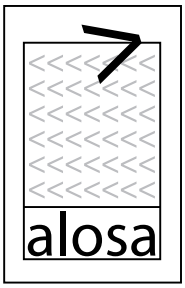
Maximizing function in the patient with impaired cognition and behavior

WHAT THE PRIMARY CARE PHYSICIAN NEEDS TO KNOW TO HELP PATIENTS AND CAREGIVERS

A PRACTICAL REVIEW OF CURRENT DATA



The Alosa Foundation

PENNSYLVANIA DEPARTMENT OF AGING

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Balanced data about medications

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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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THE BURDEN OF DEMENTIA

Introduction

Cognitive impairment (dementia) is more common in advanced age, but it is **not** a normal part of aging. It poses major physical and emotional challenges for patients, families and other caregivers. With the aging of the population, the problem also places a heavy burden on health care systems.[1]

This monograph summarizes the current medical literature about cognitive impairment and dementia and offers pragmatic strategies for diagnosing and managing these problems, including their associated behavioral and psychological disturbances. Although there is still no truly satisfactory treatment for these problems, appropriate use of available interventions can have a substantial effect on the well-being of elderly patients. In some cases, this could mean the difference between the ability to continue living independently in the community and the need for institutional care.

MILD COGNITIVE IMPAIRMENT, DELIRIUM, AND DEMENTIA: DEFINITIONS AND RISK FACTORS

Mild cognitive impairment

Mild cognitive impairment (MCI) is a condition in which a person has problems with memory, language, or other mental function that are severe enough to be noticeable to other people and be documented on tests, but not serious enough to interfere with daily life. MCI most commonly involves memory problems but can also affect language, attention, judgment, reading and writing. Symptoms are not as severe as those seen in dementia, and people with MCI do not have the personality changes or cognitive problems that often occur in dementia. The estimated prevalence of MCI is 12-20% in people aged ≥ 70 years. A significant number of patients with MCI progress to dementia each year, most commonly as a result of Alzheimer's disease.

Dementia

Dementia is a progressive, irreversible impairment in cerebral functioning. It can involve memory loss, loss of social and occupational functioning, impaired executive function, speech deficits, personality changes, and behavioral and psychological disturbances. These functional impairments distinguish dementia from MCI.

Clinical features of dementia

Dementia follows a deteriorating course, with a median life expectancy after diagnosis of 5 to 6 years. The cardinal features of several types of dementia are summarized in Table 1 on page 3.[1-5]

Table 1. Features of dementia.

Type of dementia	Prevalence	Clinical features	Comments
Alzheimer's disease (AD)	50–70% of dementia cases	Insidious symptom onset; initial forgetfulness progressing to profound memory loss with one or more of: aphasia, apraxia, agnosia, or impaired executive function	Symptoms generally begin after age 60. May coexist with vascular dementia (mixed-picture dementia).
Vascular dementia (VD)	15–20% of dementia cases	Stepwise rather than gradual deterioration; focal neurological deficits, emotional lability, impaired judgment, early neuropsychiatric symptoms and/or gait disorders	Sudden decline usually indicates a stroke. Progressive subcortical small vessel ischemia may cause slow progression.
Dementia with Lewy bodies (DLB)	Up to 10–20% of dementia cases	Involves any two of the following: visual hallucinations, parkinsonism or repeated unexplained falls, and fluctuation in mental state in the absence of delirium	Cognitive impairment affects both memory and ability to carry out complex tasks and can fluctuate within one day, so may be confused with delirium.
Parkinson's disease dementia (PDD)	Estimated to be 6 times higher in PD than in the general population	Diagnosis of PDD may be difficult as there is often overlap with AD, VD, and DLB	Older age and the severity of parkinsonism are risk factors for the development of PDD.
Fronto-temporal dementia (FTD)	Up to 10% of dementia cases	Personality changes, mood lability, and alterations in behavior (such as disinhibition and lack of insight)	Cognitive deficits may be poorly detected by the Mini-Mental Status Examination (MMSE). Anger, apathy and withdrawal may make it difficult to differentiate from depression.

A key feature differentiating DLB from PDD is time course. In DLB, onset of dementia and parkinsonism generally occur within a year of each other. In PDD, parkinsonism is usually diagnosed years before dementia.

Given that disinhibition, mood lability, and poor impulse control can occur in FTD, it may be difficult to differentiate FTD from bipolar disorder.

Epidemiology

The U.S. population 65 years of age and older is expected to double in size to about 72 million people within the next 25 years,[6] and the 85+ age group is now the fastest growing segment of the population. This has particular relevance for AD, because the number of people with the condition doubles with every 5 years age beyond age 65.[6] Alzheimer's disease is the most common cause of dementia in older people; recent estimates suggest that between 2.4 million and 4.5 million Americans have AD.[1]

In addition to its enormous human toll, the growing number of people with AD and the costs associated with the disease also impose a heavy economic burden. The national direct and indirect costs of caring for people with AD are estimated to be more than $100 billion a year. If current AD trends continue, total Federal Medicare spending to treat beneficiaries with this disease will increase from $62 billion in 2000 to $189 billion in 2015.

Etiology and risk factors

Many conditions and diseases cause cognitive impairment and dementia. Genetic, environmental, and lifestyle factors can also play an important role. Non-modifiable risk factors for dementia include:[1]

- Advanced age (> 90% of AD cases develop in people > age 60)[7]
- Family history
- Female gender
- Down's syndrome
- Low IQ
- Genetic predisposition (see page 12)

Potentially modifiable risk factors for cognitive impairment include:[8]

- Medication adverse effects
- Depression
- Risk factors for vascular disease (hypertension, diabetes, dyslipidemia, smoking, obesity)
- Excessive alcohol consumption
- Diabetes
- Poor nutrition
- Dehydration
- Thyroid, kidney, or liver disorders

Many of these conditions can be treated and may be reversible, making a brief workup a key element of initial assessment.

Delirium

By contrast, delirium is an acute, reversible organic mental disorder characterized by a reduced ability to maintain attention to external stimuli, and disorganized thinking with rambling, irrelevant or incoherent speech. Delirium generally follows a waxing and waning course. Other symptoms include disorientation to time, place and person, a reduced level of consciousness, sensory misperceptions, sleep disturbances, and memory impairment.

Delirium is often caused by medical conditions including infection (including urinary and respiratory tract), pain, drug intoxication or withdrawal, seizures, head trauma, and metabolic disturbances such as hypoxia, hypoglycemia, fluid/electrolyte disturbance, and hepatic or renal impairment. Patients with dementia are more prone to develop delirium.

Delirium can mask as dementia and may take weeks or months to resolve. It can involve hallucinations and therefore complicate a diagnosis of dementia, particularly dementia with Lewy Body Disease. Up to one-third of elderly people discharged from the hospital have delirium.[5]

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioral and psychological symptoms of dementia are also referred to as neuropsychiatric symptoms of dementia, or behavioral disturbance in dementia. They represent a diverse constellation of symptoms [9, 10] including calling out, screaming, verbal and physical aggression, agitation, apathy, hostility, sexual disinhibition, resistiveness, wandering, intrusiveness, repetitive behavior and/or vocalizations, hoarding, nocturnal restlessness, psychosis (hallucinations or delusions), emotional lability, and paranoid behaviors.[11, 12]

This constellation of symptoms is often used as a primary outcome measure in clinical trials. As a result, the efficacy of therapies for specific symptoms is difficult to determine.[13] Clinically, the key symptoms are aggression, agitation, psychosis, and mood disorders[9, 13]

Prevalence

The prevalence of behavioral symptoms is greater in nursing homes than in community settings.[10] Up to 90% of patients with dementia have such symptoms at some stage during their illness.[9, 10, 12-14] The prevalence in community dwelling patients with dementia is estimated at 60–88%.[15, 16] Apathy, depression and agitation/aggression are the most common features, followed (in descending order) by sleep disturbance, anxiety, delusions, and hallucinations.[9, 17] In patients with MCI, the most prevalent symptoms (in descending order) are depression, apathy, irritability, and sleep disturbance.[17]

Natural History

These behavioral symptoms usually fluctuate over the course of dementia and may actually remit in severe dementia.[9, 12, 18] A study of patients with mild AD found that wandering and purposeless/inappropriate activities persisted or increased in severity over two years in about 85% of patients who had these symptoms at baseline, while paranoid ideation persisted in approximately 66% of patients.[19] Hallucinations and depressive symptoms were the least persistent symptoms: less than half of the patients with depressive symptoms still had the symptoms one year later.

Burden

Behavioral symptoms, especially paranoia and aggression, and incontinence often contribute more to caregiver burden than the cognitive impairment itself, and are frequently responsible for placement in nursing homes.[9, 10, 13, 20] Patients with these symptoms also have a poorer prognosis, accelerated rate of cognitive decline, greater impairment in activities of daily living and diminished quality of life,[9] compared with patients with cognitive impairment alone. These behaviors become problematic when they are disruptive, unsafe, or interfere with the delivery of care.

Symptom clustering

Depressive symptoms often occur in the early stages of dementia. As dementia progresses, other behavioral and psychological symptoms may predominate. Adverse symptoms tend to occur in clusters, as outlined below.[9, 21, 22]

Table 2. BPSD clusters.

Cluster	Symptoms
Depression	Sadness, tearfulness, hopelessness, low self esteem, anxiety, guilt
Apathy	Withdrawal, anhedonia
Aggression	Aggressive resistance, physical or verbal aggression (often accompanies delusions)
Psychomotor agitation	Aimless walking, pacing, shadowing, restlessness, repetitive actions, dressing/undressing, sleep disturbance
Psychosis	Delusions: that others are stealing, misidentification (patient no longer recognizes home or spouse/family), delusions of abandonment and sexual infidelity. Hallucinations: less common than delusions in patients with Alzheimer's disease. Visual hallucinations are more common than other forms of hallucinations and are particularly prevalent in Lewy body dementia. Hallucinations are not necessarily disturbing and may not need treatment if the patient has some degree of insight.

▲ DIAGNOSING DEMENTIA

Elderly people who present with memory impairment, decline in functional status, mood disorders, or behavioral abnormalities should be screened for dementia. Many geriatricians screen all their patients on the first visit and regularly thereafter over age 65. It is important to detect dementia early, when interventions can have a greater effect. Early detection also allows patients and family more time to plan for the future and take part in decision making.

A diagnosis of dementia usually requires:

- a report of cognitive decline from a reliable informant;
- the presence of memory loss on direct examination; and
- a meaningful decline in function.

There is no single simple test for identifying dementia, but patient interviews and collaborative information from family, as well as a cognitive test, may establish the diagnosis or identify patients for specialist referral.[23] If available, consider referral to a memory disorders clinic when there is difficulty with symptoms or diagnosis. Assessment by a specialist may be helpful to establish diagnoses such as dementia with Lewy bodies, vascular dementia, or Parkinson's disease dementia.

Emotional problems in the elderly can be mistaken for dementia. For example, people may feel sad, lonely, or worried when coping with the death of a loved one. This can leave people feeling confused or forgetful. Support from friends, family, and a physician can help people cope with these changes. Depressive symptoms are common in patients with dementia, and depression in Alzheimer's dementia may occur in 30-50% of patients. Depression co-existing in individuals with dementia is associated with increased rates of institutionalization and suicide. Referral to a geriatric psychiatrist may be helpful.

History

Table 1 on page 3 describes the features of the various forms of dementia, but symptoms often co-exist, and there is no simple way of differentiating between the potential etiologies. A medical history should be taken from both the patient and family/caregiver. The following 12-point checklist provides a list of the signs of dementia, to assist in early detection (adapted from: http://www.alz.org/alzheimers_disease_symptoms_of_alzheimers.asp).

