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

Peter V. Rabins, M.D., M.P.H., Chair
Deborah Blacker, M.D., Sc.D.
Barry W. Rovner, M.D.
Teresa Rummans, M.D.
Lon S. Schneider, M.D.
Pierre N. Tariot, M.D.
David M. Blass, M.D., Consultant

STEERING COMMITTEE ON PRACTICE GUIDELINES

John S. McIntyre, M.D., Chair
Sara C. Charles, M.D., Vice-Chair
Daniel J. Anzia, M.D.
Ian A. Cook, M.D.
Molly T. Finnerty, M.D.
Bradley R. Johnson, M.D.
James E. Nininger, M.D.
Barbara Schneidman, M.D.
Paul Summergrad, M.D.
Sherwyn M. Woods, M.D., Ph.D.

AREA AND COMPONENT LIAISONS

Joseph Berger, M.D. (Area I)
C. Deborah Cross, M.D. (Area II)
Harry A. Brandt, M.D. (Area III)
Philip M. Margolis, M.D. (Area IV)
John P. D. Shemo, M.D. (Area V)
Barton J. Blinder, M.D. (Area VI)
David L. Duncan, M.D. (Area VII)
Mary Ann Barnovitz, M.D.
Anthony J. Carino, M.D.
Zachary Z. Freyberg, M.D., Ph.D.
Sheila Hafter Gray, M.D.
Tina Tonnu, M.D.

STAFF

Robert Kunkle, M.A., Senior Program Manager
Amy B. Albert, B.A., Project Manager
Thomas J. Craig, M.D., M.P.H., Director, Dept. of Quality Improvement and Psychiatric Services
Darrel A. Regier, M.D., M.P.H., Director, Division of Research

MEDICAL EDITOR

Laura J. Fochtmann, M.D.

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

A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available in the Psychiatric Practice section of the APA Web site at www.psych.org.

The Work Group on Alzheimer's Disease and Other Dementias reports the following potentially competing interests for the period January 2003 to December 2006: Dr. Rabins has received speaking fees from Pfizer, AstraZeneca, Janssen, Eli Lilly and Company, Forest Pharmaceuticals, Inc., and Wyeth Pharmaceuticals. Dr. Blacker reports no competing interests. Dr. Rovner has served on speakers bureaus for Pfizer and Forest Pharmaceuticals, Inc. Dr. Rummans has received a research grant from the Linse Bock Foundation. Dr. Schneider has received research or other grants from Abbott Laboratories, AstraZeneca, Forest Pharmaceuticals, Inc., Johnson & Johnson, Eli Lilly and Company, Novartis, Pfizer, and Myriad. Dr. Schneider has served on speakers bureaus or performed other work relating to continuing medical education for Abbott Laboratories, AstraZeneca, Forest Pharmaceuticals, Eli Lilly and Company, Solvay, Bristol-Myers Squibb, and Lundbeck. Dr. Schneider has served on advisory panels for Abbott Laboratories, AstraZeneca, Forest Pharmaceuticals, Inc., Johnson & Johnson, Eli Lilly and Company, and Novartis. Dr. Tariot has received consulting fees from Memory Pharmaceuticals Corp. and Novartis; consulting fees and research support from Abbott Laboratories, Bristol-Myers Squibb, Eisai Inc., GlaxoSmithKline, Janssen, Eli Lilly and Company, Merck and Company, Myriad, Pfizer, Sanofi-Synthélabo, Dr. Willmar Schwabe Pharmaceuticals, and Takeda Pharmaceuticals North America, Inc.; educational fees from Lundbeck; consulting fees, research support, and educational fees from AstraZeneca, Eisai Inc., Forest Pharmaceuticals, Inc., and Pfizer; and research support from Elan Corporation, Mitsubishi Pharma Corporation, Neurochem, Inc., Ono Pharmaceuticals Co., Ltd., and Wyeth Pharmaceuticals. Dr. Tariot has received other research support from the National Institute of Aging, the National Institute of Mental Health, the Alzheimer's Association, the Arizona Department of Health Services, and the Institute for Mental Health Research. Dr. Tariot has served on speakers bureaus for AstraZeneca, Eisai Inc., Forest Pharmaceuticals, Inc., and Pfizer, Inc. Dr. Blass reports no competing interests. The Executive Committee on Practice Guidelines has reviewed this guideline and found no evidence of influence from these relationships.

CONTENTS

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 treatment 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.

To share feedback on this or other published APA practice guidelines, a form is available at http://www.psych.org/psych_pract/pg/reviewform.cfm.

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).

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 psychiatric 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 re-

duce 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, medications 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 in-

somnia, 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. Appropriate 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 patients, usually together with their caregivers, at regular follow-up visits. Patients who are clinically stable or are taking stable doses of medications should gen-

erally 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 subtle 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 tech-

niques 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 specific 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 instru-

mental 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 often 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, loneli-

ness, 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 circum-

stances, 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 patient'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 efficacy 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 fam-

ily 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 childcare 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, nonpharmacological 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, confusion, 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 func-

tion 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 agitated 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 in-

creases 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 problem. 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 contraindication 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 contrib-

ute 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 common 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 spe-

cific 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 de-

velopment 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.

INDIVIDUALS AND ORGANIZATIONS THAT SUBMITTED COMMENTS

George S. Alexopoulos, M.D.
Paul Appelbaum, M.D.
Steven Barczi, M.D.
Dan G. Blazer, M.D., M.P.H., Ph.D.
Frank W. Brown, M.D.
Kathleen C. Buckwalter, Ph.D., R.N., F.A.A.N.
Debra Cherry, Ph.D.
Mirean Coleman, M.S.W., L.C.S.W., C.T.
Christopher Colenda, M.D., M.P.H.
Yeates Conwell, M.D.
John R. M. Copeland, M.D., F.R.C.P., F.R.C.Psych.
Jeffrey L. Cummings, M.D.
M. L. Donnelly, M.D., F.R.C.P.C.
Brian Draper, M.B.B.S., M.D., F.R.A.N.Z.C.P.
Elizabeth Edgerly, Ph.D.
Barbara Else, M.P.A., MT-BC
Serge Gauthier, M.D., F.R.C.P.C.
David S. Geldmacher, M.D.
George T. Grossberg, M.D.
Elizabeth Heck Gould, M.S.W., L.C.S.W.
Nathan Herrmann, M.D., F.R.C.P.C.
Al Herzog, M.D.
Dilip V. Jeste, M.D.
Jason Karlawish, M.D.
Daniel Kaufer, M.D.
Kristy Klein, M.S.W.
David Knopman, M.D.
Edward C. Lauterbach, M.D., F.A.N.P.A., D.F.A.P.A.
J. Kenneth Le Clair, M.D., F.R.C.P.C
Peter A. Lichtenberg, Ph.D., A.B.P.P.
Benjamin Liptzin, M.D.
Constantine Lyketsos, M.D., M.H.S.
Katie Maslow, M.S.W.
Helen S. Mayberg, M.D.
Barnett S. Meyers, M.D.
Jacobo Mintzer, M.D.
Gary S. Moak, M.D.
Victor Molinari, Ph.D., A.B.P.P.
Lawrence J. Nardozzi, M.M.M., M.D., D.F.A.P.A., C.P.E.
Suzann Ogland-Hand, Ph.D.
Ronald C. Petersen, M.D., Ph.D.
Jill Pettigrew, M.B.B.S., F.R.A.N.Z.C.P.
Kiran Rabheru, M.D., F.R.C.P.C.
Barry Reisberg, M.D.
Robert G. Robinson, M.D.
Robert M. Rohrbaugh, M.D.
Jules Rosen, M.D.
Eugene H. Rubin, M.D., Ph.D.
Kenneth M. Sakauye, M.D.
Stephen F. Signer, M.D., C.M.
Elizabeth Sloan, M.S., L.C.P.C.
Gary W. Small, M.D.
John A. Snowdon, M.D., M.Phil., F.R.C.Psych.
Ann M. Steffen, Ph.D.
David C. Steffens, M.D., M.H.S.
Robert Stern, M.D., Ph.D.
Nicholas E. Stratas, M.D., D.L.F.A.P.A.
David L. Sultzer, M.D.
Trey Sunderland, M.D.
Can H. Tang, M.D.
Linda Teri, Ph.D.
Larry E. Tune, M.D.
Peter J. Whitehouse, M.D., Ph.D.
Antonette Zeiss, Ph.D.

Alzheimer's Association
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

REFERENCES

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.

