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THE DIAGNOSIS AND MANAGAMENT OF DEMENTIA

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The Increasing Burden of Dementing Disease

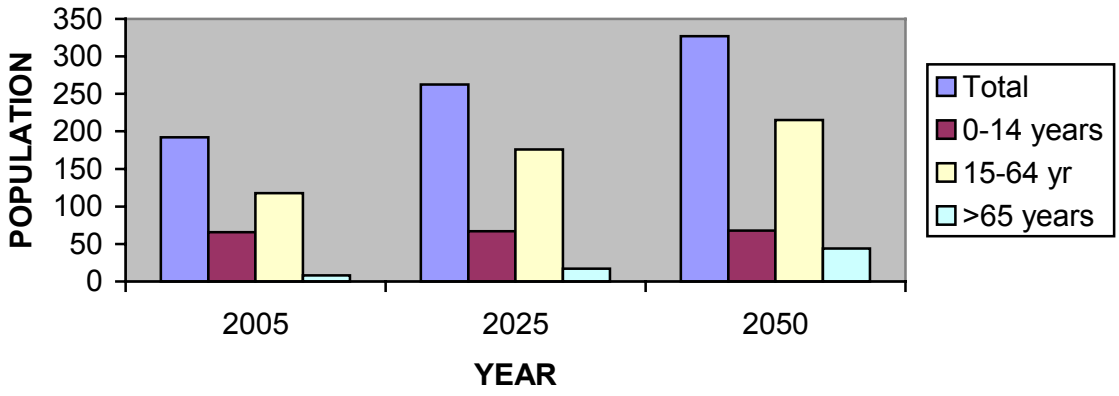
Dementia is a common, disabling and distressing neurological disorder and should not be considered a feature of normal aging. Many people reach old age without developing disabling cognitive impairment, although some aspects of cognition routinely change with age. These changes vary among aged individuals and involve slowing of reaction times and reduction of memory capacity and visuospatial skills (1). Despite the presence of measurable neuropsychological alterations in the majority of elderly people, those who experience these changes typically retain their ability to conduct their daily social and occupational activities. These mild alterations stand in stark contrast to the derangements of cognition that lead to dementia, with loss of normal function. The proportion of aging individuals who develop dementia is substantial, and the aging segment of the population is expanding worldwide.

According to World Health Organization (WHO) estimates, the total population of ten selected Middle Eastern nations (Algeria, Bahrain, Egypt, Iraq, Israel, Kuwait, Lebanon,

Libya, Saudi Arabia and Syria) will continue to expand through the first half of this century, exceeding 326 million by the year 2050. During this interval the proportion of the population over the age of 65 will grow at a greater rate than other segments of the populace. Thus, although only 6.2% of the adult population of these countries is projected to be over the age of 65 in 2005, this percentage will rise to 17.1% by the year 2050 (2) (Figure 1). The expansion of the number of aged individuals in the population will inevitably be accompanied by an increasing number of persons with dementia and pre-dementia mild cognitive impairment (MCI). A further concern is that this will not be accompanied by a comparable increase in the occupationally productive segment of the population. While the 15-64 year old age group is projected to increase by 81%, the over-65 year-old group will increase by 468%.

Diseases that result in cognitive impairment are common and increase in prevalence with age. The aged segment of the population is growing rapidly in most countries of the world and high rates of dementing disease are expected during the next fifty years. In the United States there were 2.32 million individuals with Alzheimer's disease (AD) in 1997 and this number is expected to increase to at least 8.64 million by the year 2050 (3). The proportion of new AD cases in Middle Eastern nations may be similar to that of the US, although few studies are available to guide predictions. Unless a means is found to prevent or delay the onset of AD, many of the people in the over-65 age group will become demented, constituting an overwhelming social and economic burden as well as a personal tragedy and a challenge to family

Figure 1 Demography of Aging in Ten Middle Eastern Nations (population in millions)



Mild Cognitive Impairment

Studies of aging that address the epidemiology of dementia have revealed the presence of three groups of individuals: those who are cognitively normal, those who are demented and a third group that have cognitive impairment but do not meet criteria for dementia. These individuals may have impairment in a single domain, usually memory. This third group of patients cannot be classified as "normal" or as "demented," since the definition

of dementia requires abnormalities in at least two cognitive domains and social or occupational disability. These individuals have been labeled as **mild cognitive impairment** (MCI). The most clearly characterized form of MCI is known as the "amnestic form"; these patients are characterized by subjective memory complaints and evidence objective memory impairment but have normal cognitive function in other domains and intact ability to carry out activities of daily living (4)(See Table 1). In research studies, patients typically meet an operational criterion of 1.5 or more standard deviations below the mean for age-matched controls on standard neuropsychological tests of memory (5).