Warning sign	Features	What's normal?
1. Memory loss that affects job skills	Forgetting recently learned information is one of the earliest signs of dementia. A person with dementia becomes forgetful more often and is unable to recall information.	Occasionally forgetting names or appointments
2. Difficulty performing activities of daily living	A person with dementia often finds it hard to plan or complete everyday tasks. Individuals may lose track of the steps to prepare a meal, place a telephone call, or play a game.	Occasionally forgetting why you came into a room or what you planned to say
3. Problems with language	A person with dementia often forgets simple words or substitutes unusual words, making their speech or writing hard to understand. For example, they may be unable to name their watch, for example, and instead ask for "that thing for the time."	Sometimes having trouble finding the right word
4. Disorientation to time and language	A person with dementia can become lost in their own neighborhoods, forget where they are and how they got there, and not know how to get back home.	Forgetting the day of the week or where you were going
5. Poor or decreased judgment	A person with dementia may dress inappropriately, wearing several layers on a warm day or little clothing in the cold. They may show poor judgment about money, like giving away large sums to telemarketers.	Making a questionable or debatable decision from time to time
6. Problems with abstract thinking	A person with dementia may have unusual difficulty performing complex mental tasks, like forgetting what numbers are and how they should be used.	Finding it challenging to balance a checkbook
7. Misplacing things	A person with dementia may put things in unusual places: a toothbrush in the freezer or keys in the sugar bowl.	Temporarily misplacing keys or a wallet
8. Changes in mood	A person with dementia may show rapid mood swings – from calm to tears to anger – for no apparent reason.	Occasionally feeling sad or moody
9. Changes in behavior	A person with dementia may exhibit uncharacteristic agitation, aggression, wandering, or sexual disinhibition.	Occasionally losing your temper or feeling frustrated
10. Changes in personality	The personality of a person with dementia can change dramatically. They may become extremely confused, suspicious, fearful or dependent on a family member.	People's personalities do not usually change dramatically or suddenly with age
11. Loss of initiative	A person with dementia may become very passive and unresponsive, sitting in front of the TV for hours, sleeping more than usual, or not wanting to do usual activities.	Sometimes feeling weary of work or social obligations
12. Psychosis	A person with dementia may experience hallucinations (audio or visual) and/or delusions (often paranoid in nature).	Hallucinations and delusions are never normal

The medical history should also assess:

- drug and alcohol intake;
- past medical history;
- family history;
- bowel/bladder incontinence; and
- educational history.

It is vital to be alert for elder neglect and abuse in these vulnerable patients.

Cognitive testing

Several validated screening and assessment tools can be used in primary care. The clock drawing test and Mini-Cog test are quick screening tests for cognitive impairment:

- The **Clock Drawing Test** (see page 61) provides a quick screen for impaired executive function. It may be useful for identifying patients with MCI or early dementia.[24, 25]
- The **Mini-Cog Test**[26] (see Appendix 1, page 58) uses a simply scored 3-item recall test and a clock-drawing test. It is quick and easy to administer, even in a busy practice.

These simple screening tests may identify cognitive deficits and the need for further evaluation with an easily administered test such as the Mini Mental State Examination (MMSE)[27] (see Appendix 2, The Folstein Mini-Mental Status Examination (MMSE), page 59-61). Impaired recall, anomia, disorientation (to time, place and eventually person), and impaired executive functioning are common in patients with dementia. Test scores should be interpreted cautiously, especially in the context of socio-cultural diversity, level of education, or developmental disability.

The St Louis University Mental Status (SLUMS) examination[28] and the Montreal Cognitive Assessment (MOCA)[29] may be more sensitive than the MMSE in picking up mild cognitive impairment. The MOCA is also valuable in its assessment of fronto-temporal functioning.

Another test of cognitive function is the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[30] (see Appendix 3, Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), page 62). This test can take up to 60 minutes to administer and is used more commonly in clinical trials and memory disorder clinics, rarely or never in primary care.

Physical examination

Physical examination may be unremarkable, but it can reveal clues to the etiology of cognitive impairment. In addition to all vital signs and a search for evidence of potentially related co-morbidity, a careful neurological examination is crucial, including gait assessment. In advanced disease, the patient may exhibit sloppy dress, a slow shuffling gait, and stooped posture. The focus of the physical examination in more advanced stages of dementia shifts from cognitive assessment to vigilance for evidence of complications such as infections (UTI, pneumonia), bed sores, and falls.

Investigations

Laboratory tests and imaging aim to identify organic and potentially reversible causes of cognitive impairment. Testing should be done initially, but need not be repeated over time. A reasonable initial assessment would include:

- Complete blood count
- Serum electrolytes
- Thyroid function tests (TSH)
- Vitamin B_{12} level
- Liver function tests (to rule out hepatic encephalopathy)
- Erythrocyte sedimentation rate (to screen for inflammatory disease, e.g., vasculitis)
- Urine drug screen (when there is suspicion of drug-induced cognitive impairment)
- Urine analysis and culture (to rule out UTI-induced cognitive impairment)
- CT or MRI head (to rule out tumor, infarction, subdural hematoma, normal pressure hydrocephalus, etc.; some authorities recommend imaging studies primarily for patients with evidence of specific focal neurological deficits.)

Other investigations such as EEG are not part of the initial workup, but can be considered depending on individual clinical circumstance.

Genetic testing for Alzheimer's disease

A blood test can identify a patient's apolipoprotein (APOE) alleles. Although the epsilon 4 allele is a risk factor for AD, its presence does not mean that a person will develop AD. APOE testing is currently used in research to identify study participants who may have an increased risk of developing AD. The APOE test is useful for studying AD risk in large groups of people, but not for determining any one person's specific risk. A fact sheet on the genetics of Alzheimer's disease is available from The Alzheimer's Disease Education and Referral (ADEAR) Center of the U.S. National Institute on Aging (NIA) at: http://www.nia.nih.gov/NR/rdonlyres/3C4B634E-A2D8-4415-927F-4B79BEC47EA6/11207/84206ADEARFactsheetGeneticsFINAL08DEC23.pdf

Differential diagnosis

It is vital to attempt to diagnose the cause of dementia or other forms of cognitive impairment, and to consider each of the problems listed below, since many forms of cognitive impairment can be ameliorated or reversed:

- Delirium (typically has an acute onset and a fluctuating course; multiple causes, often due to medications or infection)
- Depression
- Substance intoxication or withdrawal
- Alcohol-related dementia
- Hypothyroidism
- Mild cognitive impairment
- Sleep apnea
- Vitamin B deficiency
- Normal pressure hydrocephalus
- Brain tumor
- HIV dementia
- Huntington's disease
- Syphilis
- Creutzfeldt-Jakob disease (rare)

▲ NON-PHARMACOLOGIC MANAGEMENT OF DEMENTIA

General

Resources

Independent of any other therapeutic approaches, referral to a social worker or psychologist can provide emotional support and psychosocial input. Additionally, this will facilitate work on important decisions regarding legal issues, financial planning, health care proxies and advanced directives.

Education, support, and resources can help the patient and family understand and cope with dementia. The Alzheimer's Disease Education and Referral (ADEAR) Center of the U.S. National Institute on Aging (NIA) provides information about managing cognitive and behavioral problems. Information on these issues can be found at http://www.nia.nih.gov/alzheimers and from the ADEAR center at **800-438-4380** (toll-free).

The National Institute of Aging produces a number of publications including:

- "Alzheimer's Disease: Unraveling the Mystery," an 80-page color booklet available at http://www.nia.nih.gov/NR/rdonlyres/0FA2EE06-0074-4C45-BAA3-34D56170EB8B/0/Unraveling_final.pdf
- "Legal and Financial Planning for People with Alzheimer's Disease," available at http://www.nia.nih.gov/Alzheimers/Publications/legaltips.htm
- "Understanding Memory Loss," available at http://www.nia.nihgov/Alzheimers/Publications/UnderstandingMemoryLoss/
- "Understanding Alzheimer's Disease," available at http://www.nia.nih.gov/Alzheimers/Publications/UnderstandingAD/

The Alzheimer's Association website at http://www.alz.org/index.asp offers a great deal of information, education and support to patients and caregivers. The website provides contact details for both the national office and offices in all 50 states. The Association also provides advice on the management of challenging behavior in dementia, including a 12-page booklet, "Behaviors: What causes dementia-related behavior like aggression, and how to respond." It describes five common behaviors (aggression, anxiety or agitation, confusion, repetition, suspicion) and provides recommended responses. The booklet is available at: http://www.alz.org/living_with_alzheimers_behaviors.asp.

The International Psychogeriatric Association (IPA) has produced educational materials on how to cope with the behavioral symptoms of dementia. Module 5 provides a comprehensive review of non-pharmacological interventions and is available at: http://www.ipa-online.org/ipaonlinev3/ipaprograms/bpsdarchives/bpsdrev/5BPSDfinal.pdf.

A national, non-profit organization for caregivers, "Children of Aging Parents (CAPS)" provides information and referrals for nursing homes, retirement communities, elder-law attorneys, adult day-care centers, insurance providers, respite care, assisted living centers, support groups, and state and county agencies. It also offers fact sheets, a newsletter, and conferences and workshops. Contact details are:

P.O. Box 167
Richboro, PA 18954-0167
800-227-7294 (toll-free)
www.caps4caregivers.org

Driving

A diagnosis of dementia does not always exclude driving, and on-road assessment is available. The Alzheimer's Disease Education and Referral (ADEAR) Center of the U.S. National Institute on Aging (NIA) produces a booklet "Home Safety for People with Alzheimer's Disease," available at: http://www.nia.nih.gov/Alzheimers/Publications/homesafety.htm. The booklet includes a section on driving, containing practical information for both healthcare professionals and caregivers.

Cognitive impairment

Non-pharmacologic interventions to improve, or slow deterioration of, cognitive function are at an early stage of development. There are few well-designed trials of cognitive intervention for dementia,[31] and few systematic assessment of outcomes.[8]

Despite limited evidence of its efficacy, cognitive interventions are increasingly used to preserve autonomy and quality of life. For elderly adults with normal cognition, these interventions focus on training in cognitive skills to enhance current function, with the goal of delaying or preventing future cognitive decline. For people with AD, the goals are to optimize and extend cognitive and functional skills for the longest possible period.[32]

Three major types of psychological interventions focus on cognition:[8, 31]

- **Cognitive stimulation**: engagement with activities and materials involving some degree of cognitive processing, usually within a social context and often group based, with an emphasis on enjoyment of activities.
- **Cognitive training**: training exercises geared to specific cognitive functions. It includes practice and repetition, may be computer-assisted, and may be individual or group based.
- **Cognitive rehabilitation**: working on personal goals, often using external cognitive aids and/or learning strategies.

Other approaches include reminiscence work, characterized by use of memory triggers, prompting discussion of remote memories, which may be individual or group based; validation therapy, a group-based approach which encourages communication at an emotional level in a safe, facilitative environment; and "snoezelen" – stimulation of a number of senses using aromas, hand massage and other tactile stimulation, visual light displays and atmospheric music and sounds.[8]

Some evidence supports the use of cognitive stimulation for people with mild to moderate dementia. There are improvements in quality of life in addition to modest improvements in cognitive function, and the intervention is likely to be cost effective.[8, 33] One study evaluated the effect of 6 months of cognitive stimulation with donepezil (Aricept) compared to donepezil alone in patients with mild to moderate AD. All participants had been treated with donepezil for at least 3 months. There was a small, statistically significant benefit of combined therapy compared to donepezil alone, with a net difference between the two groups of 2.9 points on ADAS-Cog ($P = 0.01$).[34] No randomized studies have directly compared cognitive stimulation with medications such as cholinesterase inhibitors, so it is difficult to compare the magnitude of effects with these treatments.[8]

Another trial examined the effect of a cognitive stimulation program in patients with mild to moderate dementia.[35] The program involved 14 sessions over 7 weeks using money, word games, and famous faces. None of the participants had been prescribed a cholinesterase inhibitor. There was a small, statistically significant benefit of the intervention compared to the control group (no intervention), with a net difference between the 2 groups of 1.14 points on the MMSE (P = 0.044) and 2.37 points on ADAS-Cog (P = 0.014).

Cognitive training has not been associated with benefits beyond the particular tasks trained. There is insufficient evidence to fully evaluate the effects of cognitive rehabilitation, reminiscence therapy, or validation therapy in relation to cognitive function in dementia.[8] A Cochrane review found no evidence for the efficacy of snoezelen for dementia.[36]

A recent review of non-pharmacological interventions for cognition found that techniques effective in improving memory in Alzheimer's disease include "spaced-retrieval technique," procedural motor memory training, and dual cognitive support. The goals of these interventions are to optimize and extend cognitive and functional skills for the longest possible period.[32]

Spaced-retrieval technique involves incorporating progressive increases of intervals between the presentation of information to be remembered and the recall of that information.[32] These intervals are filled with distracting conversation to prevent rehearsal. If an error occurs when retrieving the information, feedback is provided to the patient, and the interval between stimulus presentation and recall is decreased to the previous interval in which recall was correct. The approach has been effectively used to teach a range of skills to patients with AD, including object naming, recalling of personal information, and learning face-name and object-location associations.[37-40]

Another technique that has been effectively used in patients with AD is the activation of procedural motor memory, which is often preserved in mild and moderate AD. For example, patients with severely impaired recent memory are often able to achieve normal motor learning and skill retention in tasks such as learning to dance.[32]

Dual cognitive support involves activating prior knowledge by linking the recall of new material to personal and salient life events. This type of support may be particularly effective when the information to be recalled has an emotional significance to the patient.[32]

BOTTOM LINE

Non-pharmacologic interventions to improve, or slow deterioration of, cognitive function are at an early stage of development. There is some limited evidence to support the use of cognitive stimulation approaches for people with mild to moderate dementia, with modest improvement in quality of life and cognitive function. Cognitive stimulation may add somewhat to the effects of treatment with a cholinesterase inhibitor in mild to moderate Alzheimer's disease.

