NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™) GUIDELINE SYNTHESIS

MANAGEMENT OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Guidelines

1. **American College of Physicians/American Academy of Family Physicians (ACP/AAFP)**. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008 Mar 4;148(5):370-8. [63 references]
2. **American Medical Directors Association (AMDA)**. Dementia. Columbia (MD): American Medical Directors Association (AMDA); 2005. 28 p. [20 references]
3. **American Psychiatric Association (APA)**. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Arlington (VA): American Psychiatric Association (APA); 2007 Oct. 85 p. [554 references]
4. **Scottish Intercollegiate Guidelines Network (SIGN)**. Management of patients with dementia. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2006 Feb. 53 p. (SIGN publication; no. 86). [183 references]
5. **Singapore Ministry of Health (SMOH)**. Dementia. Singapore: Singapore Ministry of Health; 2007 Mar. 80 p. [162 references]

INTRODUCTION

A direct comparison of the American College of Physicians/American Academy of Family Physicians (ACP/AAFP), American Medical Directors Association (AMDA), American Psychiatric Association (APA), Scottish Intercollegiate Guidelines Network (SIGN) and Singapore Ministry of Health (SMOH) recommendations for management of Alzheimer's disease (AD) and related dementias is provided in the tables below.

The guidelines are similar in scope. In addition to addressing AD, all of the guidelines also encompass related dementias, such as vascular dementia. In addition to management, the AMDA, SIGN and SMOH guidelines also consider diagnosis and assessment; these topics are addressed in a separate synthesis (see Alzheimer's Disease and Related Dementias. Part II. Assessment and Diagnosis).

The tables below provide a side-by-side comparison of key attributes of each guideline, including specific interventions and practices that are addressed. The

language used in these tables, particularly that which is used in Table 3, Table 4, and Table 5, is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group.
- Table 2 provides a comparison of the overall scope of the guidelines.
- Table 3 provides a more detailed comparison of the specific recommendations offered by each group for the topics under consideration in this synthesis, including:
    - General Management Recommendations
    - Non-Pharmacologic Interventions
    - Pharmacological Interventions
    - Patient And Caregiver Education
    - Monitoring
- Table 4 lists the potential benefits and harms associated with the implementation of each guideline as stated in the original guidelines.
- Table 5 presents the rating schemes used to rate the level of evidence and/or the strength of the recommendations.

A summary discussion of the areas of agreement and areas of differences among the guidelines is presented following the content comparison tables.

Abbreviations:

- ACP/AAFP, American College of Physicians/American Academy of Family Physicians
- AD, Alzheimer's disease
- AMDA, American Medical Directors Association
- APA, American Psychiatric Association
- NMDA, N-methyl-D-aspartate
- NSAID, nonsteroidal anti-inflammatory agents
- SIGN, Scottish Intercollegiate Guidelines Network
- SMOH, Singapore Ministry of Health

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	ACP/AAFP (2008)	AMDA (2005)	APA (2007)	SIGN (2006)	SMOH (20067)
General Management Recommendations		✓	✓		✓
Non-Pharmacologic Interventions		✓	✓	✓	✓
Pharmacologic Interventions	✓	✓	✓	✓	✓

Patient And Caregiver Education		✓	✓	✓	
Monitoring		✓	✓		✓

TABLE 2: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
ACP/AAFP (2008)	To present the available evidence on the effectiveness of five U.S. Food and Drug Administration (FDA)-approved pharmacologic therapies for dementia for outcomes in the domains of cognition, global function, behavior/mood, and quality of life/activities of daily living
AMDA (2005)	• To offer care providers and practitioners in long-term care facilities a systematic approach to recognizing, assessing, treating, and monitoring patients with dementia, including impaired cognition and problematic behavior • To help practitioners to provide dementia patients with a systematic assessment and care plan, leading to appropriate management that maximizes functioning and quality of life and minimizes the likelihood of complications and functional decline
APA (2007)	• To assist the psychiatrist in caring for a patient with dementia • 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
SIGN (2006)	• To present evidence-based recommendations for the management of dementia • To consider investigations and interventions in which direct benefit to the patient can be demonstrated
SMOH (2007)	To provide an approach for healthcare professionals to assess, evaluate, and manage dementia (using local evidence where possible)
Target Population	
ACP/AAFP	Adults 18 years or older with a diagnosis of dementia

(2008)	
AMDA (2005)	• United States • Elderly individuals and/or residents of long-term care facilities who have, or are suspected of having, dementia
APA (2007)	• United States • Patients with dementia of the Alzheimer's type 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.
SIGN (2006)	• Scotland • Patients with all stages of dementia excluding mild cognitive impairment
SMOH (2007)	• Singapore • Adults with progressive cognitive or behavioural complaints suggestive of dementia, as well as patients who arouse the physician's or caregiver's suspicion of cognitive impairment despite absence of complaints
Intended Users	
ACP/AAFP (2008)	Physicians
AMDA (2005)	Advanced Practice Nurses Allied Health Personnel Dietitians Nurses Pharmacists

	Physicians Social Workers
APA (2007)	Allied Health Personnel Physicians
SIGN (2006)	Advanced Practice Nurses Nurses Occupational Therapists Physical Therapists Physician Assistants Physicians Psychologists/Non-physician Behavioral Health Clinicians
SMOH (2007)	Advanced Practice Nurses Hospitals Nurses Physician Assistants Physicians Psychologists/Non-physician Behavioral Health Clinicians

