oxidase inhibitors (MAOIs), SSRIs tend to have a more favorable side-effect profile and generally have fewer anticholinergic and cardiovascular side effects. However, SSRIs can produce nausea and vomiting, agitation and akathisia, parkinsonian side effects, sexual dysfunction, weight loss, and hyponatremia. Some of these effects are more common with specific SSRIs than with the entire class. As with most psychotropic medications, SSRI use is associated with an increased risk of falls in elderly patients (300). Physicians prescribing SSRIs should also be aware of the many possible medication interactions associated with the metabolism of these agents through the cytochrome P450 system.

Alternative agents to SSRIs include but are not limited to venlafaxine, mirtazapine, and bupropion. The serotonin-norepinephrine reuptake inhibitor venlafaxine is metabolized through the cytochrome P450 system, but because it does not induce or inhibit these enzymes, it is less likely to interact with other drugs metabolized through the same system. One side effect more commonly seen with venlafaxine than other antidepressants is an elevation in blood pressure, which may be less likely with the sustained release formulation. Duloxetine, another inhibitor of serotonin and norepinephrine reuptake, is commonly used to treat major depression, but clinical experience with its use in geriatric patients with dementia is limited, and there are no published clinical trials to support its use. Mirtazapine, a noradrenergic/specific serotonergic antidepressant, can produce sedation and weight gain, especially at low doses. Rare but potentially serious side effects of mirtazapine are liver toxicity and neutropenia. Bupropion, a norepinephrine-dopamine reuptake inhibitor, has been associated with a risk of seizures, especially at high doses, in patients with anorexia or with structural neurological problems. Trazodone, a serotonin-2 antagonist/reuptake inhibitor, has sedative side effects and can be used when insomnia or severe agitation are prominent. At higher doses, significant side effects include postural hypotension and priapism.

Cyclic antidepressants or MAOIs can be used to treat depression in patients with dementia if other classes of agents have failed or are contraindicated. However, the prominent cardiovascular and anticholinergic side effects associated with these agents make them undesirable first- or second-line agents. The most problematic side effects are cardiovascular effects, including orthostatic hypotension and cardiac conduction delay, and anticholinergic effects, including blurred vision, tachycardia, dry mouth, urinary retention, constipation, sedation, impaired cognition, and delirium. If a cyclic antidepressant is used, agents with significant anticholinergic properties such as imipramine and amitriptyline should be avoided. In terms of MAOI treatment, only the reversible MAOI moclobemide has been studied for treating depression in patients with dementia. Although moclobemide is less toxic than the irreversible MAOIs, it is not currently available in the United States. If nonselective irreversible MAOIs are prescribed, the required dietary restrictions necessitate close

monitoring of food intake, because a patient with dementia cannot be relied on to adhere to these restrictions.

As with most other medications, low starting doses, small dose increases, and long intervals between dose increases are generally necessary when implementing antidepressants for elderly patients. Citalopram is started at 5–10 mg/day and increased at several-week intervals to a maximum of 40 mg/day. Sertraline may be started at 12.5–25.0 mg/day and increased at 1–2-week intervals up to a maximum dosage of 150–200 mg/day.

If these agents are ineffective and other agents are chosen, the starting doses are as follows. Venlafaxine can be started at a dosage as low as 25 mg/day (extended release, 37.5 mg/day) and increased at approximately weekly intervals up to a maximum dosage of 375 mg/day in divided doses (extended release, 225 mg/day). If venlafaxine is prescribed, careful monitoring of blood pressure is indicated. Mirtazapine can be started at a dosage as low as 7.5 mg at bedtime and increased by 7.5-mg or 15-mg increments to 45–60 mg at bedtime. Lower dosages have been associated with sedation and appetite increase, both of which may be beneficial for depressed patients with insomnia or anorexia. Less sedation is found in dosages over 15 mg/day. Caution should be used in prescribing this agent for patients with liver dysfunction or renal impairment and for patients who develop signs of infection. Bupropion can be started at 37.5 mg once or twice per day (sustained release, 100 mg/day) and increased slowly to a maximum dosage of 300 mg/day in divided doses (sustained release, 300 mg/day). No more than 150 mg of immediate release bupropion should be given within any 4-hour period because of the risk of seizures. Duloxetine can be started at 20–40 mg/day and increased slowly to a maximum of 60–80 mg/day, typically in divided doses.

2. Psychostimulants and dopamine agonists

There is a small amount of evidence (301, 302) that dopaminergic agents such as psychostimulants (*d*-amphetamine, methylphenidate), amantadine, bromocriptine, and bupropion may be helpful in the treatment of severe apathy in patients with dementia. Psychostimulants have also received some support for the treatment of depression in elderly individuals with severe general medical disorders (303–305). In general, these agents may be associated with tachyarrhythmias, hypertension, restlessness, agitation, sleep disturbances, psychosis, confusion, dyskinesias, and appetite suppression, particularly at high doses, and amantadine may also be associated with significant anticholinergic effects. Starting dosages of dextroamphetamine and methylphenidate are 2.5–5.0 mg in the morning. The starting dose can be increased by 2.5 mg every 2 or 3 days to a maximum of 30–40 mg/day.

3. Electroconvulsive therapy

Although the data supporting the efficacy and safety of ECT in the treatment of depression in dementia are limited to one small retrospective chart review study, there are significant data supporting its use in geriatric depression in patients without dementia (306–308). Therefore, in the presence of dementia, ECT should only be considered for treating depression that is severe, life-threatening, or does not respond to other treatments. The most common significant side effect is transient confusion, which in turn increases the risk of falls, dehydration, and other complications. Twice weekly rather than thrice weekly and high-dose unilateral (309) or bifrontal rather than bitemporal ECT may decrease the risk of cognitive side effects after ECT. Clinicians should refer to *The Practice of Electroconvulsive Therapy. Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association* (310) for a full discussion of the use of ECT and other potential side effects of ECT treatment.

d. Treatments for Sleep Disturbance

Sleep problems have been reported in 25%–50% of patients with dementia (311, 312), and provisional criteria for sleep disturbances associated with Alzheimer's disease have been proposed (313). Major causes of sleep disturbances in this population include physiological changes associated with aging (fragmented nocturnal sleep, multiple and prolonged awakenings, relative decrease in slow-wave sleep percentage, and increased daytime napping), pathological involvement of the suprachiasmatic nucleus, the effects of co-occurring medical or psychiatric disorders or medications, untreated pain, and poor sleep hygiene (314, 315). Cholinesterase inhibitors can also cause insomnia (141). Some over-the-counter sleep medications (e.g., diphenhydramine) can contribute to delirium and paradoxically worsen sleep. Thus, it is important to ask if the patient is using over-the-counter diphenhydramine or other over-the-counter or herbal preparations to treat sleep disturbance.

Treatment of sleep disturbance in dementia is aimed at decreasing the frequency and severity of insomnia, interrupted sleep, and nocturnal confusion in patients with dementia. In addition to addressing the sleep complaints of people with dementia, treatment goals are to increase patient comfort, decrease disruption to families and caregivers, and decrease nocturnal wandering and nighttime accidents.

Available data do not support the recommendation of a specific course of action for treating sleep disturbances in patients with dementia. Although the data are sparse, clinical practice favors beginning with nonpharmacological approaches when the sleep disorder is an isolated prob-

lem. There are few studies of behavioral, environmental, or pharmacological interventions to improve sleep in this population, although there is some evidence that training caregivers in how to implement proper sleep hygiene can result in improved sleep for patients with dementia (316, 317). A number of trials of bright light therapy have been conducted but have failed to demonstrate significant clinical benefit (315, 318–322). Nevertheless, the psychiatrist treating a patient for a sleep disorder can follow a number of general clinical guidelines in developing a treatment plan. In meeting the needs of both the patient and his or her caregivers, clinicians should consider behavioral and environmental interventions, combine nonpharmacological and pharmacological therapies, and seek to avoid use of multiple psychotropic medications (314). Other initial steps may include establishing regular sleep and waking times, limiting daytime sleeping, avoiding fluid intake in the evening, establishing calming bedtime rituals, and providing adequate daytime physical and mental activities (323–325). Underlying medical and psychiatric conditions that could disturb sleep should be evaluated and treated. Medications that could interfere with sleep should be adjusted if possible. If the patient lives in a setting that can provide adequate supervision without causing undue disruption to others, allowing the patient to sleep in the daytime and be awake at night is an alternative to pharmacological intervention. Pharmacological treatment should be instituted only after other measures have been unsuccessful and the potential benefits outweigh the risk of side effects. It is particularly important to identify sleep apnea (326), which may affect 33%–70% of patients with dementia (324). This condition is a relative contra-indication to the use of benzodiazepines or other agents that suppress respiratory drive.

If another behavioral or neuropsychiatric condition is present, and medications used to treat that condition have sedative properties, clinical practice favors prescribing that agent at bedtime, if appropriate, to assist with treatment of insomnia. For example, an antidepressant with sedative properties (e.g., mirtazapine or trazodone) can be given at bedtime if both sleep disorder and depression are present. If the patient has psychotic symptoms and sleep disturbance, second-generation antipsychotics may be the initial treatment of choice. If there are clear deficits in the patient's sleep hygiene, then education and behavioral management might be the preferred treatment course.

Pharmacological interventions include a number of agents. Some clinicians prefer 25–100 mg of trazodone at bedtime for sleep disturbances, whereas others prefer the nonbenzodiazepine hypnotics such as zolpidem (5–10 mg at bedtime) or zaleplon (5–10 mg at bedtime). Benzodiazepines (e.g., 0.5–1.0 mg of lorazepam, 7.5–15.0 mg of oxazepam) may be used but are generally recommended only for short-term sleep problems because of the possibility of tolerance, daytime sleepiness, rebound insomnia, worsening cognition, falls, disinhibition, and delirium. Rebound insomnia and daytime sleepiness can occur with any of these agents (327). Triazolam is not recommended for individuals with dementia because of its association with amnesia. Diphenhydramine, which is found in most over-the-counter sleep preparations, is used by some clinicians, but it is not recommended for the treatment of patients with dementia because of its anticholinergic properties.

III. SPECIFIC CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

A. DEMOGRAPHIC AND SOCIAL FACTORS

1. Age
Patients and families with dementia occurring in middle age (e.g., frontotemporal dementia or early-onset Alzheimer's disease) may have unique and particularly difficult challenges in coping with the diagnosis and its impact on their lives. Early age of onset may be associated with a more rapid rate of decline (328). In addition, they may require assistance with problems not generally seen with older patients, such as relinquishing work responsibilities (particularly if their jobs are such that their dementia puts others at risk), obtaining disability benefits, and arranging care for minor children. On the other hand, older patients may be frail and have multiple other general medical problems that create difficulties in diagnosis and treatment as well as greater disability for a given stage of dementia.

2. Gender
Another important demographic factor affecting treatment is gender. There are more women with dementia, partly because of greater longevity, but also because Alzheimer's disease is more prevalent among women for reasons that are not known. In addition, because of their greater life expectancy (and tendency to marry men older than themselves), women with dementia are more likely

to have an adult child rather than a spouse as caregiver. Unlike an elderly spouse caregiver, who is more likely to be retired, adult child caregivers (most often daughters or daughters-in-law) are more likely to have jobs outside the home and/or to be raising children. These additional caregiver responsibilities may contribute to earlier institutionalization for elderly women with dementia.

3. Ethnic and Cultural Background

Ethnic diversity affects the presentation, diagnosis, and treatment of dementia. Although *APOE4* was initially believed to be a stronger risk factor for Alzheimer's disease in whites than in Asians or blacks, it is now believed that *APOE4* is associated with similar risks for developing Alzheimer's disease across ethnic groups (329, 330).

Prevalence rates of dementia vary across ethnic groups. For example, compared with whites, blacks may have a higher prevalence of vascular dementia and a lower prevalence of Parkinson's disease (331). These differences are also affected by economic, educational, and co-occurring conditions (70, 332). One study of 240 blacks of U.S. and Caribbean origin indicated that in both Alzheimer's disease and vascular dementia, blacks may have higher rates of psychosis, whereas whites may have higher rates of depression (333).

Cultural differences may affect the family's perception of cognitive symptoms and therefore their report of them to the physician, as well as attitudes toward treatment (334). Ethnicity, race, and culture may influence interpretation of symptoms as well as attitudes toward nursing home placement; the clinician should be sensitive to varying beliefs about the desirability of such a step (70, 335). Cultural background also has an impact on social networks, caregiving style, presentation of disease symptoms such as depression, and acceptance of behavioral symptoms.

4. Other Demographic and Psychosocial Factors

Another critical demographic factor affecting the care of patients with dementia is social support. The availability of a spouse, adult child, or other loved one with the physical and emotional ability to supervise and care for the patient, communicate with treating physicians, and otherwise coordinate care may influence the patient's quality of life as well as the need for institutionalization. In addition, a social network of friends, neighbors, and community may play a key role in supporting the patient and primary caregivers. Spiritual supports and religious beliefs have been shown to have positive benefits for caregivers' well-being. These findings should be taken into account in assessment and treatment planning.

Resource availability varies widely by geographic region and socioeconomic status. This issue should be considered in all treatment decisions but has a particular impact on decisions about long-term care. A referral to the local chapter of the Alzheimer's Association or to a social worker or another individual knowledgeable about local resources, treatment centers, and Medicaid laws can be important in helping families find local treatment options that fit their needs and budget.

B. CO-OCCURRING CONDITIONS AND OTHER DEMENTIAS

1. General Medical Conditions

Because the likelihood of chronic general medical illnesses and the likelihood of dementia both increase with age, the two commonly coexist. Memory impairment and aphasia, both of which interfere with the patient's ability to provide a reliable description of symptoms, complicate the assessment and treatment of general medical conditions. Resistance to physical examination can also complicate assessment, so laboratory testing and radiological procedures may become particularly important. The involvement of family members and other caregivers in providing history is essential.

Many medical conditions are known to have a significant impact on cognitive functioning. The identification and treatment of medical and psychiatric disorders that can adversely affect cognition are especially important. For example, appropriate management of diabetes mellitus may have beneficial effects on cognition (336, 337).