Behavorial and psychological symptoms of dementia (BPSD)

There is evidence that non-pharmacological approaches to BPSD may produce equivalent outcomes, in a much shorter time and at less overall risk and cost, than pharmacological therapy.[41] Much of the use of psychotropic medication for BPSD appears to be based more on clinical tradition and limited knowledge of psychosocial approaches than on established clinical superiority.

Several non-controlled unrandomized studies and systematic reviews of non-pharmacological interventions for BPSD point out the need to match interventions to the patient's specific needs and capabilities.[42, 43] This includes learning about the patient's life before dementia and personal history, to help identify unmet needs. It is also critical to address any sensory and nutritional deficits.[44] Vision or hearing loss in a patient with dementia can reduce functioning and increase fearfulness, anxiety, restlessness and paranoia. If there is any suspicion of these deficits, much benefit can be achieved by referral to an optometrist or ophthalmologist, or an audiologist, as indicated, for glasses and/or hearing aids.

It is also important to optimize nutrition: up to 92% of patients with dementia will experience significant weight loss. Difficulty preparing meals, confusion about mealtimes, apathy, agitation, and paranoid ideation about food and fluids may all contribute to weight loss.[44]

Non-pharmacological interventions should be first-line therapy in the management of BPSD unless there is a treatable medical condition such as delirium or concomitant medication contributing to the symptoms, **or** if the behavior may cause imminent danger to the patient or others.[44] Symptoms most responsive to non-pharmacological interventions include depression, apathy, wandering, pacing, and repetitive questions or declarations.[44]

When assessing BPSD, **consider the "ABC:"**

- **A**ntecedents: What are the triggers for the behavior?
- **B**ehavior: What is the behavior being targeted?
- **C**onsequences: What are the consequences of the behavior for self and others?

Family, caregivers, and nurses are often in the best position to identify these issues. An understanding of these factors may reveal simple and effective behavioral and environmental interventions (e.g., providing a quiet personal space at mealtimes). Complex, expensive interventions and major environmental modifications are often not required.

Environmental factors can cause disorientation, loneliness, boredom, worry, discomfort or humiliation that lead to BPSD. These may include sitting all day in an uncomfortable position, hunger or thirst, poor lighting, improper heating, excessive noise, being surrounded by unfamiliar people, disruption of normal routines, lack of opportunity to participate in meaningful and useful activities, needing assistance with private tasks such as bathing or toileting, and feeling pressured to do tasks that are difficult.

Psychological interventions include individual, family, or group psychotherapy. Patients benefit from an empathetic approach that makes it possible for them to focus on their feelings, the practical aspects of their dementia, and their mourning response to progressive cognitive deficits.

Behavioral interventions include reminiscence therapy,[45] validation therapy,[45] music therapy,[46] light therapy,[47] massage, aromatherapy, and simulated presence therapy (recorded voice of a family member or friend). Such interventions, tailored to individual needs, may reduce agitation, anxiety, aggression, and wandering.

Wandering may be aimless or purposeful (e.g., to abscond from residential care), and may result from agitation or depression. Recommended strategies are as follows: [44]

- Reassurance about where a person is and why they are there.
- Involving the patient in any planned move, and visiting a new setting before a move.
- Day care centers have found that people are less likely to wander when they are not required to stay long for the first few visits, that the caregiver stays with them for initial visits, and that someone from the daycare center visits them at home before the transition.
- If the person is getting lost and is still able to understand and follow instructions, give them a card with simple reminders such as "Stay calm and don't walk away", or "Call home on this telephone number 123-456-7890."
- Patients can wear a bracelet stating "Memory impaired person." The bracelet should also provide contact details of the caregiver and should be visible and securely fastened.

A summary of the evidence for non-pharmacological interventions to improve functional status and behavior in dementia is provided on page 21.

Figure 1. Interventions to improve fuctional performance and behavior.

Improving functional performance	Supporting evidence
Behavior modification, scheduled toileting, prompted voiding to reduce urinary incontinence	Strong
Graded assistance, practice, and positive reinforcement to increase functional independence	Good
Low lighting levels, music and simulated nature sounds to improve eating	Weak
Intensive multi-modality group training to improve activities of daily living	Weak
Improving behavior	**Supporting evidence**
Music, particularly during meals and bathing	Good
Walking or other forms of light exercise	Good
Simulated presence therapy, such as use of videotapes of family	Weak
Massage	Weak
Comprehensive psychosocial care programs	Weak
Pet therapy	Weak
Commands tailored to the patient's comprehension level	Weak
Bright light, white noise	Weak
Cognitive remediation	Weak

Adapted from American Academy of Neurology Guideline Summary for Clinicians: Detection, Diagnosis, and Management of Dementia. Available at: http://www.aan.com/professionals/practice/pdfs/dementia_guideline.pdf

BOTTOM LINE

Consider the "ABC" in assessing and managing BPSD:

- **A**ntecedents – What causes the behavior, what leads up to it?
- **B**ehavior – What is the behavior being targeted?
- **C**onsequences – What are the consequences of the behavior for self and others?

In many cases, simple, non-drug approaches can help address behavioral issues in dementia. These focus on management of medications, changes to the physical environment, psychotherapy, and behavior modification.

PHARMACOLOGIC MANAGEMENT OF DEMENTIA

Medications in dementia are used to address cognition, behavior, or both. Some agents may be useful in both domains, while others address only one. A medication providing benefit in one area might be detrimental in the other. For example, antipsychotics and benzodiazepines may provide some benefit for BPSD, but can exacerbate cognitive decline. Because of this, although the pharmacologic treatment of cognitive impairment and BPSD are described separately below, there is overlap between the two. Outcomes other than cognition and behavior, such as time to nursing home placement, can also be important endpoints in dementia.[48] Some but not all clinical trials suggest that cholinesterase inhibitors and memantine may delay the time to nursing home placement, but this remains controversial.[48, 49]

Cognitive impairment

Background

The two major classes of medication available to manage the cognitive symptoms of dementia are **cholinesterase inhibitors** and **memantine**. These drugs do not alter the underlying pathology of dementia.

Many of these drugs have been evaluated and approved based on changes in scores of cognition assessment tools, but these outcomes may not be meaningful or even noticeable in daily life. For example, a ≥ 4 point reduction in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) or a ≥ 3 point increase on the Mini-Mental Status Exam (MMSE) are often accepted as clinically significant improvements in cognition in clinical trials. However, this may not make a detectable impact on a patient's functional status or quality of life. Therefore, assessment of global functioning with tools such as the Clinician's Interview-Based Impression of Change (CIBIC) or Clinical Global Impression of Change (CGIC) is important. These are subjective tools performed by a clinician who makes an assessment of whether a patient has changed in any important way. They assess concentration, orientation, memory, language, behavior, initiative, and activities of daily living. The CIBIC-Plus allows for caregiver input, and the 7-point rating scale ranges from very much improved (1), to no change (4), to very much worse (7). By definition, a change in CIBIC or CGIC is likely to be clinically significant.

Because of patient and caregiver expectation and the placebo effect, it is difficult to objectively assess the effectiveness of drugs like memantine and the cholinesterase inhibitors in routine practice, and some patients/caregivers may think they are working even in the face of progressive deterioration in cognitive function. For this reason, in the absence of randomized controls it is difficult to make judgments regarding the efficacy of these agents in an individual patient. If it occurs, improvement should be seen within 3 months of beginning treatment. Many patients will be back to or below baseline 6-12 months later, and all will be below baseline 18-24 months later. However, a good initial response means that a slowing of disease progression has been achieved, which can be an important therapeutic outcome.

Before starting pharmacological therapy for cognitive impairment in dementia:

- Consider and treat reversible causes of impaired cognition, such as depression, delirium, hypothyroidism, B group vitamin deficiencies, sleep apnea, and normal pressure hydrocephalus.
- Review medication profile and minimize exposure to drugs that can impair cognition, e.g., benzodiazepines, antipsychotics, indomethacin, opiates, corticosteroids, antihistamines, and anticholinergics including amitriptyline, doxepin, imipramine and oxybutynin.

Mechanism of action

CHOLINESTERASE INHIBITORS

Cholinesterase inhibitors (donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon)) increase activity of the neurotransmitter acetylcholine in the central nervous system. Most randomized controlled trials (RCTs) of these drugs in patients with dementia have typically lasted only 12–24 weeks, with only a few trials of longer duration. Many have involved community-dwelling patients with mild to moderate Alzheimer's disease.[50, 51] A small number of trials have involved patients with MCI, severe Alzheimer's disease in institutional care, vascular dementia, Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB).[51, 52]

MEMANTINE

Memantine (Namenda) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Most trials with memantine have been for 6 months or less, and there are no head-to-head trials comparing memantine with cholinesterase inhibitors.

Efficacy

ALZHEIMER'S DISEASE

Cholinesterase inhibitors

A Cochrane systematic review found that use of a cholinesterase inhibitor to treat mild, moderate, or severe dementia due to Alzheimer's disease for periods of 6 months and one year produced statistically significant improvements in cognitive function.[53] However, while statistically significant, these changes were, on average, very small. The mean improvement in cognition was 2.37 points on the 70 point ADAS-Cog scale and 1.4 points on the 30 point MMSE, which are not likely to translate into a clinically meaningful effect. There were significant but modest improvements in the CIBIC-plus (odds ratio of improvement or stabilization 1.84; odds ratio of improvement 1.56) and other measures of global functioning in treated patients. Benefits of treatment were also seen on measures of activities of daily living. There is no clear evidence that any one of the three cholinesterase inhibitors is more effective than any other, and it is not possible to predict which patients will respond to a cholinesterase inhibitor.[53]

In 2007, the British National Institute of Clinical Excellence (NICE) assessed the usefulness of these drugs for the treatment of Alzheimer's disease, in terms of improvement of ≥ 4 points in ADAS-Cog score, considered the smallest gain needed to see a clinically significant response.[54] Response rates over ≥ 24 weeks were as follows:

- 39% for donepezil compared to 22% for placebo;
- 41% for galantamine compared to 27% for placebo; and
- 37% for rivastigmine compared to 24% for placebo.[54]

Five recent systematic reviews found similar modest improvements in cognition, and improvement or stabilization in global assessment, with cholinesterase inhibitors.[55-59] Data from these studies support the findings of the Cochrane and NICE reviews above.

A 2008 meta-analysis likewise found statistically significant but small improvements in cognition with cholinesterase inhibitors in patients with AD. Effect sizes on ADAS-Cog were as follows: [55, 60]

- -2.80 with donepezil for patients with any level of AD
- -2.45 with galantamine for patients with mild to moderate AD
- -1.60 to -3.78 with rivastigmine for patients with any level of AD

The analysis also found improvements in the CIBIC-plus, with effect sizes as follows:

- Donepezil: Odds ratio (OR) of improvement 2.01(any severity of AD)
- Galantamine: Odds ratio of improvement/stabilization 1.22 (mild to moderate AD)
- Rivastigmine: Odds ratio of improvement 1.76 (any severity level of AD).

Memantine

A 2006 Cochrane systematic review[61] found that treatment with memantine (20 mg daily) for 6 months had a statistically significant beneficial effect on cognitive function, clinical impression of change (CIBIC-plus), activities of daily living, and behavior in patients with moderate to severe Alzheimer's dementia, compared to placebo. These effects were also small (e.g., 0.28 points on the 7 point CIBIC-Plus). In patients with mild to moderate AD, pooled data from 3 studies indicated a small statistically significant beneficial effect at 6 months on cognition (-0.99 points on the ADAS-Cog). There was also a small statistically significant improvement in the CIBIC-plus (0.13 points), but no effect on behavior or activities of daily living. Patients taking memantine were slightly less likely to develop agitation, but there was no evidence on whether the drug had an effect on agitation that is already present.[61]

A 2008 systematic review found that patients with any severity level of Alzheimer's disease were significantly more likely to show improvement or stabilization from baseline in global functioning with memantine compared to placebo (odds ratio of improvement or stabilization 1.25 for the CIBIC-Plus).[55, 60]

A study of memantine in patients with mild to moderate AD found statistically significant improvements in cognition relative to placebo after 12 and 18 weeks of therapy, but not at 24 weeks.[62]

Dual therapy with memantine and a cholinesterase inhibitor

The effect of adding memantine to a cholinesterase inhibitor remains unclear. A trial comparing memantine added to a cholinesterase inhibitor vs. placebo added to a cholinesterase inhibitor found that memantine did not show an advantage over placebo in patients with mild to moderate AD.[63] On the other hand, another trial adding memantine or placebo to donepezil in patients with moderate to severe AD found significantly better outcomes with adding memantine vs. placebo on measures of cognition, activities of daily living, global outcome, and behavior.[64] However, there is no evidence that the combination of memantine with a cholinesterase inhibitor is better than memantine alone.