TABLE 3: COMPARISON OF RECOMMENDATIONS FOR MANAGEMENT OF ALZHEIMER'S DISEASE AND RELATED DISORDERS	
General Management Recommendations	
ACP/AAFP (2008)	No recommendations offered.
AMDA (2005)	**Prepare an Interdisciplinary Care Plan** An appropriate, individualized care plan for managing the patient

	with dementia should include the categories of approaches discussed in detail in Steps 10 through 15 (see Non-Pharmacologic Interventions section below). The care plan should: • Define treatment goals that are appropriate for the individual patient, taking into account the wishes of the patient and/or family; • Incorporate definite, measurable objectives derived from those treatment goals; and • Allow for modification as the patient's needs change. Ensure that all parts of the care plan are consistent and are based on appropriate assessment of the patient. Effective care of patients with dementia requires a unified care plan based on extensive coordination of functions (i.e., an *interdisciplinary* approach) rather than a composite of separately formulated approaches (i.e., a *multidisciplinary* approach). Individual opinions must be consistent with the broader goals and objectives for the patient's care. **Note**: For additional details of each step, see the original guideline document. This guideline includes an algorithm, Dementia that is to be used in conjunction with the clinical practice guideline.
APA (2007)	**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**].
SIGN (2006)	No recommendations offered
SMOH (2007)	**Social and Caregiver Management of Dementia and Community Resources** **A** - Caregiver interventions via a multifaceted approach should be considered in the total management of the person with dementia. (**Grade A, Level 1+**) **GPP** - Where appropriate, respite care can be offered to relieve the burden of caregiving on the family caregiver. (**GPP**) **GPP** - Referral to community resources to meet the care needs of

	the person with dementia and his/her carer should always be considered. (**GPP**)
Non-Pharmacologic Interventions	
ACP/AAFP (2008)	No recommendations offered.
AMDA (2005)	**Optimize Function and Quality of Life and Capitalize on Remaining Strengths** Patients with dementia often benefit from efforts to optimize their function and quality of life. Such efforts often include activities that target cognitive function (e.g., solving puzzles, engaging in arts and crafts), physical function (e.g., exercise, games), and spiritual well-being (e.g., attending religious services). • Consider using complementary and alternative therapies. • Prevent excess disability. • Consider medical interventions if appropriate. **Note**: Refer to the original guideline document for a discussion of complementary and alternative therapies. **Address Socially Unacceptable or Disruptive Behaviors** The management of socially unacceptable or disruptive behavior should be based on a careful evaluation and description of the behavior (refer to Table 20 in the original guideline document). The interdisciplinary team, in conjunction with the practitioner, should define the target symptoms (e.g., self-injury, severe agitation related to delusions) to be addressed and identify care goals. Generally, unless the behavior potentially endangers the patient or others, nonpharmacological interventions should be considered first while efforts are made to identify the causes of the problem. **Manage Functional Deficits** Patients with dementia invariably have functional deficits. Caregivers need to be aware of these deficits and should be trained to help the patient to compensate for them while also helping to maximize unimpaired function. Focus on maintaining the patient's dignity and encouraging him or her to use whatever capacities remain. Train staff to help patients with activities of daily living (ADLs) without provoking negative reactions. **Address Pertinent Psychosocial and Family Issues** Pertinent issues may include personal and family relationships, and other family issues. Facilitate appropriate activities and

	interpersonal relationships among patients with dementia. Work closely with families to help them understand the patient's situation and the plans for optimizing his or her function. Obtain and use some of the many resources available on these issues (e.g., publications from the Alzheimer's Association; see Resources in original guideline document). Train staff to address family concerns and issues. Practitioners should help to identify for families the implications of the patient's underlying condition, reassure them about the appropriateness of the selected management approach, and help to identify and address treatable medical conditions as appropriate. Other members of the interdisciplinary team also play important roles in providing information and support to family members. **Address Ethical Issues** Ethical issues relevant to patients with dementia include: • Defining decision-making capacity and identifying situations that require substitute decision-making, • Addressing situations related to everyday life (e.g., patient preferences, boundaries on sexual expression and socially questionable behaviors), and • Discussing possible limitations on medical interventions such as hospitalization, resuscitation, and artificial nutrition and hydration (tube feeding). **Manage Risks and Complications Related to Dementia** Patients with dementia often have complications directly related to their disease (e.g., impaired mobility, urinary incontinence). They may also be at risk for indirect complications such as falls, adverse medication reactions, and aspiration related to tube feeding. Caregivers and the practitioner should anticipate these significant risks and complications and be prepared to address them when they occur. Such plans should address not only medical management (e.g., what to do in case of an abrupt worsening of confusion) but also ethical issues (e.g., when and whether to perform an extensive diagnostic work-up or transfer the patient to a hospital).
APA (2007)	**Specific Psychotherapies and Other Psychosocial Treatments** In addition to the general psychosocial interventions subsumed under psychiatric management, a number of specific interventions are appropriate for some patients. Few of these treatments have been subjected to double-blind randomized evaluation, but some

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

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 Item 2 above 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**].

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**]. **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**]. **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**].
SIGN (2006)	**<u>Non-Pharmacological Interventions</u>**

Behaviour Management

B - Behaviour management may be used to reduce depression in people with dementia.

Good Practice Point: Multilevel behavioural management interventions may be more effective than individual interventions at improving behaviour and well-being in people with dementia.

Caregiver Intervention Programmes

B - Caregivers should receive comprehensive training on interventions that are effective for people with dementia.

Cognitive Stimulation

B - Cognitive stimulation should be offered to individuals with dementia.

Environmental Design

Good Practice Point: Measures which should be considered when planning an environment for people with dementia include:

- Incorporating small size units
- Separating non-cognitively impaired residents from people with dementia
- Offering respite care as a complement to home care
- Relocating residents, when necessary, in intact units rather than individually
- Incorporating non-institutional design throughout the facility and in dining rooms in particular
- Moderating levels of stimulation
- Incorporating higher light levels
- Using covers over fire exit bars and door knobs to reduce unwanted exiting
- Incorporating outdoor areas with therapeutic design features
- Considering making toilets more visible to potentially reduce incontinence
- Eliminating factors that increase stress when bathing

Multisensory Stimulation and Combined Therapies

Good Practice Points:

- In people with dementia who show behavioural disturbance despite the use of psychotropic medication, aromatherapy may influence behaviour but cannot be recommended as a direct alternative to antipsychotic drugs, nor for the reduction of specific behavioural problems.