2. Delirium

Dementia predisposes to the development of delirium (338–341), especially in the presence of general medical and other neurological illnesses. Delirium in persons with dementia negatively affects cognitive and functional ability, quality of life, and life span, as well as increases the need for institutionalization and rehospitalization and increases mortality (340).

Medications prescribed to treat co-occurring general medical conditions can lead to further cognitive impairment or to delirium, even when doses are appropriate and blood levels are in the nontoxic range. Prescribed and over-the-counter compounds with anticholinergic activity (e.g., tricyclic antidepressants, low-potency antipsychotics, diphenhydramine, disopyramide phosphate, benztropine), histamine-2 blockade (cimetidine, ranitidine), and narcotic properties are particularly likely to cause delirium (342–344), as are many other classes of medications. Of particular relevance to psychiatrists, delirium has been associated with virtually all psychotropic medications, including lithium, other mood stabilizers,

antidepressants (including SSRIs), antipsychotics, and benzodiazepines (345). A comprehensive approach to delirium includes prevention by avoidance of unnecessary medications and use of the lowest effective dosage, early recognition of delirium through vigilant monitoring at regular intervals, and—when delirium does develop—a thorough search for other causes and prompt treatment to decrease the associated morbidity.

3. Parkinson's Disease Spectrum Illnesses (Including Parkinson's Disease and Dementia With Lewy Bodies)

The cognitive impairment associated with Parkinson's disease and related illnesses (including dementia with Lewy bodies) requires a broad treatment approach that targets both cognitive and noncognitive neuropsychiatric symptoms. Mild cognitive impairment may be partially ameliorated by dopaminergic agents prescribed for the treatment of motor symptoms (346), so both cognitive and motor symptoms should be carefully monitored in assessing the benefits of dopaminergic enhancing therapies. However, the use of dopaminergic agents predisposes patients to the development of visual hallucinations and other psychotic phenomena (347), especially in patients with coexisting dementia, so these agents must be used with particular care, and the minimal dosage needed to control the motor symptoms should be prescribed. In addition, patients with Parkinson's disease spectrum illnesses are vulnerable to delirium from medications and concomitant general medical conditions, as discussed in Section III.B.2. Therefore, the development of these symptoms deserves a thorough evaluation. Both pharmacological and behavioral interventions have been shown to have beneficial effects for specific patients with dementia. However, strong evidence guiding when to use one form over another is lacking. A number of clinical trials have demonstrated the efficacy of acetylcholinesterase inhibitors on cognition in dementia with Lewy bodies and dementia with Parkinson's disease with effects similar to those seen in Alzheimer's disease (168, 348, 349).

Noncognitive neuropsychiatric symptoms often require treatment in patients with dementia with Lewy bodies. Behavioral disturbances are often difficult to control. If psychotic symptoms result in distress or danger, the judicious use of an antipsychotic agent, often at low doses, is indicated. Although all antipsychotic agents can aggravate the motor disturbances of Parkinson's disease, open-label data support the efficacy of second-generation antipsychotics for the treatment of psychotic symptoms associated with these conditions (350–353). Because antipsychotics can dramatically worsen dementia with Lewy bodies, they should be prescribed very cautiously. Depression is com-

mon in Parkinson's disease (354) and may exacerbate functional impairment or be misinterpreted as dementia. Data supporting the efficacy of psychotherapy or antidepressants for the treatment of depression associated with Parkinson's disease are modest, but clinical experience supports their use.

4. Cerebrovascular Disease

Cerebrovascular disease can directly cause or contribute to dementia by means of single and multiple infarcts, hemorrhagic lesions, subcortical white matter disease, arteritis, and hypertension. For patients with dementia who have a history of cerebrovascular disease or who have evidence on neurological examination or neuroimaging of cerebrovascular disease, a careful evaluation is essential to determine the etiology of the vascular changes (e.g., hypertension, atrial fibrillation, or valvular disease) and to make any needed referrals for further evaluation and treatment. Epidemiological evidence suggests that good control of blood pressure and low-dose aspirin might prevent or lessen further cognitive decline (355, 356). The acetylcholinesterase inhibitors donepezil and galantamine have shown at most modest efficacy in treating cognitive impairment in patients with vascular dementia or mixed vascular dementia and Alzheimer's disease (357, 358), and there are safety concerns about the use of this class of medications in this population. Because there are no data on the specific treatment of neuropsychiatric complications of vascular dementia (359, 360), clinical practice extrapolates from studies of Alzheimer's disease or studies of dementia in general.

5. Frontotemporal Dementia Spectrum Disorders

The spectrum of frontotemporal lobar degenerative syndromes includes frontotemporal dementia, primary progressive aphasia, semantic dementia, corticobasal ganglionic degeneration, progressive supranuclear palsy, and hippocampal sclerosis (361) and account for about 5%–10% of patients with dementia. Patients with frontotemporal dementia typically have significant alterations of personality and behavior, and the typical staging schema used for Alzheimer's disease (mild, moderate, severe) does not conform well to the typical natural history of frontotemporal dementia. Overall, there is very limited evidence supporting the use of any particular agent for frontotemporal dementia spectrum disorders (362). Only one small randomized controlled trial has evaluated the safety and/or efficacy of a treatment for associated cognitive or behavioral features (264, 362). This trial demonstrated that trazodone may be beneficial in decreasing problematic behaviors such as irritability, agitation, depressive symptoms, or eating

problems in patients with frontotemporal dementias. In helping families understand and address specific aspects of frontotemporal dementia spectrum disorders, psychiatrists may want to recommend the book *What If It's Not Alzheimer's? A Caregiver's Guide to Dementia* (363).

C. SITE-SPECIFIC ISSUES

The development of a treatment plan for a patient with dementia focuses not only on the identification of specific symptoms and associated general medical problems but also depends on features of the environment in which the patient is cared for, as certain issues are specific to particular care settings.

1. Home Care

The majority of Americans with dementia reside in the community (364), although as many as 90% will receive long-term care during their lifetimes (365). Caring for patients with dementia at home presents challenges of social isolation for the patient and emotional and physical strain on caregivers and others in the home. Care at home is complicated by the need for many family caregivers to work outside the home during the day. Providing care at home can also have adverse emotional effects on caregivers, as well as their children. The psychological stress on families of individuals with Alzheimer's disease and other dementias appears to be more complex than simply the burden of caring for a disabled family member (366). Older spousal caregivers who experience mental or physical strain are at higher risk for health problems and mortality than other caregivers (367, 368). It has been estimated that 30% of spousal caregivers experience a depressive disorder while providing care for a husband or wife with Alzheimer's disease (369). The prevalence of depressive disorders among adult children caring for a parent with Alzheimer's disease ranges from 22%, among those with no prior history of affective disorder, to 37%, among those with a prior history of depression (369, 370). Particularly difficult behavior problems for patients with dementia living at home include poor sleep, wandering, accusations directed toward caregivers, threatening or combative behavior, and reluctance to accept help. However, with assessment and treatment, these symptoms are potentially modifiable. Multifaceted interventions with the family that provide emotional support, focus on the management of the specific behavior problem, and, where appropriate, include careful monitoring of the pharmacological treatment of behavioral symptoms have demonstrated efficacy in reducing caregiver depression, caregiver burden, and rate of nursing home placement (84, 87, 371). The use of home health aides, day care, and respite care may provide stimulation for patients and needed relief for caregivers. End-of-life care for patients with dementia is extremely demanding of family caregivers, with many reporting high levels of depressive symptoms while caring for their relatives with dementia. However, within 3 months of the death, caregivers experience significant declines in depressive symptoms (372).

2. Day Care

Day care provides a protected environment and appropriate stimulation to patients during the day and gives caregivers a needed break to attend to other responsibilities. Some day care centers specialize in the care of individuals with dementia and may offer more appropriate activities and supervision. Anecdotal reports and clinical experience support the benefit to patients of scheduled activities. However, behavioral symptoms can be precipitated by overstimulation as well as understimulation, so activities must be selected with care, and participation should be adjusted according to each patient's response. It is noteworthy that problems can arise when patients with different levels of dementia severity are expected to participate together in the same activities.

3. Long-Term Care

A high proportion of patients with dementia eventually require placement in a long-term-care facility such as a nursing home, assisted living facility, or group home. Placement is usually due to the progression of the illness, the emergence of behavioral problems, the development of intercurrent medical illness, or the loss of social support. Both the patient's characteristics (e.g., race, functional dependence, impaired cognition, behavior) and caregivers' characteristics (e.g., older age, level of caregiver burden) are determinants of nursing home placement (335, 373). Approximately two-thirds of the residents of long-term-care facilities have dementia (374–376), and as many as 90% of them have behavioral symptoms. The number of individuals with dementia living in assisted living facilities is now equivalent to the number living in nursing homes (377). Thus, these facilities should be tailored to meet the needs of patients with dementia and to adequately address behavioral symptoms (120, 378). Well-trained staff are crucial to the humane care of patients with dementia. Knowledge about dementia, neuropsychiatric and behavioral symptoms, and approaches to improving caregiver well-being are essential elements of a staff training program (379, 380).

There is little evidence from randomized controlled trials that addresses the optimum care of individuals in

nursing homes. One important element is employing staff who are committed to working with patients with dementia and are knowledgeable about dementia and the management of its noncognitive symptoms. Structured activity programs can improve both behavior and mood (120). Controlled research on psychotherapeutic interventions has been limited (see Section V.A). Other factors valued in nursing homes include privacy, adequate stimulation, maximization of autonomy, and adaptation to change with the progression of the disease (see references 381 and 382). Whether design features such as particular colors for walls, doors, and door frames affect quality of care remains unknown.

There is no evidence that specialized dementia care units produce better outcomes than traditional nursing home units. However, some such units may offer a model for the optimal care of patients with dementia in any nursing home setting. For example, Reimer et al. (383) reported that quality of life for older residents with dementia was the same or better in a purpose-built and -staffed specialized care facility than in traditional institutional settings.

A particular concern in nursing homes relates to the use of physical restraints and antipsychotic medications, which are regulated by the Omnibus Budget Reconciliation Act of 1987. Use of restraints and antipsychotic medications is fairly common in nursing homes, and psychiatrists practicing in such settings must be familiar with these regulations, which generally can be obtained from the nursing home administrator, local public library, or regional office of the Center for Medicare and Medicaid Services. Although few studies are available to guide the appropriate use of restraints in nursing homes, restraint use can be decreased by strong administrative support for a restraint-free culture, adoption of philosophy statements that promote a restraint-free environment, staff education programs, effecting environmental changes that reduce the risk of falls or wandering, and careful assessment and treatment of possible causes of agitation. Rates of restraint use have also been shown to vary with specific resident characteristics, the number of residents in a facility, and the nurse/resident ratio (384–386). Although chest or wrist restraints are occasionally used for patients who pose an imminent risk of physical harm to themselves or others (e.g., during evaluation of a delirium or during an acute-care hospitalization for an intercurrent illness), the use of staff to provide constant, close supervision is preferable. For long-term-care facilities, geri-chairs may have a place in the care of patients at extreme risk of falling and for whom all other options have failed. Regular use of restraints is not recommended unless alternatives have been exhausted. When they are used, they require periodic reassessment and careful documentation.

The use of antipsychotic medications in nursing homes, as elsewhere, for the treatment of behavioral and psychotic symptoms (see reference 387 for a review) requires consideration of the potential benefits and side effects. When used appropriately and cautiously (see Sections II.C.5.b.1, and V.B.2.a.2), these medications can be modestly effective in reducing patient distress and increasing safety for the patient, other residents, and staff. Excessive dosing, on the other hand, and sometimes even appropriate use, can lead to worsening cognition, oversedation, falls, and numerous other complications including increased mortality, and place patients at risk for tardive dyskinesia and other serious medical adverse events (see Section V.B.2.a.2). Thus, regulations resulting from the Omnibus Budget Reconciliation Act of 1987 and good clinical practice require documentation of the indications for antipsychotic medication treatment, a discussion of available alternatives with the family or other surrogate decision makers, and the identification of treatment outcomes. In the context of these regulations, the psychiatrist should regularly reassess patients for medication response and adverse effects, consider which patients may be appropriate for withdrawal of antipsychotic medications, document the clinical reasoning for maintaining their use, and reinstate their prescription, as deemed clinically necessary (229). It is noteworthy that a structured education program for nursing and medical staff has been shown to decrease antipsychotic usage in the nursing home setting without adverse outcomes (120, 229, 388).

Additional aspects of physical restraint use and antipsychotic medication prescribing are described in Sections II.B.4.b and II.C.5.b.1, respectively.

4. Inpatient General Medical or Surgical Services

Patients with dementia on general medical and surgical services are at particular risk for three problems, all of which can lead to aggressive behavior, wandering, climbing over bed rails, removal of intravenous lines, and resistance to needed medical procedures. First, cognitive impairment makes patients with dementia vulnerable to behavioral problems owing to fear, lack of comprehension, and lack of memory of what they have been told. No data are available to guide treatment recommendations, but general practice supports a preventive approach of having family members or aides stay with the patient. Frequent reorientation and explanation of hospital procedures and plans, writing down important information for the patient, maintaining adequate light, and avoidance of overstimulation may also be useful.

Second, persons with dementia are at high risk for delirium, as discussed in Section III.B.2 (338–340, 389). Prevention of delirium by judicious use of any necessary

medications and elimination of any unnecessary ones, attention to fluid and electrolyte status, and prompt treatment of infectious diseases can also diminish morbidity. Inouye et al. (26) showed the efficacy of a protocol of orientation strategies and therapeutic activities to prevent delirium in hospitalized older adults, many of whom had dementia. Occasionally, psychopharmacological treatment for cognitive impairment (e.g., with a cholinesterase inhibitor) and for behavior disorders (antipsychotic agents) is used in the management of patients with delirium, but no controlled trials exist (340).

Third, patients with dementia may have difficulty understanding and communicating pain, hunger, and other uncomfortable states. For this reason, the development of irritability and/or agitation should prompt a thorough evaluation to identify an occult medical problem or a possible source of discomfort. A significant part of the psychiatrist's role in this setting is educating other physicians and hospital staff regarding the diagnosis and management of dementia and its behavioral manifestations.

