

Diagnosis and Treatment of Alzheimer's Disease

George T. Grossberg, M.D.

The defining characteristic of Alzheimer's disease is cognitive impairment, but commonly this impairment is accompanied by mood and behavioral symptoms such as depression, anxiety, irritability, inappropriate behavior, sleep disturbance, psychosis, and agitation. The symptoms of Alzheimer's disease are not normative to the aging process. Diagnosis of Alzheimer's disease in the majority of cases can be made with confidence through office-based clinical assessment and informant interview. Alzheimer's disease is the most common of the dementing disorders and is exponentially increasing in incidence, projected to affect 8.64 million people in the United States by the year 2047. At present, no treatment can prevent or cure Alzheimer's disease, and the fact that Alzheimer's affects a geriatric population makes treatment all the more challenging. Therapies that could delay onset of symptoms even briefly would have a major impact on public health. As the prevalence of Alzheimer's disease increases, researchers are examining the efficacy of treatment options beyond the realm of the established cholinesterase inhibitors.

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Alzheimer's disease is a progressive, irreversible neurodegenerative illness and the most common of the dementing disorders. Onset occurs generally after 60 years of age but may be earlier in rare cases.¹ Time between symptom onset and death may span 8 to 10 years. The gradual and continuous decline caused by Alzheimer's disease is characterized by cognitive deterioration, changes in behavior, loss of functional independence, and increasing requirements for care.²

Dementia (defined as cognitive impairment accompanied by aphasia, apraxia, or agnosia) is the critical feature of Alzheimer's disease. Associated symptoms include depression, irritability, mood lability, anxiety, and sleep disturbance. Individuals with Alzheimer's disease may also exhibit wandering, motor disturbances, disinhibition that can appear as disregard for normative social conduct, and catastrophic reactions to relatively minor stressors as well as hypervulnerability to stressors like bereavement.^{1,3} Thirty percent to 50% of persons with Alzheimer's disease have psychotic symptoms,⁴ particularly delusions of persecution and visual hallucinations. Agitation—encompassing aggression, combativeness, shouting, and hyperactivity—may be manifested by as many as 50% of Alzheimer's

sufferers⁵ and, when it peaks during the evening hours, is known as sundowning.

While depression and sleep disturbance are unfortunately common in older populations, the symptoms of Alzheimer's disease are not normative to the aging process.¹ The insidious character and increasing severity of these symptoms exact enormous tolls in terms of quality of life and financial resources from those with Alzheimer's disease and their caretakers.

DIAGNOSIS

Most patients with symptoms of dementia present first to primary care physicians.¹ Ninety percent of Alzheimer's disease diagnoses can be made on the basis of a general medical and psychiatric evaluation.⁶ The major diagnostic resources are the office-based clinical assessment and the informant interview. The informant is usually a family member who can provide quotidian observation of the patient's cognition, function, and behavior. Helpful informant-based tools include the Functional Activities Questionnaire and the Revised Memory and Behavior Problems checklist.¹ It is also helpful to ask about a family history of Alzheimer's. In particular, the presence of the apolipoprotein E-4 allele on chromosome 19, which has been found in many individuals who developed Alzheimer's late in life, may point to genetic heritability.⁷

Complaints regarding cognitive function may fit a number of different diagnoses, including major depression, anxiety disorder, and dementia due to illness other than Alzheimer's disease. Small et al.¹ highlighted the delicate diagnostic differentiation of cognitive symptoms by noting that while late-life depression may present with subjective cognitive complaints, Alzheimer's disease pre-

From the Department of Psychiatry, St. Louis University School of Medicine, St. Louis, Mo.

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Corresponding author and reprints: George T. Grossberg, M.D., St. Louis University School of Medicine, Department of Psychiatry, 1221 South Grand Blvd., St. Louis, MO 63104 (e-mail: grossbgt@slu.edu).

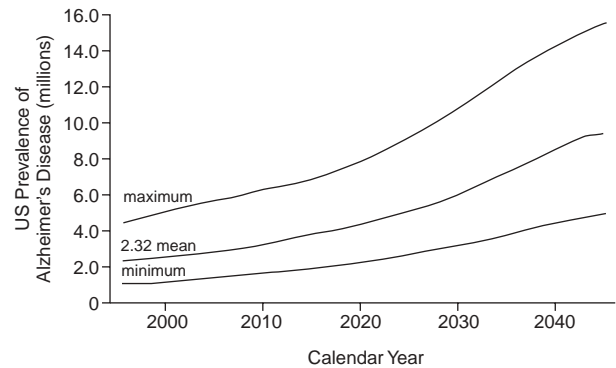
sents with objective cognitive signs. However, clinicians are advised to administer dementia screening instruments to all older patients with memory or other cognitive complaints, even in the absence of functional impairment, as well as to older patients without such complaints who arouse suspicion of cognitive impairment during the office interview.⁸

