Management of Alzheimer's Disease and Related Dementias

Guidelines Being Compared:


A direct comparison of recommendations presented in the above guidelines for the management of Alzheimer's disease (AD) and related dementias is provided below.

**Areas of Agreement**

**Pharmacological Management of Dementia**

Three groups—APA, NICE, and SMOH—provide explicit recommendations regarding appropriate medications for a certain type and/or severity of dementia. The guideline developers agree that the three cholinesterase inhibitors donepezil, rivastigmine and galantamine are the primary medications used in the management of
AD, and should be considered for the management of patients with mild to moderate disease. There is less agreement regarding their use in severe AD—refer to Areas of Difference below for information.

With regard to the use of cholinesterase inhibitors for types of dementia other than AD, APA and SMOH agree that they can be considered for patients with dementia with Lewy bodies and dementia associated with Parkinson's disease. APA specifies that only rivastigmine has been approved by the FDA for the latter indication, but that there is no reason to believe the benefit is specific to this cholinesterase inhibitor. NICE did not assess the benefits of cholinesterase inhibitors for patients with forms of dementia other than AD.

There is consensus that the NMDA antagonist memantine can be considered for the management of moderate and severe AD (NICE specifies that use in people with moderate disease should be reserved for those who are intolerant of or have a contraindication to cholinesterase inhibitors). There is less agreement regarding its use in mild AD—refer to Areas of Difference below for information.

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. The ACP/AAFP guideline focuses primarily 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.

NICE specifies that pharmacological treatment be initiated only by specialists in the care of patients with dementia; that patients who continue treatment should be reviewed regularly using cognitive, global, functional, and behavioral assessment; and that carers' views on the patient's condition should be sought at baseline and at follow-up. NICE also cites circumstances in which it is inappropriate to rely solely on the patient's cognition scores when assessing the severity of AD and the need for treatment. In such cases, they recommend healthcare professionals use another appropriate method of assessment.

Other Pharmacologic Agents

APA and SMOH agree 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 trazodone 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.

APA and SMOH further 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.

The NICE technology appraisal only addresses donepezil, galantamine, rivastigmine and memantine.

**Patient and Caregiver Education**

APA emphasizes the importance of communicating with the patient (as appropriate) and caregivers regarding the patient's status, treatment plan, and approaches to behavioral management. APA also underscores 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 Difference**

**Cholinesterase Inhibitors for the Management of Severe AD**

While NICE recommends cholinesterase inhibitors as options for managing AD of mild to moderate severity only, SMOH states that they can be considered for the management of moderate to severe AD. APA similarly states that cholinesterase inhibitors may be helpful for patients with severe AD.

**Memantine for the Management of Mild AD**

NICE recommends memantine as an option only for managing moderate AD (in people who are intolerant of or have a contraindication to cholinesterase inhibitors) and severe AD. SMOH, in contrast, deems it an option for the management of mild to moderate AD if cholinesterase inhibitor therapy is contraindicated, not tolerated, or if there is disease progression despite an adequate trial of a cholinesterase inhibitor. APA notes that there is some evidence of memantine's benefit in mild AD, but the developer does not make an explicit recommendation for its use for this level of severity.

**Cholinesterase Inhibitors for the Management of Vascular Dementia**

SMOH states that cholinesterase inhibitors have been shown to be of clinical benefit and may be considered for use in the management of mild to moderate vascular dementia. APA, in contrast, states that the constructs of mild cognitive impairment and vascular dementia are evolving and have ambiguous boundaries with AD. The efficacy and safety of cholinesterase inhibitors for patients with these disorders are uncertain, APA continues, and therefore makes no specific recommendation, noting that individual patients may benefit from these agents.

NICE did not assess the benefits of the three cholinesterase inhibitors for patients with forms of dementia other than AD.

**Memantine for the Management of Vascular Dementia**
While APA and SMOH agree on the use of memantine for AD, there is less agreement regarding its efficacy in the management of vascular dementia. According to APA, there is very limited evidence of its benefit in vascular dementia. SMOH, in contrast, 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.

General Management Recommendations

|-----------------|-----------------------------|
| 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].

**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 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 [1].

All patients and families should be informed that even mild dementia increases the risk of vehicular accidents [1]. Mildly impaired patients should be advised to limit their driving to safer situations or to stop driving [1], and moderately impaired patients should be instructed not to drive [1]. Advice about driving cessation should also be communicated to family members, as the implementation of the recommendation often falls on them [1]. Relevant state laws regarding notification should be followed [1].

| NICE (2011) | No recommendations offered. |
| SMOH (2007) | **Social and Caregiver Management of Dementia and Community Resources**

  - 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** - Referral to community resources to meet the care needs of the person with dementia and his/her carer should always be considered.

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<th>Non-pharmacologic Interventions (Back to top)</th>
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| **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 [III]. 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 [III]. Among the emotion-oriented treatments, supportive psychotherapy can be employed to address issues of loss in the early stages of dementia [III]. 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 [III]. 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].

| NICE (2011) | No recommendations offered. |
| 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. |
**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
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 AD. Patients with mild vascular dementia have shown mild benefit from memantine. However, memantine use in mild AD 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.