	• The use of aromatherapy to reduce associated symptoms in people with dementia should be discussed with a qualified aromatherapist who can advise on contraindications. • Bright light therapy is not recommended for the treatment of cognitive impairment, sleep disturbance or agitation in people with dementia. • For people with moderate dementia who can tolerate it, multisensory stimulation may be a clinically useful intervention. • Multisensory stimulation is not recommended for relief of neuropsychiatric symptoms in people with moderate to severe dementia. **Physical Activities** Good Practice Point: For people with dementia a combination of structured exercise and conversation may help maintain mobility. **Reality Orientation Therapy** **D** - Reality orientation therapy should be used by a skilled practitioner, on an individualised basis, with people who are disorientated in time, place and person. **Recreational Activities** **B** - Recreational activities should be introduced to people with dementia to enhance quality of life and well-being. Good Practice Point: Individualised activities adapted to maximise the person's remaining abilities and based on previous interests may be more beneficial to people with dementia than generic activities.
SMOH (2007)	**Management of Behavioural and Psychological Symptoms of Dementia (BPSD)** **GPP** - Non-pharmacological methods to manage behavioural and psychological symptoms of dementia should be instituted, prior to consideration of pharmacological measures. (**GPP**)
Pharmacologic Interventions	
ACP/AAFP (2008)	***Recommendation 1****: Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment. (Grade: weak recommendation, moderate-quality evidence.)* The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. In particular, in more advanced dementia, family or other decision

	makers may not view stabilization or slowing of decline as a desirable goal if quality of life is judged to be poor. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of dementia, these benefits, on average, are not clinically significant for cognition and are modest for global assessments. However, limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvements. These findings should be interpreted cautiously because many trials did not report the proportion of patients who achieved clinically important improvements, and for trials that did, these outcomes were often not the primary end point of the trial. In addition, many trials that did report the proportion of patients who achieved clinically important improvements did not report the statistical significance of these findings. Currently, we have no way to predict which patients might have a clinically important response. Therefore, the evidence does not support prescribing these medications for every patient with dementia. Evidence is insufficient to determine the optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months on the basis of duration of trials. This effect could be an improvement or stabilization. In addition, no evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. However, if slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate. ***Recommendation 2****: Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. (Grade: weak recommendation, low-quality evidence.)* Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. Therefore, tolerability, adverse effect profile, ease of use, and cost of medication are reasonable criteria to help select a treatment. For example, when the benefits and harms related to a drug are being evaluated, the severe side effects associated with tacrine make it an unreasonable choice. Cholinesterase inhibitors discussed in this guideline are approved for treatment of mild to moderate dementia, and memantine is approved by the FDA for the treatment of moderate to severe Alzheimer disease. Patients with mild vascular dementia have

	shown mild benefit from memantine. However, memantine use in mild Alzheimer disease has not been well studied. Major contraindications of cholinesterase inhibitors and memantine include, but are not limited to, uncontrolled asthma, angle-closure glaucoma, the sick sinus syndrome, and left bundle-branch block. ***Recommendation 3****: There is an urgent need for further research on the clinical effectiveness of pharmacologic management of dementia.* Further research is needed to evaluate the effectiveness of pharmacologic therapy for dementia and to assess whether treatment affects outcomes, such as institutionalization. Evaluation of the appropriate duration of therapy and more head-to-head comparisons of agents are needed. Finally, assessment of the effectiveness of combination therapy is lacking.
AMDA (2005)	**Consider Medical Interventions if Appropriate** Patients with dementia related to specific causes may benefit from certain medical interventions. For example, medical interventions such as the use of anticoagulants, antihypertensive agents, and lipid-lowering or antiplatelet agents may prevent worsening of symptoms in a patient with multi-infarct dementia. Cholinesterase inhibitors may reduce the rate of decline in cognitive function (notably memory and attention) and may improve behavioral symptoms in patients with mild to moderate dementia. Three agents of this class (donepezil, rivastigmine, and galantamine) are currently approved by the U.S. Food and Drug Administration (FDA) to treat patients with dementia of the Alzheimer's type. Table 18 in the original guideline document compares the characteristics of these medications. Consider the use of a cholinesterase inhibitor in patients with a diagnosis of dementia who have mild to moderate cognitive and functional decline that is not caused by an underlying treatable condition and in whom drug therapy is not clinically contraindicated. In patients who do not appear to be benefiting from these medications or whose cognition is deteriorating despite treatment, consider discontinuing therapy if no other clear indication exists. Explain the rationale for discontinuing these medications to the patient and involved family members. In some cases, discontinuation maybe associated with worsening cognitive and physical function. Memantine hydrochloride (an N-methyl-D-aspartate receptor antagonist) is the only medication currently approved by the U.S. FDA to treat patients with moderate to severe dementia of the Alzheimer's type. The recommended starting dose of memantine

	hydrochloride is 5 mg once daily; the dose should be increased by 5 mg every week to a target dose of 20 mg/day. This agent may be used alone or in combination with a cholinesterase inhibitor. Other agents, including selegiline, NSAIDs, estrogen, and vitamin E have been tried in the treatment of dementia. However, strong evidence is not available to support their use and some of them may be associated with adverse effects. **Address Socially Unacceptable or Disruptive Behaviors** Table 22 in the original guideline document lists medication options used to manage behavioral and psychological symptoms in patients with dementia. They should be utilized only after careful consideration of the causes of symptoms and only when a clear indication is present and non-pharmacological strategies or other treatments are not pertinent or have failed. These medications have modest effectiveness and also have associated risks. Their effects should be monitored regularly—especially when the patient has other risk factors related to, or is also taking other medications affecting, the cardiovascular or central nervous system.
APA (2007)	**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**]. **Treatment of Cognitive Symptoms** Three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—are approved by the U.S. 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 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 (alpha-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**].