1. Pasternak R, Rovner BW: Psychogeriatric programs: inpatient hospital units and partial hospital programs, in Comprehensive Textbook of Geriatric Psychiatry. Edited by Sadavoy J, Jarvik LF, Grossberg GT, Meyers BS. New York, W. W. Norton & Co., 2004, pp 1103–1118 [G]
2. Rabins P, Nicholson M: Acute psychiatric hospitalization for patients with irreversible dementia. Int J Geriatr Psychiatry 1991; 6:209–211 [G]
3. Zubenko GS, Rosen J, Sweet RA, Mulsant BH, Rifai AH: Impact of psychiatric hospitalization on behavioral complications of Alzheimer's disease. Am J Psychiatry 1992; 149:1484–1491 [B]
4. Callahan CM, Boustani MA, Unverzagt FW, Austrom MG, Damush TM, Perkins AJ, Fultz BA, Hui SL, Counsell SR, Hendrie HC: Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. JAMA 2006; 295:2148–2157 [A–]
5. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, Small GW, Miller B, Stevens JC: Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56:1143–1153 [G]
6. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST: Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56:1133–1142 [G]
7. Agency for Health Care Policy and Research: Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias: Clinical Practice Guideline, vol. 19. Washington, DC, US Department of Health and Human Services, Agency for Health Care Policy and Research, 1996 [G]
8. American Psychiatric Association: Practice guideline for psychiatric evaluation of adults, 2nd edition. Am J Psychiatry 2006; 163(June suppl):1–36 [G]
9. Crum RM, Anthony JC, Bassett SS, Folstein MF: Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993; 269:2386–2391 [G]
10. Tang-Wai DF, Knopman DS, Geda YE, Edland SD, Smith GE, Ivnik RJ, Tangalos EG, Boeve BF, Petersen RC: Comparison of the Short Test of Mental Status and the Mini-Mental State Examination in mild cognitive impairment. Arch Neurol 2003; 60:1777–1781 [G]
11. Chui H, Zhang Q: Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. Neurology 1997; 49:925–935 [G]
12. Coimbra A, Williams DS, Hostetler ED: The role of MRI and PET/SPECT in Alzheimer's disease. Curr Top Med Chem 2006; 6:629–647 [F]
13. Masters CL, Cappai R, Barnham KJ, Villemagne VL: Molecular mechanisms for Alzheimer's disease: implications for neuroimaging and therapeutics. J Neurochem 2006; 97:1700–1725 [F]
14. Sunderland T, Hampel H, Takeda M, Putnam KT, Cohen RM: Biomarkers in the diagnosis of Alzheimer's disease: are we ready? J Geriatr Psychiatry Neurol 2006; 19:172–179 [F]
15. Sanchez-Juan P, Green A, Ladogana A, Cuadrado-Corrales N, Saanchez-Valle R, Mitrovaa E, Stoeck K, Sklaviadis T, Kulczycki J, Hess K, Bodemer M, Slivar-

ichova D, Saiz A, Calero M, Ingrosso L, Knight R, Janssens AC, van Duijn CM, Zerr I: CSF tests in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology 2006; 67:637–643 [D]

16. Hedera P, Turner RS: Inherited dementias. Neurol Clin 2002; 20:779–808, vii [G]
17. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD: Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 1993; 90:1977–1981 [G]
18. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD: Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993; 43:1467–1472 [G]
19. Locke PA, Conneally PM, Tanzi RE, Gusella JF, Haines JL: Apolipoprotein E4 allele and Alzheimer disease: examination of allelic association and effect on age at onset in both early- and late-onset cases. Genet Epidemiol 1995; 12:83–92 [G]
20. Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, Hyman BT, Crain B, Tang MX, Phelps CH: Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. N Engl J Med 1998; 338:506–511 [G]
21. American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer Disease: Statement on use of apolipoprotein E testing for Alzheimer disease. JAMA 1995; 274:1627–1629 [G]
22. National Institute on Aging/Alzheimer's Association Working Group: Apolipoprotein E genotyping in Alzheimer's disease. Lancet 1996; 347:1091–1095 [G]
23. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor MN, Owen M, Hardy J: Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991; 349:704–706 [G]
24. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, Tsuda T, Mar L, Foncin JF, Bruni AC, Montesi MP, Sorbi S, Rainero I, Pinessi L, Nee L, Chumakov I, Pollen D, Brookes A, Sanseau P, Pollinsky RL, Wasco W, Da Silva HA, Haines JL, Pericak-Vance MA, Tanzi RE, Roses A, Frazer P, Rommens J, St. George-Hyslop P: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995; 375:754–760 [G]
25. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K, Crowley AC, Fu Y-H, Guenette SY, Galas D, Nemens E, Wijsman EM, Bird TD, Schellenberg GD, Tanzi RE: Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269:973–977 [G]
26. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM Jr: A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999; 340:669–676 [B]
27. Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB: The clinical introduction of genetic testing for Alzheimer disease: an ethical perspective. JAMA 1997; 277:832–836 [G]
28. Blacker D: New insights into genetic aspects of Alzheimer's disease: does genetic information make a difference in clinical practice? Postgrad Med 2000; 108:119–122, 125–126, 129 [G]
29. Goldman JS, Farmer JM, Van Deerlin VM, Wilhelmsen KC, Miller BL, Grossman M: Frontotemporal dementia: genetics and genetic counseling dilemmas. Neurologist 2004; 10:227–234 [G]
30. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M: Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442:916–919 [G]
31. MacMillan JC, Snell RG, Tyler A, Houlihan GD, Fenton I, Cheadle JP, Lazarou LP, Shaw DJ, Harper PS: Molecular analysis and clinical correlations of the Huntington's disease mutation. Lancet 1993; 342:954–958 [G]
32. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssiere C, Cruaud C, Maciazek J, Weissenbach J, Bousser MG, Bach JF, Tournier-Lasserve E: Strong clustering and stereotyped nature of Notch 3 mutations in CADASIL patients. Lancet 1997; 350:1511–1515 [G]
33. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S: Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 2002; 288:1475–1483 [C]
34. Steinberg M, Corcoran C, Tschanz JT, Huber C, Welsh-Bohmer K, Norton MC, Zandi P, Breitner JC, Steffens DC, Lyketsos CG: Risk factors for neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry 2006; 21:824–830 [C]
35. Warner ML: The Complete Guide to Alzheimer's-Proofing Your Home, revised ed. West Lafayette, IN, Purdue University Press, 2000 [G]

36. American Psychiatric Association: Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry 2003; 160(Nov suppl):1–60 [G]
37. Kovach CR, Taneli Y, Dohearty P, Schlidt AM, Cashin S, Silva-Smith AL: Effect of the BACE intervention on agitation of people with dementia. Gerontologist 2004; 44:797–806 [A]
38. Leibovici A, Tariot PN: Agitation associated with dementia: a systematic approach to treatment. Psychopharmacol Bull 1988; 24:49–53 [G]
39. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A: Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987; 48(May suppl):9–15 [G]
40. Devanand DP, Sackeim HA, Mayeux R: Psychosis, behavioral disturbance, and the use of neuroleptics in dementia. Compr Psychiatry 1988; 29:387–401 [F]
41. Rabins PV, Lyketsos CG, Steele CD: Practical Dementia Care, 2nd ed. New York, Oxford University Press, 2006 [G]
42. Burton LC, German PS, Rovner BW, Brant LJ: Physical restraint use and cognitive decline among nursing home residents. J Am Geriatr Soc 1992; 40:811–816 [C]
43. Capezuti E, Evans L, Strumpf N, Maislin G: Physical restraint use and falls in nursing home residents. J Am Geriatr Soc 1996; 44:627–633 [D]
44. Neufeld RR, Libow LS, Foley WJ, Dunbar JM, Cohen C, Breuer B: Restraint reduction reduces serious injuries among nursing home residents. J Am Geriatr Soc 1999; 47:1202–1207 [B]
45. Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH: Interventions for preventing falls in elderly people. Cochrane Database Syst Rev 2003; (4):CD000340 [E]
46. Klein DA, Steinberg M, Galik E, Steele C, Sheppard JM, Warren A, Rosenblatt A, Lyketsos CG: Wandering behaviour in community-residing persons with dementia. Int J Geriatr Psychiatry 1999; 14:272–279 [D]
47. Price JD, Hermans DG, Grimley EJ: Subjective barriers to prevent wandering of cognitively impaired people. Cochrane Database Syst Rev 2000; (4):CD001932 [E]
48. Dubinsky RM, Stein AC, Lyons K: Practice parameter: risk of driving and Alzheimer's disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2000; 54:2205–2211 [G]
49. Cox DJ, Quillian WC, Thorndike FP, Kovatchev BP, Hanna G: Evaluating driving performance of outpatients with Alzheimer disease. J Am Board Fam Pract 1998; 11:264–271 [G]
50. Gilley DW, Wilson RS, Bennett DA, Stebbins GT, Bernard BA, Whalen ME, Fox JH: Cessation of driving and unsafe motor vehicle operation by dementia patients. Arch Intern Med 1991; 151:941–946 [G]
51. Carr D, Jackson T, Alquire P: Characteristics of an elderly driving population referred to a geriatric assessment center. J Am Geriatr Soc 1990; 38:1145–1150 [D]
52. O'Neill D, Neubauer K, Boyle M, Gerrard J, Surmon D, Wilcock GK: Dementia and driving. J R Soc Med 1992; 85:199–202 [G]
53. Drachman DA, Swearer JM: Driving and Alzheimer's disease: the risk of crashes. Neurology 1993; 43:2448–2456 [D]
54. Hopkins RW, Kilik L, Day DJ, Rows C, Tseng H: Driving and dementia in Ontario: a quantitative assessment of the problem. Can J Psychiatry 2004; 49:434–438 [G]
55. American Psychiatric Association: The Role of the Psychiatrist in Assessing Driving Ability: Position Statement. Washington, DC, American Psychiatric Association, 1993 [G]
56. Reger MA, Welsh RK, Watson GS, Cholerton B, Baker LD, Craft S: The relationship between neuropsychological functioning and driving ability in dementia: a meta-analysis. Neuropsychology 2004; 18:85–93 [E]
57. Ott BR, Anthony D, Papandonatos GD, D'Abreu A, Burock J, Curtin A, Wu CK, Morris JC: Clinician assessment of the driving competence of patients with dementia. J Am Geriatr Soc 2005; 53:829–833 [G]
58. Duchek JM, Carr DB, Hunt L, Roe CM, Xiong C, Shah K, Morris JC: Longitudinal driving performance in early-stage dementia of the Alzheimer type. J Am Geriatr Soc 2003; 51:1342–1347 [C]
59. Adler G, Rottunda S, Dysken M: The older driver with dementia: an updated literature review. J Safety Res 2005; 36:399–407 [F]
60. Brown LB, Ott BR: Driving and dementia: a review of the literature. J Geriatr Psychiatry Neurol 2004; 17:232–240 [F]
61. Perkinson MA, Berg-Weger ML, Carr DB, Meuser TM, Palmer JL, Buckles VD, Powlishta KK, Foley DJ, Morris JC: Driving and dementia of the Alzheimer type: beliefs and cessation strategies among stakeholders. Gerontologist 2005; 45:676–685 [G]
62. Friedland RP, Koss E, Kumar A, Gaine S, Metzler D, Haxby JV, Moore A: Motor vehicle crashes in dementia of the Alzheimer type. Ann Neurol 1988; 24:782–786 [C]
63. Odenheimer GL, Beaudet M, Jette AM, Albert MS, Grande L, Minaker KL: Performance-based driving evaluation of the elderly driver: safety, reliability, and validity. J Gerontol 1994; 49:M153–M159 [G]
64. Fitten LJ, Perryman KM, Wilkinson CJ, Little RJ, Burns MM, Pachana N, Mervis JR, Malmgren R, Siembieda DW, Ganzell S: Alzheimer and vascular dementias and driving: a prospective road and laboratory study. JAMA 1995; 273:1360–1365 [C]
65. Carr DB, Duchek J, Morris JC: Characteristics of motor vehicle crashes of drivers with dementia of the Alzheimer type. J Am Geriatr Soc 2000; 48:18–22 [D]