**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 [1]. 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 [1].

**Treatment of Cognitive Symptoms**

Three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—are approved by the U.S. FDA for treatment of mild to moderate AD, and donepezil has been approved by the FDA for severe AD. 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 AD after a thorough discussion of their potential risks and benefits [1], and they may be helpful
for patients with severe AD [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 AD. 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 AD, 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 AD [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 [III].

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 AD 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 [II]. 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].

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**NICE (2011)**

The review and re-appraisal of donepezil, galantamine, rivastigmine and memantine for the treatment of AD has resulted in a change in the guidance. Specifically:

- Donepezil, galantamine and rivastigmine are now recommended as options for managing mild as well as moderate AD, and
- Memantine is now recommended as an option for managing moderate AD for people who cannot take acetylcholinesterase (AChE) inhibitors, and as an option for managing severe AD.

**Guidance**

The three AChE inhibitors donepezil, galantamine, and rivastigmine are recommended as options for managing mild to moderate AD under all of the conditions specified below.

Memantine is recommended as an option for managing AD for people with:

- Moderate AD who are intolerant of or have a contraindication to AChE inhibitors or
- Severe AD

Treatment should be under the following conditions:

- Only specialists in the care of people with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the older people) should initiate treatment. Carers' views on the patient's
condition at baseline should be sought.

- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.

- Patients who continue on treatment should be reviewed regularly using cognitive, global, functional, and behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care. Carers' views on the patient's condition at follow-up should be sought.

If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles.

When using assessment scales to determine the severity of AD, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate. Healthcare professionals should also be mindful of the need to secure equality of access to treatment for patients from different ethnic groups, in particular those from different cultural backgrounds.

When assessing the severity of AD and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so. These include:

- If the cognition score is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning difficulties or other disabilities (for example, sensory impairments), linguistic or other communication difficulties or level of education or
- If it is not possible to apply the tool in a language in which the patient is sufficiently fluent for it to be appropriate for assessing the severity of dementia or
- If there are other similar reasons why using a cognition score, or the score alone, would be inappropriate for assessing the severity of dementia.

In such cases healthcare professionals should determine the need for initiation or continuation of treatment by using another appropriate method of assessment.
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 AD, doses of vitamin E in excess of 400 IU a day should be avoided for the treatment of AD 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 cyclooxygenase 2 inhibitors) are not recommended for the prevention of cognitive decline in AD (Aisen et al., 2003; Reines et al., 2004). (Grade A, Level 1++)

B - Prednisolone is not recommended for the prevention of cognitive decline in AD (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 AD. (Grade A, Level 1++)

B - Acetylcholinesterase inhibitors can be considered for the management of moderate to severe AD. (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 - NMDA antagonists such as memantine can be considered for the management of moderate to severe AD, either alone or in combination with acetylcholinesterase inhibitors. (Grade B, Level 1+)

B - NMDA antagonists such as memantine may be a treatment option for mild to moderate AD, 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 - 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. (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 AD. (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 NMDA 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 NMDA 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 (Back to top)

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<td>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) [1].</td>
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<tr>
<td>NICE (2011)</td>
<td>No recommendations offered.</td>
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**APA Definition of the Three Categories of Endorsement (2007)**

| 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.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>Levels of Evidence</td>
</tr>
<tr>
<td>1++ High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias</td>
<td></td>
</tr>
<tr>
<td>1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
<td></td>
</tr>
<tr>
<td>1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
<td></td>
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<tr>
<td>2++ High quality systematic reviews of case-control or cohort or studies</td>
<td></td>
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<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>2- Case-control or cohort studies with a high risk of confounding or bias and a significant risk</td>
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</tbody>
</table>
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.

Methodology

|-----------------|------------|-------------|-------------|

To collect the evidence, all four groups performed searches of electronic databases. ACP/AAFP and NICE also performed hand-searches of published literature; NICE also searched unpublished data. All of the groups, with the exception of SMOH, provide details of the literature selection/collection process, including the
names of databases used, date ranges searched, and search terms employed. Two of the groups, ACP/AAFP and NICE, differ from the others in that they commissioned external, independent systematic reviews. ACP/AAFP recommendations are based on a systematic evidence review by Raina and colleagues and the Agency for Healthcare Research and Quality–sponsored McMaster University Evidence-based Practice Center. The NICE assessment report for its technology appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG).

To assess the quality and strength of the selected evidence, ACP/AAFP and SMOH weighted it according to a rating scheme and provide the scheme. NICE employed expert consensus; APA does not state the methods used. With regard to evidence analysis, all four groups reviewed published meta-analyses and performed a systematic review. All of the systematic reviews, with the exception of SMOH’s, incorporated evidence tables. NICE and ACP/AAFP are the only two groups to perform their own meta-analysis. A description of the methods used to analyze the evidence is provided by ACP/AAFP and NICE.