Cholinesterase inhibitors for severe AD

Trials of donepezil or galantamine that have included patients with severe Alzheimer's disease (baseline MMSE score < 10) have found statistically significant improvements in cognitive and functional outcomes compared to placebo.[52, 65-69] However, as with trials involving patients with less severe dementia, the effect sizes and the durability of the response have been questioned.[70, 71]

CHOLINESTERASE INHIBITORS IN THE VERY OLD

Most RCTs of cholinesterase inhibitors have included patients with an average age of about 75. There is limited evidence to guide the initiation and continuation of cholinesterase inhibitor therapy in older patients.

EFFECT OF CHOLINESTERASE INHIBITORS ON INDEPENDENT LIVING

No firm conclusions can be drawn concerning the impact of the cholinesterase inhibitors on the ability to delay placement in institutional care. [48, 49 51, 72]

MILD COGNITIVE IMPAIRMENT (MCI)

There is insufficient evidence to support the use of cholinesterase inhibitors for slowing the progression to dementia, or preserving cognitive function, in patients with MCI. [55, 60, 65, 73-77]

There is insufficient evidence to support the use of memantine for MCI.

VASCULAR DEMENTIA

Vascular dementia and Alzheimer's disease often coexist.[78, 79] Meta-analyses and trials involving cholinesterase inhibitors in patients with vascular dementia have found small, statistically significant improvement in ADAS-Cog score with all cholinesterase inhibitors, but the clinical significance of these improvements remains uncertain.[55, 80-83]

A 2006 Cochrane systematic review found that memantine (20 mg daily) for 6 months had statistically significant beneficial effects on cognition (-1.85 ADAS-Cog points), but the effect was small and not supported by clinical global measures.[61] A 2007 meta-analysis found a statistically significant but small improvement with memantine for cognition in patients with mild to moderate vascular dementia (-1.86 points on the ADAS-Cog), but the clinical relevance of this change was not clear.[61, 80]

A 2007 meta-analysis found statistically significant but small improvements in cognition in patients with mild to moderate vascular dementia for all the cholinesterase inhibitors, ranging from -1·10 to -2.17 points on the ADAS-Cog.[61, 80] Only 5 mg daily donepezil had a statistically significant effect on the CBIC-Plus (OR of improvement or stabilization 1.51). The benefits in cognition were of uncertain clinical significance and data were insufficient to support widespread use of these drugs in vascular dementia.[61, 80]

A 2008 meta-analysis found a statistically significant but small improvement in cognition in patients with mild to moderate vascular dementia treated with donepezil (-2.17 points on ADAS-Cog) and memantine (-2.20 on the ADAS-Cog). In patients with a mixed dementia (AD and vascular), galantamine produced a statistically significant but small improvement in cognition (-2.70 points on ADAS-Cog) in one study.[55, 60] The review also found a statistically significant improvement in CIBIC-Plus in patients with a mixed picture dementia (AD and vascular) with galantamine (OR of improvement or stabilization 1.25), but not with donepezil, in patients with mild to moderate vascular dementia. [55, 60]

Table 3 on page 29 presents a summary of recent meta-analyses of the effect of cholinesterase inhibitors and memantine on cognition (ADAS-Cog) and global assessment of change (CIBIC-Plus) in Alzheimer's disease and Vascular dementia.

Table 3. Effect of cholinesterase inhibitors and memantine on cognition and global assessment of change.

Study	Condition	Drug	Cognition*	Global assessment of change**
Birks 2006[47]	Alzheimer's disease Any severity AD	Cholinesterase inhibitors (class)	-2.37	OR of improvement/stabilization 1.84 OR of improvement 1.56
McShane 2006[61]	Alzheimer's disease			
	Mild-moderate AD	Memantine	-0.99	+0.13 points
	Moderate-severe AD	Memantine	Did not assess	+0.28 points
	Vascular dementia			
	Mild-moderate VD	Memantine	-1.85	NS
Kavirajan 2007[61, 80]	Vascular dementia	Donepezil 5mg Donepezil 10mg Galantamine Rivastigmine Memantine	-1.15 -2.17 -1.60 -1.10 -1.86	OR of improvement/stabilization 1.51 NS NS NS NS
Raina 2008[55, 60]	Alzheimer's disease			
	Any severity AD	Donepezil	-2.80	OR of improvement 2.01
	Mild-moderate AD	Galantamine	-2.45	OR of improvement/stabilization 1.22
	Any severity AD	Rivastigmine	-1.60 to -3.78	OR of improvement 1.76
	Any severity AD	Memantine	NS	OR of improvement/stabilization 1.25
	Vascular dementia			
	Mild-moderate VD	Donepezil	-2.17	NS
	AD+VD	Galantamine	-2.70	OR of improvement/stabilization 1.25
	Mild-moderate VD	Memantine	-2.20	Did not assess
	Mild cog impairment	Donepezil	NS	Did not assess

* **Points change in ADAS-Cog (negative=improvement), compared to placebo**. ADAS-Cog is a 70 point scale. A change of at least 4 points is considered a clinically significant result.

** **Change in CIBIC-Plus, compared to placebo**. CIBIC-Plus is a 7 point scale. Any change may be clinically significant.

AD=Alzheimer's disease; VD=Vascular dementia; NS=not statistically significant; OR=odds ratio

PARKINSON'S DISEASE DEMENTIA

Rivastigmine may offer modest improvement in cognitive function in a minority of patients with PDD, but there is insufficient evidence to support the use of other cholinesterase inhibitors.[51, 84, 85]

There is insufficient evidence to support the use of memantine for PDD.

DEMENTIA WITH LEWY BODIES

A retrospective comparison of three independent clinical studies of donepezil (open label study), galantamine (open label study) and rivastigmine (randomized controlled trial) in patients with DLB found that all 3 agents significantly improve MMSE scores in these patients.[86] There is no compelling evidence that any one agent is better than any other.

There is limited evidence to support the use of memantine for DLB.

FRONTO-TEMPORAL DEMENTIA

There is insufficient evidence to support the use of cholinesterase inhibitors or memantine in patients with fronto-temporal dementia

Duration of therapy

There is no evidence that any benefits of cholinesterase inhibitor or memantine therapy increase with duration of therapy, and these agents do not appear to modify the pathophysiology of the disease. A number of open label extension studies and observational studies have studied the effects of cholinesterase inhibitors beyond the 12-24 weeks of RCTs.[87-90] These studies suggest that initial response may be maintained for 6-12 months, possibly up to 18 months. After this time the beneficial effect on cognition declines,[51] with cognition scores falling to below those at baseline.

How long patients should be treated with these agents remains an individualized decision, influenced by caregiver and family preferences.[51] With both cholinesterase inhibitors and memantine, it would be reasonable to discontinue the drug after 6 months if there is no improvement.

Safety

ANTICHOLINERGIC DRUGS AND CHOLINESTERASE INHIBITORS

Medications with anticholinergic activity can impair cognition and functional performance from effects such as sedation, agitation, confusion, and delirium.[91, 92] Such drugs include antihistamines, tricyclic antidepressants, antipsychotics, and drugs such as oxybutynin that are used to treat urinary incontinence. These medications may reduce or negate any beneficial effect on cognition by cholinesterase inhibitors.

Urinary incontinence is common in people with dementia. It may result from disinhibition (inappropriate voiding or lack of impulse control), physical frailty, or a number of more specific causes. It may also result from medication, such as cholinesterase inhibitors. Urinary incontinence can also be caused by common medical conditions such as heart failure causing nocturia. Any patient with urinary incontinence merits a full evaluation, including genitourinary examination, urine analysis, urine culture, voiding diary, serum electrolytes, and (in men) a prostate examination. If no treatable causes are found, consider non-anticholinergic alternatives such as scheduled toileting and incontinence pads.[93]

ADVERSE EFFECTS: CHOLINESTERASE INHIBITORS

The most common adverse effects of cholinesterase inhibitors are anorexia, nausea, vomiting and diarrhea. These drugs have also been associated with dizziness, hypertension, syncope, bradycardia, QT interval prolongation, arrhythmia, angina pectoris and heart block. Meta-analysis suggests that the mean frequency of dizziness with cholinesterase inhibitors is 10% (8% with donepezil, 10% with galantamine and 22% with oral rivastigmine).[56] Dizziness may be a clinical manifestation of changes in blood pressure and heart rhythm, and may result in syncope and falls.

Approximately 30% of patients stop therapy due to adverse effects.[53] If a patient is unable to tolerate, or does not respond to, one cholinesterase inhibitor, there is limited data to support switching to an alternate agent.[94] Donepezil may cause fewer adverse effects than oral rivastigmine.[53]

Most studies have found significant increases in adverse effects with higher doses .[52, 65] It is important to individualize upward dose titration to minimize adverse effects. Transdermal administration of rivastigmine appears to offer improved GI tolerability compared to oral rivastigmine.

MEMANTINE

Memantine has been well tolerated in clinical trials, with most finding the overall incidence of adverse effects, and dropout rates due to adverse effects, to be similar to that of placebo.[60, 95] Common adverse effects are hypertension, confusion, dizziness, drowsiness, headache, hallucinations, constipation, dyspnea, vomiting, cough, and fatigue. Serious adverse effects include Stevens-Johnson syndrome and seizures.

Dose and cost

A greater benefit with donepezil 10 mg once daily compared to a starting dose of 5 mg once daily has not been consistently demonstrated.[52] There is no significant difference in efficacy with 16 mg/day of galantamine compared to higher doses.[65] However, significant improvements in cognition and global function have been found with oral rivastigmine across the entire dose range from 1 to 12 mg daily (in two divided doses).[50] Dosages of memantine above 20 mg/day have not been studied.[96]

Table 4. Dosing of cholinesterase inhibitors and memantine.

Drug	Starting dose	Titration	Approximate monthly cost (at maximum dose)
Donepezil (Aricept)	5 mg once daily	Increase to 10 mg once daily after 4-6 weeks according to response	$170
Galantamine* (Razadyne)	4 mg orally (immediate-release) twice daily	Increase by 8 mg/day (given in 2 divided doses) every 4 weeks according to response, maximum 24 mg/day	$186
	8 mg orally (extended-release) once daily	Increase by 8 mg/day every 4 weeks, maximum 24 mg/day	$196
Rivastigmine* (Exelon) - oral	1.5 mg orally twice daily	Increase by 3 mg/day (given in 2 divided doses) every 2 weeks according to response, maximum 12 mg/day	$202
Rivastigmine (Exelon) - transdermal	4.6 mg/24 hour patch once daily	Increase to 9.5 mg/24 hour patch once daily after 4 weeks according to response; starting dose varies if switching from oral to transdermal therapy	$202
Memantine (Namenda)	5 mg once daily	Increase by 5 mg/day every week to a target dose of 10 mg twice daily; give bid if dose > 5 mg per day	$156

*FDA has recently approved the manufacture of generic galantamine and generic oral rivastigmine. Generics of donepezil, memantine, and transdermal rivastigmine will not be available until 2010 or later.

Some frequently asked questions regarding the use of cholinesterase inhibitors and memantine in dementia are provided on pages 34 and 35.

FAQs of clinical practice - cholinesterase inhibitors

Which agent do I choose?

- donepezil (Aricept) for AD (mild to severe)
- galantamine (Razadyne, generic) for AD (mild to moderate)
- rivastigmine (Exelon) for AD (mild to moderate) or PDD (mild to moderate)
- some evidence of efficacy in VD and DLB, but not FDA-approved for these indications
- no clear evidence that one agent is better than another

What do I do before I start one of these agents?

- review continence
- consider an ECG if patient has a history of cardiac disease

How long does it take to work?

If benefit for cognition occurs, it should be evident within 3 months of therapy. Perform cognitive assessment (such as MMSE) after 3 months and compare to baseline.

What about adverse effects?

- Adverse effects and drug interaction profiles may guide drug selection.
- Adverse effects are dose related and tend to occur early in treatment. However, some adverse effects, such as anorexia, weight loss, and urinary incontinence, may emerge with time.

How long do I treat for?