5.   General Psychiatric Inpatient Units

Individuals with dementia may require admission to a psychiatric unit for the treatment of psychotic, affective, or behavioral manifestations of neuropsychiatric disorders. For patients who are very frail or who have significant general medical illnesses, a geriatric psychiatry or medical psychiatric unit may be helpful when available. Hospitalization may be indicated because of the severity of symptoms, such as psychosis, depression, threats of harm to self or others, and violent or uncontrollable behavior. It may also be indicated because of the intensity of services required for treatment such as continuous skilled observation, ECT, or a medication or diagnostic test that cannot be performed on an outpatient basis (for literature review, see reference 1).

A thorough search for environmental, general medical, or other psychiatric difficulties that may be leading to the neuropsychiatric disturbance will often reveal a treatable problem. Both nonpharmacological and pharmacological interventions can be tried more readily and aggressively on inpatient units than in outpatient settings.

Part B

BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

IV.   DISEASE DEFINITION, NATURAL HISTORY, AND EPIDEMIOLOGY

Many types of dementias exist, and they have a number of features in common. This section contains a discussion of dementia in general and brief descriptions of some of the more common types of dementias.

A. DEFINITION OF DEMENTIA

The essential features of a dementia are acquired multiple cognitive deficits that usually include memory impairment and at least one of the following phenomena in the absence of a delirium that might explain the deficit: aphasia, apraxia, agnosia, or a disturbance in executive func-

tioning (the ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behavior). The order of onset and relative prominence of the cognitive disturbances and associated symptoms vary with the specific type of dementia, as discussed in Section IV.F.

Memory impairment is often a prominent early symptom. Individuals with dementia have difficulty learning new material. These short-term memory problems commonly result in losing valuables such as wallets and keys or forgetting food cooking on the stove. In more severe dementia, individuals also forget previously learned material, including the names of loved ones. Individuals with

dementia may have difficulty with spatial tasks, such as navigating around the house or in the immediate neighborhood. Poor judgment and poor insight are common as well. Individuals may exhibit little or no awareness of memory loss or other cognitive deficits. They may make unrealistic assessments of their abilities, underestimate the risks involved in activities such as driving, and make plans that are incongruent with their deficits and prognosis (e.g., planning to start a new business).

In order for a diagnosis of dementia to be made, the cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previous level of functioning. The nature and degree of impairment are variable and often depend on the particular social setting of the individual. For example, mild dementia may significantly impair an individual's ability to perform a complex job but not a less demanding one. When memory impairments and/or other cognitive deficits are present in the setting of intact functional status, the patient is usually given a diagnosis of mild cognitive impairment (390) (see Section IV.F.2). There is not yet a general consensus on the criteria for defining and diagnosing mild cognitive impairment (391).

B. ASSOCIATED FEATURES

Some individuals with dementia experience a variety of neuropsychiatric symptoms that may include disinhibited behavior, making inappropriate jokes, neglecting personal hygiene, exhibiting undue familiarity with strangers, or disregarding conventional rules of social conduct. They may also demonstrate apathy, amotivation, and withdrawal. Depressed mood, with or without neurovegetative changes, is quite common, as are sleep disturbances and anxiety independent of depression. Suicidal behavior may occur, especially in mildly impaired individuals, who are more likely to have insight into their deficits and to be capable of formulating and carrying out a plan of action. Some patients manifest "catastrophic reactions," overwhelming emotional responses to relatively minor stressors, such as changes in routine or environment. Occasionally, they may harm others by striking out. Delusions can occur, especially those involving themes of spousal infidelity and persecution such as the belief that misplaced possessions have been stolen. Misidentifications of familiar people as unfamiliar (or vice versa) frequently occur. Delusions that a spouse or caregiver is an imposter are particularly difficult for patients and their families. Hallucinations can occur in all sensory modalities, but visual hallucinations are most common. Some patients exhibit a peak period of agitation (or other behavioral disturbances) during the evening hours, which is sometimes referred to as "sundowning."

Individuals with dementia are especially vulnerable to the effects of change and psychosocial stressors (such as bereavement or going to the hospital), and these stressors can worsen intellectual deficits and exacerbate neuropsychiatric symptoms. Patients with dementia are particularly susceptible to developing delirium, as discussed in Section III.B.2. Dementia may be accompanied by neurological symptoms such as gait difficulties, dysarthria, swallowing difficulty with consequent choking or aspiration, urinary and fecal incontinence, seizures, tremor, myoclonus, and other abnormal movements.

C. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dementia is described in detail in DSM-IV-TR and is only summarized here (392, 393). Age-associated memory changes are modest and not associated with functional impairment or depression. Memory impairment occurs in both delirium and dementia. A new diagnosis of dementia cannot be made when delirium is present. Delirium, discussed in Section III.B.2, is characterized by a reduced ability to maintain and shift attention appropriately, fluctuating cognitive deficits, and impaired level of consciousness, whereas the deficits in dementia tend to be stable or progressive, and level of consciousness is unaffected. In addition, the onset of delirium may be acute, and its course is often time limited. Amnestic disorder is characterized by memory impairment without significant impairment in other cognitive domains. Mental retardation has an onset before age 18 years and is characterized by significantly subaverage general intellectual functioning, which may not include memory impairment. Schizophrenia may be associated with multiple cognitive impairments and a decline in functioning, but the cognitive impairment tends to be less severe and occurs against a background of psychotic and behavioral symptoms meeting the established diagnostic criteria.

Major depression is an important element of the differential diagnosis of memory difficulties. Particularly in elderly persons, major depressive disorder may be associated with reports of memory impairment, difficulty concentrating, and a reduction in intellectual abilities described by history or observed on mental status examination. Depression and progressive dementia may sometimes be distinguished on the basis of an assessment of the course and onset of depressive and cognitive symptoms and by response of cognitive symptoms to treatment of the depression. However, even when the onset of depressive symptoms precedes or coincides with the onset of cognitive symptoms and both resolve with antidepressant treatment, more than 50% of patients go on to develop dementia or mild cognitive impairment within several

years of the depressive episode (280, 394, 395). In addition, among patients with mild cognitive impairment (see Section IV.F.2), evidence suggests that those who are also depressed have a greater likelihood of developing Alzheimer's disease (396). Dementia must be distinguished from malingering and factitious disorder, which generally manifest patterns of cognitive deficits that are inconsistent over time and are uncharacteristic of those typically seen in dementia.

Dementia must also be distinguished from milder symptoms. Subjective memory complaints are common as people get older. Many individuals with these complaints have subtle, nonprogressive declines in memory, but some have more significant impairment that is more likely to represent the prodromal phase of Alzheimer's disease or another dementia. The category of mild cognitive impairment (390) was developed to describe individuals in this prodromal phase (see Section IV.F.2) (6, 391, 397).

D. PREVALENCE AND COURSE

Exact estimates of the prevalence of dementia depend on the definition and specific threshold used, but it is clear that the prevalence increases dramatically with age. The syndrome affects approximately 5%–8% of individuals over age 65 years, 15%–20% of individuals over age 75 years, and 25%–50% of individuals over age 85 years (398). Alzheimer's disease is the most common dementia, accounting for 50%–75% of the total number of cases of dementia, with a greater proportion of cases in the higher age ranges. Vascular dementia is probably next most common; prevalence estimates vary widely and depend on the definition of vascular dementia used; pure vascular disease may account for 5%–20% of cases of dementia, and mixed dementia—Alzheimer's disease with vascular dementia—occurs at least as frequently. Dementia with Lewy bodies may present with frequent falls, hallucinations, and cognitive fluctuation as well as mild parkinsonism and may account for up to 20% of individuals with dementia (399, 400).

The mode of onset and subsequent course of dementia depend on the underlying etiology. Typically, Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia have an insidious onset and gradual decline, whereas vascular dementia may be characterized by a more acute onset and stepwise decline. However, since both Alzheimer's disease and vascular dementia are common and the two frequently coexist, a secondary diagnosis of vascular dementia or a diagnosis of mixed dementia is often made when a gradually progressive dementia occurs in the setting of known cerebrovascular disease. Other dementias may be progressive, static, or occasionally remitting. The reversibility of a dementia is a function of the underlying etiology and of the availability and timely application of effective treatment.

E. STAGING OF DEMENTIA

Progressive dementias are generally staged globally according to the level of cognitive and functional impairment, and the same categories may be used to describe the degree of severity of any dementia (401, 402). However, the staging criteria have not been well validated for non-Alzheimer's dementias. Specific functional staging (FAST staging) has also been developed, is widely used, and can be very useful in tracking the course of Alzheimer's disease and other dementias (403). The ability to perform a specific function depends on baseline skills, acquired deficits, and the social environment. Consequently, the severity of illness should be assessed in the context of past functioning in several domains. Behavioral and neuropsychiatric symptoms are not stage specific.

The CDR is a commonly used scale to stage dementia severity (401). Individuals with a CDR of "questionable" (CDR of 0.5) show mild deficits in memory and sometimes in other areas and have doubtful or mild functional impairment. When such individuals present for clinical evaluation, they tend to have fairly significant memory impairment that is evident on objective testing as well, and they are typically assigned a diagnosis of mild cognitive impairment (see Section IV.F.2) or mild dementia. The Global Deterioration Scale (GDS) distinguishes three stages in this range (402). A GDS stage of 2 designates normal aging, in which older persons have subjective deficits in cognition and related areas only. Many studies have indicated that persons with these complaints are at increased risk for decline over subsequent years (404–406). The GDS stage 3, which includes subtle but manifest cognitive deficits, generally accompanied by executive level functional deficits, is equivalent to mild cognitive impairment (391). Such individuals should be evaluated over time. Many patients with mild cognitive impairment progress to Alzheimer's disease or another dementia, some patients' deficits remain stable without progression, and a few return to normal functioning (6). In community settings, this group of individuals is heterogeneous; some are similar to those who would be given a diagnosis of mild cognitive impairment in a memory clinic, whereas others have much more subtle symptoms that may be consistent with normal aging. Patients who have been systematically diagnosed as having mild cognitive impairment in memory clinics tend to be more homogeneous and more likely to progress to dementia.

Individuals with "mild" dementia (MMSE score of >18, GDS or FAST stage 4, CDR of 1) are likely to have diffi-

culties with balancing a checkbook, preparing a complex meal, or managing a difficult medication schedule. Those with "moderate" impairment (MMSE score of 10–18, GDS or FAST stages 5 and 6, CDR of 2) also have difficulties with simpler food preparation, household cleanup, and yard work and may require assistance with some aspects of self-care (e.g., picking out the proper clothing to wear). Those whose dementia is "severe" (MMSE score of <10, GDS or FAST stages 6 and 7, CDR of 3) require considerable or total assistance with personal care, such as dressing, bathing, and toileting. Research has shown that measurable cognitive abilities remain throughout the course of severe dementia (407). In the terminal phase, patients become bed bound, develop contractures (408), require constant care, and may be susceptible to accidents and infectious diseases, which ultimately prove fatal.

F. SPECIFIC DEMENTIAS

1. Dementia of the Alzheimer's Type

Dementia of the Alzheimer's type, commonly referred to as Alzheimer's disease, has an insidious onset and gradual progression. Various patterns of deficits are seen, but the disorder begins most commonly with deficits in recent memory, which are followed by aphasia, visuospatial perceptual impairments, apraxia, and agnosia after several years. Deficits in executive function (e.g., performing tasks involving multiple steps, such as balancing a checkbook or preparing a meal) are also typically seen early in the course of the disease. Neuropsychiatric symptoms are common in Alzheimer's disease. Depression, anxiety, irritability, apathy, and even subtle personality changes are fairly common in the early stages of the disease, whereas in the middle and later stages of the disease psychotic symptoms and behavioral disturbances are more common. Patients usually develop incontinence and gait and motor disturbances, and eventually become mute and bed bound. Seizures and myoclonus may also occur late in the disease.

The diagnosis of Alzheimer's disease should be made only when the patient exhibits the typical symptom profile of Alzheimer's disease and when other etiologies for the dementia have been ruled out by careful history, physical and neurological examinations, and clinical and laboratory tests. A definitive diagnosis of Alzheimer's disease requires both the clinical syndrome and microscopic examination of the brain at autopsy, at which time the characteristic plaques and neurofibrillary tangles widely distributed in the cerebral cortex will be seen. A careful clinical diagnosis of Alzheimer's disease conforms to the pathological diagnosis 70%–90% of the time.

Onset of Alzheimer's disease generally occurs in late life, most commonly in the 60s, 70s, and 80s and beyond, but in rare instances the disorder appears in the 40s and 50s. The incidence of Alzheimer's disease also increases with age, and it is estimated at 0.5% per year from age 65–69 years, 1% per year from age 70–74 years, 2% per year from age 75–79 years, 3% per year from age 80–84 years, and 8% per year from age 85 years onward (409). Progression is gradual but steadily downward, with an average duration from onset of symptoms to death of 8–10 years. Plateaus may occur, but progression generally resumes after 1 to several years.

In DSM-IV-TR, Alzheimer's disease is subdivided into the subtypes "With Early Onset" and "With Late Onset," as well as "With and Without Behavioral Disturbance." Other predominant features of the current clinical presentation such as psychosis, mood disorder, or personality change, are coded with their own Axis I code.

2. Mild Cognitive Impairment

Mild cognitive impairment is a term used to represent a variety of mild cognitive syndromes manifested by a modest but detectable decline in cognitive function in the setting of largely intact functional status (391). Because it is expected that new treatments will be better at preserving than restoring neuronal function, early recognition of these mild syndromes, particularly those thought to represent the prodromal phase of Alzheimer's disease and other neurodegenerative dementias, are a major focus of current research. Mild cognitive impairment is conceived of as a transitional state between normal aging and dementia (particularly Alzheimer's disease) in which cognitive deficits are present but function is preserved. As such, the population of patients meeting the criteria for mild cognitive impairment is inherently unstable, as many patients progress to meet the criteria for dementia. Moreover, because mild cognitive impairment lies along a continuum between normal aging and dementia, its precise upper and lower boundaries are difficult to determine. A variety of research definitions for mild cognitive impairment are in place, but there is no consensus on the optimal definition. The most widely accepted definition requires the following: 1) subjective cognitive complaints, 2) evidence of objective deficits in cognitive function based on age- and education-adjusted norms on standardized neuropsychological tests, 3) intact daily functioning, 4) evidence of cognitive decline from a prior level, and 5) evidence of not meeting the criteria for dementia (410).