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**].

Treatment of Psychosis and Agitation

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 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**].

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**]. **Treatment of Sleep Disturbances** 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 insomnia, worsening cognition, falls, disinhibition, and delirium [**II**]. Diphenhydramine is not recommended because of its anticholinergic properties [**II**]. Antipsychotic medications should not be used solely for the purpose of treating sleep disturbances [**I**].
SIGN (2006)	**Cholinesterase Inhibitors** **B** - Donepezil, at daily doses of 5 mg and above, can be used: • To treat cognitive decline in people with Alzheimer's disease. • For the management of associated symptoms in people with Alzheimer's disease. Good Practice Point: Age and severity of AD should not be contraindications to the use of donepezil. **B** - Galantamine, at daily doses of 16 mg and above, can be used: • To treat cognitive decline in people with Alzheimer's disease and people with mixed dementias. • For the management of associated symptoms in people with Alzheimer's disease.

Good Practice Point: Galantamine should be used with slow escalation to doses of up to 24 mg.

B - Rivastigmine, at daily doses of 6 mg and above, can be used:

- To treat cognitive decline in people with Alzheimer's disease.
- To treat cognitive decline in people with dementia with Lewy bodies.
- For the management of associated symptoms in people with Alzheimer's disease and dementia with Lewy bodies.

Ginkgo

Good Practice Point: People with dementia who wish to use Ginkgo biloba should consult a qualified herbalist for advice and should be made aware of possible interactions with other prescribed drugs.

Salvia

Good Practice Point: People with dementia who wish to use Salvia officinalis should consult a qualified herbalist for advice.

Antidepressants

D - Antidepressants can be used for the treatment of comorbid depression in dementia providing their use is evaluated carefully for each patient.

Antipsychotics

A - If necessary, conventional antipsychotics may be used with caution, given their side effect profile, to treat the associated symptoms of dementia.

Good Practice Points:

- Atypical antipsychotics with reduced sedation and extrapyramidal side effects may be useful in practice, although the risk of serious adverse events such as stroke must be carefully evaluated.
- An individualised approach to managing agitation in people with dementia is required.
- Where antipsychotics are inappropriate cholinesterase inhibitors may be considered.
- In patients who are stable antipsychotic withdrawal should be considered.

Trazadone

Good Practice Point: Trazadone may be considered for patients with depressive symptoms and dementia associated agitation.

Clinically Ineffective Interventions

Anti-Inflammatories

A - Anti-inflammatories are not recommended for treatment of cognitive decline in people with Alzheimer's disease.

B - Hydroxychloroquine is not recommended for the treatment of associated symptoms in people with dementia.

A - Prednisolone is not recommended for the treatment of associated symptoms in people with Alzheimer's disease.

Oestrogen

B - Oestrogen is not recommended for the treatment of associated symptoms in women with dementia.

Selegiline

A - Selegiline is not recommended for the treatment of core or associated symptoms in people with Alzheimer's disease.

Interventions Lacking Evidence of Clinical Effectiveness

Anticonvulsants

A - Valproate is not recommended for the treatment of behavioural symptoms associated with dementia.

Good Practice Point: Anticonvulsants may be considered for the symptomatic treatment of seizures or myoclonus associated with dementia but are not recommended for other symptoms of dementia.

Aspirin

Good Practice Point: Aspirin is only recommended for people with vascular dementia who have a history of vascular disease.

Lithium

Good Practice Point: In the absence of concurrent evidence of bipolar affective disorder lithium is not recommended for the reduction of behavioural problems in dementia.

SMOH (2007)	**Pharmacological Management of Dementia** **GPP** - Pharmacotherapy should be part of a multi-pronged strategy to dementia management that encompasses a well-established diagnosis, education of patient and caregiver, non-pharmacological measures and comprehensive caregiver psychosocial intervention. (**GPP**) **B** - Although high dose vitamin E (2000 IU per day) may have a modest effect in delaying disease progression in moderately severe Alzheimer's disease, doses of vitamin E in excess of 400 IU a day should be avoided for the treatment of Alzheimer's disease until there is further data on its safety, especially in patients with cardiovascular disease. (**Grade B, Level 1+**) **A** - Anti-inflammatory agents (such as non-steroidal anti-inflammatory agents and cyclo-oxygenase 2 inhibitors) are not recommended for the prevention of cognitive decline in Alzheimer's disease (Aisen et al., 2003; Reines et al., 2004). (**Grade A, Level 1++**) **B** - Prednisolone is not recommended for the prevention of cognitive decline in Alzheimer's disease (Aisen et al., 2000). (**Grade B, Level 1+**) **A** - Oestrogen is not recommended for the prevention of cognitive decline in women with dementia. (**Grade A, Level 1++**) **A** - Acetylcholinesterase inhibitors should be considered for the management of all patients with mild to moderate Alzheimer's disease. (**Grade A, Level 1++**) **B** - Acetylcholinesterase inhibitors can be considered for the management of moderate to severe Alzheimer's disease. (**Grade B, Level 1+**) **A** - Acetylcholinesterase inhibitors have been shown to be of clinical benefit and may be considered for use in the management of mild to moderate vascular dementia. (**Grade A, Level 1+**) **B** - Acetylcholinesterase inhibitors can be considered for the management of dementia with Lewy bodies and Parkinson's disease dementia. (**Grade B, Level 1+**) **B** - All three available acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine) can be considered for the pharmacological management of dementia, since there is no definite evidence to support a difference in clinical efficacy between them. (**Grade B, Level 1+**)