66. Shua-Haim JR, Gross JS: The "co-pilot" driver syndrome. J Am Geriatr Soc 1996; 44:815–817 [G]
67. Wang CC, Carr DB: Older driver safety: a report from the Older Drivers Project. J Am Geriatr Soc 2004; 52:143–149 [G]
68. Taylor BD, Tripodes S: The effects of driving cessation on the elderly with dementia and their caregivers. Accid Anal Prev 2001; 33:519–528 [G]
69. Drickamer MA, Lachs MS: Should patients with Alzheimer's disease be told their diagnosis? N Engl J Med 1992; 326:947–951 [G]
70. Yeo G, Gallagher-Thompson D: Ethnicity and the Dementias, 2nd ed. Philadelphia, PA, Taylor & Francis, 2006 [G]
71. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, Marder K, Sano M, Devanand D, Albert SM, Bylsma F, Tsai WY: Predicting time to nursing home care and death in individuals with Alzheimer disease. JAMA 1997; 277:806–812 [C]
72. Ostwald SK, Hepburn KW, Caron W, Burns T, Mantell R: Reducing caregiver burden: a randomized psychoeducational intervention for caregivers of persons with dementia. Gerontologist 1999; 39:299–309 [A–]
73. Lovett S, Gallagher D: Psychoeducational interventions for family caregivers: preliminary efficacy data. Behav Ther 1988; 19:321–330 [B]
74. Gallagher-Thompson D: Direct services and interventions for caregivers: a review and critique of extant programs and a look ahead to the future, in Family Caregiving: Agenda for the Future. Edited by Cantor MH. San Francisco, American Society on Aging, 1994, pp 101–122 [G]
75. Marriott A, Donaldson C, Tarrier N, Burns A: Effectiveness of cognitive-behavioural family intervention in reducing the burden of care in carers of patients with Alzheimer's disease. Br J Psychiatry 2000; 176:557–562 [A–]
76. Chang BL: Cognitive-behavioral intervention for homebound caregivers of persons with dementia. Nurs Res 1999; 48:173–182 [A–]
77. King AC, Baumann K, O'Sullivan P, Wilcox S, Castro C: Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: a randomized controlled trial. J Gerontol A Biol Sci Med Sci 2002; 57:M26–M36 [A–]
78. Chiverton P, Caine ED: Education to assist spouses in coping with Alzheimer's disease: a controlled trial. J Am Geriatr Soc 1989; 37:593–598 [C]
79. Mittelman MS, Ferris SH, Steinberg G, Shulman E, Mackell JA, Ambinder A, Cohen J: An intervention that delays institutionalization of Alzheimer's disease patients: treatment of spouse-caregivers. Gerontologist 1993; 33:730–740 [A–]
80. Gitlin LN, Winter L, Corcoran M, Dennis MP, Schinfeld S, Hauck WW: Effects of the home environmental skill-building program on the caregiver-care recipient dyad: 6-month outcomes from the Philadelphia REACH Initiative. Gerontologist 2003; 43:532–546 [A–]
81. Burgio L, Stevens A, Guy D, Roth DL, Haley WE: Impact of two psychosocial interventions on white and African American family caregivers of individuals with dementia. Gerontologist 2003; 43:568–579 [A–]
82. Coon DW, Thompson L, Steffen A, Sorocco K, Gallagher-Thompson D: Anger and depression management: psychoeducational skill training interventions for women caregivers of a relative with dementia. Gerontologist 2003; 43:678–689 [A–]
83. Hebert R, Levesque L, Vezina J, Lavoie JP, Ducharme F, Gendron C, Preville M, Voyer L, Dubois MF: Efficacy of a psychoeducative group program for caregivers of demented persons living at home: a randomized controlled trial. J Gerontol B Psychol Sci Soc Sci 2003; 58:S58–S67 [A–]
84. Brodaty H, Green A, Koschera A: Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc 2003; 51:657–664 [E]
85. Thompson C, Briggs M: Support for carers of people with Alzheimer's type dementia. Cochrane Database Syst Rev 2000; (2):CD000454 [E]
86. Brodaty H, Peters KE: Cost effectiveness of a training program for dementia carers. Int Psychogeriatr 1991; 3:11–22 [G]
87. Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B: A family intervention to delay nursing home placement of patients with Alzheimer disease: a randomized controlled trial. JAMA 1996; 276:1725–1731 [A–]
88. Eloniemi-Sulkava U, Notkola IL, Hentinen M, Kivela SL, Sivenius J, Sulkava R: Effects of supporting community-living demented patients and their caregivers: a randomized trial. J Am Geriatr Soc 2001; 49:1282–1287 [A–]
89. Flint AJ: Effects of respite care on patients with dementia and their caregivers. Int J Psychogeriatr 1995; 7:505–517 [F]
90. Burdz MP, Eaton WO, Bond JB Jr: Effect of respite care on dementia and nondementia patients and their caregivers. Psychol Aging 1988; 3:38–42 [G]
91. Conlin MM, Caranasos GJ, Davidson RA: Reduction of caregiver stress by respite care: a pilot study. South Med J 1992; 85:1096–1100 [B]
92. Wimo A, Mattsson B, Adolfsson R, Eriksson T, Nelvig A: Dementia day care and its effects on symptoms and institutionalization—a controlled Swedish study. Scand J Prim Health Care 1993; 11:117–123 [B]
93. Lee H, Cameron M: Respite care for people with dementia and their carers. Cochrane Database Syst Rev 2004; (2):CD004396 [E]
94. Mace NL, Rabins PV: 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, 4th ed. New York, Warner Books, 2006 [G]

95. Petersen RC: Mayo Clinic: Guide to Alzheimer's Disease: The Essential Resource for Treatment, Coping, and Caregiving. Rochester, MN, Mayo Foundation for Medical Education and Research, 2006 [G]
96. Schneider J, Murray J, Banerjee S, Mann A: EUROCARE: a cross-national study of co-resident spouse carers for people with Alzheimer's disease, I: factors associated with carer burden. Int J Geriatr Psychiatry 1999; 14:651–661 [G]
97. Overman W Jr, Stoudemire A: Guidelines for legal and financial counseling of Alzheimer's disease patients and their families. Am J Psychiatry 1988; 145:1495–1500 [G]
98. Hirschman KB, Xie SX, Feudtner C, Karlawish JH: How does an Alzheimer's disease patient's role in medical decision making change over time? J Geriatr Psychiatry Neurol 2004; 17:55–60 [C]
99. Grisso T, Appelbaum PS: Assessing Competence to Consent to Treatment: A Guide for Physicians and Other Health Professionals. New York, Oxford University Press, 1998 [G]
100. American Psychiatric Association: Principles of Informed Consent in Psychiatry. Resource Document No. 960001. Washington, DC, American Psychiatric Association, 1996 [G]
101. Karlawish JH: Research involving cognitively impaired adults. N Engl J Med 2003; 348:1389–1392 [G]
102. Alzheimer's Association: Research consent for cognitively impaired adults: recommendations for institutional review boards and investigators. Alzheimer Dis Assoc Disord 2004; 18:171–175 [G]
103. Spar JE, Garb AS: Assessing competency to make a will. Am J Psychiatry 1992; 149:169–174 [F]
104. Burgener SC, Twigg P: Interventions for persons with irreversible dementia. Annu Rev Nurs Res 2002; 20:89–124 [F]
105. Charney DS, Reynolds CF III, Lewis L, Lebowitz BD, Sunderland T, Alexopoulos GS, Blazer DG, Katz IR, Meyers BS, Arean PA, Borson S, Brown C, Bruce ML, Callahan CM, Charlson ME, Conwell Y, Cuthbert BN, Devanand DP, Gibson MJ, Gottlieb GL, Krishnan KR, Laden SK, Lyketsos CG, Mulsant BH, Niederehe G, Olin JT, Oslin DW, Pearson J, Persky T, Pollock BG, Raetzman S, Reynolds M, Salzman C, Schulz R, Schwenk TL, Scolnick E, Unutzer J, Weissman MM, Young RC: Depression and Bipolar Support Alliance consensus statement on the unmet needs in diagnosis and treatment of mood disorders in late life. Arch Gen Psychiatry 2003; 60:664–672 [F]
106. Lopez OL, Becker JT, Saxton J, Sweet RA, Klunk W, DeKosky ST: Alteration of a clinically meaningful outcome in the natural history of Alzheimer's disease by cholinesterase inhibition. J Am Geriatr Soc 2005;53:83–87 [C]
107. Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL, Jansson-Blixt C, Haglund A: Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet 2006; 367:1057–1065 [A]
108. McShane R, Areosa Sastre A, Minakaran N: Memantine for dementia. Cochrane Database Syst Rev 2006: (2)CD003154 [E]
109. Volicer L, Volicer BJ, Hurley AC: Is hospice care appropriate for Alzheimer patients? Caring 1993; 12:50–55 [G]
110. Lyness JM: End-of-life care: issues relevant to the geriatric psychiatrist. Am J Geriatr Psychiatry 2004; 12:457–472 [F]
111. Volicer L, Hurley AC, Lathi DC, Kowall NW: Measurement of severity in advanced Alzheimer's disease. J Gerontol 1994; 49:M223–M226 [G]
112. Cohen-Mansfield J: Nonpharmacologic interventions for inappropriate behaviors in dementia: a review, summary, and critique. Am J Geriatr Psychiatry 2001; 9:361–381 [F]
113. Spira AP, Edelstein BA: Behavioral interventions for agitation in older adults with dementia: an evaluative review. Int Psychogeriatr 2006; 18:195–225 [F]
114. Kitwood T: Dementia Reconsidered: The Person Comes First. Buckingham, UK, Open University Press, 1997 [G]
115. Opie J, Rosewarne R, O'Connor DW: The efficacy of psychosocial approaches to behaviour disorders in dementia: a systematic literature review. Aust N Z J Psychiatry 1999; 33:789–799 [F]
116. Livingston G, Johnston K, Katona C, Paton J, Lyketsos CG: Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry 2005; 162:1996–2021 [E]
117. Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, Kukull WA, LaCroix AZ, McCormick W, Larson EB: Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. JAMA 2003; 290:2015–2022 [A–]
118. Proctor R, Burns A, Powell HS, Tarrier N, Faragher B, Richardson G, Davies L, South B: Behavioural management in nursing and residential homes: a randomised controlled trial. Lancet 1999; 354:26–29 [A–]
119. Teri L: Behavioral treatment of depression in patients with dementia. Alzheimer Dis Assoc Disord 1994; 8(suppl 3):66–74 [B]
120. Rovner BW, Steele CD, Shmuely Y, Folstein MF: A randomized trial of dementia care in nursing homes. J Am Geriatr Soc 1996; 44:7–13 [A–]
121. Camberg L, Woods P, Ooi WL, Hurley A, Volicer L, Ashley J, Odenheimer G, McIntyre K: Evaluation of simulated presence: a personalized approach to enhance well-being in persons with Alzheimer's disease. J Am Geriatr Soc. 1999; 47:446–452 [A]
122. Baines S, Saxby P, Ehlert K: Reality orientation and reminiscence therapy: a controlled cross-over study of elderly confused people. Br J Psychiatry 1987; 151:222–231 [A–]