Table 1 *Criteria for mild cognitive impairment (4)*

Memory complaint, preferably corroborated by an informant
Objective memory impairment (below 1.5 standard deviations)
Normal general cognitive functioning
Intact activities of daily living
Not demented

Patients with MCI are at increased risk for the development of AD. The annual incidence of AD in the general population ranges from 0.2% among those aged 65-69 years to 3.9% among those aged 85-89, but studies estimate the incidence rate among patients previously diagnosed with MCI to be between 6 and 25% per year (6). Early recognition of these patients will become increasingly important as treatments are developed that delay the transition from MCI to AD. Delaying the onset of AD by as little as six months will have substantial economic benefits (3). Several clinical trials are under way to investigate potential pharmacological treatments for MCI (5). Patients with other forms of MCI (such as mild changes in more than one domain or in a single non-memory domain) may be at risk for other forms of dementia, such as dementia with Lewy bodies, vascular dementia or frontotemporal dementia (4).

Assessment of Dementia

A number of cognitive instruments have proven useful for screening patients at risk for dementia. The Mini-Mental Status Exam (MMSE) is widely used. It is sensitive when scores are adjusted for age and education (6,7). The validity of the MMSE in some Arab populations has been investigated and shown to provide acceptable data (8). Cognitive testing with a short mental status exam should be supplemented with the bedside evaluation of memory, language, visuospatial abilities, and frontal-executive functions. Culturally appropriate versions of these tasks should be selected. Depression can cause cognitive changes and patients should be screened with questions about their mood, tearfulness and suicidal ideation.

In addition to measures of cognitive function, it is important to identify loss of general function or of the ability to carry out activities of daily living, such as bathing, grooming, toileting, eating or more complex activities expected of aged individuals in their cultural setting. These facts can be gleaned from the history or by interviewing the patient's

caregiver with structured instruments (9). The clinician can also gain insight regarding the patient's overall level of function with global rating scales (9, 10). Such informant-based scales are useful if the informant is observant.

Every patient with suspected dementia should undergo a thorough physical and neurologic examination. Medical illnesses that can result in dementia include thyroid disease, atherosclerotic vascular disease, collagen-vascular diseases (such as systemic lupus erythematosus), and infections. Thus, the clinician must be attentive to the skin for thinning of hair and eyebrows, spider hemangiomata, palmar erythema, malar rash or Kaposi's sarcoma. The heart sounds, liver texture and size, or the presence of fever, hypertension or lymphadenopathy may also provide important diagnostic clues. Visual field defects, eye movement abnormalities, facial asymmetry, dysarthria, focal weakness or spasticity may indicate the presence of focal brain or brainstem lesions due to stroke, tumor or infectious diseases such as toxoplasmosis.

Where feasible, patients with a clinical dementia syndrome should undergo structural brain imaging with noncontrast computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate for focal lesions, deep white matter ischemic changes and regions of atrophy.

Certain laboratory tests are valuable for the initial screening of patients with cognitive changes. In particular, thyroid function tests (thyroid stimulating hormone and free T4) and the vitamin B_{12} level should be checked in patients with cognitive complaints. In cases of borderline B_{12} deficiency elevated levels of homocysteine and methylmalonic acid enhance the sensitivity of the B_{12} level. Patients with risk factors for HIV should undergo appropriate tests. The prevalence of venereal syphilis is low outside of urban areas in most Middle Eastern countries, reducing the utility of routine syphilis testing. The occurrence of non-venereal, endemic syphilis (bejel) in rural regions of North Africa and the Arabian peninsula increases the need for caution when interpreting serological tests for syphilis (11). There is little evidence that bejel ever results in neurologic complications. The 14-3-3 protein is present in higher levels in the spinal fluid of patients with Creutzfeldt-Jakob disease and can be used to support the diagnosis in patients whose clinical presentation is consistent with the disorder (12).

Diagnosis of Dementia

Dementia

The definition of dementia provided in the *Diagnostic and Statistical Manual,* 3rd edition, revised (DSM-IIIR) has been found to have adequate reliability and should be used for making the diagnosis (13,14). These criteria were not changed in the 4th edition, and are shown in Table 2.