- There is insufficient evidence to determine the optimal duration of therapy with a cholinesterase inhibitor.
- Cease treatment if there are significant adverse effects, poor compliance, or lack of stabilization or improvement in cognition after 6 months of therapy.
- When ceasing a cholinesterase inhibitor, reduce the dose gradually unless an adverse effect warrants abrupt cessation.

What do I do with missed doses?

If treatment with a cholinesterase inhibitor is interrupted for several days, it should be restarted at the low initial dose and then increased gradually.

Can I use a cholinesterase inhibitor with memantine?

Yes, these agents can be used in combination.

FAQs of clinical practice - memantine

How do I initiate?

- Initiate at 5 mg once daily.
- Increase by 5 mg/day every week to a target dose of 10 mg twice daily.
- Give bid if dose > 5 mg per day.

What adverse effects do I look for?

Common adverse effects are hypertension, confusion, dizziness, drowsiness, headache, hallucinations, constipation, dyspnea, vomiting, cough, and fatigue. Serious but rare adverse effects are Stevens-Johnson syndrome and seizures.

How long does it take to work?

- If benefit for cognition occurs, it should be evident within 3 - 6 months of therapy. Perform cognitive assessment (such as MMSE) after 3 months and compare to baseline.
- There is also some evidence that memantine can help reduce delusions, agitation, and aggression.

When do I stop treatment?

Stop if there are significant adverse effects, poor compliance, or lack of stabilization or improvement in cognition after 6 months of therapy.

Mini-Mental State Examination (MMSE)

As a rule of thumb, need a gain of at least 3 points on the MMSE for a response to be clinically significant.

BOTTOM LINE

Some patients with dementia show modest improvement or stabilization in cognition and global assessment of change with cholinesterase inhibitors and memantine. Although these improvements have been statistically significant compared to placebo, their clinical significance has not always been compelling. Most evidence of efficacy is in Alzheimer's disease and vascular dementia, with limited data for other forms of dementia. It is not possible to predict responders to these agents. No one agent has been conclusively shown to be more effective than another.

Other therapies

A number of other therapies have been suggested for cognitive impairment in dementia and these are presented on page 37. There is insufficient evidence to recommend any of them, though they can be used to treat other indications if present (e.g., hypertension, dyslipidemia, vitamin B deficiency, etc.)

Table 5. Other treatments proposed for cognitive impairment.

Therapy	Evidence
Anti-hypertensives	A 2006 Cochrane systematic review found no convincing evidence that blood pressure lowering prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease.[97]
HMG-CoA reductase inhibitors (statins)	There is insufficient evidence to recommend statins for reducing the risk of, or for the treatment of, dementia (including AD).
Estrogen	The Women's Health Initiative Memory study found that conjugated equine estrogen (with or without progesterone) in postmenopausal women aged ≥ 65 years did not improve global cognitive function, or decrease the risk of MCI or dementia, and may actually adversely affect these outcomes.[98-101] A Cochrane review concluded that there is no evidence that estrogen maintains or improves cognitive function in women who already have Alzheimer's disease.[102]
Aspirin	A meta-analysis of cohort and case-control studies found no significant benefit of aspirin in reducing the risk of Alzheimer's disease.[103] Although aspirin is widely prescribed for patients with a diagnosis of vascular dementia, there is no good evidence to support this practice.[104]
NSAIDs	Observational studies, epidemiological studies and meta-analyses have reported variable results.[105, 106] NSAIDs cannot be recommended for the prevention or treatment of Alzheimer's disease.
Folic acid, vitamin B_6 and vitamin B_{12}	Systematic reviews[107] and RCTs[108] have found no evidence that folic acid (with or without vitamin B_{12}),[109] vitamin B_6 alone,[110] vitamin B_{12} in people with low B_{12} levels at baseline,[111] or combined treatment with folic acid, vitamin B_6 and vitamin B_{12} [107, 108] have beneficial effects on cognitive function in either healthy people, or in those with cognitive impairment or dementia.
Vitamin E	There is insufficient evidence to support the use of Vitamin E to reduce the risk of, or treat, dementia. Trials have found no advantage of vitamin E (2000 IU/day) over placebo in slowing the progression of MCI to Alzheimer's disease.[112]
Exercise	Some (but not all) studies suggest physical activity may delay the onset of dementia in healthy older adults and slow cognitive decline in people with MCI.[113-118] A Cochrane review found that there is insufficient evidence of the effectiveness of physical activity programs in improving cognition in people with existing dementia.[113]
Ginkgo biloba	A 2007 Cochrane systematic review[119] and a subsequent trial[120] found no convincing evidence that ginkgo biloba has predictable and clinically significant benefit on dementia or cognitive function. A recently published 6-year RCT with 3,069 people aged ≥ 75 years with normal cognition or MCI found no advantage of ginkgo biloba over placebo in reducing the incidence of Alzheimer's disease or dementia.[121]
Omega-3 fatty acids	A recent Cochrane systematic review concluded that there is insufficient evidence to support the use of dietary or supplemental omega-3 fatty acids for the prevention of cognitive impairment or dementia.[122]
Selenium	A large clinical trial (PREADVISE) is currently assessing the role of selenium in the prevention of dementia, but results will not be available for several years.

Behavioral and psychological symptoms of dementia (BPSD)

General principles

Many medications routinely used in the elderly can cause or worsen behavioral and psychological problems. For example, anticholinergic agents increase the risk of visual hallucinations, agitation, irritability, delirium and aggressiveness.[123] Adverse drug effects are one of the most reversible conditions in geriatric medicine. They present an opportunity to effect a cure by stopping the offending drug or lowering the dose. This has led to the recommendation that "any new symptom in an older patient should be considered a possible drug side effect until proven otherwise."[124]

Psychotropic medications used for BPSD (e.g., antipsychotics, benzodiazepines, antidepressants) have been implicated in a variety of serious adverse effects including falls, fractures, delirium, and over-sedation.[125] Elderly patients are particularly vulnerable to injury from psychotropic medications because of increased frequency of use, slower metabolic clearance, increased CNS receptor sensitivity, or reduced physiologic reserve.[125] Lower starting and target doses are often needed in older people.[12] A reduced initial dose for elderly patients is endorsed by the FDA, which mandates that drug manufacturers state a recommended geriatric dose for all medications evaluated in a significant number of patients older than 65 years.[125] Unfortunately, drug trials often under-represent older patients – especially those who are over 80 or frail, so the database for such recommendations is frequently inadequate.

Despite evidence of limited efficacy, antipsychotic agents are often used as the first-line treatment for BPSD.[13] Their use is influenced not only by the patient's symptoms, but also by factors related to the caregiver and setting.[126] These may include family, care givers, nursing, other residents of an aged-care facility, and a lack of training or resources for non-pharmacological approaches, such as behavioral interventions or environmental changes.[20]

Medication should be considered for the management of BPSD only after underlying medical conditions have been assessed and treated; symptoms are confirmed as unrelated to concomitant medications; response to non-pharmacological interventions has been inadequate; or if the behavior poses an imminent risk of harm to the patient or others. Pharmacotherapy for BPSD may be required while awaiting response to the treatment of underlying conditions and/or non-pharmacological interventions.

Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) is a 12-item instrument commonly used in clinical trials to evaluate behavioral and neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behavior, night-time behavior, and appetite/eating disorder. Frequency is rated from 1 (occasional, less than once a week) to 4 (very frequent) and severity from 1 (mild) to 3 (severe). The product of frequency and severity ranges from 1 to 12, with a total score ranging from 1 to 144 for the 12 domains summed. A lower score indicates improvement. Scores < 20 indicate mild disturbance, 20–50 indicate moderate disturbance and scores > 50 indicate severe disturbance. A 30–50% reduction from baseline to endpoint in the NPI score is considered clinically significant.

Antipsychotics and mortality risk

In 2005, the FDA determined that the treatment of behavioral disorders in elderly patients with dementia with atypical antipsychotic medications causes increased mortality. Its analyses of 17 placebo-controlled trials that enrolled 5,377 elderly patients with dementia-related behavioral disorders revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Most deaths were due either to cardiac events (sudden death, heart failure) or infection (principally pneumonia). The FDA noted that none of the atypical antipsychotics are approved for the treatment of behavioral disorders in patients with dementia.[127]

A 2007 retrospective cohort study assessed mortality in 37,241 adults, 65 years of age or older, who were prescribed conventional (12,882) or atypical (24,359) antipsychotic medications for any reason between 1996 and 2004. Within the first 180 days of use 14.1% in the conventional drug group died, compared with 9.6% in the atypical drug group (mortality ratio 1.32, 95% CI (1.23–1.42). In comparison with risperidone, haloperidol was associated with the greatest increase in mortality (mortality ratio 2.14, 95% CI 1.86–2.45) and loxapine the lowest (mortality ratio 1.29, 95% CI 1.19–1.40). The greatest increase in mortality occurred among people taking higher (above median) doses of conventional antipsychotic medications (mortality ratio 1.67, 95% CI 1.50–1.86) and during the first 40 days after the start of drug therapy (mortality ratio 1.60, 95% CI 1.42–1.80).[128]

A 2005 retrospective cohort study assessed mortality in 22,890 patients 65 years of age or older who received a conventional or atypical antipsychotic medication between 1994 and 2003. Conventional antipsychotic medications were associated with a significantly higher risk of death than were atypical antipsychotic medications at all intervals studied (≤180 days: relative risk, 1.37; 95% CI, 1.27 to 1.49; <40 days: relative risk, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: relative risk, 1.37; 95% CI, 1.19 to 1.59; and 80 to 180 days: relative risk, 1.27; 95% CI, 1.14 to 1.41) and in the presence or absence of dementia or nursing home residency. The greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional agents. The results suggest that conventional antipsychotics are at least as likely as atypical agents to increase the risk of death among elderly persons, so they should not be used to replace atypical agents.[129]

In June 2008, the FDA determined that both conventional and atypical antipsychotics increase the risk of death in elderly patients treated for dementia-related psychosis, and reiterated that antipsychotics are not indicated for the treatment of dementia-related psychosis.[130] FDA determined that the conventional and atypical antipsychotics both increased the risk of death in elderly patients; all antipsychotic drugs carry the same information about this risk in a Black Box Warning and in the Warnings section.[130]

Data from retrospective analyses of RCTs suggest an increased risk of death associated with antipsychotics is most pronounced in the first 40 days of use and with higher doses.[16]

Two studies published in 2009 have added to the evidence that antipsychotics increase the risk of mortality. The first of these was an RCT assessing whether continued treatment with antipsychotics is associated with an increased risk of mortality.[131] Patients with AD (mean age 85 years) were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) or to switch to an oral placebo. Across the whole study period, the overall risk of death was 42% lower in those treated with placebo vs. those receiving antipsychotics (P = 0.03). The difference was evident at 12 months and increased over time (see below). At 42 months, about ¼ of patients in the antipsychotic group were still alive compared to about ½ in the placebo group.

Follow-up	Cumulative survival (antipsychotic group) %	Cumulative survival (placebo group) %
12 months	70	77
24 months	46	71
36 months	30	59
42 months	26	53

The second study assessed the cardiac safety of antipsychotics in a retrospective cohort study of 44,218 and 46,089 baseline users of single typical and atypical drugs, and 186,600 matched non-users of antipsychotics.[132] Results were as follows:

	Incidence-rate ratio of cardiac death
Users of any conventional antipsychotic compared to non-users	1.99 (95% CI: 1.68 to 2.34; P < 0.001)
Users of any atypical antipsychotic compared to non-users	2.26 (95% CI: 1.88 to 2.72; P < 0.001)
Users of any atypical antipsychotic compared to users of any conventional antipsychotic	Not significantly different
Former users of any antipsychotic compared to non-users	Not significantly different

Users of each of 6 antipsychotics (clozapine, haloperidol, olanzapine, quetiapine, risperidone, and thioridazine) had a significantly increased rate of sudden cardiac death. For both classes of drugs, the risk for current users increased significantly with increasing dose.

	Change in Incidence-rate ratio of cardiac death
Conventional agent: low dose compared to high dose	1.31 to 2.42 (P < 0.001)
Atypical agent: low dose compared to high dose	1.59 to 2.86 (P = 0.01)

The study adds to the body of evidence that antipsychotic use should be reduced in patients for whom the evidence of efficacy is limited, since the risk of a fatal side effect is clear.[133]

The prescribing information for antipsychotic drugs carries warnings that these agents are not approved for dementia-related psychosis; elderly patients with dementia treated with conventional or atypical antipsychotics are at an increased risk of death; most deaths were due to cardiovascular or infectious events; and the extent to which increased mortality in observational studies may be attributed to the antipsychotic drug vs. some patient characteristics is not clear.