According to the Quality Standards Subcommittee of the American Academy of Neurology,⁸ cognitive assessments for the presence of dementia should measure the patient's level of arousal, attention, orientation, remote and recent recall, language, praxis, visuospatial function, calculations, and judgment. Cognitive assessments, however, are not sufficient to offer a definitive diagnosis of dementia and are most valuable as baseline measurements for future comparisons.¹ The diagnostic workup of dementia should include a complete blood cell count; measures of serum electrolytes, serum vitamin B₁₂, glucose, and BUN/creatinine; liver and thyroid function tests; and a syphilis test.⁸

There is at present no consensus regarding the necessity or usefulness of neuroimaging when onset of dementia occurs after 60 years of age, but the Quality Standards Subcommittee⁸ advised that clinicians consider computed tomography or magnetic resonance imaging for each case of clinically identifiable dementia. Others agree that neuroimaging may be helpful, but should not be relied upon, in reaching a diagnosis.¹

All dementia is not attributable to Alzheimer's disease. There are several causes of dementia, which can be differentiated by their signs and symptoms. Alzheimer's disease is marked by an insidious onset and gradual decline. The presence of focal abnormalities, extrapyramidal symptoms, or gait disorders most likely points away from a diagnosis of Alzheimer's disease.⁸ Vascular dementia is caused by numerous small strokes resulting in brain damage and presents with a more acute onset and stepwise decline.^{1,3} Dementia due to Parkinson's disease will follow the appearance of motor disturbances, while dementia due to Lewy bodies is accompanied by visual hallucinations and alterations of alertness or attention as well as parkinsonian signs. Pick's disease is a relatively rare cause of frontal lobe dementia. This is characterized by early changes in personality, emotional blunting, prominent language abnormalities, and rapid progression. Additionally, dementia may be variously caused by, among other conditions, brain tumor, head trauma, long-term substance abuse, or human immunodeficiency virus. In general, a diagnosis of dementia due to Alzheimer's disease is supported by: (1) insidious onset and progressive worsening of dementia; (2) early and prominent difficulty with memory (especially retention and retrieval of new information); (3) onset after 60 years of age; (4) no focal signs or gait difficulties early in course; (5) exclusion of other dementing conditions.⁸

Figure 1. Projected Prevalence of Alzheimer's Disease^{a,b}



^aAdapted with permission from Brookmeyer et al.⁹

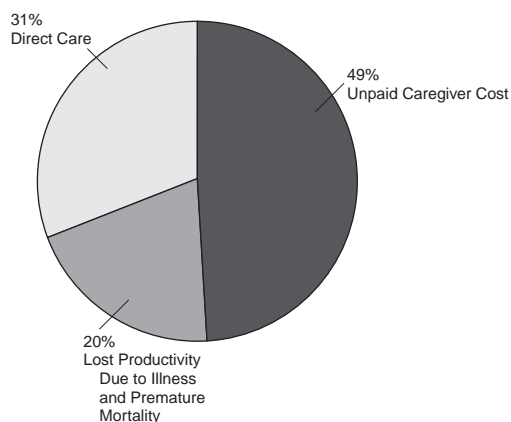
^b1997 prevalence 2.32 million (1.09–4.58), incidence per year 360,000 (200,000–600,000). Range based on age-specific incidence rates as determined by a regression model.

PREVALENCE AND BURDEN

Alzheimer's disease accounts for at least two thirds of all dementias, more than dementia with Lewy bodies and vascular dementia combined.¹ As the United States population ages, prevalence rates of Alzheimer's disease grow exponentially.⁹ According to the DSM-IV¹⁰ published in 1994, the current prevalence of Alzheimer's disease among adults at least 65 years of age is approximately 4%. However, a 1997 study by Small et al.¹ found that 6% to 8% of individuals 65 years of age or older have Alzheimer's disease. In fact, prevalence doubles every 5 years after age 60, so that in a population 85 years of age or older, prevalence of Alzheimer's disease is over 30%. A report by Brookmeyer et al.⁹ estimated the number of people with Alzheimer's in the United States in 1997 at 2.32 million and projected that prevalence could be expected to increase by a factor of 3.7, to 8.64 million individuals, by the year 2047 (Figure 1). At that time—if prevalence goes unchecked—1 in 45 Americans will have Alzheimer's disease.

Though estimates vary, the burden associated with Alzheimer's disease is tremendous. Alzheimer's presents not only an escalating financial drain on the patient's family and estate but also a public health concern (Figure 2).¹¹ Care of the individual with mild or moderate dementia is provided largely by loved ones and in part by formal sources like medical professionals and adult day care. The patient's functional deficiencies in day-to-day life—loss of skills like meal preparation, failure to remember medications, inability to recognize familiar people and objects—place a practical strain upon friends and family, while witnessing the patient's deterioration is likewise stressful and saddening. Approximately 50% of primary caregivers develop significant emotional distress,¹² which can in turn lead to the necessity of psychiatric treatment.