Table 2 *DSM-IV Criteria for dementia (13)*

Short- and long-term memory impairment
Impairment in abstract thinking, judgment, other higher cortical function or personality change
Cognitive disturbance interferes with significantly with work, social activities or relationships with others
These cognitive changes do not occur exclusively in the setting of delirium

Once the presence of dementia is established an attempt should be made to identify its etiology by use of the history, clinical exam, neuropsychological assessment, and, where feasible, imaging and laboratory studies. None of the currently available biological markers are useful for establishing with certainty the diagnosis of any of the most common forms of dementia: Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB) or frontotemporal dementia (FTD) (13). Therefore, the clinician must rely on clinical criteria for making these diagnoses.

Alzheimer's disease

Alzheimer's disease is the most common form of late-onset dementia. The National Institute of Neurological and Communicative Disorders and Stroke- AD and Related Disorders Association (NINCDS-ADRDA) criteria for AD have been shown to have adequate sensitivity and specificity (see Table 3). Patients nearly always present with the primary complaint of memory difficulty, articulated either by the patient or by the family. This is frequently associated with visuospatial disorientation or language dysfunction. These may manifest as a tendency to get lost in familiar locations, reduction in the conceptual precision of speech or impaired comprehension of complex linguistic material. Occasionally patients with the neuropathologic changes of AD present clinically with disruption of a single cognitive domain other than memory, such as loss of visuospatial or frontal-executive function or aphasia. Such patients may be diagnosed with posterior cortical atrophy, frontal variant-AD or aphasia-predominant AD (15). The diagnosis of AD should be held in question if there is evidence that the patient's cognition is being impacted by another psychiatric, systemic or central nervous system disease. Thus, in patients with depression, severe hypothyroidism or cerebrovascular disease the diagnosis of *possible* rather than *probable* AD is appropriate until the cause of the disease is evident.

Table 3 *NINCDS-ADRDA Criteria for the Diagnosis of Alzheimer's Disease (15)*

Probable AD: Core Diagnostic Features

A. Dementia established by clinical examination (including MMSE, BRDRS, and neuropsychological testing)
B. Deficit in at least two areas of cognition
    i. Memory (required)
    ii. Other area besides memory
C. Deficits characterized by gradual onset and progression, onset after age 40
D. Other systemic disorders or brain disease do not account for the progressive deficits in memory and cognition in and of themselves

II. Possible AD: Core Diagnostic Features
   A. Dementia syndrome in the absence of other neurologic, psychiatric, or systemic disorder, ***OR***
   B. Presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the primary cause of the dementia

III. Features that make a diagnosis of *Probable* or *Possible* AD unlikely or uncertain
   A. Sudden apoplectic onset
   B. Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
   C. Seizures or gait disturbances at the onset or very early in the course of the illness

IV. Criteria for diagnosis of *Definite* Alzheimer's disease:

   A. Clinical criteria for probable Alzheimer's disease
   B. Histopathologic evidence obtained from a biopsy or autopsy

As AD progresses, patients frequently suffer from neuropsychiatric complications such as agitation, apathy, delusions, hallucinations or depression. In many cases, these constitute a greater burden for caregivers than the cognitive deficits and may require treatment with psychoactive medications.

Vascular dementia

Dementia due to cerebrovascular disease should be suspected when impairment in more than one cognitive domain accompanies clinical or neuroimaging evidence of stroke. Observed loss of normal social and occupational functioning required in the definition of dementia should result from cognitive impairment and not be explained entirely by the physical disability that results from stroke. The diagnosis is more certain when there is a temporal association between clinical stroke and onset of cognitive impairment, or when family members describe a stepwise pattern of deterioration. The most common type of VaD is associated with ischemic injury to subcortical white matter and lacunar infarctions secondary to small vessel disease.

Patients with VaD often exhibit cortical deficits associated with focal cerebral lesions, such as aphasia, neglect, apraxia or dyscalculia. Frontal executive function is commonly impaired and memory defects follow the frontal-subcortical pattern, in which patients encode memories adequately but have difficulty retrieving them.

Four sets of criteria exist for the diagnosis of VaD. None have been shown to have good specificity, but all are sensitive. Of these, the Hachinski Ischemic Score (Table 4) may identify the greatest number of patients with VaD in spite of not including neuroimaging criteria (13,17). A score of ≤ 4 is suggestive of AD or other non-vascular causes of dementia, while a score of ≥ 7 is supportive of a diagnosis of VaD.