	A - Where tolerated, acetylcholinesterase inhibitors should be titrated to recommended doses (5 to 10 mg/day donepezil; 6 to 12 mg/day rivastigmine; 16 to 24 mg/day galantamine), which have been shown to confer greater benefit compared with lower doses. (**Grade A, Level 1++**) **B** - N-methyl D-aspartate (NMDA) antagonists such as memantine can be considered for the management of moderate to severe Alzheimer's disease, either alone or in combination with acetylcholinesterase inhibitors. (**Grade B, Level 1+**) **B** - N-methyl D-aspartate antagonists such as memantine may be a treatment option for mild to moderate Alzheimer's disease, if acetylcholinesterase inhibitor therapy is contra-indicated, not tolerated or if there is disease progression despite an adequate trial of acetylcholinesterase inhibitor. (**Grade B, Level 1+**) **A** - N-methyl D-aspartate antagonists have been shown to be of clinical benefit and may be considered for use in the management of mild to moderate vascular dementia. (**Grade A, Level 1+**) **B** - Practitioners who prescribe ginkgo for the treatment of dementia should be aware of the unestablished benefit, variability of active ingredient among preparations, and potential for drug interactions. (**Grade B, Level 1+**) **A** - Selegiline is not recommended for the treatment of core or associated symptoms in Alzheimer's disease. (Birks & Flicker, 2003) (**Grade A, Level 1++**) **GPP** - Appropriate treatment of vascular risk factors is recommended for all patients. However, it should be noted that whilst promising observational data exists, it remains to be shown in a randomised controlled clinical trial if any prevention strategy such as blood pressure reduction or antiplatelet treatment for the secondary prevention of stroke, will reduce the incidence of vascular dementia. (**GPP**) **GPP** - The decision to initiate costly symptomatic dementia treatment, such as acetylcholinesterase inhibitors or N-methyl D-aspartate antagonists, should always be made in consultation with the patient and family after careful consideration of the expected magnitude of benefit, side effects, comorbidities and costs of treatment. (**GPP**) **GPP** - Patients who are started on acetylcholinesterase inhibitors or N-methyl D-aspartate antagonists should be carefully monitored for side effects and response to treatment. (**GPP**) **Pharmacological Interventions to Manage Behavioural and**

	Psychological Symptoms of Dementia (BPSD) **GPP** - Antidepressants may be used for the treatment of comorbid depression in dementia provided their use has been evaluated carefully for each patient. (**GPP**) **A** - Conventional and atypical antipsychotics may be used with caution, given their side effect profile, to treat neuropsychiatric symptoms of dementia. (**Grade A, Level 1+**) **B** - Trazodone may be considered for patients with depressive symptoms and dementia associated agitation. (**Grade B, Level 1+**) **A** - Routine use of mood stabilizers, such as carbamazepine and sodium valproate, is not recommended for treatment of behavioural symptoms associated with dementia. (**Grade A, Level 1+**) **GPP** - An individualized approach to managing behavioural problems in dementia patients is required. (**LGPP**) **GPP** - Cholinesterase inhibitor therapy may be considered in treatment of patients with behavioural problems if antipsychotics are inappropriate. (**GPP**) **GPP** - The decision to start antipsychotic therapy to control behavioural problems in dementia patients should be made in consultation with the patient and family, after careful consideration of the benefit, adverse-effects and co-morbidities. (**GPP**) **B** - For patients with dementia with Lewy Body and behavioural problems, acetylcholinesterase inhibitors should be considered first for management of the behavioural problems. (**Grade B, Level 1+**) **GPP** - In all patients started on antipsychotic medication, they should be monitored carefully for side effects and response to treatment. In patients who are stable, antipsychotic withdrawal should be considered. (**GPP**)
Patient And Caregiver Education	
ACP/AAFP (2008)	No recommendations offered.
AMDA (2005)	**Prevent Excess Disability** Table 17 in the original guideline document suggests possible organizational, physical environment, and psychosocial approaches

	to environmental adaptation, including • Provide family support and education • Provide relevant staff education and training **Address Pertinent Psychosocial and Family Issues** Pertinent issues may include personal and family relationships, and other family issues. Facilitate appropriate activities and interpersonal relationships among patients with dementia. Work closely with families to help them understand the patient's situation and the plans for optimizing his or her function. Obtain and use some of the many resources available on these issues (e.g., publications from the Alzheimer's Association; see Resources in original guideline document). Train staff to address family concerns and issues. Practitioners should help to identify for families the implications of the patient's underlying condition, reassure them about the appropriateness of the selected management approach, and help to identify and address treatable medical conditions as appropriate. Other members of the interdisciplinary team also play important roles in providing information and support to family members.
APA (2007)	**Psychiatric Management** 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**].
SIGN (2006)	**Supportive Information for Patients and Carers** **C** - Patients and carers should be offered information tailored to the patient's perceived needs. Good Practice Point: Good communication between healthcare professionals, patients and carers is essential. *Disclosure of Diagnosis* **C** - Healthcare professionals should be aware that many people with dementia can understand their diagnosis, receive information and

	be involved in decision making. **C** - Healthcare professionals should be aware that some people with dementia may not wish to know their diagnosis. **D** - Healthcare professionals should be aware that in some situations disclosure of a diagnosis of dementia may be inappropriate. Good Practice Points: • The wishes of the person with dementia should be upheld at all times. • The diagnosis of dementia should be given by a health care professional skilled in communication or counselling. • Where diagnosis is not disclosed there should be a clear record of the reasons. *Information at Other Stages of the Patient Journey* Good Practice Points: • Patients and carers should be provided with information about the services and interventions available to them at all stages of the patient's journey of care. • Information should be offered to patients and carers in advance of the next stage of the illness.
SMOH (2007)	No recommendations offered.
Monitoring	
ACP/AAFP (2008)	No recommendations offered.
AMDA (2005)	**Monitor the Patient's Condition and Adjust Management as Appropriate** Monitor the patient's progress periodically, using the same methods and criteria used in the initial assessment. If the patient's condition remains stable, continue pertinent interventions. If he or she declines rapidly or progressively, the practitioner, other direct care providers, and possibly a consulting psychiatrist should assess the patient and review the medical record to identify possible reasons for the decline. Refer to the NGC summary of AMDA's clinical practice guideline Acute Change of