Mild cognitive impairment is sometimes divided into subtypes based on the most prominent symptoms. One subtype, referred to as "amnestic mild cognitive impair-

ment," may be the prodromal stage of Alzheimer's disease (410). A large proportion of patients who meet the criteria for mild cognitive impairment probably have the prodromal phase of Alzheimer's disease, particularly when short-term memory loss dominates the clinical picture (173). However, it should be noted that, no matter how it is defined, mild cognitive impairment is a heterogeneous category that includes some individuals with nonprogressive deficits, some with prodromal Alzheimer's disease and other dementias, and some for whom a diagnosis of early Alzheimer's disease or another dementia would be more appropriate.

3.　Vascular Dementia

Vascular dementia results from the effects of cerebrovascular disease on cognitive function. Several cerebrovascular mechanisms can lead to cerebral injury, including large vessel infarctions, multiple lacunar infarctions, extensive subcortical and periventricular white matter disease, and microvascular changes. These types of tissue injuries are usually due to atherosclerotic disease or amyloid angiopathy. Autoimmune mechanisms are far less likely.

The full range of clinical symptoms in vascular dementia is not well understood. The best known syndrome is cognitive impairment that occurs shortly after a clinically recognized stroke (within 3 months), with evidence of infarctions in brain areas relevant to the impaired cognitive functions. Neurological signs and symptoms consistent with cerebrovascular damage (hemiparesis or hemianopia) are usually present. There is no specific cognitive profile of vascular dementia, although executive and attentional deficits may be more pronounced than impairment in short-term memory. The pattern of cognitive deficits is often patchy, depending on which regions of the brain have been damaged (411).

The incidence and prevalence of vascular dementia mirror those of Alzheimer's disease in that vascular dementia becomes increasingly common with advanced age (412–414). The relationship between Alzheimer's disease and vascular dementia is complex. Alzheimer's disease and strokes are both common and frequently coexist (although often only one diagnosis is recognized during a person's life). In addition, a wide variety of evidence from neuroimaging, neuropathological, epidemiological, and genetic studies suggests that the two share common risk factors, such as hypertension, diabetes, hypercholesterolemia, hyperhomocysteinemia, as well as others (415). There is also considerable neuropathological overlap between the two conditions. Many patients with typical pathological signs of Alzheimer's disease have cerebrovascular disease as well, whereas other patients with clear strokes also have pathological signs of Alzheimer's disease. The degree to which strokes alone are responsible for dementia is unclear; estimates for the fraction of dementia caused by "pure" vascular dementia range from 5% to 20% (416). Early treatment of hypertension and vascular disease may prevent further progression. Vascular dementia associated with autoimmune disease occurs in concert with other symptoms of the specific illness and in the age group characteristic of the specific disease (e.g., systemic lupus erythematosus, giant cell arteritis).

Like Alzheimer's disease, vascular dementia is subtyped by DSM-IV-TR according to certain clinical features. Subtypes available for vascular dementia include "With Delirium," "With Delusions," "With Depressed Mood," and "Uncomplicated." Clinically significant behavioral disturbances can be coded as a modifier but are not considered a separate subtype. No subtyping based on age of onset is used. More formal diagnostic criteria, typically focused on differentiating pure vascular dementia from a mixture of Alzheimer's disease and vascular pathology, are used in the research setting (417). These criteria vary widely, particularly to the extent that they stress clinical versus radiographic evidence for stroke, and there is no consensus on optimal criteria for vascular dementia at this time (5, 418, 419).

4.　Dementia of Parkinson's Disease and Dementia With Lewy Bodies

Lewy bodies are commonly found at autopsy in individuals with late-life dementia. There are two subtypes of Lewy body disease depending on whether Parkinson's disease precedes cognitive impairment by more than 1 year (Parkinson's disease dementia) or whether the cognitive impairment is the dominant symptom (dementia with Lewy bodies). Whether or not these entities are best classified as one condition or as distinct ones is still unresolved. Parkinson's disease is a slowly progressive neurological condition characterized by tremor, rigidity, bradykinesia, and postural instability; its onset is typically in middle to late life. Estimates of the prevalence of dementia in Parkinson's disease vary. One large longitudinal study found that dementia developed in nearly 80% of patients followed for 8 years (420). The dementia associated with Parkinson's disease has an insidious onset and slow progression and is characterized by cognitive and motor slowing, executive dysfunction, and impairments in memory retrieval and flexibility. Parkinson's disease is important to psychiatrists because of the high prevalence of associated depression and the frequent occurrence of psychotic symptoms such as visual hallucinations during pharmacological treatment of the primary motor deficit.

Dementia with Lewy bodies has been recognized clinically only in the last 10–15 years (421, 422). In many ways it is clinically similar to Alzheimer's disease. Important clinical differences that distinguish dementia with Lewy bodies include visual hallucinations that appear earlier in the disease course and tend to be more prominent, parkinsonian features such as postural instability and falls that appear early in the disease course, cognitive fluctuations lasting days to weeks, and a somewhat more rapid evolution. Patients with dementia with Lewy bodies are markedly sensitive to the extrapyramidal effects of antipsychotic medications, and these medications should be used only with the utmost caution in these patients. Dementia with Lewy bodies may account for as many as 7%–26% of dementia cases, depending on the criteria used (423, 424). The disorder is particularly likely to come to psychiatric attention because of a patient's prominent psychotic symptoms and sensitivity to antipsychotic medications.

The neuropathology of Parkinson's disease and dementia with Lewy bodies are identical and include an abundance of Lewy inclusion bodies in both subcortical and cortical regions (422). Because autopsies often reveal both the neuropathologies of dementia with Lewy bodies and Alzheimer's disease, controversy exists about the independence of the two diseases. The development of valid clinical and pathological diagnostic criteria for dementia with Lewy bodies is an area of active research.

5. Dementia Due to Frontotemporal Dementia Spectrum Disorders

Frontotemporal dementia (formerly referred to as Pick's disease and sometimes referred to as frontotemporal lobar degeneration) is characterized in its early stages by changes in personality, significant apathy, executive dysfunction, deterioration of social skills, emotional blunting, behavioral disinhibition, and prominent language abnormalities. Difficulties with memory, apraxia, and other features of dementia usually follow later in the course. As the dementia progresses, it may be accompanied by extreme agitation. Individuals may develop such severe problems with language, attention, or behavior that it may be difficult to assess the degree of cognitive impairment. Early prominent changes in personality and behavior, severe apathy, and/or early language deficits help to distinguish this group of disorders from Alzheimer's disease. Two sets of diagnostic criteria for frontotemporal dementia spectrum disorders have been proposed (361, 425). The criteria of McKhann et al. include several disorders previously considered to be distinct: progressive supranuclear palsy, corticobasal ganglionic degeneration, amyotrophic lateral sclerosis with dementia, and hippo-

campal sclerosis (361, 426). Argyrophilic grain disease may also be included in this group of conditions (427). In frontotemporal dementia spectrum disorders, structural brain imaging typically reveals prominent frontal and/or temporal atrophy, with relative sparing of the parietal and occipital lobes. The formal diagnosis of Pick's disease, which is only one of the numerous neuropathological subtypes of this condition, depends on the neuropathological finding of Pick inclusion bodies (361). About one-third of cases are familial, and a number of specific genetic defects have been identified (29). The disorder most commonly manifests in patients ages 50–60 years, although it can occur among older or younger individuals. The course is progressive and can be more rapid than that of Alzheimer's disease, although there is significant heterogeneity. Once thought to be rare, these conditions have been found to be more common, and careful assessment may reveal cases previously missed. These conditions are important for psychiatrists because they often present with a variety of psychiatric symptoms, including disinhibition, apathy, depression, anxiety, personality change, substance abuse, family conflict, and impaired work performance, that initially overshadow the cognitive impairment, complicating and delaying the proper diagnosis.

6. Other Progressive Dementing Disorders

Other disorders that can lead to progressive dementia include Huntington's disease and Creutzfeldt-Jakob disease. Huntington's disease is an autosomal dominant disorder that affects the basal ganglia and other subcortical structures and includes motor, behavioral, mood, and cognitive symptoms. Creutzfeldt-Jakob disease is a rapidly progressive spongiform encephalopathy associated with a prion (proteinaceous infectious particle). Variant Creutzfeldt-Jakob disease, thought to be due to introduction into the human food chain of scrapie-like prion disease, usually presents before age 40 years with psychiatric symptoms. Cognitive decline is rapid, with death usually occurring within 1.5 years.

7. Dementia Due to Other Causes

In addition to the preceding categories, a number of general medical conditions can cause dementia (428). These conditions include structural lesions (e.g., primary or secondary brain tumors, subdural hematoma, slowly progressive or normal-pressure hydrocephalus), head trauma, endocrine conditions (e.g., hypothyroidism, hypercalcemia, hypoglycemia), nutritional conditions (e.g., deficiency of vitamin B_{12}, thiamine, or niacin), other infectious conditions (e.g., HIV, neurosyphilis, *Cryptococcus*), derangements of renal and hepatic function, neu-

rological conditions (e.g., multiple sclerosis), effects of medications (e.g., benzodiazepines, beta-blockers, anticholinergics), autoimmune diseases (e.g., lupus erythematosus, vasculitis, Hashimoto's encephalopathy, neurosarcoidosis), environmental toxins (e.g., heavy metals, organic hydrocarbons), and the toxic effect of long-standing substance abuse, especially alcohol abuse. It is critical that psychiatrists caring for individuals with dementia be familiar with the general medical and neurological causes of dementia in order to ensure that the diagnosis is accurate and, in particular, that potentially treatable conditions are not missed.

V.   REVIEW OF AVAILABLE EVIDENCE

A. SPECIFIC PSYCHOTHERAPIES/PSYCHOSOCIAL TREATMENTS

Specific psychosocial treatments for dementia can be divided into four broad groups: behavior oriented, emotion oriented, cognition oriented, and stimulation oriented. Few of these treatments have been subjected to rigorous double-blind, randomized, controlled trials, although some are supported by research findings and have gained clinical acceptance. Published studies have generally been based on small samples and have been of limited duration, and many of the reports fail to fully characterize the intervention, the nature or stage of the subjects' dementia, their baseline status, or the persistence of any improvement.

1.   Behavior-Oriented Approaches

Behavioral interventions have not been shown to improve the overall functioning of patients with dementia, but there is some evidence that they can be effective in lessening or eliminating some specific problem behaviors, as described in literature reviews (112, 115). For example, behavioral interventions such as scheduled toileting can reduce frequent urinary incontinence (429). The evidence from a few well-designed studies of behavioral management therapy shows that behavioral interventions can be somewhat beneficial for improving mood and disruptive behavior. A body of literature consisting of small trials or single case studies supports the short-term benefits of behaviorally focused interventions (118, 430–436). For example, results of a small randomized controlled study (32 subjects in each group) of a four-session aggressive behavior management training program for caregivers showed a trend toward lower rates of aggression in the experimental group, compared to the control group ($P = 0.071$), but that difference was not statistically significant (431). In addition, a review of the literature revealed modest effectiveness of such treatments (113). Nonetheless, with some exceptions, the limited available follow-up data have suggested that the benefits do not persist beyond the duration of the interventions (116, 437).

At this time there is insufficient evidence to claim superiority of either behavioral approaches or pharmacological approaches (117, 214). Studies combining the two types of approaches are almost nonexistent, although they are often combined in clinical practice. In a randomized placebo-controlled trial that included 149 patients with Alzheimer's disease and agitation, haloperidol (mean dose of 1.8 mg/day), trazodone (mean dose of 200 mg/day), and behavior management techniques were compared over a 16-week period. Overall, 34% of the patients improved, but there were no differences between treatment groups, although fewer episodes of bradykinesia and parkinsonian gait occurred in the behavior management group (214). In a study that included 153 community-dwelling patients with Alzheimer's disease, routine medical care was compared with a structured program combining exercise training and caregiver training in the management of problematic behaviors; the results showed no statistically significant reduction in nursing home admissions due to behavioral disturbances but did show improvement in mood and physical role function (117). In another study, 12 nursing homes or residential homes were randomly assigned to receive a 6-month training and education intervention or to provide usual care. The patients in the intervention homes did slightly better in cognition and mood than the patients in the homes that provided usual care, but there was no difference between groups on measures of behavior (118).

2.   Emotion-Oriented Approaches

Emotion-oriented interventions include reminiscence therapy (438), validation therapy (439, 440), supportive psychotherapy (441), sensory integration (442), and simulated presence therapy (443).

Reminiscence therapy, in which the aim is to stimulate memory and mood in the context of the patient's life history, has been shown in three studies of "confused" elderly persons (122–124) to be associated with modest short-lived gains in mood, behavior, and cognition. A single small study of validation therapy, in which the aim is to re-

store self-worth and reduce stress by validating emotional ties to the past, found that validation therapy did not improve cognitive, functional, and mood measures more than reality orientation or no intervention (444). For nursing home residents with moderate to severe dementia, a staff training program emphasizing emotion-oriented care (which combined validation therapy, sensory stimulation, and reminiscence) found no effects on cognitive, functional, or behavioral outcomes (445). Supportive psychotherapy has received little or no formal scientific study, but some clinicians find it useful in helping mildly impaired patients adjust to their illness. Cochrane reviews of validation therapy, reminiscence, and Snoezelen (controlled multisensory stimulation) did not identify reliable empirical evidence of efficacy of these interventions (446–448).

3. Cognition-Oriented Approaches

Cognition-oriented techniques include reality orientation (449) and skills training (450). The aim of these treatments is to restore cognitive deficits, often in a classroom setting. In a number of studies of both institutionalized and non-institutionalized patients, reality orientation has produced modest but transient improvement in verbal orientation (122, 451–460). Some studies have also demonstrated slight transient improvement in other measures of cognition, function, behavior, and social interaction. However, there have also been case reports of anger, frustration, and depression precipitated by reality orientation (127).