Table 4 Hachinski Ischemic Score (16)

Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Preservation of personality	1
Depression	1

Somatic complaints	1
Emotional incontinence	1
Hypertension	1
History of stroke	2
Associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) has been defined clinically as a dementia syndrome with parkinsonism, delusions, hallucinations (especially visual), fluctuating alertness and sensitivity to neuroleptic medications (See Table 5) (18). The criteria have poor sensitivity but are very specific (19). The cognitive profile is remarkable for deficits in attention, visuospatial reasoning and frontal-subcortical function. When patients with DLB are compared to patients with AD, memory is significantly worse in AD, while visuospatial function and executive abilities are worse in DLB (20). The core clinical features that may be present include fluctuating cognition, visual hallucinations and parkinsonism. Depression and rapid eye movement (REM) sleep behavior disorder are also common in DLB.

Parkinson's disease (PD) is characterized by rigidity, bradykinesia, rest tremor, loss of righting reflexes, and beneficial response to dopaminergic therapy. Approximately 40% of patients with idiopathic PD meet criteria for dementia (21). This usually follows a frontal-subcortical pattern, in which frontal executive functions and memory retrieval are the most impaired. Patients with PD and dementia typically have Lewy bodies in the cortex at autopsy. The dementia of PD may represent a variant of DLB.

Table 5 *Criteria for Dementia with Lewy Bodies (17)*

I. Progressive cognitive decline interfering with social and occupational functioning, usually including deficits of attention, frontal subcortical skills and visuospatial ability; memory impairment tends to be a later finding

II. Two of the following core features are necessary for the diagnosis of probable DLB, one for the diagnosis of possible DLB:
- A. Fluctuating cognition with pronounced variations in attention and alertness
- B. Recurrent visual hallucinations which are typically well-formed and detailed
- C. Spontaneous motor features of parkinsonism

III. Supportive features:
- A. Repeated falls
- B. Syncope
- C. Transient loss of consciousness
- D. Neuroleptic sensitivity
- E. Systematized delusions
- F. Hallucinations in other modalities

IV. A diagnosis of DLB is less likely in the presence of:
- A. Clinical or neuroimaging evidence of stroke

Clinical, laboratory or neuroimaging evidence for other physical illness or brain disorder that accounts for

the clinical picture

Frontotemporal Dementia

Frontotemporal dementia (FTD) features early behavioral changes preceding loss of memory, perception, spatial skills or praxis (22). This disorder is less common than AD, VaD or DLB. As is the case with other neurodegenerative diseases, the onset is insidious and progressive. Those close to the patient frequently notice a change in personality characterized by tactlessness, disinhibition, poor impulse control, poor grooming and hygiene, emotional blunting, mental rigidity and ritualized behaviors (22). Some patients demonstrate hyperorality, which may manifest as a craving for sweets, but patients have been described who chewed compulsively on nonfood objects. Language is often impacted, and may be characterized by stereotypies and echolalia. Anomia and reduced verbal output are common. Snout, grasp and palmomental reflexes may be present (see Table 6.) Onset of the disorder is typically between the ages of 45 and 65 years.

The clinical syndromes of progressive nonfluent aphasia and semantic dementia are most often associated with the neuropathologic changes of FTD. The former is typically manifested as the insidious onset of anomia that progresses to nonfluent aphasia, while the latter is characterized by early loss of word meaning that manifests as failure of single-word production and comprehension (22). Patients with semantic dementia often lose conceptual knowledge in other spheres, resulting in prosopagnosia or visual agnosia (23). Primary progressive aphasia often leads to complete or nearly complete mutism.