	Condition in the Long-term Care Setting. Periodically, the practitioner should document functional decline that appears to be medically unavoidable (i.e., decline that results from the effects of aging or illness, including the progression of dementia that cannot or should not be treated). Periodic attempts to taper one or more psychoactive medications are sometimes warranted, unless the nature of the condition (e.g., psychotic delusions) or past experience suggest that doing so may result in a return or an exacerbation of the patient's symptoms. The practitioner should periodically review the patient's condition and risk factors with the nursing staff and the family. As appropriate, review the staging of a patient whose behavior or function changes (improves or declines) significantly from a previous baseline. Medication reduction efforts should follow published recommendations and should be consistent with the guidelines in the OBRA '87 federal nursing facility regulations and future supplements.
APA (2007)	**General Treatment Principles and Alternatives** 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 to 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**].
SIGN (2006)	No recommendations offered.
SMOH (2007)	**GPP** - Patients who are started on acetylcholinesterase inhibitors or N-methyl D-aspartate antagonists should be carefully monitored for side effects and response to treatment. (**GPP**) **GPP** - In all patients started on antipsychotic medication, they should be monitored carefully for side effects and response to treatment. In patients who are stable, antipsychotic withdrawal should be considered. (**GPP**)

TABLE 4: BENEFITS AND HARMS	
Benefits	
ACP/AAFP (2008)	Appropriate pharmacologic treatment of dementia based on tolerability, adverse effect profile, ease of use, and cost of medications
AMDA (2005)	**Expected Outcomes from Implementation of this Clinical Practice Guideline** Implementation of this guideline should: • Identify patients who are at risk for new or progressive dementia • Identify the nature and causes of dementia in different patients • Make appropriate environmental modifications to maximize patient dignity, comfort and safety • Identify and manage potential sources of excess disability • Minimize preventable complications and functional decline • Manage dementia symptoms, consequences, and complications effectively and appropriately • Respond appropriately to the changing needs of patients with dementia *Anticipated care outcomes:* As a result of the above, the following patient-related outcomes may be anticipated: • Maintained or improved function and quality of life prior to the end of life • Reduced complications and negative consequences of the condition or its management • Improved resource utilization
APA (2007)	**Potential Benefits** Effective treatment and management of patients with Alzheimer's disease and other dementias
SIGN (2006)	Implementation of this guideline should: • Improve early identification of dementia • Allow early involvement of professional services in treatment • Ensure that people receive clinically effective treatment at a point where both they and their carers will be able to appreciate the benefits • Ensure that patients and carers have a better understanding of the illness and are able to adjust to difficulties as they arise • Aid management of problems and difficulties, which can delay

	the need to go into a care home
SMOH (2007)	**Potential Benefits** Appropriate assessment, evaluation, and management of patients with dementia
Harms	
ACP/AAFP (2008)	**Adverse Effects of Medications** • **Donepezil:** Withdrawal rates because of adverse events associated with donepezil ranged from 0% to 57% in the treatment groups (0% to 20% in placebo groups). No study showed a statistically significant difference between the treatment and placebo groups for serious adverse events except for the expected side effects of cholinesterase inhibitors (diarrhea, nausea, and vomiting). Six studies reported a dose—response effect with increasing frequency of adverse events as dosage increased. • **Galantamine:** Withdrawal for adverse events for galantamine ranged from 8% to 54% in the treatment group (4% to 17% in the placebo group). Four studies showed a dose—response relationship for adverse events during titration. Although most trials did not report statistical analysis of adverse effects, 2 studies reported statistically significant weight loss in the treatment group. Commonly reported adverse effects included gastrointestinal symptoms (nausea, vomiting, and diarrhea), eating disorders/weight loss, and dizziness. • **Rivastigmine:** Withdrawal rates related to adverse events ranged from 12% to 29% in the treatment group (0% to 11% in the placebo group). The frequency of adverse events between treatment and control groups did not differ. However, 2 studies showed a dose—response relationship for adverse events. The types of adverse events were consistent with those related to cholinesterase inhibitor use and included dizziness, nausea, vomiting, eating disorder/weight loss, and headache. • **Tacrine:** The withdrawal rate related to adverse events ranged from 0% to 55% in the treatment group (0% to 12% in the placebo group). The evidence showed that adverse events related to tacrine were serious and increased with higher doses. Elevated alanine aminotransferase level and other hepatic abnormalities were reported in 6 of 7 studies. Nausea, vomiting, gastrointestinal problems, and dizziness were reported in addition to the serious liver abnormalities. • **Memantine:** The withdrawal rates related to adverse effects varied from 9% to 12% in the treatment group (7% to 13% in the placebo group), including nausea, dizziness, diarrhea, and

	agitation. Refer to the original guideline document for more information on adverse effects of medications.
AMDA (2005)	The medical treatment of problematic behavior and impaired cognition may also cause complications that resemble an acute illness or a worsening of the underlying condition. • Adverse drug interactions • Worsening of disruptive or socially unacceptable behavior • Cardiac arrhythmias • Orthostatic hypotension
APA (2007)	**<u>Psychosocial Treatment</u>** Short-term adverse emotional consequences have occasionally been reported with some psychosocial treatments. This is especially true of the cognitively oriented treatments, during which frustration, catastrophic reactions, agitation, and depression have been reported. **<u>Pharmacological Treatment</u>** 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. 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. Side effects of specific medications are discussed further in the original guideline document.
SIGN (2006)	**Subgroups Most Likely to be Harmed** • Practitioners should be aware that up to 60% of patients with dementia with Lewy bodies suffer adverse reactions to *antipsychotic drugs*.