There is some evidence of benefit from cognitive remediation and from skills (or memory) training. Spector et al. (125) conducted a single-blind, multicenter, controlled clinical trial comparing a cognitive stimulation program with routine care for 201 patients with dementia attending day treatment programs or residing in nursing homes. They found improvements in scores on the MMSE and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) and in quality-of-life measures. Other studies have reported short-lived gains with ultimate return to baseline levels of cognition and behavior and no generalization of skills to other areas of cognition (450, 461–467). In addition, there have been reports of frustration in patients and depression in caregivers associated with this type of intervention (86). The modest and transient improvements observed with some of these treatments may not justify the cost of the intervention or the risk of adverse effects.

4. Stimulation-Oriented Approaches

These treatments include recreational activities or therapies (e.g., crafts, games, pets), art therapies (e.g., music, dance, art), exercise, multisensory stimulation, simulated presence, and aromatherapy, some of which overlap with emotion-oriented interventions in their content. They are intended to mobilize the patient's available cognitive resources by providing stimulation and enrichment. Benefits of music therapy may include improving mood, decreasing behavior problems, enhancing socialization and quality of life, and encouraging emotional expression (468).

There is some evidence that, while they are in use, these interventions decrease behavioral problems and improve mood. Rovner et al. (120) tested the efficacy of an intervention combining activities, guidelines for psychotropic drug use, and educational rounds to reduce behavior disorders in 89 nursing home patients with moderate to severe dementia. After 6 months, the prevalence of behavior disorders and psychotropic drug and restraint use was significantly lower in the experimental group, compared with usual care controls. Camberg et al. (121) tested the efficacy of simulated presence to reduce agitation and withdrawn behaviors in 54 nursing home residents with severe dementia. Simulated presence was an audiotaped, individualized telephone conversation consisting of recollections of the person's life; control comparisons were a placebo audiotape (e.g., someone reading a newspaper) and usual care. Whenever study subjects exhibited agitated or withdrawn behaviors, they were exposed to the assigned intervention. According to staff observation logs (with raters blind to treatment assignment), simulated presence significantly reduced rates of agitation, compared with usual care or placebo (121).

Baker et al. (469) tested the effectiveness of multisensory stimulation in 50 patients with moderate to severe dementia attending a day treatment program and found short-lived improvements in mood, attention, and behavior. However, a second trial (470) involving 136 patients failed to find differences in these outcomes, compared to outcomes of a control condition consisting of an activities program. Robichaud et al. (442) similarly found no improvements in mood, cognition, or behavior in response to a sensory integration intervention in 40 nursing home residents with dementia. Two studies have investigated the efficacy of aromatherapy to reduce agitation in nursing home residents with severe dementia. Ballard et al. (471) reported reduced agitation and improved quality of life, whereas Snow et al. (472) found no benefit. Five recent studies have investigated the benefits of exercise; four studies (117, 473–475) reported improved mobility, physical endurance, strength, and mood, whereas one study (476) found no change in mobility and function. Additional support for this approach comes from the work of Teri et al. (119, 477), who have developed a behavioral protocol for managing Alzheimer's disease that includes a number of stimulation-oriented interventions. The core

of this protocol, identifying and increasing the number of previously enjoyed pleasant activities, has been shown in preliminary studies to improve the mood of patients and caregivers alike.

In general, the data supporting efficacy for stimulation-oriented therapies are limited either by small numbers of subjects (459, 478, 479) or use of multiple interventions (478); nevertheless, there is anecdotal and common sense support for their inclusion as part of the humane care of patients with dementia.

B. SOMATIC TREATMENTS

1. Treatments for Cognitive and Functional Losses

a. Cholinesterase Inhibitors

1. *Alzheimer's disease*

a. Tacrine

The efficacy of tacrine in mild to moderate Alzheimer's disease has been extensively studied, although its effects on patients with more severe or very mild Alzheimer's disease or with other forms of dementia have not been assessed. At least five double-blind placebo-controlled trials with parallel-group comparisons including a total of more than 2,000 patients have been reported (131–135). Overall, these clinical trials consistently demonstrated differences between tacrine and placebo. Approximately 30%–40% of patients taking tacrine who completed the trials showed modest improvements in cognitive and functional measures over study periods ranging from 6 to 30 weeks, compared to up to 10% of those taking placebo. Modest improvement in these studies corresponded to maintaining or improving function by an amount typically lost over 6 months in untreated groups of similar patients with Alzheimer's disease. Response appeared to be related to dose, at least in the largest clinical trial (133), in which patients who could tolerate 120–160 mg/day were more likely to respond. However, only approximately 60% of the patients were able to complete the tacrine trials even at moderate doses; 30% of the subjects were dropped from these trials prior to completion because of elevation in hepatic transaminases, and another 10% had to leave because of other adverse effects, mainly cholinergic effects (e.g., nausea and vomiting). The benefits and adverse effects of administration beyond 30 weeks are unknown.

b. Donepezil

The efficacy of donepezil has been evaluated in more than 15 randomized, double-blind, placebo-controlled trials (136–146). Trial sizes have varied from fewer than 20 subjects to 818 subjects (138), and many trials have been multicentered. Most trials have been 12–24 weeks in duration, although at least two have lasted 1 year (137, 139), and one lasted more than 2 years (136). Studies have generally been conducted with community-dwelling patients, although one trial included nursing home residents with moderate to severe dementia (145). The majority of studies have enrolled patients with mild to moderate Alzheimer's disease (MMSE scores in the 10–26 range), although at least two have focused on patients with moderate to severe dementia (MMSE scores in the 5–17 range) (107, 142), and one focused exclusively on patients with early Alzheimer's disease with MMSE scores in the 21–26 range (146, 480).

Published studies consistently have found a benefit of donepezil over placebo in both cognitive and functional measures, including measures of clinicians' impressions of improvement. The size of the effect of donepezil has likewise been consistent across most studies, with improvement over placebo of about 1 point on the MMSE and 3 points on the ADAS-cog. On cessation of donepezil, improvement was lost over a 3–6-week period in all studies that examined this outcome. In one study in which donepezil treatment was interrupted for 6 weeks and then reinstated at the original dose, patients' cognition and function did not return to the level achieved prior to donepezil discontinuation (166). Most studies comparing 5 mg/day dosing with 10 mg/day found greater benefit with the higher dosage (138, 140), although this result has not been found in some studies comparing these dosages (141). Donepezil is administered once daily.

The question of whether donepezil treatment delays nursing home placement is an important one and has been addressed in two studies. One study found a delay in nursing home placement in patients treated with open-label donepezil for up to 240 weeks (481). However, these findings have been contested on methodological grounds (482). The AD2000 trial conducted in the United Kingdom followed 565 community-dwelling patients randomly assigned to receive donepezil or placebo for more than 2 years (136). Although donepezil-treated patients had better cognitive and activities of daily living scores than the placebo group, there was no difference in the primary endpoint of time to institutionalization. However, the trial was underpowered, had a high dropout rate, and may have been influenced by treatment interruptions (483).

c. Rivastigmine

The efficacy of rivastigmine has been evaluated in at least eight randomized, placebo-controlled, double-blind studies of patients with Alzheimer's disease (147–152). The sizes of the studies have varied from 50 subjects (148) to as many as 725 subjects (149). The duration of most trials was

26 weeks or shorter, although one trial lasted 12 months (150). All trials thus far have been conducted with community-dwelling patients with mild to moderate dementia severity (480).

These studies consistently have found a benefit of rivastigmine over placebo on both cognitive and functional measures, including measures of clinicians' impressions of improvement. The size of the effect of rivastigmine has likewise been consistent across most studies, with improvement over placebo of about 1 point on the MMSE and 3 points on the ADAS-cog, a magnitude of effect similar to that of donepezil. The dosage range found to have maximum efficacy is 6–12 mg/day in divided doses.

d.   Galantamine
The efficacy of galantamine has been evaluated in at least eight randomized, placebo-controlled, double-blind studies (153–159). The numbers of subjects have ranged from under 100 to 978 (157). Duration of most trials was one-half year or shorter. All trials thus far have been conducted with community-dwelling patients with mild to moderate Alzheimer's disease (480).

These studies consistently have found a benefit of galantamine over placebo in both cognitive and functional measures, including measures of clinicians' impressions of improvement. The size of the effect of galantamine has likewise been consistent across most studies, with improvement over placebo of about 1 point on the MMSE and 3 points on the ADAS-cog, a magnitude of effect similar to that of donepezil. The dosage range found to have maximum efficacy is 16–24 mg/day in divided doses. An extended release, once-daily dosing form of galantamine has recently been released.

2.   Vascular dementia
A number of randomized, double-blind, placebo-controlled trials have been conducted in patients with vascular dementia or mixed Alzheimer's disease and vascular dementia. In two 24-week trials conducted with patients with probable or possible vascular dementia (616 subjects and 603 subjects, respectively), donepezil (5 mg/day and 10 mg/day) was compared to placebo (484, 485). Improvements in measures of cognition and function were found in patients given either dose of donepezil, although in one of the trials (484) one of the two primary outcome measures did not demonstrate benefit of donepezil, compared with placebo. The effect size was comparable to that found in Alzheimer's disease trials. Two 6-month trials of galantamine (592 and 786 subjects, respectively) in patients with vascular dementia or mixed Alzheimer's disease and vascular dementia had similar findings (358, 486).

Of concern, in one unpublished trial of donepezil for vascular dementia, there was a significantly higher rate of death in the subjects taking donepezil than in the placebo group (167), raising a significant safety concern that requires further study.

3.   Dementia with Lewy bodies
One 20-week, randomized, double-blind, placebo-controlled study with 120 subjects examined the effects on cognition of 6–12 mg/day of rivastigmine in patients with Lewy body dementia (168). The results showed overall cognitive benefits with rivastigmine, compared with placebo, although differences were not statistically significant for all measures. A small 4-week, placebo-controlled, double-blind, double-crossover, randomized trial of donepezil also demonstrated cognitive benefits in subjects with Lewy body dementia (169).

4. Parkinson's disease dementia
In a 24-week, randomized, double-blind, placebo-controlled study with 541 subjects, the effects on cognition and function of 3–12 mg/day of rivastigmine were examined in patients with mild to moderate Parkinson's disease dementia (170). Improved cognition and function were found in the rivastigmine group, compared with the placebo group, and rivastigmine was tolerated by this patient population. In a 48-week open-label active treatment (3–12 mg/day of rivastigmine) extension study that included 334 subjects who completed the above-mentioned 24-week study, cognitive and functional benefits appeared to continue over time (171). Patients treated with placebo in the initial study who were then treated with rivastigmine in the open-label study had improvements in cognitive and functional scores similar to those of the patients who received rivastigmine in the initial study.

5.   Mild cognitive impairment
Two randomized, double-blind, placebo-controlled studies have investigated donepezil for the treatment of mild cognitive impairment, neither of which demonstrated benefit in the primary study outcomes. In one study of 270 subjects, there was no benefit of donepezil on most (but not all) cognitive tests studied, including the primary efficacy measures (172). The second study included 769 subjects with mild cognitive impairment and used a primary endpoint of progression from mild cognitive impairment to meeting the criteria for the diagnosis of possible or probable Alzheimer's disease over a 3-year period (173). Although fewer donepezil-treated subjects had progressed to Alzheimer's disease in the first year of the study, compared to placebo-treated subjects, there was no difference between the groups by the end of 3 years. Donepezil-

treated subjects did better than the placebo group on a number of cognitive tests, but this modest difference did not persist beyond 18 months.

There have been two randomized, placebo-controlled, clinical trials of galantamine in subjects with mild cognitive impairment. Each study was of 2 years' duration and included approximately 1,000 patients. Overall, there were no statistically significant benefits for galantamine compared to placebo, either in increasing the time to the onset of dementia or improving cognitive function, activities of daily living, or global assessment ratings. Of concern in these two trials together, 13 subjects who were taking galantamine died, compared to one subject who received placebo. This finding was statistically significant and represents a precaution in the use of galantamine in this patient population. It is noteworthy that the rates of death in these two trials were much lower in both the placebo and the galantamine groups than would have been expected based on previously conducted clinical trials in patients with actual dementia. As in trials of cholinesterase inhibitors for Alzheimer's disease subjects, there were substantial dropouts due to adverse events in the trials for subjects with mild cognitive impairment.

b. Memantine

1. *Alzheimer's disease*

Memantine, a noncompetitive NMDA antagonist, has been studied extensively in recent years for the treatment of Alzheimer's disease and vascular dementia. Trials have ranged from 6 weeks to 6 months in duration and have primarily included outpatients, although one study included nursing home residents (180). Studies have enrolled patients with moderate to severe dementia (MMSE scores ranging from 3 to 15) as well as mild to moderate dementia (MMSE scores ranging from 10 to 24).

Among randomized placebo-controlled trials that have included patients with mild to moderate Alzheimer's disease, two unpublished trials did not find benefit of memantine over placebo (487), whereas one trial demonstrated cognitive and functional improvement with memantine, compared to placebo (177). A meta-analysis of these three trials showed a statistically significant but very small advantage to memantine over placebo (108). Nonetheless, the FDA has not approved the use of memantine for treatment of mild Alzheimer's disease.

Among studies of patients with moderate to severe Alzheimer's disease, two published trials (with 252 and 404 subjects, respectively) (174, 175) found cognitive and functional improvement with memantine, compared with placebo. In one of those studies, which included only patients who were already taking stable dosages of done-

pezil, random assignment to treatment with memantine led to improvement in cognition and function, compared to random assignment to the placebo group (175). One unpublished study did not show any benefit of memantine over placebo (487). In a trial that included 166 subjects with severe dementia due to Alzheimer's disease or vascular dementia, cognitive and functional improvement was greater with memantine than with placebo (180).

In summary, there is evidence supporting the use of memantine for moderate to severe Alzheimer's disease, and memantine is approved by the FDA for this use. Data are not yet available to argue for or against the use of memantine beyond 6 months (108, 176).