Table 6 *Criteria for Frontotemporal Lobar Degeneration (21)*

I. Core diagnostic features
   - A. Insidious onset and gradual progression
   - B. Early decline in social interpersonal conduct
   - C. Early impairment in regulation of personal conduct
   - D. Early emotional blunting
   - E. Early loss of insight

II. Supportive diagnostic features
   - A. Decline in personal hygiene and grooming
     1. Mental rigidity and inflexibility
     2. Distractibility and impersistence
     3. Hyperorality and dietary changes
     4. Perseverative and stereotyped behavior
     5. Utilization behavior
   - B. Speech and language
     1. Altered speech output
        - a. Aspontaneity and economy of speech
        - b. Press of speech
     2. Stereotypy of speech
     3. Echolalia
     4. Perseveration
     5. Mutism
   - C. Physical signs
     1. Primitive reflexes
     2. Incontinence

3. Akinesia, rigidity and tremor
4. Low and labile blood pressure

D. Investigations

1. Neuropsychology: significant impairment of frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
2. Electroencephalography: normal on conventional EEG despite clinically evident dementia

Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

Treatment of Alzheimer's Disease

A great deal of research has focused on identifying medications capable of slowing or delaying the progression of AD. A placebo-controlled, double-blind study comparing selegiline, vitamin E (alpha-tocopherol) and a combination of both drugs demonstrated that all three treatments delayed the onset of functional dependence and the need for institutionalization compared to placebo (24). Combination of the two drugs did not offer significant benefit over either drug alone. Since vitamin E is inexpensive and relatively safe in patients who are not on anticoagulation, it is now the standard of care to administer 1000 IU twice daily to patients diagnosed with AD. The value of vitamin E in ameliorating other forms of dementia is not known.

Four medications that block the action of acetylcholinesterase have been proven to be beneficial for AD. The first of these to be approved, tacrine, is associated with liver toxicity and requires QID dosing. Newer agents are less toxic and easier to use, and tacrine is no longer frequently prescribed (25,26). Donepezil is a cholinesterase inhibitor that does not require monitoring of liver function tests and is dosed once per day. The starting dose of 5 mg is therapeutic; many patients benefit from titration to 10 mg. Rivastigmine is a cholinesterase inhibitor that is dosed twice daily, starting with 1.5 mg tablets. The dose can be increased at 4-week intervals to 3 mg BID, then 4.5 mg BID and finally 6 mg BID if desired (27). Gastrointestinal side effects (such as nausea or weight loss) have been reported in 15 to 45% of subjects and result in discontinuation of the drug in up to 25% (25). Galantamine is a cholinesterase inhibitor with comparable cognitive benefits (28). The optimal dose identified is 16 to 24 mg/d, divided into two daily doses. Galantamine typically is titrated from 4 mg BID, to 8 mg BID, and finally to 12mg BID. Cholinesterase inhibitors have been shown to improve cognition and global function compared to placebo. Improved behavior, delayed decline in function, decreased caregiver burden and deferral of institutionalization have been suggested by some studies (28,29). Cholinesterase inhibitors may be useful in other dementias with cholinergic deficits including the dementia of Parkinson's disease and DLB (29).

Another approach to treating AD pharmacologically is to prevent excitotoxicity by blocking N-methyl-D-aspartate (NMDA) receptors in the brain. This is the rationale for the use of memantine, which delays the onset of severe functional disability in patients with AD (30), even in patients who are already receiving donepezil (32). The medication is started at 5 mg once per day is titrated weekly in increments of 5 mg, with a target dose of 10 mg BID after four weeks. From a neuropsychiatric standpoint, the drug seems to reduce agitation (31-33). Although memantine fares well against placebo in terms of side

effects, it may be associated rarely with confusion or headaches (32). Table 7 summarizes the medications commonly used in the treatment of AD.

The benefits of memantine and cholinesterase inhibitors are modest, and new approaches will be important for the prevention or postponement of AD. Amyloid accumulation in the cortex is considered the primary lesion of AD and research currently is focused on preventing amyloid aggregation. Trials of a vaccine against amyloid have been disappointing thus far, due to the development of encephalopathy in some patients (34), but efforts will continue to focus on vaccination strategies as well as on beta and gamma secretase inhibitors, copper and zinc chelators, statins, antioxidants and non-steroidal anti-inflammatory drugs as means of limiting amyloid or amyloid-related neuronal injury.