Atypical antipsychotics for BPSD

Most trials of atypical antipsychotics for BPSD have used risperidone, have been of short (6–12 weeks) duration, and have involved elderly patients in long term care facilities who have Alzheimer's disease (+/- vascular dementia). These trials provide little information on concurrent non-pharmacological interventions and concomitant medications. Outcomes are typically reported in terms of BPSD, with few trials differentiating which specific symptoms were affected by the intervention.

META-ANALYSIS

Although some clinical trials provide some support for using atypical antipsychotics to treat BPSD, there is limited evidence of the clinical value of these agents.[134] A 2006 meta-analysis of the use of atypical agents for psychosis and behavioral disorders in dementia concluded that modest efficacy, uncertain response rates, and risks caused by these drugs suggest that they should only be used after deliberate consideration.[135] Clinical improvement should be expected well within the 10-12 weeks of most clinical trials. If no improvement is seen, the medication should be stopped, non-pharmacological approaches (behavioral and environmental changes) should be revisited, and/or another antipsychotic should be tried. The authors of the meta-analysis acknowledge that psychosis and aggression in people with dementia are difficult to manage, that antipsychotics are modestly effective when used judiciously, and that there are no effective alternative medications.[135]

COCHRANE REVIEW

A 2006 Cochrane review of atypical antipsychotics for aggression and psychosis in Alzheimer's disease concluded that risperidone and olanzapine have modest efficacy in reducing aggression, and that risperidone reduces the symptoms of psychosis. There was a high placebo response rate in all of the studies involving risperidone.[13] However, risperidone and olanzapine substantially increase risk of stroke and other adverse effects, and there is a general increase in mortality associated with the use of atypical antipsychotics in people with dementia. Therefore, the review concluded that these treatments should be used only if there is severe distress or risk of physical harm to the patient or those living and working with the patient. There was insufficient evidence to systematically evaluate the efficacy of any of the other atypical antipsychotics.[13]

COMMUNITY-DWELLING PATIENTS (THE CATIE-AD STUDY)

The Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease (CATIE-AD) study examined the effectiveness of atypical antipsychotics in patients with Alzheimer's disease and psychosis, aggression or agitation.[136] The study was conducted over 36 weeks, with 421 outpatients randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo. Doses were adjusted by study physicians as clinically indicated, reflecting 'real-life' clinical practice. The main outcome measures were the time from initial treatment to discontinuation for any reason and the number of patients with some improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks. Main results were:

- No significant differences among any of the drugs studied in time to discontinuation of treatment for any reason (5.3 to 8.1 weeks, p=0.52).
- Median time to discontinuation of treatment due to a lack of efficacy favored olanzapine (22 weeks) and risperidone (27 weeks) compared to quetiapine (9 weeks) and placebo (9 weeks) (p = 0.002).
- Median time to discontinuation of treatment due to adverse effects favored placebo.
- No significant differences among the groups in clinical improvement measured by the CGIC. Improvement was observed in 32% of patients taking olanzapine, 26% taking quetiapine, 29% taking risperidone, and 21% taking placebo.
- The rate of discontinuation due to adverse effects, intolerance to study drug or death was 5% in the placebo group compared to 24% with olanzapine, 18% with risperidone and 16% with quetiapine. Approximately half of the patients discontinued the study drug during the first eight weeks.[16, 136, 137]
- There was no significant difference between the groups in quality of life measures or daily function.[138]

In this study of BPSD in community-dwelling patients with Alzheimer's dementia, there was no benefit of treatment with atypical antipsychotic medications as compared to placebo.[136]

OTHER

Other aspects of studies of atypical antipsychotics for BPSD:

- In patients who responded to treatment, improvement tended to occur within the first two to four weeks. Increased attention to the patient, non-drug interventions, and symptom fluctuation may have contributed to the improvement.[135]
- Despite improvement, many patients still experienced symptoms such that most would have still met the trials' inclusion criteria even after treatment.[135]
- Risperidone (1 mg/day) and olanzapine (5–10 mg/day) significantly reduced aggression and agitation.[13, 135]
- Quetiapine significantly improved agitation at a dose of 200 mg/day compared to placebo, but not at lower doses.[139] However, this is not a recommended starting dose for this drug.
- Aripiprazole (10 mg/day) and risperidone (1 mg/day) significantly reduced psychosis compared to placebo.[13, 140]
- Risperidone was associated with a clinically significant improvement in BPSD with a clinical response rate of 65% versus 47% with placebo. The 18% absolute difference in response rate suggests a NNT of 6; that is, 6 patients need to be treated with risperidone rather than placebo for up to 12 weeks for one patient to respond.[13] A meta-analysis of conventional antipsychotics for management of agitation in patients with dementia also found an 18% improvement over placebo.[141]
- About a third of patients withdrew from trials due to lack of efficacy or adverse effects.[14, 135, 142]

Conventional (typical) antipsychotics for BPSD

Reviews and meta-analyses of clinical trials involving conventional antipsychotics (e.g., haloperidol [Haldol], thioridazine [Mellaril] and chlorpromazine [Thorazine]) in the management of BPSD found modest improvement in aggression over 3-8 weeks of treatment compared to placebo.[14, 51, 141, 143]

Approximately 60% of patients taking conventional antipsychotics showed improvement in behavioral symptoms compared to 40% in the placebo group.[51] These response rates are consistent with those found in trials of atypical antipsychotics.[51] Discontinuation rates due to adverse effects were significantly higher with conventional antipsychotics than with placebo.[141]

Comparative trials of antipsychotics for BPSD

Two studies found no significant difference between olanzapine and risperidone for the treatment of dementia-related psychosis and behavioral disturbances (agitation, aggression)[144, 145] although in the larger of those 2 studies, neither antipsychotic was significantly better than placebo.[144] A small study of 72 outpatients found that quetiapine and risperidone were equally effective in the treatment of BPSD.[146] There are insufficient data from comparative trials to support one atypical antipsychotic over another.

There is no consistent evidence that any one conventional antipsychotic is more effective than another,[141] and there are insufficient data to make conclusions about the efficacy of conventional vs. atypical antipsychotics for BPSD.[147]

Withdrawal of antipsychotics in BPSD

Withdrawal of an antipsychotic in patients treated for at least 3 months does not appear to lead to deterioration in behavior after 6-12 months, compared to continuing therapy.[148-151] One randomized trial in nursing home patients found that patients randomized to a physician education program that achieved a reduction in antipsychotic drug use had a significant improvement in their memory function, compared to controls.[152] These results, together with the known fluctuating course of BPSD symptoms, suggest that patients who have been treated with an antipsychotic for three months can safely undergo a trial withdrawal of the drug.

Tapering of antipsychotics should be done slowly to avoid a withdrawal syndrome (unless significant adverse effects or a drug interaction necessitates abrupt cessation). One regimen recommends reducing the antipsychotic dose by 25–50% every 2 weeks and ceasing after 2 weeks on the minimum dose. Close attention should be paid to behavior in response to reducing doses.

Summary: benefits and risks of antipsychotic therapy for BPSD

Although several clinical trials provide some support for using atypical antipsychotics to treat BPSD, their clinical value is clearly a double-edged sword.[134, 136] Although these agents may be modestly effective when used judiciously,[12, 135] the elderly are particularly susceptible to serious adverse effects and these drugs should be used with great caution, if at all. The risks and benefits of antipsychotics for BPSD are summarized below.[153]

1. The symptoms of BPSD with some evidence supporting the efficacy of antipsychotics are agitation, aggression, psychosis.

2. The symptoms of BPSD with little or no evidence supporting the efficacy of antipsychotics are anxiety, withdrawn states, apathy, demanding behaviors, hoarding, calling out/screaming, sexual disinhibition, shadowing, sundowning, swearing, psychomotor agitation, wandering, and depression.

3. Of the atypical agents, risperidone has the most evidence supporting efficacy, but:
   - cannot predict responders to any agent,
   - insufficient data from comparative trials to support one atypical antipsychotic over another,
   - insufficient data to make definitive conclusions regarding relative efficacies of atypical vs. conventional agents.

4. There is an increased risk of death with both atypical and conventional agents in elderly people with dementia. Antipsychotics are not FDA-approved for use in the elderly with dementia. Serious adverse effects (see also page 63) include: stroke, TIA, seizures, increased mortality, Extrapyramidal side effects, drowsiness, cognitive decline, confusion, increased risk of falls, parkinsonism, akathisia, tardive dyskinesia, social withdrawal, QT prolongation, diabetes, postural hypotension, neuroleptic malignant syndrome, angioedema, blood dyscrasias, Stevens-Johnson syndrome.

Before starting an antipsychotic medication:

- Assess and treat any potential reversible causes of dementia, as well as any underlying medical conditions such as delirium or depression that may cause behavioral problems
- Assess and review any medications that may be contributing to BPSD, such as psychotropics and anticholinergics.
- Explore non-pharmacological interventions such as environmental changes and behavior modification for patients with BPSD. [12, 154]
- Antipsychotics are associated with only a modest improvement in BPSD.[135] The symptoms for which benefit has been observed are aggression, agitation and psychosis (hallucinations and delusions).[155]
- Symptoms unresponsive to antipsychotic therapy include anxiety, withdrawn states, apathy, demanding behaviors, hoarding, calling out/screaming, sexual disinhibition, shadowing, sundowning, swearing, psychomotor agitation, wandering and cognitive deficits.[155]
- Antipsychotics are associated with significant adverse effects and an increased risk of mortality in elderly patients with dementia. These agents are not FDA-approved for use in elderly patients with dementia.
- If the consequences of the behavior are significant enough, initiation of pharmacological therapy may be required at the same time as treatment of underlying medical conditions and/or non-pharmacological intervention.
- Use of an antipsychotic may be indicated for agitation, aggression or psychosis, **if** the target behavior:
  — is persistent or recurrent **and** can cause harm or significant distress to the patient or others;
  — has not adequately responded to non-pharmacological interventions;
  — is not due to reversible or treatable causes.[16, 51, 156]
- The decision to use an antipsychotic should involve the patient (where possible), family and caregivers, with realistic guidance around expected benefit, time course of response, duration of therapy and potential adverse effects.[8, 157]
- Antipsychotics should not be used for the management of sleep disorders or anxiety.[51]
- Patients with PDD and DLB have an increased risk of extrapyramidal side effects and neuroleptic sensitivity reactions, and antipsychotics should be avoided in these patients
- If an antipsychotic agent is necessary, get an ECG before and shortly after initiation of treatment. This enables screening for existing or emergent QT interval prolongation. If QT prolongation is detected, a reduction of the dose or discontinuation of the drug should be attempted, concurrent medications examined for known interactions, other risk factors for sudden cardiac death reduced, and follow-up ECGs obtained.[133]

Initiating an antipsychotic
• Non-pharmacological interventions should be continued in combination with any pharmacological therapy of BPSD.[51]
• The target symptoms or behavior should be identified prospectively, and methodically documented both before and following medication initiation for at least two weeks, with regular review for response, adverse effects and drug interactions.[158]
• Initiate antipsychotics at the lowest possible dose, and very gradually titrate upwards according to tolerability and response.[10] The dose of the antipsychotic, or other agent trialed for BPSD, should take into account the physical size, age, and general condition of the patient. A maximal daily dose including p.r.n. doses should be clearly specified (e.g., "total dose within any 24 hour period is not to exceed [specify dose] mg").
• Consider a p.r.n. regimen for the management of episodic or rapidly changing agitation, aggression, or psychosis. Specifically define the clinical circumstances warranting use, including the symptoms to trigger administration, dose, frequency, duration and maximum dose for any 24 hour period. Carefully defined p.r.n. regimens and drug-free days can help minimize overall psychotropic load. If appropriate, consent should also be sought from the patient's family or guardian. The administration of p.r.n. medication may be difficult in the community with a sole caregiver. If symptoms begin to flare, the patient may be suffering from delirium and need a full medical workup
• There is no evidence to support the use of more than one antipsychotic at a time (for example, a regularly dosed antipsychotic with another antipsychotic dosed on a p.r.n. basis).[8] Using more than 1 antipsychotic at a time is likely to significantly increase the risk of serious adverse effects.

Dosing.

Agent	Dose	Maximum dose
Risperidone (Risperdal)	A total daily dose of 0.5 to 2 mg, administered in 1 or 2 divided doses.	Maximum total dose (including any p.r.n medication) not to exceed 2 mg in 24 hours.
Olanzapine (Zyprexa)	A total daily dose of 2.5 to 10 mg, administered in 1 or 2 divided doses.	Maximum total dose (including any p.r.n medication) not to exceed 10 mg in 24 hours.
Haloperidol (Haldol, generics)	0.5 mg at night, increase up to 1 mg twice daily as necessary.	Normal final dose is 1-2 mg daily.