2. *Vascular dementia*

There have been two large 6-month clinical trials (with 579 and 321 subjects, respectively) of memantine to treat patients with mild to moderate vascular dementia (178, 179). In both trials, cognition and behavior improved, but there was no demonstrated functional improvement and no improvement on clinical global ratings of change (Clinician's Interview-Based Impression of Change Plus). No studies of memantine have been conducted with patients with severe vascular dementia alone. Nonetheless, in one randomized placebo-controlled trial that included 166 patients with severe dementia, of which 51% had vascular dementia and 49% had Alzheimer's disease, there was improvement in cognitive and functional outcome measures for both the Alzheimer's disease and vascular dementia subjects (180).

c. Vitamin E

There has been considerable interest in vitamin E (α-tocopherol) as a treatment for Alzheimer's disease and other dementias because of its antioxidant properties and efficacy in Parkinson's disease. Vitamin E has been shown to slow nerve cell damage and delay death in animal models and cell cultures (including damage associated with amyloid deposition) and thus may be relevant to the development and progression of Alzheimer's disease (183, 488–490).

One large clinical trial of vitamin E for treatment of Alzheimer's disease has been conducted (183). This placebo-controlled, double-blind, multicenter trial included 341 subjects with moderate Alzheimer's disease (CDR of 2) who were randomly assigned to receive 1,000 IU b.i.d. of vitamin E alone, 5 mg b.i.d. of selegiline alone, both agents, or placebo. Vitamin E alone, selegiline alone, and the combination each delayed reaching the study endpoints (defined as a poor outcome, namely death, institutionalization, or significant functional decline). The benefit observed was equivalent to a delay of approximately 5–7 months in reaching the composite endpoint. It is note-

worthy that no evidence was found for improvement in function or cognition, compared to baseline. Despite the evidence for a better functional outcome in the treatment groups, compared to the placebo group, all groups showed similar rates of cognitive decline during the 2-year study period. There are no studies of the effects of vitamin E in subjects with Alzheimer's disease with mild or severe impairment or in subjects with other dementias. There are also no data concerning the effect of vitamin E in combination with medications other than selegiline.

In one clinical trial, the effects of donepezil, vitamin E, and placebo were compared in patients with mild cognitive impairment (173). These patients were followed for 3 years. Overall, no differences were found between vitamin E (2,000 IU/day) and placebo on measures of cognition, level of function, or progression to dementia.

Although vitamin E has been widely used clinically and in numerous clinical trials for a variety of indications and has been considered to have low toxicity, more recent evidence suggests that vitamin E may be associated with a small but significantly increased risk for morbidity and possibly even mortality. At high doses, it may worsen blood coagulation defects in patients with vitamin K deficiency (184). Of greater concern is evidence linking vitamin E usage in clinical trials to increased mortality in a dose-dependent fashion. A meta-analysis of 11 clinical trials of vitamin E in a mixed population that included some individuals with significant cardiac disease found a very small but statistically significant increase in mortality in trials using doses greater than 400 IU/day and a dose-dependent increase in mortality with doses above 150 IU/day (181). In addition, a carefully conducted large, randomized clinical trial of vitamin E (400 IU/day) for the prevention of heart disease or cancer in patients with diabetes mellitus and/or vascular disease had an unanticipated finding that vitamin E was associated with an increased risk of heart failure (182).

d.   Other Agents

A number of medications marketed for other indications have been proposed for the treatment of dementia on the basis of epidemiological data or pilot studies. Aspirin and other NSAIDs have been proposed because of epidemiological data suggesting that they protect against the development of dementia (185–189) and because of hypotheses regarding the involvement of inflammatory mechanisms in the pathogenesis of Alzheimer's disease (491). In a single small treatment trial for patients with Alzheimer's disease, patients receiving 100–150 mg/day of indomethacin experienced less decline over 6 months than did a matched control group (186). However, a number of larger studies with other NSAIDs (rofecoxib,

naproxen, and diclofenac) did not show benefit over placebo in slowing the cognitive decline in Alzheimer's disease (190–192). Moreover, several studies have suggested cardiac toxicity, especially with more selective cyclooxygenase-2 inhibitors. Finally, use of aspirin and NSAIDs can be associated with other significant adverse events such as gastrointestinal bleeding and impairment of renal function. Thus, NSAIDs are not recommended for the treatment of Alzheimer's disease.

Hormone replacement therapy is known to affect cognitive function (492) and was shown to be beneficial in the treatment of dementia in at least two case series (493, 494). It was also associated with later onset and/or decreased risk of cognitive decline in at least two observational studies of postmenopausal women (495, 496). In contrast, in the prospective Women's Health Initiative Memory Study (WHIMS), increased rates of conversion to Alzheimer's disease were found in women age 65 years or older who were randomly assigned to receive an estrogen/progestin combination compared with those who received placebo (193). Results of a number of other prospective trials also showed no benefit of estrogen over placebo in the treatment of cognitive symptoms of Alzheimer's disease (194, 195). Therefore, hormone replacement therapy is not recommended for use in the treatment of cognitive symptoms of Alzheimer's disease.

There is also interest in the hormone melatonin and in botanical agents such as ginkgo biloba, which are available without a prescription. There are no data supporting the use of most of these agents in Alzheimer's disease. Numerous clinical trials of ginkgo biloba have been conducted. Most of these have been small trials with considerable methodological problems (497). In one randomized placebo-controlled trial that included 309 subjects, 1-year efficacy of ginkgo was found in subjects with Alzheimer's disease or vascular dementia, but there were significant methodological problems with the trial, including a very high dropout rate (498). In a large, 26-week, randomized, double-blind, placebo-controlled trial that included 513 subjects with mild to moderate Alzheimer's disease (MMSE score of 10–24), the effects of 120 mg/day of ginkgo, 240 mg/day of ginkgo, and placebo were compared (196). There was no advantage to ginkgo over placebo for cognitive function, but these results are qualified by the fact that there was very little cognitive decline in the placebo group as well. At this point, the preponderance of the evidence does not support the routine use of ginkgo for the treatment of dementia (197, 198).

The chelating agent desferrioxamine has also been studied as a possible treatment for Alzheimer's disease on the basis of hypotheses regarding heavy metals in the pathogenesis of the disease. In one small single-blind trial,

there was some evidence of a decrease in cognitive decline over 2 years (499). One study of another chelating agent failed to confirm this finding (500). Because chelating agents are quite toxic and support for them is so weak, they are not recommended for the treatment of dementia. Newer agents that chelate copper and zinc are in clinical development as potential Alzheimer's disease therapies because they may lower beta-amyloid burden (501).

As reviewed in a Cochrane meta-analysis that included negative trials, the irreversible MAO-B inhibitor selegiline has been studied in a large number of randomized controlled clinical trials, with mixed results (199). One large trial comparing selegiline with vitamin E and placebo demonstrated some benefit of selegiline over placebo (183), but numerous other trials have not shown clinically meaningful benefit. Although use of selegiline at dosages of 5–10 mg/day is generally safe and well tolerated, few clinicians actually use this medication in clinical practice for the treatment of cognitive decline in dementia. Selegiline use is considered contraindicated in combination with meperidine, SSRIs, or tricyclic antidepressants. Use of the selegiline patch for treatment of dementia has not been studied.

A mixture of ergoloid mesylates is currently marketed under the trade name Hydergine for the treatment of nonspecific cognitive impairment. It has been available for at least 40 years and has been studied in at least 150 clinical trials, seven of which were double-blind, placebo-controlled, randomized trials with a parallel-group design involving a total of 297 patients with diagnoses consistent with Alzheimer's disease. Studies have been conducted in patients with vascular dementia as well. Although a number of trials have produced weakly positive results, these have generally been on isolated cognitive measures or on measures of psychiatric symptoms, and the overall evidence suggests little or no effect (200). Side effects are usually mild and affect the gastrointestinal system. Dosages used in the studies ranged from 3 to 9 mg/day.

2. Treatments for Psychosis and Agitation

Because treatments for psychosis and behavioral disturbances overlap to a considerable extent, and because investigations often include subjects with both groups of symptoms, they are grouped together in this discussion.

a. Antipsychotics

1. Efficacy

First-generation antipsychotic medications (also known as "conventional" or "typical" antipsychotic agents) have been extensively studied in the treatment of psychosis and agitation in individuals with dementia. For example, a

1990 review (210) identified seven double-blind, placebo-controlled, randomized, parallel-group clinical trials including 252 patients studied over periods of 3–8 weeks (203–209). Despite some methodological flaws, notably small numbers of subjects and a lack of diagnostic specificity, these studies, when taken together, constitute reasonable evidence for a modest improvement in target symptoms in some patients treated with first-generation antipsychotic medications. A meta-analysis of these seven trials (210), using clinician assessment of improvement in a variety of behavioral symptoms as the primary outcome, showed improvement in 59% of the subjects taking antipsychotics and 41% of those taking placebo. The studies used a wide variety of dosages (ranging from 66 to 267 mg/day in chlorpromazine equivalents), and efficacy for behavioral symptoms was not correlated with standardized dose. Adverse effects were common, but specific rates are not available. Dropout rates were also high, whether associated with side effects or poor efficacy.

In a more recent meta-analysis of studies of first-generation antipsychotics in patients with dementia, clinically significant improvement was found in 64% of patients treated with active medication versus 38% of patients treated with placebo, translating to an effect size of 26% (211). No differences in efficacy were seen among the different agents used. Significant side effects were found in 25% more of the patients who received active treatment, compared with those who received placebo. This meta-analysis did not include a number of more recent studies (212–216); however, the data from these newer studies generally conformed to the results of the meta-analyses (210, 211). In another review of antipsychotics used in dementia (217), which also included several trials of second-generation antipsychotic agents, mean improvement rates were 61% with antipsychotics and 35% with placebo, yielding a treatment effect of 26%. The modest treatment effects estimated by these meta-analyses and reviews are generally consistent with results from placebo-controlled trials of second-generation antipsychotics.

Second-generation antipsychotic agents have also been studied in well-controlled trials in patients with dementia. Three placebo-controlled trials of risperidone have been conducted among nursing home residents with severe dementia complicated by agitation and/or psychosis (212, 218). In the first trial, a fixed-dose study that included 625 patients, the response rates of 45% and 50% for 1 mg/day and 2 mg/day, respectively, were significantly different than placebo (33%) (the 0.5-mg/day dose was not more effective than placebo). Parkinsonism was seen in 21% of patients who received 2 mg/day, and it was concluded that 1 mg/day represented the most effective dose. In the second trial, a flexible-dose study that included 344 patients,

response rates were 47%, 63%, and 54%, respectively, for placebo, haloperidol (mean dosage 1.2 mg/day), and risperidone (mean dosage 1.1 mg/day); these response rates did not differ statistically. Secondary outcomes related to aggression decreased in the two active treatment groups, compared with the placebo group, but cognitive and functional outcomes were not different across treatment groups. In the third trial, the effects of flexibly dosed risperidone were compared to those of placebo in 337 nursing home patients with severe dementia who required treatment for aggression; a significant difference in response rates of 37% for placebo and 63% for risperidone (mean dosage 1 mg/day) was found (219).

Three clinical trials have been conducted to study the effects of oral olanzapine for the treatment of persisting agitation and/or psychosis in patients with severe dementia. The first trial, reported only as an abstract, compared flexibly dosed olanzapine (mean dosage of about 2.3 mg/day) with placebo in 238 patients, and no difference in efficacy or tolerability was found. This negative result may in part be explained by the mean dosage's being too low (502). In the second trial, in which participants consisted of 206 nursing home residents, response rates of 66%, 57%, and 43% were found with fixed dosages of 5, 10, and 15 mg/day of olanzapine, respectively, versus 36% for placebo (the response rates with 5 mg/day and 10 mg/day were significantly different from those with placebo) (220). Some patients from this trial received follow-up open-label, flexible-dose treatment for 18 weeks; the results were consistent with the findings of the original report (221). The third trial included 652 residents of nursing homes or continuing care hospitals who met the operational criteria for psychosis (222). Patients were assigned to treatment with olanzapine at doses of 1, 2.5, 5, or 7.5 mg/day or placebo; no drug-placebo differences were seen in measures of psychosis or other behavioral features.

Meehan et al. (223) studied acute treatment of agitation with intramuscular olanzapine in a group of 272 inpatients or nursing home residents with Alzheimer's disease and/or vascular dementia. Olanzapine at doses of 2.5 and 5.0 mg was found to be superior to placebo in treating agitation at 2 hours; the response rates were 62%, 66.7%, and 37.3%, respectively. The response rate for those treated with intramuscular lorazepam was 72.1%; all response rates for participants who received active treatment were different from those for participants who received placebo group but not from each other. Adverse events were not significantly different between groups.

Evidence for the use of quetiapine is limited to findings from three open-label trials that suggested possible benefits for agitation (503–505). A 10-week, multicenter, placebo-controlled trial of flexibly dosed quetiapine versus haloperidol was conducted in a group of elderly nursing home patients with operationally defined psychosis, criteria for which were implemented before the development of the recently proposed clinical criteria for the psychosis of Alzheimer's disease (201). Results from the subgroup of 284 patients with Alzheimer's disease were analyzed separately. In these subjects, the mean daily dosage of haloperidol was 2 mg/day at endpoint, whereas that of quetiapine was about 120 mg/day. Neither of the treatment groups differed with respect to reduction in measures of psychosis, the primary outcome of the trial. One secondary measure of agitation showed improvement with both haloperidol and quetiapine treatment but not placebo. These studies led to a second placebo-controlled trial of 100 mg/day of quetiapine, achieved by day 4, or 200 mg/day, achieved by day 8, in which the participants were 333 nursing home residents with dementia (227). A dose of quetiapine at 200 mg/day was superior to placebo on numerous outcomes, with less benefit seen at 100 mg/day. A more critical review of the data will be possible once the trial results are published. A placebo-controlled trial of quetiapine in a group of 93 subjects with Alzheimer's disease and agitation failed to show any benefit over placebo for the medication (506).