Most patients will develop neuropsychiatric symptoms during the course of the illness. These symptoms constitute a weighty burden on caregivers who should be advised that modification of the patient's environment may reduce the frequency and severity of these symptoms. Such modifications may include avoiding overstimulation, following a regular schedule, and keeping the patient active during the day but providing quiet relaxing evenings. Cholinesterase inhibitors and memantine have behavioral as well as cognitive benefits. Many patients, however, will require psychotropic medications for neuropsychiatric symptoms. Depression is a feature that commonly accompanies AD and responds most readily to a non-sedating serotonin-selective reuptake inhibitor (SSRI), such as sertraline or escitalopram. Tricyclic antidepressants are of limited usefulness because of sedation and anticholinergic side effects. Agitation is a common complaint that may be associated with depression, delusions, hallucinations or insomnia. Depending on the associated features, clinicians may find use of an atypical antipsychotic, antidepressant or anticonvulsant to be useful for reducing agitation. In one trial for agitation in dementia, risperidone was shown to be as effective as haloperidol, with fewer extrapyramidal side effects (36). The effective dose of risperidone is typically 1.0 to 1.5 mg/day. Low-dose olanzapine (5-10 mg) reduced psychosis and agitation in an 18-week study of patients with possible or probable AD, with no significant increase in extrapyramidal side effects (37). Quetiapine represents a feasible alternative to these agents and may produce fewer extrapyramidal side effects. One preliminary study of sertraline use for agitation and aggression in severe AD indicated that some patients responded favorably (38). Trazodone is an unconventional antidepressant with hypnotic properties that is useful for insomnia and intermittent agitation in demented patients (21). In some cases, neuropsychiatric symptoms may respond to an anticonvulsant with mood stabilizing properties (39,40).

The late stages of AD and most dementias are marked by complete functional dependence. Patients are non-ambulatory, unable to communicate needs and may be unable to feed themselves. End of life issues must be addressed with patients and family members before this stage is reached, as many people have strong feelings regarding use of intravenous hydration or nasogastric or percutaneous gastrostomy tubes for life support. As with all bedridden patients, there is high risk for the development of decubitus ulcers, dehydration, urinary tract infection, pneumonia and deep venous thrombosis. These risks may be reduced by adequate physical therapy, frequent turning,

and hydration. Encephalopathy, rather than fever, is often the earliest sign of infection and should warrant prompt evaluation, as infections are frequently the cause of death in patients with dementia.

The Caregiver Alliance

Those caring for demented patients bear a great physical and emotional burden. Studies of medications for AD have begun to take this into account; for example, use of memantine is associated with a reduction in the caregiver time requirement of about 45.8 hours per month (31). Regardless of such modest improvements, caregivers remain responsible for numerous time-consuming tasks, such as supervising patients in activities of daily living, administering medications, and restricting driving. In addition, the difficulty of caring for a patient with dementia has a negative impact on the health of the caregiver (41). As dementia becomes more prevalent in society, resources that mitigate the suffering of caregivers and assist them in coping with the daily management of the patient will become increasingly necessary.

Table 7 Medications used in the treatment of AD

	Starting Dose	**Target Dose**	**Uses**
Cognitive Agents			
Donepezil	5 mg daily	10 mg daily	Improve cognition, may reduce apathy and hallucinations
Galantamine	4 mg BID	12 mg BID	
Rivastigmine	1.5 mg BID	6 mg BID	
Memantine	5 mg daily	10 mg BID	Slow functional decline, may improve agitation
Antidepressants			
Sertraline	25 mg daily	75-100 mg daily	Depression and agitation
Escitalopram	5 mg daily	10-20 mg daily	Depression
Trazodone	25 mg QHS	100-400 mg daily	Agitation, insomnia
Atypical Antipsychotics			
Risperidone	0.25 mg daily	0.75-1.5 mg daily	Agitation, delusions, hallucinations
Olanzapine	2.5 mg daily	5-10 mg daily	
Quetiapine	25 mg BID	200-300 mg daily	
Anticonvulsants			
Carbamazepine	200 mg BID	200-500 mg BID	Mood stabilization, outburst control
Valproic acid	125 mg BID	250-500 mg BID	

Conclusion

The prevalence of dementia is rising as the aged segment of the population grows larger. This growth is out of proportion to growth in the younger segments of the population, and dementia will impose an increasing social and economic burden during the next several decades. Middle-Eastern nations will experience a marked growth in aged segments of their populations in the impending decades. The diagnosis of dementia is best made with clinical assessment including cognitive testing. Treatments that delay the progression or improve the symptoms of AD include cholinesterase inhibitors and vitamin E. The management of neuropsychiatric symptoms is important for improving quality of life for patients and caregivers. Researchers and clinicians must recognize cognitive decline early and identify treatments that will delay or prevent the onset of dementia. Current trials are focused on identifying reliable biological markers of dementia, preventing the advancement of MCI to AD, and finding treatments to slow or halt the progression of AD and other dementing diseases.

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