123. Kiernat JM: The use of life review activity with confused nursing home residents. Am J Occup Ther 1979; 33:306–310 [B]
124. Cook JB: Reminiscing: how it can help confused nursing home residents. Soc Casework 1984; 65:90–93 [B]
125. Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, Orrell M: Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry 2003; 183:248–254 [A]
126. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A: Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev 2003; (4):CD003260 [E]
127. Dietch JT, Hewett LJ, Jones S: Adverse effects of reality orientation. J Am Geriatr Soc 1989; 37:974–976 [B]
128. Copeland JRM, Abou-Saleh MT, Blazer DG: Principles and Practice of Geriatric Psychiatry. New York, Wiley, 1994 [G]
129. Jacobson SA, Pies RW, Greenblatt DJ: Handbook of Geriatric Psychopharmacology. Washington, DC, American Psychiatric Publishing, 2002 [G]
130. Sunderland T, Weingartner H, Cohen RM, Tariot PN, Newhouse PA, Thompson KE, Lawlor BA, Mueller EA: Low-dose oral lorazepam administration in Alzheimer subjects and age-matched controls. Psychopharmacology (Berl) 1989; 99:129–133 [D]
131. Davis KL, Thal LJ, Gamzu ER, Davis CS, Woolson RF, Gracon SI, Drachman DA, Schneider LS, Whitehouse PJ, Hoover TM, Morris JC, Kawas CH, Knopman DS, Earl NL, Kumar V, Doody RS: A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. N Engl J Med 1992; 327:1253–1259 [A]
132. Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J: A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA 1992; 268:2523–2529 [A]
133. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI: A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 1994; 271:985–991 [A]
134. Forette F, Hoover T, Gracon S, de Rotrou J, Hervy MP: A double-blind, placebo-controlled, enriched population study of tacrine in patients with Alzheimer's disease. Eur J Neurology 1995; 2:1–10 [A]
135. Foster NL, Petersen RC, Gracon SI, Lewis K: An enriched-population, double-blind, placebo-controlled, crossover study of tacrine and lecithin in Alzheimer's disease. The Tacrine 970-6 Study Group. Dementia 1996; 7:260–266 [A]
136. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P: Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004; 363:2105–2115 [A]
137. Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD: A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001; 57:481–488 [A]
138. Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Moller HJ, Rogers SL, Friedhoff LT: The effects of donepezil in Alzheimer's disease—results from a multinational trial. Dement Geriatr Cogn Disord 1999; 10:237–244 [A]
139. Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P: A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001; 57:489–495 [A]
140. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT: A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998; 50:136–145 [A]
141. Rogers SL, Doody RS, Mohs RC, Friedhoff LT: Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med 1998; 158:1021–1031 [A]
142. Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E: A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001; 57:613–620 [A]
143. Tune L, Tiseo PJ, Ieni J, Perdomo C, Pratt RD, Votaw JR, Jewart RD, Hoffman JM: Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: results of a 24-week, double-blind, placebo-controlled study. Am J Geriatr Psychiatry 2003; 11:169–177 [A]
144. Greenberg SM, Tennis MK, Brown LB, Gomez-Isla T, Hayden DL, Schoenfeld DA, Walsh KL, Corwin C, Daffner KR, Friedman P, Meadows ME, Sperling RA, Growdon JH: Donepezil therapy in clinical practice: a randomized crossover study. Arch Neurol 2000; 57:94–99 [A]
145. Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM, Whalen E: A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001; 49:1590–1599 [A]
146. Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S: Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol 2004; 61:1852–1856 [A]
147. Forette F, Anand R, Gharabawi G: A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon). Eur J Neurol 1999; 6:423–429 [A]

148. Sramek JJ, Anand R, Wardle TS, Irwin P, Hartman RD, Cutler NR: Safety/tolerability trial of SDZ ENA 713 in patients with probable Alzheimer's disease. Life Sci 1996; 58:1201–1207 [A]
149. Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal Bianco P, Stahelin HB, Hartman R, Gharabawi M: Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999; 318:633–638 [A]
150. Karaman Y, Erdogan F, Koseoglu E, Turan T, Ersoy AO: A 12-month study of the efficacy of rivastigmine in patients with advanced moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2005; 19:51–56 [A–]
151. Agid Y, Dubois B, Anand R, Gharabawi G: Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Curr Ther Res Clin Exp 1998; 59:837–845 [A]
152. Corey-Bloom J, Anand R, Veach J, ENA 713 B352 Study Group: A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. International Journal of Geriatric Psychopharmacology 1998; 1:55–65 [A]
153. Wilkinson D, Murray J: Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2001; 16:852–857 [A]
154. Wilcock GK, Lilienfeld S, Gaens E: Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000; 321:1445–1449 [A]
155. Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D: Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2001; 71:589–595 [A]
156. Raskind MA, Peskind ER, Wessel T, Yuan W: Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000; 54:2261–2268 [A]
157. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C: A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000; 54:2269–2276 [A]
158. Brodaty H, Corey-Bloom J, Potocnik FC, Truyen L, Gold M, Damaraju CR: Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2005; 20:120–132 [A]
159. Suh GH, Yeon JH, Uk LC, Hoon OB, Nam BJ, Jung HY, Ju YS, Kil YB, Park J, Hong I, Choi S, Ho LJ: A prospective, double-blind, community-controlled comparison of three doses of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population. Clin Ther 2004; 26:1608–1618 [A]
160. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, Maud CM, Engelbrecht I, Hock C, Ieni JR, Bahra RS: A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. Int J Clin Pract 2002; 56:441–446 [B]
161. Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, Zhang R, Bahra R: A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19:58–67 [A–]
162. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, Bullock R, Kershaw P: A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging 2003; 20:777–789 [A–]
163. Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, Nagel J, Lane R: Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin 2005; 21:1317–1327 [A]
164. Hogan DB, Goldlist B, Naglie G, Patterson C: Comparison studies of cholinesterase inhibitors for Alzheimer's disease. Lancet Neurol 2004; 3:622–626 [G]
165. Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW: Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 1994; 271:992–998 [C]
166. Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD: Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001; 58:427–433 [B]
167. Eisai Inc: Press Release: Eisai Reports Results From Latest Donepezil Study in Vascular Dementia. Tokyo, Eisai Corporate Communications Department, March 16, 2006. http://www.leaddiscovery.co.uk/prlink.asp?reclink= http://www.eisai.co.jp/enews/enews200609.html [G]
168. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R: Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000; 356:2031–2036 [A]
169. Beversdorf DQ, Warner JL, Davis RA, Sharma UK, Nagaraja HN, Scharre DW: Donepezil in the treatment of dementia with Lewy bodies. Am J Geriatr Psychiatry 2004; 12:542–544 [A]
170. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S, Lane R: Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004; 351:2509–2518 [A]