Three placebo-controlled studies of aripiprazole have been published or presented in abstract form. In all three studies, the primary outcomes were not reached, but significance on individual outcomes was shown. In a placebo-controlled trial that included 208 outpatients who met the clinical criteria for psychosis of Alzheimer's disease (201), there was no difference between flexibly dosed aripiprazole (mean dosage of 10 mg/day) and placebo on the primary outcome variable of psychosis, although post hoc analyses showed benefits at some time points (224). The second study, with findings presented in abstract form, was a placebo-controlled study of fixed-dose aripiprazole conducted with 587 nursing home residents with dementia and psychotic features (507). A significant effect was found only for the 10-mg/day dose on the primary outcome, a measure of psychosis, with 50% of patients who received placebo and approximately 68% who received 10 mg/day of aripiprazole considered to have responded clinically. The third study, with findings presented in abstract form, was a placebo-controlled flexible-dose study conducted with 256 nursing home residents with dementia and psychotic features (508). The results showed no drug-placebo difference in the primary outcome with a mean aripiprazole dosage of 8.6 mg/day. A fuller appreciation of these studies will be possible once the results are published.

Clozapine has been found to be useful in controlling psychotic symptoms in patients with Parkinson's disease

(233) and dementia with Lewy bodies (234) and may also be useful for patients with Alzheimer's disease who are sensitive to the extrapyramidal effects of first-generation antipsychotic agents (509). Currently no specific data are available on the use of ziprasidone in the treatment of elderly patients.

A recent meta-analysis that included the randomized controlled trials described in preceding paragraphs showed that benefits tended to be greater for symptoms of agitation than for psychosis (225). These data also demonstrate a significant placebo response, a finding that underscores the importance of nonpharmacological interventions for relief of these signs and symptoms. The nonspecific aspects of clinical trial participation (e.g., increased attention from staff), as well as the frequent clinical evaluations that occur during a clinical trial, may contribute to the improvement seen in patients in the placebo arm of a trial. Finally, much of the data discussed earlier are from studies that have not been published yet, so they will need to be reevaluated.

The available studies comparing antipsychotics to one another are of limited power but suggest no clinically significant differences in efficacy (40, 210, 212, 215, 225). The first direct comparison of second-generation antipsychotics with placebo in patients with Alzheimer's dementia has been undertaken as part of the NIMH-funded CATIE-AD (228). In this trial 421 outpatients with Alzheimer's disease and psychosis and/or aggression were randomly assigned to treatment with olanzapine, quetiapine, risperidone, or placebo with dosages adjusted as needed and followed for as long as 36 weeks. There were no differences among treatments in the main outcome, time to all-cause discontinuation, with initial treatments maintained for about 8 weeks. Time to discontinuation due to lack of efficacy, however, favored olanzapine and risperidone, both of which were maintained for about 24 weeks, whereas quetiapine and placebo were maintained for approximately 9 weeks. Time to discontinuation due to adverse events or intolerability favored placebo, with discontinuation in 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received placebo. Although there were no differences in improvement as rated with the Clinical Global Impression of Change (olanzapine 32%, quetiapine 26%, risperidone 29%, placebo 21%), some symptom ratings favored the drugs over the first 12 weeks. Adverse effects offset advantages in efficacy of second-generation antipsychotic drugs for treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease.

It is important to note that there are limited data on the efficacy of antipsychotic medications for patients with dementia beyond 8–12 weeks of follow-up, although these medications are often used for much longer periods of time in clinical practice. Extensive clinical experience has suggested that they are sometimes helpful for longer periods of time. Several studies of the effects of withdrawal of treatment have suggested that a substantial proportion of patients can be withdrawn from treatment successfully after a period of time (40, 229).

2. Side effects and toxicity

a. Serious side effects

Antipsychotic agents are associated with a risk of serious complications that must be considered in weighing the risks and benefits of antipsychotic treatment.

Tardive dyskinesia, whose incidence increases with increasing dose and duration of treatment and which occurs more commonly in women, is also more common in individuals with dementia and in elderly patients in general. The risk may be as high as 30% for elderly patients with significant exposure to first-generation antipsychotic agents (510–512). This risk may be considerably lower with the use of second-generation antipsychotics. For example, Jeste et al. (513) reported a cumulative incidence of tardive dyskinesia of 2.6% in 330 patients with dementia treated openly with risperidone (mean dosage of about 1 mg/day) for a median of 273 days. This figure is much lower than that reported for older people treated with first-generation antipsychotics (511) and is consistent with data reported in a recent prospective longitudinal study of risperidone and haloperidol in older subjects with mixed psychiatric disorders (514). There are, however, no placebo-controlled studies addressing this issue and no studies employing withdrawal maneuvers. Clozapine is the agent least associated with tardive dyskinesia, although the rare occurrence of clozapine-induced tardive dyskinesia has been reported (515).

Neuroleptic malignant syndrome is a rare but potentially lethal adverse effect of antipsychotic medications. It occurs less frequently with second-generation antipsychotic agents than with first-generation agents, but it has been reported with both types (516–520). The core features of this syndrome are muscle rigidity (leading to elevated serum creatinine phosphokinase levels), fever, leukocytosis, tremor, delirium, autonomic instability, and diaphoresis. Older age and dementia may increase the risk of neuroleptic malignant syndrome.

Clozapine is associated with risk of **agranulocytosis** (about 1%), which is more common in elderly patients than in younger patients (509), and regular monitoring of blood counts is required. Other antipsychotics may rarely be associated with this adverse event, but its incidence is so infrequent that routine monitoring of blood counts for

this syndrome is not required for patients who take other antipsychotics.

Metabolic abnormalities caused by second-generation antipsychotic medications are not well studied in individuals with dementia but may be more common with use of these agents in older individuals (258). These metabolic abnormalities include hyperlipidemia, weight gain, and diabetes mellitus (228).

There is also evidence of an increased risk of **cerebrovascular adverse events** with at least three of the second-generation antipsychotics (aripiprazole, olanzapine, and risperidone) when used in the treatment of patients with dementia. In October 2002, Health Canada issued a letter to health care professionals stating that risperidone use may be associated with cerebrovascular events in elderly patients with dementia (521). In April 2003, the FDA issued a similar warning regarding risk of cerebrovascular events with risperidone in patients with dementia and noted that risperidone had not yet been shown to be safe or effective in treating dementia-related psychosis (522). Pooled data from four placebo-controlled trials suggested a rate of "cerebrovascular events" (variably defined) of 4% in patients treated with risperidone, compared with about 2% in those treated with placebo. The available data suggest that the risk is greater among those with pre-existing risk factors for cerebrovascular disease.

In January 2004, Eli Lilly and Company issued a warning to prescribers that there was an increased incidence of cerebrovascular adverse events in patients with dementia who were treated with olanzapine (1.3%) versus placebo (0.4%), as well as increased mortality (3.5% vs. 1.5%) (523). In February 2005, Bristol-Myers Squibb issued a warning to prescribers that there was an increased risk of cerebrovascular adverse events in patients with dementia who were treated with aripiprazole (1.3% vs. 0.6% in those given placebo).

At present no warning has been issued regarding quetiapine and increased risk of cerebrovascular events. Schneider et al. (225, 524) reported an event rate of 0.8% for quetiapine and 1.9% for placebo among placebo-controlled studies of quetiapine in the dementia population. They also noted that the 95% confidence intervals (CIs) for the relative risks for risperidone, olanzapine, and aripiprazole all indicated increased risk for such events, whereas the CI for quetiapine could not distinguish among increased risk, decreased risk, or no risk. It is possible that patients with existing cerebrovascular disease or other risk factors might be most susceptible to these events. However, this possibility has yet to be definitively addressed with studies designed to assess side effects or efficacy as a function of baseline medical condition.

Finally, a recent meta-analysis of randomized controlled clinical trials of second-generation antipsychotics in patients with dementia performed by Schneider et al. (525) compared **mortality** in the treatment and placebo groups during the clinical trial period. In total, the meta-analysis included 15 trials, three of aripiprazole, five of olanzapine, three of quetiapine, and five of risperidone. The subjects were nursing home residents in 11 of the trials and outpatients in the remaining four trials; a total of 3,353 subjects received medication and 1,757 received placebo. When data from all the trials were pooled, the odds ratio for death in subjects who received second-generation antipsychotics was 1.54, compared to the placebo group, with a 95% CI of 1.06–2.23. Although for no individual medication or individual trial was the odds ratio of death in the medication group statistically different from that for the placebo group, for all medications and for 12 of the 15 trials the odds ratio favored placebo over the medication.

This finding has been underscored by the "black box" warning applied by the FDA on April 11, 2005, to all of the second-generation antipsychotics, stating that analysis of 17 placebo-controlled trials of aripiprazole, olanzapine, quetiapine, or risperidone in patients with dementia showed a death rate of about 4.5% in those receiving active treatment versus about 2.6% in those receiving placebo. Causes of death were varied, with the most common being cardiovascular (heart failure, sudden death) or infectious (pneumonia) in nature (231).

There is also evidence that first-generation antipsychotics are similarly associated with increased mortality among patients who take them and that this increased mortality may exceed that found with second-generation antipsychotics. In a large retrospective review of 22,890 patients over age 65 years in Pennsylvania who received either first- or second-generation antipsychotic agents between 1994 and 2003, Wang et al. (230) found a 1.37 relative risk (CI, 1.27–1.49) of death among users of first-generation agents versus users of second-generation agents. The risk was highest with higher doses and closer to the initiation of treatment. The increased risk was independent of the presence of dementia and of residence (nursing home versus community). The magnitude of this difference was such that the authors concluded that for every 100 patients treated with first-generation antipsychotics instead of second-generation agents, there would be seven additional deaths. At this time, there is no FDA "black box" warning on first-generation antipsychotics.

Clinicians facing the challenge of treating patients with significant psychosis or behavioral disturbances must weigh the risk of not treating these complications of dementia against the risks of active treatment described

in this section. Clinicians must take into account the evidence supporting the efficacy of the agent in question, the morbidity and risk associated with the target symptoms, the patient's general medical condition, and the evidence of risk and benefit of any alternative treatment being considered.

b.   Mild to moderate side effects
In addition to their association with the serious side effects described in Section V.B.2.a.2.a, antipsychotic medications are associated with numerous more common but milder side effects.

First-generation antipsychotic agents have a broad range of common side effects that vary with medication potency, although any side effect can be seen with any agent. Reviews regarding first-generation agents have cited side effects including akathisia, parkinsonism, sedation, peripheral and central anticholinergic effects, postural hypotension, cardiac conduction defects, and falls (211). Most of these data come from short-term controlled trials; evidence regarding long-term safety is generally lacking. Data available from other studies in the elderly population, however, indicate that caution is warranted. For instance, rates of tardive dyskinesia are five- to sixfold greater in older than in younger populations after long-term treatment with first-generation agents (511). For practical purposes, side effects often guide selection of these agents when used in patients with dementia. High-potency agents (e.g., haloperidol, fluphenazine) are most strongly associated with akathisia (which can worsen the target symptoms) and parkinsonian symptoms. Low-potency agents (e.g., thioridazine, chlorpromazine) are associated with sedation (which can lead to worsening cognition or falls), central anticholinergic effects (e.g., confusion, delirium), postural hypotension (which can also lead to falls), and a variety of peripheral anticholinergic effects (e.g., dry mouth, constipation, bladder dysfunction, tachycardia). When individuals with dementia have co-occurring extrapyramidal disorders (as in dementia with Lewy bodies), extraordinary sensitivity to first-generation antipsychotic agents may be seen (526).

Risperidone treatment of patients with dementia is associated with a low to moderate risk of dose-related parkinsonism. In the large trial by Katz et al. (218), the rates of parkinsonism were 21%, 13%, and 7% among patients who received 2 mg/day of risperidone, 1 mg/day of risperidone, and placebo, respectively. In the trial of De Deyn et al. (212), the incidence of parkinsonism was 15% for subjects who received risperidone at a mean endpoint dosage of 1.1 mg/day and 11% for subjects who received placebo. Brodaty et al. (219) found an incidence of parkinsonism of 23% among subjects who received risperidone (mean dos-

age of 0.95 mg/day) and 16% among subjects who received placebo. These results are similar to those from a smaller study by Chan et al. (215) in which risperidone and haloperidol were compared and are also consistent with the results of a large meta-analysis of randomized controlled trials of risperidone, which found an overall odds ratio for extrapyramidal signs and symptoms of 1.80 (CI, 1.35–2.42) for risperidone versus placebo (225). These studies also showed a greater risk of sedation. In the trial of De Deyn et al. (212), sedation affected 12% of patients taking risperidone but only 4.4% of those who received placebo, a finding also confirmed by the meta-analysis (odds ratio, 2.43; CI, 1.78–3.32). In the meta-analysis, a higher rate of peripheral edema was found in patients treated with risperidone, compared to those who received placebo (225). Risperidone may also cause an abnormal gait in some patients (225).

For olanzapine, side effect information is primarily available from the one randomized controlled trial that demonstrated clear clinical efficacy (220); in one other clinical trial, the doses used were not sufficient to help or harm or to provide meaningful information about side effects (502), and in the other trial specific characteristics were not described for the side effects that occurred (222). In the one trial with side effect information, sedation (at rates of 25%–36%) and abnormal gait (at rates of 14%–20%) were observed at all dosages used (5–15 mg/day). Results of the meta-analysis of randomized controlled trials of olanzapine showed substantially increased risk with the medication, compared to placebo, of sedation (odds ratio, 4.00; CI, 2.27–7.04) and urinary tract infections or incontinence (odds ratio, 6.69; CI, 1.27–35.10) (225). Gait abnormalities also developed in more subjects taking olanzapine than in those who received placebo (225).

In the one trial comparing quetiapine to haloperidol, tolerability of quetiapine was superior, with comparable effects on a simple measure of agitation (527). Several measures of parkinsonism showed worsening with haloperidol but no difference between quetiapine and placebo (527). Sedation was seen in 4.1% of patients who received placebo versus 25.3% and 36.2% of those who received quetiapine and haloperidol, respectively. In the subsequent trial in which the most efficacious dosage of quetiapine was 200 mg/day, sedation occurred in 17.6% of patients taking 200 mg/day, compared with 11.3% of those taking 100 mg/day and 6.5% of those who received placebo (227). A recent meta-analysis of randomized controlled trials of quetiapine similarly found an odds ratio for sedation of 3.90 (CI, 1.41–10.78) for quetiapine versus placebo (225).