	• *Ginkgo* causes bleeding when combined with warfarin or aspirin, raises blood pressure when combined with a thiazide diuretic and possibly causes coma when combined with trazodone.
SMOH (2007)	**Adverse Effects of Medications** • Although generally well tolerated, dose-related gastrointestinal side effects (nausea, vomiting, diarrhea, anorexia) are common with *acetylcholinesterase inhibitors (AchEI)* use. These are transient and often circumvented to a large extent by a slower titration and taking the medication with food. Great caution should be exercised in those with bradycardia, sick sinus syndrome or cardiac conduction disturbances, in view of possible adverse effects of symptomatic bradycardia and syncope. Other less common side effects that have been reported include muscle cramps, insomnia, vivid dreams and weight loss. Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) patients commenced on AchEI should be carefully monitored for worsening of motor symptoms. • Compared with AchEI, gastrointestinal-related side effects are uncommon with *memantine* use. Common adverse events of *memantine* include dizziness, headache, fatigue, hallucinations and confusion, but these tend to be transient. Memantine should be used with caution in patients with epilepsy and renal impairment, and the clinician should be aware of interactions involving commonly prescribed medications such as dextromethorphan and L-dopa. • Doses of *vitamin E* in excess of 400 IU a day should be avoided for the treatment of Alzheimer's disease until there is further data on its safety, especially in patients with cardiovascular disease. • Conventional antipsychotics are associated with extrapyramidal side effects and somnolence • *Atypical antipsychotics* are associated with somnolence and gait disturbance. These adverse effects are 7.5 to 11 times more common in olanzepine-treated group compared to placebo. Serious adverse events occurred in 16.8% of risperidone versus 8.8% of placebo group, including 5 strokes and 1 transient ischaemic attacks, all in risperidone group. Meta-analysis of adverse events performed showed 3-fold statistically increased risk of cerebrovascular adverse events with risperidone and olanzepine (no statistically significant increase in mortality) while another meta-analysis comparing risk of death with atypical antipsychotics (Aripiprazole, Olanzepine, Risperidone and Quetiapine) with placebo showed increased risk of death. Other serious adverse events reported included somnolence and metabolic complications of hyperglycemia and weight gain. • A recent retrospective cohort study had shown increased mortality among subjects using *conventional antipsychotics*

	compared to atypical antipsychotics. Antipsychotic medication should be used cautiously in patients suspected to have dementia with Lewy Body as these patients have marked sensitivity to neuroleptic agents, including life-threatening neuroleptic malignant syndrome.

TABLE 5: EVIDENCE RATING SCHEMES AND REFERENCES

ACP/AAFP (2008)	**American College of Physicians' Clinical Practice Guidelines Grading System***		
	Quality of Evidence	Strength of Recommendation	
		Benefits Clearly Outweigh Risks and Burden **OR** Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
	High	Strong	Weak
	Moderate	Strong	Weak
	Low	Strong	Weak
	Insufficient evidence to determine net benefits or risks	I recommendation	
	*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.		
AMDA (2005)	The type of evidence supporting the recommendations is not specifically stated. The guideline was developed by interdisciplinary work groups using a process that combines evidence and consensus-based approaches.		
APA (2007)	**<u>Definition of the Three Categories of Endorsement</u>**		

	[**I**] Recommended with substantial clinical confidence [**II**] Recommended with moderate clinical confidence [**III**] May be recommended on the basis of individual circumstances **Nature of Supporting Evidence** [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, e.g., 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 opinion, case reports, and other reports not included above.
SIGN (2006)	**Levels of Evidence** **1++**: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias **1+**: Well-conducted meta-analyses, systematic reviews of RCTs,

or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++: High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Grades of Recommendations

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

Grade A: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

Grade B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

Grade C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 2++

Grade D: Evidence level 3 or 4; *or*

	Extrapolated evidence from studies rated as 2+ **Good Practice Points**: Recommended best practice based on the clinical experience of the guideline development group.
SMOH (2007)	**Levels of Evidence** **1++** High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias. **1+** Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias. **1-** Meta-analyses, systematic reviews, or RCTs with a high risk of bias. **2++** High quality systematic reviews of case-control or cohort or studies. High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal. **2+** Well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal. **2-** Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal. **3** Non-analytic studies (e.g., case reports, case series) **4** Expert opinion. **Grades of Recommendation** **A**. At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or A body of evidence, consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results **B**. A body of evidence, including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or

	Extrapolated evidence from studies rated as 1++ or 1+ **C**. A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ **D**. Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **GPP**: (good practice points) Recommended best practice based on the clinical experience of the guideline development group.

GUIDELINE CONTENT COMPARISON

The American College of Physicians/American Academy of Family Physicians (ACP/AAFP), American Medical Directors Association (AMDA), American Psychiatric Association (APA), Scottish Intercollegiate Guidelines Network (SIGN) and Singapore Ministry of Health (SMOH) present recommendations for the management and treatment of Alzheimer's disease (AD) and related dementias.

As mentioned above, the guidelines are similar in scope. In addition to addressing AD, all of the guidelines also encompass related dementias, such as vascular dementia. In addition to management, the AMDA, SIGN and SMOH guidelines also consider diagnosis and assessment; these topics are addressed in a separate synthesis (see Alzheimer's Disease and Related Dementias. Part II. Assessment and Diagnosis).

Areas of Agreement

General Management Recommendations

The two groups that address care plans, AMDA and APA, agree that the care plans should be individualized and multimodal, and should evolve and allow for modification to address newly emerging issues and the patient's changing needs. SMOH agrees that care should be provided via a multifaceted approach, and also makes recommendations regarding respite care and referral to community resources.

Non-pharmacologic Interventions

Among the guidelines that provide specific recommendations for non-pharmacologic interventions (AMDA, APA, and SIGN), there is general agreement that activities that target cognitive function, physical activity, and overall well-being should be encouraged. Although all three guidelines indicate that

stimulation-oriented treatments (e.g. recreational activity, art therapy, music therapy, pet therapy, aromatherapy) may be useful, they do not make unqualified recommendations for their use given the absence of sufficient data concerning effectiveness.