Reviewing antipsychotic therapy
• After starting an antipsychotic or changing dose, the patient should be reviewed one week later for adverse effects.[159] In particular, postural hypotension should be assessed prior to initiation of an antipsychotic and then once a day for the first three days after initiation, as well as after any dose increase.
• Patients should be regularly assessed for adverse effects.[10, 16]
• If a positive response occurs, it is usually evident within two weeks, but may take longer.[16] If improvement is not evident, discontinue the antipsychotic.
• In patients who do respond to antipsychotic therapy, use for no longer than 3 months before considering tapering the dose (see below) and undertaking a trial cessation to assess continuing need.[10, 135, 156, 158] Certain behaviors may abate as the dementia progresses,[10, 51] and the use of any pharmacological intervention for BPSD should be re-evaluated regularly.[51]
• Do not stop antipsychotics abruptly; they should be gradually withdrawn to avoid withdrawal symptoms (e.g., dizziness, nausea, vomiting, headache, tremors, insomnia, and anxiety), unless significant adverse effects or a drug interaction necessitates abrupt cessation. Dose should be tapered by 25-50% every 2 weeks and stopped after 2 weeks on the minimum dose.

BOTTOM LINE

Antipsychotic drugs may provide modest benefit for some aspects of BPSD in the elderly, but the risks of serious adverse events often outweigh the benefits. Most evidence of efficacy from clinical trials is for aggression, agitation, and psychosis. The use of antipsychotics in elderly patients increases the risk of death, and no antipsychotic is FDA-approved for this purpose.

Other drugs for BPSD

BENZODIAZEPINES

A p.r.n. short-acting benzodiazepine (rather than an antipsychotic) may be useful for acute anxiety or agitation, but can also cause a paradoxical response in which agitated behavior is exacerbated. Most guidelines suggest that benzodiazepines should not be used continuously for longer than 2 weeks. These agents may exacerbate cognitive impairment in dementia and may increase the risk of falls in older people. They may also increase risk for accidents while driving. Oxazepam and lorazepam are preferred as they do not have active metabolites and tend to be relatively rapidly absorbed.[51] Oral lorazepam may be given as required 0.5–1 mg every four to six hours, to a maximum dose of 2 mg/24 hours.[51] Oxazepam may be given as required 10–15 mg one to four times a day, to a maximum dose of 60 mg/24 hours.[51]

CHOLINESTERASE INHIBITORS

The clinical efficacy of the cholinesterase inhibitors [donepezil (Aricept); galantamine (Razadyne); rivastigmine (Exelon)] and memantine (Namenda)] for BPSD has not been well established in prospective trials. Rivastigmine may modestly improve behavioral and psychological symptoms (in particular visual hallucinations) in patients with DLB.[160]

A number of reviews have examined the effects of cholinesterase inhibitors using the Neuropsychiatric Inventory (NPI, see page 39, a lower score indicates improvement) to assess BPSD. A 2006 Cochrane systematic review found that treatment of mild, moderate, or severe Alzheimer's disease with a cholinesterase inhibitor for 6 months produced a small, statistically significant improvement in the NPI (-2.44 points).[53] A 2007 meta-analysis of cholinesterase inhibitors in patients with mild to moderate vascular dementia found no behavioral or functional benefits except with 10 mg daily donepezil.[61, 80]

A 2008 meta-analysis examined the efficacy of cholinesterase inhibitors in treating BPSD in patients with AD. The analysis included only studies that measured the BPSD with the NPI in patients with any stage of AD and living in any clinical setting. The analysis found that cholinesterase inhibitors led to a statistically significant improvement on BPSD, but the effect size was small (-1.38 points on the NPI overall; -1.92 points in mild AD; -0.06 points in patients with severe AD). The clinical significance of this was unclear.[161] The analysis concluded that the use of cholinesterase inhibitors for BPSD does not appear to produce an effect large enough to be used as monotherapy in patients with dementia.

MEMANTINE

A 2006 Cochrane review found a small, statistically significant (-2.76 points on the NPI), beneficial effect of memantine on behavior in moderate to severe AD, but no benefit in mild to moderate disease.[61] The review also found a small beneficial effect of memantine on behavior (-0.84 points on the NPI) in mild to moderate vascular dementia, but this was not supported by clinical global measures. A 2007 meta-analysis of memantine in patients with mild to moderate vascular dementia found no behavioral or functional benefits.[61, 80]

A 2008 pooled analysis of 6 RCTs of patients with moderate to severe AD (MMSE < 20) found statistically significant effects of memantine on the NPI in treatment and prevention of behavioral symptoms. Specifically, benefits were demonstrated for delusions, hallucinations, disinhibition, irritability, agitation, and aggression.[162] A 2008 systematic review of memantine for BPSD found a statistically significant improvement in NPI scores with memantine treatment of AD. However, the effect size was small (-1.99 points on the NPI) and it was unclear if the drug produced significant clinical benefit.[163]

A summary of results from recent meta-analyses and reviews assessing the effects of cholinesterase inhibitors and memantine on BPSD in dementia (as measured with the NPI) are shown in Table 6 on page 53.

Table 6. Effect of cholinesterase inhibitors and memantine on BPSD.

		Points change in NPI compared to placebo (% change from baseline)
Birks 2006[47]	Alzheimer's disease Cholinesterase inhibitors as a class	-2.44 (% change from baseline not stated)
McShane 2006[61]	Alzheimer's disease Memantine Vascular dementia Memantine	-2.76 (moderate to severe AD) NS (mild to moderate AD) -0.84 (mild to moderate VD) (% changes from baseline not stated)
Kavirajan 2007[61, 80]	Vascular dementia Donepezil 5 mg Donepezil 10 mg Galantamine Rivastigmine	 NS NS NS NS
Maidment 2008[163]	Alzheimer's disease Memantine	-1.99 (9%-17%)
Campbell 2008[161]	Alzheimer's disease Cholinesterase inhibitors as a class	-1.38 (overall) -1.92 (mild to moderateAD) NS (moderate to severe AD) (% changes from baseline not stated)
Gauthier 2008[162]	Alzheimer's disease (moderate to severe) Memantine	Approx -2.0 at 12 weeks of therapy (13%) Approx -1.4 at 24/28 weeks of therapy (9%)

NS = not significant; NPI = Neuropsychiatric Inventory (a 30–50% reduction from baseline to endpoint in the NPI score is considered clinically significant)

BOTTOM LINE

Studies of anticholinesterases and memantine have found small, statistically significant beneficial effects on BPSD, as measured by the Neuropsychiatric Inventory. However, the clinical significance of these changes has not always been clear. Most studies have involved patients with Alzheimer's disease or vascular dementia.

ANTIDEPRESSANTS

Antidepressants are a reasonable choice for treating depressive symptoms in dementia, and SSRIs appear to be superior to placebo in this population.[164] While there is little compelling evidence to support their use for other aspects of BPSD, one recent 12-week randomized controlled trial in non-depressed patients with dementia did show that citalopram was as effective as risperidone in decreasing psychosis and agitation, with a more desirable side effect profile.[165]

CARBAMAZEPINE

A time-limited trial of low dose carbamazepine (e.g., 50–100 mg/day, increased by 50–100 mg after 3 or more days to a b.i.d. regimen according to response and tolerability) may be considered for dementia-related agitation/aggression if other interventions have been exhausted, with close monitoring for response, adverse effects and drug interactions.[10, 51] Specialist referral is probably warranted.

VALPROATE

A 2004 Cochrane review concluded that valproate therapy cannot be recommended for management of agitation in dementia.[166] A more recent trial of sodium valproate for agitation found it to be no more effective than placebo.[167]

OTHER (LITHIUM, GABAPENTIN)

There is insufficient evidence to support the use of these drugs for BPSD.

▲ SUMMARY OF PHARMACOLOGIC AGENTS USED IN DEMENTIA

Cognition.

Drug	Efficacy						Adverse Effects							Overall
	AD	VD	PPD	DLB	FTD	Other	GI	sed	EPS	Other CNS	CV	incont	death	
donepezil (Aricept)														
galantamine (Razadyne)														
rivastigmine (Exelon)														
memantine (Namenda)														
atypical antipsychotics														
conventional antipsychotics														

AD = Alzheimer's disease; VD = vascular dementia; PDD = Parkinson's disease dementia;
DLB = dementia with Lewy bodies; FTD = fronto-temporal dementia; Other = other forms of dementia;
GI = gastrointestinal; sed = sedation; CNS = central nervous system (e.g., seizures);
CV = cardiovascular; incont = incontinence; EPS = Extrapyramidal symptoms

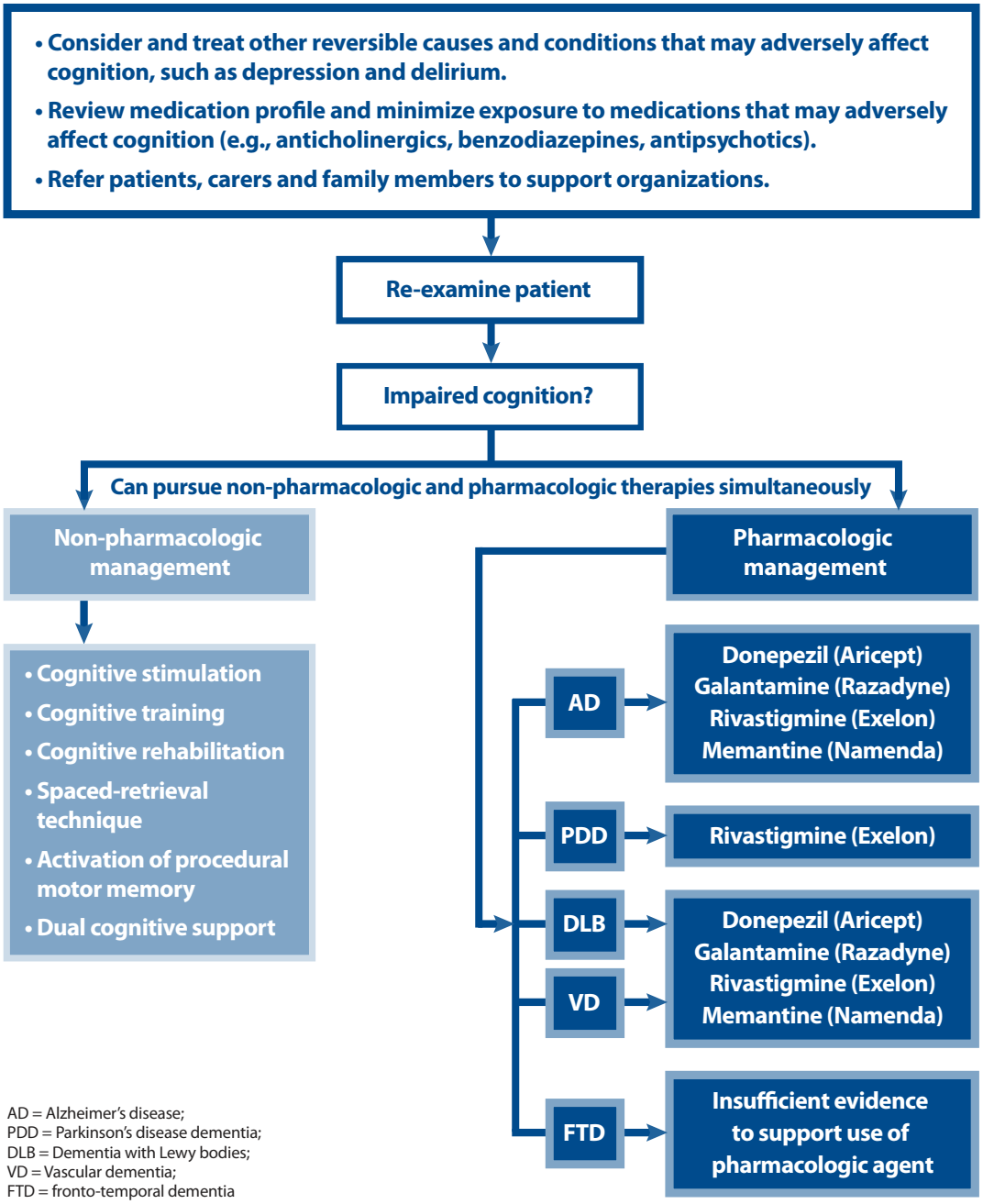
Best outcome	Intermediate	Problem	Unknown or no effect

Behavorial and psychological symptoms of dementia.