Aripiprazole treatment of patients with dementia is commonly associated with sedation, occurring in 5%–15% of those treated versus 1% of those receiving placebo.

In the one published randomized controlled trial, 8% of aripiprazole-treated subjects but only 1% of placebo-treated subjects experienced sedation (224). This finding was confirmed in a recent meta-analysis that focused on adverse events (225). Regarding ziprasidone in the treatment of patients with dementia, there are insufficient data to make assertions regarding safety and tolerability.

Most short-term side effects can be minimized by using the lowest effective dose. This principle is particularly important in order to minimize sedation and akathisia, both of which can actually worsen target symptoms (528). It may also be helpful to select an agent with the side effect profile most suited to a given patient. Anticholinergic agents may be effective in the treatment of parkinsonian side effects, but the high risk of associated cognitive decline, delirium, and other anticholinergic effects suggests that they should be used only with extreme caution for elderly patients both with and without dementia.

b. Benzodiazepines

The use of benzodiazepines in the treatment of behavioral symptoms in dementia has been studied in at least eight randomized clinical trials. In six studies including a total of 873 subjects, benzodiazepines were compared to antipsychotics administered orally (238–243). In two studies, benzodiazepines were compared to placebo (529, 530). Most of these studies were limited by the presence of poorly specified diagnoses, a mixture of target symptoms, limited outcome measures, and, in most cases, high doses of long-acting agents. Nonetheless, they demonstrated that benzodiazepines perform better than placebo but not as well as antipsychotics in reducing behavior problems. These results are supported by a more recent randomized controlled trial of comparing intramuscular lorazepam with intramuscular olanzapine, which showed equal efficacy of lorazepam and olanzapine at 2 hours but inferior efficacy of lorazepam at 24 hours (223). There are no data concerning the efficacy of benzodiazepines after 8 weeks or whether one benzodiazepine is more effective than another.

c. Anticonvulsants

Use of carbamazepine has support from several case series (248), a small open trial (249), a double-blind nonrandomized trial (250a), and two double-blind randomized trials (250b, 250c) that showed modest benefit for agitation at low doses, with low side-effect rates over a short treatment period. One of these trials was followed by an open-label extension that further supported efficacy, safety, and tolerability (251). One small randomized crossover trial showed nonsignificant decreases in behavioral measures (252).

Although several favorable case reports and open trials have been reported for the anticonvulsant valproate (531–

533), four placebo-controlled trials have not demonstrated efficacy. In a 6-week, randomized, placebo-controlled trial that included 172 nursing home residents with Alzheimer's disease and secondary mania, subjects treated with divalproex sodium had no more improvement in symptoms of mania than did subjects treated with placebo (253). In another randomized placebo-controlled study conducted with 42 patients with Alzheimer's disease and behavioral disturbances, valproic acid (dosage of 480 mg/day) was not more effective than placebo in reducing overall agitation, although in secondary analyses certain individual symptoms were improved (254). However, because these results were derived from an analysis of secondary outcomes, they are not sufficient to define practice. In another 6-week, randomized, placebo-controlled trial that included 56 nursing home residents with dementia and behavioral disturbance, results were suggestive of benefit with divalproex sodium; 68% of the treatment group had improvement in agitation, compared with 52% of the control group (256). The largest study, which prospectively addressed agitation as the primary outcome in 153 nursing home residents with Alzheimer's disease, found no difference between divalproex sodium (mean dosage of 800 mg/day) and placebo in either the primary outcome (agitation) or secondary outcome measures (255).

There are no controlled trials of newer anticonvulsants such as lamotrigine, gabapentin, and topiramate. The few case reports and case series that suggest benefit with gabapentin (e.g., reference 534) do not provide sufficient evidence to recommend their use.

d. Other Agents

A number of other agents have been proposed for the treatment of agitation in patients with dementia (reviewed in references 210, 535, 536). Efficacy data for these agents generally come from case reports or small open trials, often of mixed populations.

For example, data on trazodone are primarily from case reports, case series (260, 261), and a few small trials (262) in which decreased irritability, anxiety, restlessness, and affective disturbance was reported in a total of 13 patients. In a small double-blind, randomized clinical trial that was not placebo controlled, improvement in agitation with trazodone was comparable to that seen with haloperidol (263). However, in the largest and only placebo-controlled trial, which included 37 patients receiving trazodone, no benefit of trazodone, compared to placebo, was found (214). A small randomized, placebo-controlled, double-blind study of trazodone in patients with frontotemporal dementia showed benefit over placebo (264).

Preliminary data suggest that SSRIs may be useful in the treatment of agitation (262, 270). These preliminary

reports are supported by two case series and a small controlled trial showing benefit of a variety of SSRIs for reduction of agitation in patients with frontotemporal dementia (537–539), although one trial of paroxetine in patients with frontotemporal dementia did not demonstrate improvement in symptoms but did show worsening of cognition (540). A rigorous placebo-controlled trial examined the short-term benefit of citalopram versus perphenazine in inpatients with agitation or psychotic features (271). Double-blind treatment lasted no more than 3 weeks. Although both perphenazine and citalopram, compared to placebo, produced clinical improvement on general measures of behavior, improvement in agitation and aggression specifically was seen only with citalopram. Patients taking citalopram had few side effects.

The effects of buspirone for treatment of agitation or anxiety in elderly patients with dementia have been reported in a number of case reports (265–267) and assessed in two open trials (268, 269). These limited data are insufficient to establish efficacy.

A 6-week, randomized, double-blind, placebo-controlled trial of propranolol that included 31 subjects with Alzheimer's disease and behavioral disturbance who resided in nursing homes showed benefit of the medication, compared with placebo, for certain symptoms, although it was noted that use of beta-blockers was contraindicated for many subjects who would otherwise have been eligible for the study (277). The mean dose was 106 mg/day. The benefits noted in the 6-week trial were lost to a great extent over the ensuing 6 months of open-label treatment.

3. Treatments for Depression and Related Symptoms

a. Antidepressants

Over the last 15 years, eight placebo-controlled studies have examined the efficacy of antidepressants in patients with dementia. Four trials were conducted with SSRIs, one with citalopram, one with fluoxetine, and two with sertraline (289–292). Three trials assessed cyclic antidepressants (imipramine, maprotiline, and clomipramine) (293–295), and one trial examined an MAOI (moclobemide) (296). The available evidence is mixed for the efficacy of these medications for the treatment of depression in patients with dementia, with some trials demonstrating superiority over placebo and others failing to show differences in efficacy. Among the explanations for the variability in trial results are differences in patient selection criteria and differences in the sensitivity of the rating scales used in the various trials (541). Studies that have used the most restrictive criteria for depression generally reported better response to active treatment, compared

with placebo. Selective serotonin reuptake inhibitors appear to be the most promising for treating depression in patients with dementia, with sertraline having superior efficacy, compared with placebo (292) and citalopram improving affective symptoms in one study of patients with dementia (289). The cyclic antidepressants, however, were either no more effective than placebo or produced significant side effects. Head-to-head comparisons of SSRIs to cyclic antidepressants and a SSRI (sertraline) to a serotonin-norepinephrine reuptake inhibitor (venlafaxine) showed equal efficacy in treating depression but better tolerability of SSRIs over cyclic antidepressants (297–299).

Although clinical trials support the efficacy of antidepressants in the treatment of depressed elderly patients without dementia (285), extrapolating these data to patients with co-occurring dementia should be done cautiously. The reader is referred to APA's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*, 2nd edition (284) for a summary of this literature.

Data concerning the treatment of other affective symptoms such as apathy are much sparser. There is minimal evidence that dopaminergic agents, such as psychostimulants (*d*-amphetamine, methylphenidate), amantadine, bromocriptine, and bupropion, are helpful in the treatment of severe apathy, but case reports have suggested that efficacy studies are warranted (301, 302). Psychostimulants have also received some support for the treatment of depression in elderly individuals with severe general medical disorders (303–305).

b. Electroconvulsive Therapy

The data supporting the efficacy and safety of ECT in the treatment of depression in dementia are limited to the results of one small retrospective chart review (306). Several larger, prospective studies have supported the efficacy of ECT in the acute treatment of geriatric depression (307, 308).

4. Treatments for Sleep Disturbance

The available data do not suggest a specific course of action for treating sleep disturbances in patients with dementia. Several small trials of bright light therapy exist, but they have not shown effectiveness in improving sleep problems and their associated behavioral and mood disturbances (315, 318–322). In one small study, improvement in MMSE scores (3 points) was reported with bright light therapy (320). In another small study, patients with vascular dementia, but not patients with Alzheimer's disease, had a decrease in nighttime activity with bright light therapy (318). However, four randomized controlled trials of bright light therapy have failed to show increases in nocturnal sleep time or

decreases in nighttime activity, sleep latency time, agitation, or depression (315, 318, 319, 321, 322, 542).

Behavioral interventions and pharmacological agents are often utilized to address the sleep problems of patients with dementia. In one study, nocturnal sleep was improved by targeting daytime activities of nursing home residents during periods when they were most likely to nap (543). In another study, caregiver education and improved sleep hygiene were found to improve sleep quality in patients with dementia (316). A sleep hygiene behavioral intervention for patients with dementia was evaluated in a small trial (317). In this study, training for caregivers in how to implement proper sleep hygiene principles (e.g., consistent rising times, minimizing day-time napping, daily exercise) resulted in improved sleep, better maintenance of a consistent bedtime and rising time, fewer naps during the day, and more physical activity in the form of walking (317). Likewise, only a few pharmacological agents used to treat sleep problems have been rigorously studied in this population. Although 3 mg of melatonin at bedtime was found to prolong sleep and decrease nighttime activity in a small sample (544), a randomized controlled trial that included 157 individuals showed no benefit of 10 mg of melatonin or 2.5 mg of slow-release melatonin, compared with placebo (545). Galantamine, an acetylcholinesterase inhibitor, did not improve sleep quality in patients with dementia (546).

Part C
FUTURE RESEARCH NEEDS

A review of currently available treatments suggests a number of areas for further study. Several of these are in the realm of evaluation and assessment. Better detection and evaluation of dementia, especially in the prodromal and early stages, will be particularly important if treatments are developed that slow progression. Identification of specific biomarkers and refinements in imaging techniques may facilitate diagnosis and treatment planning as well as provide insight into categorization of dementia syndromes (13, 14). Earlier and more accurate detection of noncognitive symptoms may facilitate optimal intervention.

More accurate assessments of potentially dangerous behaviors such as driving are needed (54, 61). The development of more clinically meaningful outcome measures and more refined neuropsychological tests, the development of functional assessments, and wider use of "hard" endpoints, such as institutionalization and mortality, would allow for more confidence in making treatment recommendations.

In the realm of pharmacological treatments, there is a critical need for medications with greater ability to improve cognition or halt the progression of dementia (547). Among the leads being actively studied are agents that prevent plaque deposition, inhibit beta and gamma secretase, remove plaque and insoluble amyloid fragments, and prevent the formation of and remove neurofibrillary tangles (tau deposition); other approaches currently being studied include neuroprotective strategies, neurotropic approaches such as use of nerve cell growth factors and cell transplants, and use of antioxidants (548, 549). In addition, medications that directly enhance cognition by activating intact cognitive systems might improve performance and function. As the understanding of other dementing disorders advances, targeted therapies must be developed and tested for these illnesses as well. Efforts to prevent stroke and to decrease its destructive effect on brain tissue are particularly important avenues for dementia prevention (550, 551).

Another arena is the optimal pharmacological treatment of behavioral and neuropsychiatric symptoms, including psychosis, agitation, depression, and sleep disturbance (225, 552). Many current recommendations are extrapolated from small uncontrolled studies of agents no longer in common use and/or at doses well above those used in current practice. There is a critical need for well-designed, randomized, controlled trials of potential treatments for these neuropsychiatric symptoms.

Further research into psychosocial, psychotherapeutic, and behavioral interventions is also needed (116). Randomized controlled trials or alternative methods that apply randomized controlled trial methods to the study of behavioral interventions are of particular importance. One aspect of dementia care that deserves further study is the rehabilitation model, which focuses on identifying and maximizing

remaining abilities as a way to maximize function. Further research into this and other strategies may help to identify specific aspects of these therapies that benefit persons with dementia. Similarly, research is needed to better characterize the aspects of nursing homes and other environments most likely to improve patient outcomes.

Research is needed on models of care delivery for patients with dementia and their family (4). There is also a need to study how changes in payment for health services affect the care of individuals with dementia.

Research is also needed to identify which patients will benefit from alternative living environments and supplemental caregiving and to support the development of treatment sites that are more comfortable, less costly, and equally safe and effective for the care of individuals with moderate to severe dementia (553).

Further studies of caregivers should identify the most effective interventions for relieving burden and identifying those caregivers at highest risk for developing adverse outcomes (554).

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American Academy of Psychoanalysis and Dynamic Psychiatry
American Association for Geriatric Psychiatry
American Association of Directors of Psychiatric Residency Training
American Association of Suicidology
American College of Neuropsychopharmacology
American Music Therapy Association
American Neuropsychiatric Association
American Psychiatric Nurses Association
Association for Behavioral and Cognitive Therapies

Association of Family Psychiatrists
Canadian Academy of Geriatric Psychiatry
Canadian Coalition for Seniors' Mental Health
Canadian Psychiatric Association
Group for the Advancement of Psychiatry
Magellan Health Services, Inc.
National Association of Social Workers
National Sleep Foundation
Royal Australian and New Zealand College of Psychiatrists
Society for Behavioral and Cognitive Neurology
Society of Biological Psychiatry
World Federation for Mental Health

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The following coding system is used to indicate the nature of the supporting evidence in the references:

[A] *Double-blind, randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.

[A–] *Randomized clinical trial.* Same as above, but not double-blind.

[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.

[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.

[D] *Case-control study.* A study in which a group of patients is identified in the present and information about them is pursued retrospectively or backward in time.

[E] *Review with secondary data analysis.* A structured analytic review of existing data, for example, a meta-analysis or a decision analysis.

[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.

[G] *Other.* Textbooks, expert opinions, case reports, and other reports not included above.

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