171. Poewe W, Wolters E, Emre M, Onofrj M, Hsu C, Tekin S, Lane R: Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. Mov Disord 2006; 21:456–461 [B]
172. Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D, Richardson S: Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 2004; 63:651–657 [A]
173. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ: Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; 352:2379–2388 [A]
174. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ: Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003; 348:1333–1341 [A]
175. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291:317–324 [A]
176. Areosa Sastre A, McShane R, Sherriff F: Memantine for dementia. Cochrane Database Syst Rev 2004; (4):CD003154 [E]
177. Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, McDonald S. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14:704–715 [A]
178. Wilcock G, Mobius HJ, Stoffler A: A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002; 17:297–305 [A]
179. Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F: Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002; 33:1834–1839 [A]
180. Winblad B, Poritis N: Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999; 14:135–146 [A]
181. Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005; 142:37–46 [E]
182. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, Ross C, Arnold A, Sleight P, Probstfield J, Dagenais GR: Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 2005; 293:1338–1347 [A]
183. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336:1216–1222 [A]
184. Kappus H, Diplock AT: Tolerance and safety of vitamin E: a toxicological position report. Free Radic Biol Med 1992; 13:55–74 [G]
185. McGeer PL, Rogers J: Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease. Neurology 1992; 42:447–449 [G]
186. Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, Zalinski J, Cofield M, Mansukhani L, Willson P, Kogan F: Clinical trial of indomethacin in Alzheimer's disease. Neurology 1993; 43:1609–1611 [A]
187. Breitner JC, Gau BA, Welsh KA, Plassman BL, McDonald WM, Helms MJ, Anthony JC: Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. Neurology 1994; 44:227–232 [D]
188. Stewart WF, Kawas C, Corrada M, Metter EJ: Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997; 48:626–632 [C]
189. Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP, Brooks WS, Halliday GM: Anti-inflammatory drugs protect against Alzheimer disease at low doses. Arch Neurol 2000; 57:1586–1591 [D]
190. Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, Norman BA, Baranak CC: Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 2004; 62:66–71 [A]
191. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, Farlow MR, Jin S, Thomas RG, Thal LJ: Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003; 289:2819–2826 [A]
192. Scharf S, Mander A, Ugoni A, Vajda F, Christophidis N: A double-blind, placebo-controlled trial of diclofenac/misoprostol in Alzheimer's disease. Neurology 1999; 53:197–201 [A]
193. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN III, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J: Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003; 289:2651–2662 [A]
194. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, Koss E, Pfeiffer E, Jin S, Gamst A, Grundman M, Thomas R, Thal LJ: Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 2000; 283:1007–1015 [A]
195. Henderson VW, Paganini-Hill A, Miller BL, Elble RJ, Reyes PF, Shoupe D, McCleary CA, Klein RA, Hake

AM, Farlow MR: Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 2000; 54:295–301 [A]
196. Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M: A randomized, double-blind, placebo-controlled trial of two doses of Ginkgo biloba extract in dementia of the Alzheimer's type. Curr Alzheimer Res 2005; 2:541–551 [A]
197. van Dongen MC, van Rossum E, Kessels AG, Sielhorst HJ, Knipschild PG: The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial. J Am Geriatr Soc 2000; 48:1183–1194 [A]
198. van Dongen M, van Rossum E, Kessels A, Sielhorst H, Knipschild P: Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. J Clin Epidemiol 2003; 56:367–376 [A]
199. Birks J, Flicker L: Selegiline for Alzheimer's disease. Cochrane Database Syst Rev 2003; (1):CD000442 [E]
200. Olin J, Schneider L, Novit A, Luczak S: Hydergine for dementia. Cochrane Database Syst Rev 2001; (2):CD000359 [E]
201. Jeste DV, Finkel SI: Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 2000; 8:29–34 [G]
202. Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, Bannister C, McShane R, Swann A, Juszczak E, O'Brien JT: A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 2004; 65:114–119 [A]
203. Rada RT, Kellner R: Thiothixene in the treatment of geriatric patients with chronic organic brain syndrome. J Am Geriatr Soc 1976; 24:105–107 [A]
204. Barnes R, Veith R, Okimoto J, Raskind M, Gumbrecht G: Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. Am J Psychiatry 1982; 139:1170–1174 [A]
205. Sugerman AA, Williams BH, Adlerstein AM: Haloperidol in the psychiatric disorders of old age. Am J Psychiatry 1964; 120:1190–1192 [A]
206. Petrie WM, Ban TA, Berney S, Fujimori M, Guy W, Ragheb M, Wilson WH, Schaffer JD: Loxapine in psychogeriatrics: a placebo- and standard-controlled clinical investigation. J Clin Psychopharmacol 1982; 2:122–126 [A]
207. Hamilton LD, Bennett JL: The use of trifluoperazine in geriatric patients with chronic brain syndrome. J Am Geriatr Soc 1962; 10:140–147 [A]
208. Hamilton LD, Bennett JL: Acetophenazine for hyperactive geriatric patients. Geriatrics 1962; 17:596–601 [A]
209. Abse DW, Dahlstrom WG: The value of chemotherapy in senile mental disturbances: controlled comparison of chlorpromazine, reserpine-pipradrol, and opium. JAMA 1960; 174:2036–2042 [A]
210. Schneider LS, Pollock VE, Lyness SA: A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990; 38:553–563 [E]
211. Lanctot KL, Best TS, Mittmann N, Liu BA, Oh PI, Einarson TR, Naranjo CA: Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. J Clin Psychiatry 1998; 59:550–561 [E]
212. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, Lawlor BA: A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999; 53:946–955 [A]
213. Allain H, Dautzenberg PH, Maurer K, Schuck S, Bonhomme D, Gerard D: Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. Psychopharmacology (Berl) 2000; 148:361–366 [A]
214. Teri L, Logsdon RG, Peskind E, Raskind M, Weiner MF, Tractenberg RE, Foster NL, Schneider LS, Sano M, Whitehouse P, Tariot P, Mellow AM, Auchus AP, Grundman M, Thomas RG, Schafer K, Thal LJ: Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. Neurology 2000; 55:1271–1278 [A]
215. Chan WC, Lam LC, Choy CN, Leung VP, Li SW, Chiu HF: A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 2001; 16:1156–1162 [A]
216. Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, Cooper TB, Pelton GH, Mayeux R: A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. Am J Psychiatry 1998; 155:1512–1520 [A]
217. Kindermann SS, Dolder CR, Bailey A, Katz IR, Jeste DV: Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs Aging 2002; 19:257–276 [F]
218. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M: Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry 1999; 60:107–115 [A]
219. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, Lee E, Lyons B, Grossman F: A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003; 64:134–143 [A]

220. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, Mitan SJ, Kadam DL, Sanger TM, Feldman PD, Tollefson GD, Breier A: Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000; 57:968–976 [A]
221. Street JS, Clark WS, Kadam DL, Mitan SJ, Juliar BE, Feldman PD, Breier A: Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. Int J Geriatr Psychiatry 2001; 16(suppl 1):S62–S70 [A]
222. De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, Young CA, Lehman DL, Breier A: Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2004; 19:115–126 [A]
223. Meehan KM, Wang H, David SR, Nisivoccia JR, Jones B, Beasley CM Jr, Feldman PD, Mintzer JE, Beckett LM, Breier A: Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002; 26:494–504 [A]
224. De Deyn P, Jeste DV, Swanink R, Kostic D, Breder C, Carson WH, Iwamoto T: Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. J Clin Psychopharmacol 2005; 25:463–467 [A]
225. Schneider LS, Dagerman K, Insel PS: Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006; 14:191–210 [E]
226. Tariot PN, Schneider L, Katz IR, Mintzer JE, Street J, Copenhaver M, Williams-Hughes C: Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry 2006; 14:767–776 [A]
227. Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA: Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. Curr Alzheimer Res 2007; 4:81–93 [A]
228. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006; 355:1525–1538 [A]
229. Horwitz GJ, Tariot PN, Mead K, Cox C: Discontinuation of antipsychotics in nursing home patients with dementia. Am J Geriatr Psychiatry 1995; 3:290–299 [C]
230. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, Brookhart MA: Risk of death in elderly users of conventional vs atypical antipsychotic medications. N Engl J Med 2005; 353:2335–2341 [D]
231. US Food and Drug Administration: FDA Public Health Advisory: Death With Antipsychotics In Elderly Patients With Behavioral Disturbances, April 11, 2005. http://www.fda.gov/cder/drug/advisory/antipsychotics.htm [G]
232. McKeith IG, Ballard CG, Harrison RW: Neuroleptic sensitivity to risperidone in Lewy body dementia (letter). Lancet 1995; 346:699 [G]
233. Friedman JH, Lannon MC: Clozapine in the treatment of psychosis in Parkinson's disease. Neurology 1989; 39:1219–1221 [G]
234. Chacko RC, Hurley RA, Jankovic J: Clozapine use in diffuse Lewy body disease. J Neuropsychiatry Clin Neurosci 1993; 5:206–208 [G]
235. Madhusoodanan S, Brenner R, Araujo L, Abaza A: Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995; 56:514–518 [G]
236. Baskys A: Lewy body dementia: the litmus test for neuroleptic sensitivity and extrapyramidal symptoms. J Clin Psychiatry 2004; 65(suppl 11):16–22 [G]
237. Mancini F, Tassorelli C, Martignoni E, Moglia A, Nappi G, Cristina S, Pacchetti C: Long-term evaluation of the effect of quetiapine on hallucinations, delusions and motor function in advanced Parkinson disease. Clin Neuropharmacol 2004; 27:33–37 [B]
238. Kirven LE, Montero EF: Comparison of thioridazine and diazepam in the control of nonpsychotic symptoms associated with senility: double-blind study. J Am Geriatr Soc 1973; 21:546–551 [A]
239. Covington JS: Alleviating agitation, apprehension, and related symptoms in geriatric patients: a double-blind comparison of a phenothiazine and a benzodiazepine. South Med J 1975; 68:719–724 [G]
240. Stotsky B: Multicenter study comparing thioridazine with diazepam and placebo in elderly, nonpsychotic patients with emotional and behavioral disorders. Clin Ther 1984; 6:546–559 [A]
241. Coccaro EF, Kramer E, Zemishlany Z, Thorne A, Rice CM III, Giordani B, Duvvi K, Patel BM, Torres J, Nora R: Pharmacologic treatment of noncognitive behavioral disturbances in elderly demented patients. Am J Psychiatry 1990; 147:1640–1645 [G]
242. Cevera AA: Psychoactive drug therapy in the senile patient: controlled comparison of thioridazine and diazepam. Psychiatry Digest 1974;15–21 [A]
243. Christensen DB, Benfield WR: Alprazolam as an alternative to low-dose haloperidol in older, cognitively impaired nursing facility patients. J Am Geriatr Soc 1998; 46:620–625 [A]
244. Ashton H: Guidelines for the rational use of benzodiazepines: when and what to use. Drugs 1994; 48:25-40 [G]