All four groups employed expert consensus to develop the recommendations and provide a description of the process. Moreover, all of the groups, with the exception of NICE, rate the strength of the recommendations according to a scheme. Concerning issues of cost, ACP/AAFP and NICE reviewed published cost analyses; NICE undertook additional cost analyses of its own. See the original guideline document for details of the cost analysis. To validate the guidelines, ACP/AAFP, APA, and NICE sought either internal peer review, external peer review, or both. SMOH does not provide information regarding any methods used to validate its guideline.

Sources of Funding

<table>
<thead>
<tr>
<th>Source</th>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP/AAFP</td>
<td>2008</td>
<td>American College of Physicians&lt;br&gt;American Academy of Family Physicians</td>
</tr>
<tr>
<td>APA</td>
<td>2007</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>NICE</td>
<td>2011</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>SMOH</td>
<td>2007</td>
<td>Singapore Ministry of Health</td>
</tr>
</tbody>
</table>
## Benefits

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP/AAFP (2008)</td>
<td>Appropriate pharmacologic treatment of dementia based on tolerability, adverse effect profile, ease of use, and cost of medications</td>
</tr>
<tr>
<td>APA (2007)</td>
<td>Effective treatment and management of patients with AD and other dementias</td>
</tr>
<tr>
<td>NICE (2011)</td>
<td>Appropriate use of donepezil, galantamine, rivastigmine and memantine for the treatment of patients with AD</td>
</tr>
<tr>
<td>SMOH (2007)</td>
<td>Appropriate assessment, evaluation, and management of patients with dementia</td>
</tr>
</tbody>
</table>

## Harms

<table>
<thead>
<tr>
<th>Source</th>
<th>Adverse Effects of Medications</th>
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</table>
| ACP/AAFP (2008)   | • **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.

**Psychosocial Treatment**

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.

**Pharmacological Treatment**

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 AD, 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.

<table>
<thead>
<tr>
<th>NICE (2011)</th>
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<tbody>
<tr>
<td>- Common undesirable effects of donepezil include diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.</td>
</tr>
<tr>
<td>- Common undesirable effects of galantamine and rivastigmine are mainly gastrointestinal including nausea and vomiting.</td>
</tr>
<tr>
<td>- Common undesirable effects of memantine are dizziness, headache, constipation, somnolence and hypertension.</td>
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</tbody>
</table>

For full details of side effects and contraindications, see the Summaries of Product Characteristics.

<table>
<thead>
<tr>
<th>SMOH (2007)</th>
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</thead>
<tbody>
<tr>
<td><strong>Adverse Effects of Medications</strong></td>
</tr>
<tr>
<td>- Although generally well tolerated, dose-related gastrointestinal side effects (nausea, vomiting, diarrhea, anorexia) are common with acetylcholinesterase inhibitor (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.</td>
</tr>
<tr>
<td>- 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.</td>
</tr>
<tr>
<td>- Doses of vitamin E in excess of 400 IU a day should be avoided for the treatment of AD until there is further data on its safety, especially in patients with cardiovascular disease.</td>
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<tr>
<td>- Conventional antipsychotics are associated with extrapyramidal side effects and</td>
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</tbody>
</table>
Atypical antipsychotics are associated with somnolence and gait disturbance. These adverse effects are 7.5 to 11 times more common in olanzapine-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 attack, all in risperidone group. Meta-analysis of adverse events performed showed 3-fold statistically increased risk of cerebrovascular adverse events with risperidone and olanzapine (no statistically significant increase in mortality) while another meta-analysis comparing risk of death with atypical antipsychotics (aripiprazole, olanzapine, 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.

## Contraindications

<table>
<thead>
<tr>
<th>ACP/AAFP (2008)</th>
<th>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.</th>
</tr>
</thead>
</table>
| APA (2007)      | - Side effects occur infrequently with cholinesterase inhibitors, but bradycardia should be considered a relative contraindication to their use.  
- The main contraindication to use of cholinesterase inhibitors is hypersensitivity to the individual drugs.  
- Sleep apnea is a relative contraindication to the use of benzodiazepines or other agents that suppress respiratory drive.  
- Selegiline use is considered contraindicated in combination with meperidine, SSRIs, or tricyclic antidepressants. |
| NICE (2011)     | For full details of side effects and contraindications, see the Summaries of Product |
Characteristics.

| SMOH (2007) | Not stated |

Abbreviations

ACP/AAFP, American College of Physicians/American Academy of Family Physicians

AD, Alzheimer's disease

APA, American Psychiatric Association

FDA, U.S. Food and Drug Administration

NICE, National Institute for Health and Clinical Excellence

NMDA, N-methyl-D-aspartate

NSAID, nonsteroidal anti-inflammatory agents

SMOH, Singapore Ministry of Health

SSRI, selective serotonin reuptake inhibitor

Status

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 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. This synthesis was updated in June 2010 to add NICE recommendations. This synthesis was updated in March 2012 to remove SIGN recommendations and update NICE recommendations.