Pharmacologic Interventions

Four guidelines, AMDA, APA, SIGN and SMOH, provide explicit recommendations regarding appropriate medications for a certain type and/or severity of dementia. ACP/AAFP states that many of the improvements demonstrated in the clinical trials, although statistically significant, were not clinically important or their relative importance could not be determined at this time. In addition, the ACP/AAFP guideline raises the issue that few trials compare one drug with another and that evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. As a result, the ACP/AAFP guideline focuses on prescribing practices, more specifically the decision to initiate pharmacologic therapy, factors to consider in choosing a pharmacological agent, and research needed on the clinical effectiveness of pharmacologic management of dementia.

The four guidelines that provide specific pharmacological recommendations agree that cholinesterase inhibitors are the drug of choice for the treatment of AD. Donepezil, rivastigmine, and galantamine are currently approved by the U.S. FDA for the treatment of mild to moderate AD, and are recommended by all four groups for this indication. SIGN also notes that there is evidence to suggest that the efficacy of donepezil may extend to the treatment of people with more severe forms of AD and adds that age and severity of AD should not be contraindications to its use. APA similarly notes that donepezil has been approved by the FDA for severe Alzheimer's disease and that it may be helpful in this population. According to SMOH, acetylcholinesterase inhibitors can be considered for the management of moderate to severe AD.

In addition, there is overall agreement between the four guidelines that other classes of medication may be appropriate for the treatment of dementia-related symptoms including depression, psychosis, and anxiety. The groups agree that antidepressants may be used for the treatment of comorbid depression, provided their use has been evaluated carefully for each patient, and that the antidepressant Trazadone may be appropriate for patients with dementia-associated agitation. The guidelines agree that, if necessary, antipsychotics may be recommended with caution, given their side effect profile, to treat the neuropsychiatric symptoms of dementia.

There is also agreement that in addition to being the pharmacologic therapy of choice for AD, cholinesterase inhibitors can also be considered for the management of other dementias, including dementia with Lewy bodies and Parkinson's disease dementia.

The groups agree that the available effectiveness and safety data for other agents, including vitamin E, *Ginkgo biloba*, hydroxychloroquine, prednisolone, statin medications, selegiline, estrogen and NSAIDs, do not support recommendations for the treatment of core or associated symptoms in people with AD at this time. There is also agreement that anticonvulsants (e.g., sodium

valproate) and mood stabilizers (e.g., lithium) are not indicated for routine use in the management of AD and its associated symptoms.

ACP/AAFP does not provide recommendations for the use of particular pharmacological agents, but rather recommends clinicians base this choice on tolerability, adverse effect profile, ease of use, and cost of medication. They add that the evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia.

Monitoring

AMDA, APA and SMOH agree that patients receiving medications to treat dementia or behavioral and mood problems should be carefully monitored for side effects and drug interactions, including periodic laboratory tests. In addition, the need for the medication should be periodically reassessed.

Patient and Caregiver Education

AMDA, APA, and SIGN emphasize the importance of communicating with the patient (as appropriate) and caregivers regarding the patient's status, treatment plan, and approaches to behavioral management. In addition, the guidelines emphasize the need for the physician to be familiar with and make referrals to community support services, such as adult day care programs and AD support organizations.

Areas of Differences

Pharmacologic Interventions

The AMDA, APA and SMOH guidelines recommend memantine, which is currently approved by the U.S. FDA to treat moderate to severe AD. According to APA, it may provide modest benefits and has few adverse effects, and thus may be recommended for such patients. SMOH notes that it may also be a treatment option for mild to moderate AD if acetylcholinesterase inhibitor therapy is contraindicated, not tolerated, or if there is disease progression despite an adequate trial of acetylcholinesteraste inhibitor.

In contrast to AMDA, APA and SMOH, SIGN states there is insufficient evidence to recommend memantine for the treatment of core or associated symptoms in people with dementia. They cite the Scottish Medicines Consortium assessment of memantine, which concluded that the magnitude of any beneficial effect was small and the clinical importance unclear.

Recommendations also differ regarding the use of achetylcholinesterase inhibitors and memantine for the treatment of vascular dementia. Regarding the use of the former, SMOH makes a grade "A" recommendation that they have been shown to be of clinical benefit and may be considered for use in the management of mild to moderate vascular dementia. In contrast, APA notes that the efficacy and safety of cholinesterase inhibitors for patients with mild cognitive impairment and vascular dementia are uncertain; therefore, no specific recommendation can be made at this time, although individual patients may benefit from these agents.

SIGN does not address this issue at length, but notes that galantamine can be used to treat cognitive decline in people with mixed dementias. They also cite a systematic review of the use of donepezil in people with vascular dementia, noting that it demonstrated some benefit to patients with mild to moderate cognitive impairment examined over a six month period.

With regard to the use of memantine, SMOH provides a grade "A" recommendation, stating that NMDA antagonists have been shown to be of clinical benefit and may be considered for use in the management of mild to moderate vascular dementia. ACP/AAFP notes that patients with mild vascular dementia have shown mild benefit from memantine. They add, however, that memantine use in mild AD has not been well studied. According to APA however, there is very little evidence of memantine's benefit in vascular dementia.

This Synthesis was prepared by ECRI on September 27, 2006. It was reviewed by SIGN on October 23, 2006 and CWGAD/AALA on October 26, 2006. This synthesis was revised on November 26, 2007 following the removal of the CWGAD/AALA recommendations from the Web site. This synthesis was updated most recently on May 12, 2008 to include ACP/AAFP, APA and SMOH recommendations. The updated recommendations were verified by ACP on May 27, 2008 and by APA on June 23, 2008.

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