245. Salzman C: Clinical Geriatric Psychopharmacology, 2nd ed. Baltimore, Williams & Wilkins, 1992 [G]
246. Grad RM: Benzodiazepines for insomnia in community-dwelling elderly: a review of benefit and risk. J Fam Pract 1995; 41:473–481 [F]
247. Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F: Benzodiazepines and the risk of falling leading to femur fractures: dosage more important than elimination half-life. Arch Intern Med 1995; 155:1801–1807 [D]
248. Gleason RP, Schneider LS: Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. J Clin Psychiatry 1990; 51:115–118 [G]
249. Lemke MR: Effect of carbamazepine on agitation in Alzheimer's inpatients refractory to neuroleptics. J Clin Psychiatry 1995; 56:354–357 [B]
250a. Tariot PN, Erb R, Leibovici A, Podgorski CA, Cox C, Asnis J, Kolassa J, Irvine C: Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. J Am Geriatr Soc 1994; 42:1160–1166 [B]
250b. Olin JT, Fox LS, Pawluczyk S, Taggart NA, Schneider LS: A pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. Am J Geriatr Psychiatry 2001;9:400–405 [A]
250c. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, Irvine C: Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998;155:54–61 [A]
251. Tariot PN, Jakimovich LJ, Erb R, Cox C, Lanning B, Irvine C, Podgorski CA: Withdrawal from controlled carbamazepine therapy followed by further carbamazepine treatment in patients with dementia. J Clin Psychiatry 1999; 60:684–689 [B]
252. Chambers CA, Bain J, Rosbottom RBBR, McLaren S: Carbamazepine in senile dementia and overactivity: a placebo controlled double blind trial. IRCS Med Sci 1982; 10:505–506 [A]
253. Tariot PN, Schneider LS, Mintzer JE, Cutler AJ, Cunningham MR, Thomas JW, Sommerville KW: Safety and tolerability of divalproex sodium for the treatment of signs and symptoms of mania in elderly patients with dementia: results of a double-blind, placebo-controlled trial. Curr Ther Res Clin Exp 2001; 62:51–67 [A]
254. Sival RC, Haffmans PM, Jansen PA, Duursma SA, Eikelenboom P: Sodium valproate in the treatment of aggressive behavior in patients with dementia—a randomized placebo controlled clinical trial. Int J Geriatr Psychiatry 2002; 17:579–585 [A]
255. Tariot PN, Raman R, Jakimovich L, Schneider L, Porsteinsson A, Thomas R, Mintzer J, Brenner R, Schafer K, Thal L: Divalproex sodium in nursing home residents with possible or probable Alzheimer disease complicated by agitation: a randomized, controlled trial. Am J Geriatr Psychiatry 2005; 13:942–949 [A]
256. Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, Noviasky J, Kowalski N, Holt CJ, Irvine C: Placebo-controlled study of divalproex sodium for agitation in dementia. Am J Geriatr Psychiatry 2001; 9:58–66 [A–]
257. Lonergan ET, Cameron M, Luxenberg J: Valproic acid for agitation in dementia. Cochrane Database Syst Rev 2004; (2):CD003945 [E]
258. Alexopoulos GS, Streim J, Carpenter D, Docherty JP: Using antipsychotic agents in older patients. J Clin Psychiatry 2004; 65(suppl 2):5–99 [G]
259. American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002; 159(Apr supp):1–50 [G]
260. Simpson DM, Foster D: Improvement in organically disturbed behavior with trazodone treatment. J Clin Psychiatry 1986; 47:191–193 [G]
261. Nair NP, Ban TA, Hontela S, Clarke R: Trazodone in the treatment of organic brain syndromes, with special reference to psychogeriatrics. Curr Ther Res Clin Exp 1973; 15:769–775 [G]
262. Lebert F, Pasquier F, Petit H: Behavioral effects of trazodone in Alzheimer's disease. J Clin Psychiatry 1994; 55:536–538 [B]
263. Sultzer DL, Gray KF, Gunay I, Berisford MA, Mahler ME: A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. Am J Geriatr Psychiatry 1997; 5:60–69 [A]
264. Lebert F, Stekke W, Hasenbroekx C, Pasquier F: Frontotemporal dementia: a randomised, controlled trial with trazodone. Dement Geriatr Cogn Disord 2004; 17:355–359 [A]
265. Colenda CC III: Buspirone in treatment of agitated demented patient (letter). Lancet 1988; 1:1169 [G]
266. Tiller JW, Dakis JA, Shaw JM: Short-term buspirone treatment in disinhibition with dementia (letter). Lancet 1988; 2:510 [G]
267. Cooper JP: Buspirone for anxiety and agitation in dementia (letter). J Psychiatry Neurosci 2003; 28:469 [G]
268. Sakauye KM, Camp CJ, Ford PA: Effects of buspirone on agitation associated with dementia. Am J Geriatr Psychiatry 1993; 1:82–84 [B]
269. Herrmann N, Eryavec G: Buspirone in the management of agitation and aggression associated with dementia. Am J Geriatr Psychiatry 1993; 1:249–253 [B]
270. Nyth AL, Gottfries CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. Br J Psychiatry 1990; 157:894–901 [B]
271. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A, Marin R, Jacob NJ, Huber KA, Kastango KB, Chew ML: Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. Am J Psychiatry 2002; 159:460–465 [A]

272. Weiner MF, Denke M, Williams K, Guzman R: Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men. Lancet 1992; 339:1121–1122 [G]
273. Kyomen HH, Nobel KW, Wei JY: The use of estrogen to decrease aggressive physical behavior in elderly men with dementia. J Am Geriatr Soc 1991; 39:1110–1112 [G]
274. Rich SS, Ovsiew F: Leuprolide acetate for exhibitionism in Huntington's disease. Mov Disord 1994; 9:353–357 [G]
275. Levitsky AM, Owens NJ: Pharmacologic treatment of hypersexuality and paraphilias in nursing home residents. J Am Geriatr Soc 1999; 47:231–234 [F]
276. Weiler PG, Mungas D, Bernick C: Propranolol for the control of disruptive behavior in senile dementia. J Geriatr Psychiatry Neurol 1988; 1:226–230 [G]
277. Peskind ER, Tsuang DW, Bonner LT, Pascualy M, Riekse RG, Snowden MB, Thomas R, Raskind MA: Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease: a placebo-controlled study. Alzheimer Dis Assoc Disord 2005; 19:23–28 [A]
278. Bains J, Birks JS, Dening TR: The efficacy of antidepressants in the treatment of depression in dementia. Cochrane Database Syst Rev 2002; (4):CD003944 [E]
279. Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, Bruce ML, Caine ED, Cummings JL, Devanand DP, Krishnan KR, Lyketsos CG, Lyness JM, Rabins PV, Reynolds CF III, Rovner BW, Steffens DC, Tariot PN, Lebowitz BD: Provisional diagnostic criteria for depression of Alzheimer disease. Am J Geriatr Psychiatry 2002; 10:125–128 [G]
280. Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T: The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry 1993; 150:1693–1699 [C]
281. Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, Reynolds CF III: Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry 2000; 157:1949–1954 [C]
282. Lyketsos CG, Steele C, Galik E, Rosenblatt A, Steinberg M, Warren A, Sheppard JM: Physical aggression in dementia patients and its relationship to depression. Am J Psychiatry 1999; 156:66–71 [G]
283. Bassiony MM, Warren A, Rosenblatt A, Baker A, Steinberg M, Steele CD, Sheppard JM, Lyketsos CG: The relationship between delusions and depression in Alzheimer's disease. Int J Geriatr Psychiatry 2002; 17:549–556 [D]
284. American Psychiatric Association: Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry 2000; 157(Apr suppl):1–45 [G]
285. Wilson K, Mottram P, Sivanranthan A, Nightingale A: Antidepressant versus placebo for depressed elderly. Cochrane Database Syst Rev 2001; (2):CD000561 [E]
286. Schatzberg A, Roose S: A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. Am J Geriatr Psychiatry 2006; 14:361–370 [A]
287. Sheikh JI, Cassidy EL, Doraiswamy PM, Salomon RM, Hornig M, Holland PJ, Mandel FS, Clary CM, Burt T: Efficacy, safety, and tolerability of sertraline in patients with late-life depression and comorbid medical illness. J Am Geriatr Soc 2004; 52:86–92 [A]
288. Schneider LS, Nelson JC, Clary CM, Newhouse P, Krishnan KR, Shiovitz T, Weihs K: An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. Am J Psychiatry 2003; 160:1277–1285 [A]
289. Nyth AL, Gottfries CG, Lyby K, Smedegaard-Andersen L, Gylding-Sabroe J, Kristensen M, Refsum HE, Ofsti E, Eriksson S, Syversen S: A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand 1992; 86:138–145 [B]
290. Magai C, Kennedy G, Cohen CI, Gomberg D: A controlled clinical trial of sertraline in the treatment of depression in nursing home patients with late-stage Alzheimer's disease. Am J Geriatr Psychiatry 2000; 8:66–74 [A]
291. Petracca GM, Chemerinski E, Starkstein SE: A double-blind, placebo-controlled study of fluoxetine in depressed patients with Alzheimer's disease. Int Psychogeriatr 2001; 13:233–240 [A]
292. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, Baker AS, Sheppard JM, Frangakis C, Brandt J, Rabins PV: Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. Arch Gen Psychiatry 2003; 60:737–746 [A]
293. Reifler BV, Teri L, Raskind M, Veith R, Barnes R, White E, McLean P: Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. Am J Psychiatry 1989; 146:45–49 [A]
294. Fuchs A, Hehnke U, Erhart C, Schell C, Pramshohler B, Danninger B, Schautzer F: Video rating analysis of effect of maprotiline in patients with dementia and depression. Pharmacopsychiatry 1993; 26:37–41 [B]
295. Petracca G, Teson A, Chemerinski E, Leiguarda R, Starkstein SE: A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1996; 8:270–275 [A]
296. Roth M, Mountjoy CQ, Amrein R: Moclobemide in elderly patients with cognitive decline and depression:

an international double-blind, placebo-controlled trial. Br J Psychiatry 1996; 168:149–157 [A]
297. Taragano FE, Lyketsos CG, Mangone CA, Allegri RF, Comesana-Diaz E: A double-blind, randomized, fixed-dose trial of fluoxetine vs amitriptyline in the treatment of major depression complicating Alzheimer's disease. Psychosomatics 1997; 38:246–252 [A]
298. Katona CL, Hunter BN, Bray J: A double-blind comparison of the efficacy and safety of paroxetine and imipramine in the treatment of depression with dementia. Int J Geriatr Psychiatry 1998; 13:100–108 [A]
299. Oslin DW, Ten Have TR, Streim JE, Datto CJ, Weintraub D, DiFilippo S, Katz IR: Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. J Clin Psychiatry 2003; 64:875–882 [A]
300. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA: Antidepressants and the risk of falls among nursing home residents. N Engl J Med 1998; 339:875–882 [D]
301. Marin RS, Fogel BS, Hawkins J, Duffy J, Krupp B: Apathy: a treatable syndrome. J Neuropsychiatry Clin Neurosci 1995; 7:23–30 [G]
302. Galynker I, Ieronimo C, Miner C, Rosenblum J, Vilkas N, Rosenthal R: Methylphenidate treatment of negative symptoms in patients with dementia. J Neuropsychiatry Clin Neurosci 1997; 9:231–239 [B]
303. Wallace AE, Kofoed LL, West AN: Double-blind, placebo-controlled trial of methylphenidate in older, depressed, medically ill patients. Am J Psychiatry 1995; 152:929–931 [A]
304. Pickett P, Masand P, Murray GB: Psychostimulant treatment of geriatric depressive disorders secondary to medical illness. J Geriatr Psychiatry Neurol 1990; 3:146–151 [G]
305. Lazarus LW, Moberg PJ, Langsley PR, Lingam VR: Methylphenidate and nortriptyline in the treatment of poststroke depression: a retrospective comparison. Arch Phys Med Rehabil 1994; 75:403–406 [G]
306. Rao V, Lyketsos CG: The benefits and risks of ECT for patients with primary dementia who also suffer from depression. Int J Geriatr Psychiatry 2000; 15:729–735 [G]
307. O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, Mueller M, Snyder K, Bernstein H, Rush AJ, Fink M, Kellner C: The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. Am J Geriatr Psychiatry 2001; 9:382–390 [A]
308. Tew JD Jr, Mulsant BH, Haskett RF, Prudic J, Thase ME, Crowe RR, Dolata D, Begley AE, Reynolds CF III, Sackeim HA: Acute efficacy of ECT in the treatment of major depression in the old-old. Am J Psychiatry 1999; 156:1865–1870 [A]
309. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM: Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 1993; 328:839–846 [A]
310. American Psychiatric Association: The Practice of Electroconvulsive Therapy. Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association, 2nd ed. Washington, DC, American Psychiatric Press, 2001 [G]
311. Ritchie K: Behavioral disturbances of dementia in ambulatory care settings. Int Psychogeriatr 1996; 8(suppl 3):439–442 [G]
312. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA: Sleep disturbance in mild to moderate Alzheimer's disease. Sleep Med 2005; 6:347–352 [G]
313. Yesavage JA, Friedman L, Ancoli-Israel S, Bliwise D, Singer C, Vitiello MV, Monjan AA, Lebowitz B: Development of diagnostic criteria for defining sleep disturbance in Alzheimer's disease. J Geriatr Psychiatry Neurol 2003; 16:131–139 [G]
314. Vitiello MV, Borson S: Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. CNS Drugs 2001; 15:777–796 [F]
315. Forbes D, Morgan DG, Bangma J, Peacock S, Pelletier N, Adamson J: Light therapy for managing sleep, behaviour, and mood disturbances in dementia. Cochrane Database Syst Rev 2004; (2):CD003946 [E]
316. McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, Teri L: Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial. J Am Geriatr Soc 2005; 53:793–802 [A–]
317. McCurry SM, Gibbons LE, Logsdon RG, Vitiello M, Teri L: Training caregivers to change the sleep hygiene practices of patients with dementia: the NITE-AD project. J Am Geriatr Soc 2003; 51:1455–1460 [A–]
318. Mishima K, Hishikawa Y, Okawa M: Randomized, dim light controlled, crossover test of morning bright light therapy for rest-activity rhythm disorders in patients with vascular dementia and dementia of Alzheimer's type. Chronobiol Int 1998; 15:647–654 [A–]
319. Lyketsos CG, Lindell VL, Baker A, Steele C: A randomized, controlled trial of bright light therapy for agitated behaviors in dementia patients residing in long-term care. Int J Geriatr Psychiatry 1999; 14:520–525 [A–]
320. Graf A, Wallner C, Schubert V, Willeit M, Wlk W, Fischer P, Kasper S, Neumeister A: The effects of light therapy on Mini-Mental State Examination scores in demented patients. Biol Psychiatry 2001; 50:725–727 [A]
321. Ancoli-Israel S, Martin JL, Kripke DF, Marler M, Klauber MR: Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. J Am Geriatr Soc 2002; 50:282–289 [A–]

322. Fontana GP, Krauchi K, Cajochen C, Someren E, Amrhein I, Pache M, Savaskan E, Wirz-Justice A: Dawn-dusk simulation light therapy of disturbed circadian rest-activity cycles in demented elderly. Exp Gerontol 2003; 38:207–216 [B]
323. Hoch CC, Reynolds CF III, Houck PR: Sleep patterns in Alzheimer, depressed, and healthy elderly. West J Nurs Res 1988; 10:239–256 [G]
324. Chong MS, Ayalon L, Marler M, Loredo JS, Corey-Bloom J, Palmer BW, Liu L, Ancoli-Israel S: Continuous positive airway pressure reduces subjective daytime sleepiness in patients with mild to moderate Alzheimer's disease with sleep disordered breathing. J Am Geriatr Soc 2006; 54:777–781 [A]
325. Richards KC, Beck C, O'Sullivan PS, Shue VM: Effect of individualized social activity on sleep in nursing home residents with dementia. J Am Geriatr Soc 2005; 53:1510–1517 [A–]
326. Strollo PJ Jr, Rogers RM: Obstructive sleep apnea. N Engl J Med 1996; 334:99–104 [G]
327. Mendelson WB: A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry 2005; 66:469–476 [F]
328. Swearer JM, O'Donnell BF, Ingram SM, Drachman DA: Rate of progression in familial Alzheimer's disease. J Geriatr Psychiatry Neurol 1996; 9:22–25 [C]
329. Shadlen MF, McCormick WC, Larson EB: Research agenda for understanding Alzheimer disease in diverse populations: work group on cultural diversity, Alzheimer's association. Alzheimer Dis Assoc Disord 2002; 16(suppl 2):S96–S100 [G]
330. Graff-Radford NR, Green RC, Go RC, Hutton ML, Edeki T, Bachman D, Adamson JL, Griffith P, Willis FB, Williams M, Hipps Y, Haines JL, Cupples LA, Farrer LA: Association between apolipoprotein E genotype and Alzheimer disease in African American subjects. Arch Neurol 2002; 59:594–600 [D]
331. Froehlich TE, Bogardus ST Jr, Inouye SK: Dementia and race: are there differences between African Americans and Caucasians? J Am Geriatr Soc 2001; 49:477–484 [G]
332. Valle R, Lee B: Research priorities in the evolving demographic landscape of Alzheimer disease and associated dementias. Alzheimer Dis Assoc Disord 2002; 16(suppl 2):S64–S76 [G]
333. Cohen CI, Magai C: Racial differences in neuropsychiatric symptoms among dementia outpatients. Am J Geriatr Psychiatry 1999; 7:57–63 [G]
334. Alarcon RD, Bell CC, Kirmayer LJ, Lin K-H, Ustun TB, Wisner KL: Beyond the funhouse mirrors: research agenda on culture and psychiatric diagnosis, in A Research Agenda for DSM-V. Edited by Kupfer DJ, First MB, Regier DA. Washington, DC, American Psychiatric Association, 2002, pp 219–289 [G]
335. Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K, Covinsky KE: Patient and caregiver characteristics and nursing home placement in patients with dementia. JAMA 2002; 287:2090–2097 [D]
336. Stolk RP, Breteler MM, Ott A, Pols HA, Lamberts SW, Grobbee DE, Hofman A: Insulin and cognitive function in an elderly population: the Rotterdam Study. Diabetes Care 1997; 20:792–795 [G]
337. Sinclair AJ, Girling AJ, Bayer AJ: Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services: All Wales Research into Elderly (AWARE) Study. Diabetes Res Clin Pract 2000; 50:203–212 [D]
338. Levkoff SE, Evans DA, Liptzin B, Cleary PD, Lipsitz LA, Wetle TT, Reilly CH, Pilgrim DM, Schor J, Rowe J: Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med 1992; 152:334–340 [G]
339. Erkinjuntti T, Wikstrom J, Palo J, Autio L: Dementia among medical inpatients: evaluation of 2000 consecutive admissions. Arch Intern Med 1986; 146:1923–1926 [C]
340. Fick DM, Agostini JV, Inouye SK: Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc 2002; 50:1723–1732 [F]
341. Elie M, Cole MG, Primeau FJ, Bellavance F: Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 1998; 13:204–212 [E]
342. Tune LE: Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001; 62(suppl 21):11–14 [F]
343. Meagher DJ: Delirium: optimising management. BMJ 2001; 322:144–149 [F]
344. Fong HK, Sands LP, Leung JM: The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 2006; 102:1255–1266 [E]
345. Gaudreau JD, Gagnon P, Roy MA, Harel F, Tremblay A: Association between psychoactive medications and delirium in hospitalized patients: a critical review. Psychosomatics 2005; 46:302–316 [F]
346. Funkiewiez A, Ardouin C, Cools R, Krack P, Fraix V, Batir A, Chabardes S, Benabid AL, Robbins TW, Pollak P: Effects of levodopa and subthalamic nucleus stimulation on cognitive and affective functioning in Parkinson's disease. Mov Disord 2006; 21:1656–1662 [B]
347. Young BK, Camicioli R, Ganzini L: Neuropsychiatric adverse effects of antiparkinsonian drugs: characteristics, evaluation and treatment. Drugs Aging 1997; 10:367–383 [F]
348. Wild R, Pettit T, Burns A: Cholinesterase inhibitors for dementia with Lewy bodies. Cochrane Database Syst Rev 2003; (3):CD003672 [E]
349. Emre M: Dementia in Parkinson's disease: cause and treatment. Curr Opin Neurol 2004; 17:399–404 [G]
350. Reddy S, Factor SA, Molho ES, Feustel PJ: The effect of quetiapine on psychosis and motor function in parkinsonian patients with and without dementia. Mov Disord 2002; 17:676–681 [G]
351. Workman RH Jr, Orengo CA, Bakey AA, Molinari VA, Kunik ME: The use of risperidone for psychosis