Drug	Symptom control	Adverse Effects							Overall
		GI	sed	EPS	Other CNS	CV	incont	death	
rivastigmine (Exelon)	‡								
memantine (Namenda)	‡‡								
benzodiazepines									
atypical antipsychotics									
conventional antipsychotics									
valproate	*								

‡ may modestly improve BPSD (in particular visual hallucinations) in patients with DLB
‡‡ some evidence of efficacy for delusions, agitation, and aggression, but unclear whether the drug produces important clinical benefit
* valproate is commonly used for BPSD but there is little evidence supporting its efficacy
GI = gastrointestinal; sed = sedation; CNS = central nervous system (e.g., seizures);
CV = cardiovascular; incont = incontinence; EPS = Extrapyramidal side effects

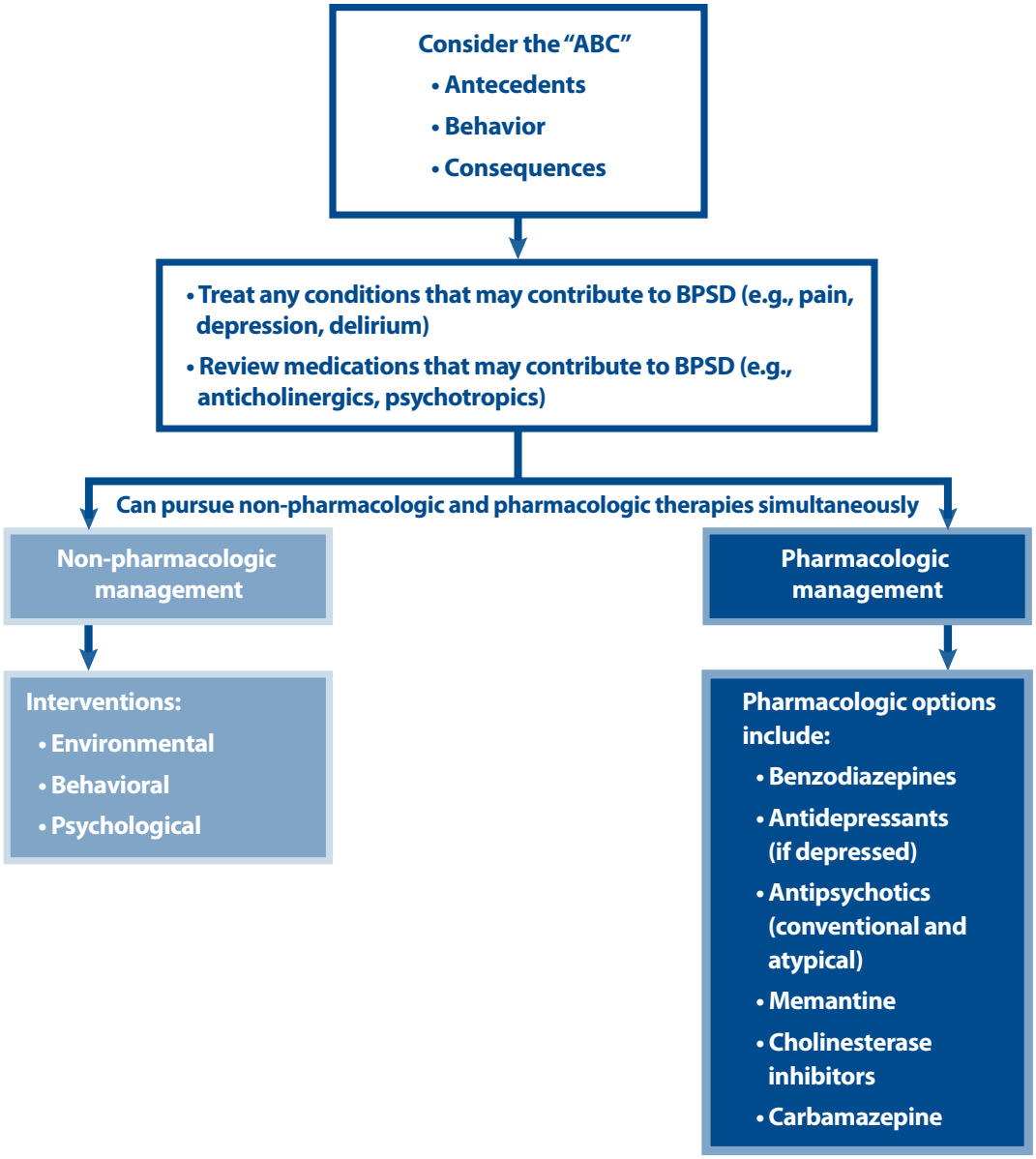
PUTTING IT ALL TOGETHER- A MANAGEMENT ALGORITHM FOR COGNITION IN DEMENTIA



AD = Alzheimer's disease;
PDD = Parkinson's disease dementia;
DLB = Dementia with Lewy bodies;
VD = Vascular dementia;
FTD = fronto-temporal dementia

This algorithm should be interpreted in the context of the more detailed information provided in the body of this document.

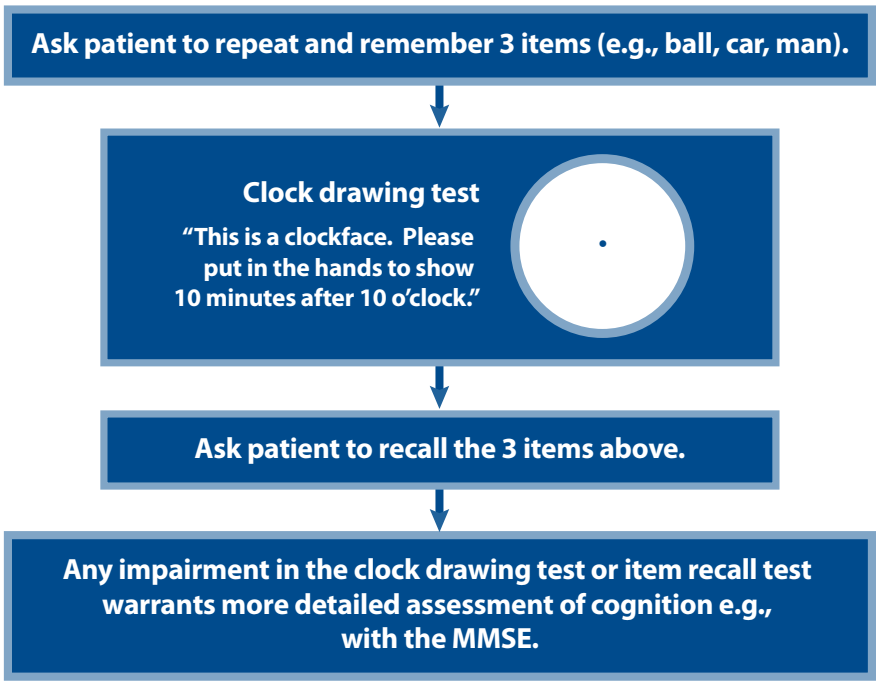
PUTTING IT ALL TOGETHER- A MANAGEMENT ALGORITHM FOR BEHAVORIAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)



This algorithm should be interpreted in the context of the more detailed information provided in the body of this document.

▲ APPENDIX 1. THE MINI-COG TEST

The Mini-Cog Test uses a 3 item recall test to assess memory and the clock drawing test. It is a non-specific test designed to quickly screen for gross abnormalities and a trigger for further evaluation. A person who scores well does not necessarily have normal cognition.



APPENDIX 2. THE FOLSTEIN MINI-MENTAL STATUS EXAMINATION (MMSE)

The MMSE is a tool for screening cognitive decline associated with dementia.[27] This version is adapted from and available at: http://rgp.toronto.on.ca/dmcourse/toolkit/Folstein.htm

The MMSE evaluates cognition in five areas: orientation; immediate recall; attention and calculation; delayed recall; and language.

Question	Correct answer	Incorrect answer
1. What year is it?		
2. What season are we in?		
3. What month are we in?		
4. What is today's date?		
5. What day of the week is it?		
6. What country are we in?		
7. What state are we in?		
8. What city are we in?		
9. What street are we on (or, what building? - if in hospital or clinic)		
10. What is the street number? (or, what floor? - if in hospital or clinic)		
Name three objects ("Ball", "Car", "Man"). Take a second to pronounce each word. Then ask the patient to repeat all 3 words. Take into account only correct answers given on the first try. Repeat these steps until the subject learns all the words.		
11. Ball?		
12. Car?		
13. Man?		
Either "please spell the word WORLD and now spell it backwards" or "Please count from 100 by subtracting 7 every time".		
14. "D" or 93?		
15. "L" or 86?		
16. "R" or 79?		
17. "O" or 72?		
18. "W" or 65?		
What were the 3 words I asked you to remember earlier?		
19. Ball?		
20. Car?		
21. Man?		

The Folstein Mini-Mental Status Examination (MMSE) *continued*

Question	Correct answer	Incorrect answer
Show the subject a pen and ask:		
22. Could you please name this object?		
Show the subject your watch and ask:		
23. Could you please name this object?		
Listen and repeat after me:		
24. "No ifs, ands or buts."		
Put a sheet of paper on the desk and show it while saying: "Listen carefully and do as I say."		
25. "Take the sheet with your left/right (opposite to dominant) hand."		
26. "Fold it in half."		
27. "Put it on the floor."		
Show the patient a written instruction directing him/her to "CLOSE YOUR EYES" and say:		
28. "Do what is written on this page."		
Give the subject a blank sheet and a pen and ask:		
29. "Write a sentence, whatever you want, but a complete sentence."		
Give the patient a sheet of paper with a drawing of intersecting pentagons and ask:		
30. "Could you please copy this drawing?"		

Test scores should always be interpreted cautiously, especially in the context of socio-cultural diversity, level of education, or developmental disability.

Scores range from zero to 30.[54]

27-30 = normal cognition

21–26 = mild dementia

10–20 = moderate dementia

< 10 = severe dementia

If the patient scores in the normal range, but his/her family report declining behavioral integrity and cognitive problems, consider more detailed assessment by a geriatric psychologist or behavioral neurologist.

The average rate of decline in MMSE is 3.35 points/year in patients with Alzheimer's disease. The MMSE is not sensitive to small changes in cognition.[168] A change of at least 3 points in the MMSE is usually needed to see a clinically significant effect.[169] The MMSE exhibits a floor effect because it poorly detects changes in cognition in severe dementia.

The MMSE does not test executive functioning affected by frontal deficits; a quick screen to assess some aspects of frontal function is a clock face drawing test as below.

Clock drawing test

"This is a clockface. Please put in the hands to show 10 minutes after 10 o'clock."

▲ APPENDIX 3. ALZHEIMER'S DISEASE ASSESSMENT SCALE-COGNITIVE SUBSCALE (ADAS-COG)

The ADAS-Cog is a 70 point scale comprising individual tests that cover memory (word recall and recognition); orientation; language (comprehension, spoken language, naming and word finding); and praxis (constructional and ideational).[30]

Higher scores on ADAS-Cog indicate greater dysfunction. Scores > 40 indicate severe impairment and scores of 10–25 indicate mild impairment.[168] The average change/year in an untreated patient with Alzheimer's disease on ADAS-Cog is approximately 8 points, but individual changes may vary by –5 to 40 points.

A change of at least 4 points in the ADAS-Cog is usually needed for a clinically significant effect.[169] The ADAS-Cog exhibits a floor effect because it poorly detects cognitive changes in severe dementia.

This test is used in clinical trials, but is rarely used in clinical practice because it can take up to 60 minutes to administer.

APPENDIX 4. ADVERSE EFFECTS OF SELECTED ANTIPSYCHOTICS

Antipsychotic adverse effects.[170]

	aripiprazole	haloperidol	olanzapine	quetiapine	risperidone
Anticholinergic	–	+	++	+	–
Hyperglycemia	–	–	++	+	–/+
Extrapyramidal side effects	+	+++	+	+	++
Hyperprolactinemia	–/+	+	+	–	++
Postural hypotension	–/+	+	+	++	+++†
Sedation	++	+	+++	+++	++
Seizures	–/+	–/+	–/+	–/+	–/+
Weight gain	+	++	+++	++	++

– no or negligible effect (< 2% frequency)
–/+ Uncertain effect
+ Infrequent effect (> 2% frequency);
++ Moderate effect (> 10% frequency)
+++ Frequent effect (> 30% frequency)
‡ Particularly at initiation

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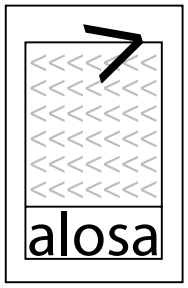

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