and agitation in demented patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1997; 9:594–597 [B]

352. Marsh L, Lyketsos C, Reich SG: Olanzapine for the treatment of psychosis in patients with Parkinson's disease and dementia. Psychosomatics 2001; 42:477–481 [B]
353. Walker Z, Grace J, Overshot R, Satarasinghe S, Swan A, Katona CL, McKeith IG: Olanzapine in dementia with Lewy bodies: a clinical study. Int J Geriatr Psychiatry 1999; 14:459–466 [B]
354. Marsh L, McDonald WM, Cummings J, Ravina B: Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord 2006; 21:148–158 [G]
355. Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M: Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. Arch Neurol 1999; 56:991–996 [C]
356. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R: Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352:1347–1351 [A]
357. Malouf R, Birks J: Donepezil for vascular cognitive impairment. Cochrane Database Syst Rev 2004; (1):CD004395 [E]
358. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV: Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002; 359:1283–1290 [A]
359. Erkinjuntti T: Diagnosis and management of vascular cognitive impairment and dementia. J Neural Transm Suppl 2002; (63):91–109 [G]
360. Nyenhuis DL, Gorelick PB: Vascular dementia: a contemporary review of epidemiology, diagnosis, prevention, and treatment. J Am Geriatr Soc 1998; 46:1437–1448 [G]
361. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ: Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001; 58:1803–1809 [G]
362. Litvan I: Therapy and management of frontal lobe dementia patients. Neurology 2001; 56:S41–S45 [G]
363. Radin L, Radin G: What If It's Not Alzheimer's? A Caregiver's Guide to Dementia. Amherst, NY, Prometheus Books, 2003 [G]
364. Rice DP, Fox PJ, Max W, Webber PA, Lindeman DA, Hauck WW, Segura E: The economic burden of Alzheimer's disease care. Health Aff (Millwood) 1993; 12:164–176 [G]
365. Smith GE, Kokmen E, O'Brien PC: Risk factors for nursing home placement in a population-based dementia cohort. J Am Geriatr Soc 2000; 48:519–525 [D]
366. Boss P, Caron W, Horbal J, Mortimer J: Predictors of depression in caregivers of dementia patients: boundary ambiguity and mastery. Fam Process 1990; 29:245–254 [G]
367. Schulz R, Beach SR: Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. JAMA 1999; 282:2215–2219 [C]
368. Vitaliano PP, Zhang J, Scanlan JM: Is caregiving hazardous to one's physical health? A meta-analysis. Psychol Bull 2003; 129:946–972 [E]
369. Dura JR, Stukenberg KW, Kiecolt-Glaser JK: Chronic stress and depressive disorders in older adults. J Abnorm Psychol 1990; 99:284–290 [D]
370. Covinsky KE, Newcomer R, Fox P, Wood J, Sands L, Dane K, Yaffe K: Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. J Gen Intern Med 2003; 18:1006–1014 [G]
371. Schulz R, Burgio L, Burns R, Eisdorfer C, Gallagher-Thompson D, Gitlin LN, Mahoney DF: Resources for Enhancing Alzheimer's Caregiver Health (REACH): overview, site-specific outcomes, and future directions. Gerontologist 2003; 43:514–520 [B]
372. Schulz R, Mendelsohn AB, Haley WE, Mahoney D, Allen RS, Zhang S, Thompson L, Belle SH: End-of-life care and the effects of bereavement on family caregivers of persons with dementia. N Engl J Med 2003; 349:1936–1942 [G]
373. Chan DC, Kasper JD, Black BS, Rabins PV: Presence of behavioral and psychological symptoms predicts nursing home placement in community-dwelling elders with cognitive impairment in univariate but not multivariate analysis. J Gerontol A Biol Sci Med Sci 2003; 58:548–554 [C]
374. Rovner BW, German PS, Broadhead J, Morriss RK, Brant LJ, Blaustein J, Folstein MF: The prevalence and management of dementia and other psychiatric disorders in nursing homes. Int Psychogeriatr 1990; 2:13–24 [G]
375. Magaziner J, German P, Zimmerman SI, Hebel JR, Burton L, Gruber-Baldini AL, May C, Kittner S: The prevalence of dementia in a statewide sample of new nursing home admissions aged 65 and older: diagnosis by expert panel. Epidemiology of Dementia in Nursing Homes Research Group. Gerontologist 2000; 40:663–672 [G]
376. Tariot PN, Podgorski CA, Blazina L, Leibovici A: Mental disorders in the nursing home: another perspective. Am J Psychiatry 1993; 150:1063–1069 [G]
377. Rosenblatt A, Samus QM, Steele CD, Baker AS, Harper MG, Brandt J, Rabins PV, Lyketsos CG: The Maryland Assisted Living Study: prevalence, recognition, and treatment of dementia and other psychiatric disorders in the assisted living population of central

Maryland. J Am Geriatr Soc 2004; 52:1618–1625 [G]

378. Sloane PD, Barrick AL: Improving long-term care for persons with Alzheimer's disease. J Am Geriatr Soc 1996; 44:91–92 [G]
379. Teri L, Huda P, Gibbons L, Young H, van Leynseele J: STAR: a dementia-specific training program for staff in assisted living residences. Gerontologist 2005; 45:686–693 [A–]
380. Testad I, Aasland AM, Aarsland D: The effect of staff training on the use of restraint in dementia: a single-blind randomised controlled trial. Int J Geriatr Psychiatry 2005; 20:587–590 [A–]
381. Lawton MP, Brody EM, Saperstein AR: A controlled study of respite service for caregivers of Alzheimer's patients. Gerontologist 1989; 29:8–16 [B]
382. Pynoos J, Regnier V: Improving residential environments for frail elderly: bridging the gap between theory and application, in The Concept and Measurement of Quality of Life in the Frail Elderly. Edited by Birren JE, Lubben JE, Cichowlas Rowe J, Deutchman DE. San Diego, CA, Academic Press, 1991, pp 91–119 [G]
383. Reimer MA, Slaughter S, Donaldson C, Currie G, Eliasziw M: Special care facility compared with traditional environments for dementia care: a longitudinal study of quality of life. J Am Geriatr Soc 2004; 52:1085–1092 [C]
384. Sullivan-Marx EM, Strumpf NE, Evans LK, Baumgarten M, Maislin G: Predictors of continued physical restraint use in nursing home residents following restraint reduction efforts. J Am Geriatr Soc 1999; 47:342–348 [B]
385. Castle NG, Fogel B: Characteristics of nursing homes that are restraint free. Gerontologist 1998; 38:181–188 [G]
386. Tinetti ME, Liu WL, Marottoli RA, Ginter SF: Mechanical restraint use among residents of skilled nursing facilities: prevalence, patterns, and predictors. JAMA 1991; 265:468–471 [G]
387. Katz IR: Optimizing atypical antipsychotic treatment strategies in the elderly. J Am Geriatr Soc 2004; 52:S272–S277 [F]
388. Fossey J, Ballard C, Juszczak E, James I, Alder N, Jacoby R, Howard R: Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. BMJ 2006; 332:756–761 [A–]
389. Inouye SK: Delirium in older persons. N Engl J Med 2006; 354:1157–1165 [F]