Figure 2. Estimated Annual U.S. Cost of Alzheimer's Disease to Society: \$67.3 Billion^a



^aData from Ernst and Hay.¹¹

In the last stages of the illness, the individual with Alzheimer's requires the round-the-clock care setting of a nursing home where he or she will stay, possibly for years, until death.

In an analysis of 1996 data, Leon et al.¹³ estimated the monthly costs of informal and formal care for 1 patient with mild (early onset) Alzheimer's disease at \$1534, moderate Alzheimer's disease at \$2058, and severe (advanced) Alzheimer's disease at \$3011. Total U.S. annual costs of care for patients with Alzheimer's reached approximately \$51.3 billion. Another study¹¹ included resource loss and caregivers' lost productivity in the tally and found that the economic costs of Alzheimer's disease total almost \$100 billion annually in the United States.

According to Brookmeyer and colleagues,⁹ an intervention that could delay the mean onset of Alzheimer's disease by approximately 5 years would reduce the projected prevalence by 1.15 million in 2007 and by 4.04 million in 2047. Even a delay of onset as short as 6 months to 1 year could have a major impact on public health. According to limited 1990 data, an average 1-year delay of onset would save \$10 billion total in formal and informal care costs over 10 years.

Henke and Burchmore² analyzed the economic impact of the use of the cholinesterase inhibitor tacrine—1 of 4 drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's disease—in newly diagnosed patients. Excluding indirect costs and informal/unpaid care, tacrine use was associated with a savings of \$9250 (or 7.5% of total expenditure) from a patient's diagnosis to his or her death. This reduction in costs was largely attributable to reduced time spent in a nursing home, e.g., higher sustained functionality and delayed nursing home entrance compared with patients who never used tacrine. In fact, nursing home entrance was

delayed by up to 433 days among patients who used tacrine. Those who continued taking the most effective dose of tacrine had the largest cost savings (> \$36,500 from diagnosis to death) due primarily to higher functionality across years 3 and 4 following diagnosis. By year 5 after diagnosis, however, there was no difference in functional level between patients who had taken tacrine and those who had not.

AVAILABLE TREATMENTS

At present, no treatment can prevent or cure Alzheimer's disease. Therapies other than cholinesterase inhibitors that may prove useful in delaying symptom onset include estrogen replacement (for women), antioxidants, and nonsteroidal anti-inflammatory drugs.⁹

The fact that Alzheimer's disease affects a geriatric population complicates its treatment. Older patients metabolize drugs more slowly and are more vulnerable to adverse effects; they are also likely to be taking multiple medications, heightening the risk of drug-drug interactions.¹ The primary goal of any treatment for Alzheimer's disease is to boost the patient's functioning and quality of life. Providing the patient with pleasant and stimulating activities, such as recreational therapy or pet therapy, can safely assist in this goal.³ On the other hand, some psychosocial therapies, particularly cognition-oriented therapies, can provoke frustration in demented patients and should be avoided. Treatment of Alzheimer's disease requires an alliance with both the patient and the patient's family.

The 4 drugs approved by the FDA for the treatment of Alzheimer's disease are tacrine, donepezil, galantamine, and rivastigmine, all of which are cholinesterase inhibitors. Although the exact mechanism of action is not fully understood, each improves cholinergic neurotransmission by preventing the breakdown of acetylcholine in the brain. Deficits of acetylcholine, a cholinergic neurotransmitter, have been observed in the brains of patients with Alzheimer's disease, suggesting that this neurotransmitter plays a role in cognition and memory. Though the cholinesterase inhibitors can produce modest improvements in cognition, their side effects include nausea, diarrhea, and vomiting.

Researchers are now testing alternative pharmacotherapies, including estrogen replacement (for women), nonsteroidal anti-inflammatory agents, ginkgo biloba, vitamin E, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, and the selective monoamine oxidase-B inhibitor selegiline, which is currently indicated for the treatment of Parkinson's disease.¹ Data show that vitamin E, as monotherapy or in combination with a cholinesterase inhibitor, may prevent further cognitive decline among patients with moderate Alzheimer's.³ Selegiline as an alternative to anticholinergic therapy may be as effective as vitamin E but with the risk of adverse effects including orthostatic hypotension.

The myriad mood and behavioral symptoms associated with Alzheimer's disease pose further challenges to treatment. Depression with Alzheimer's disease may be treated with an antidepressant that lacks substantial anticholinergic effects. First-line treatment for depression associated with Alzheimer's is generally one of the newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs). Treatments for apathy are not well-documented but, according to the American Psychiatric Association, they may include psychostimulants, the antidepressant bupropion, the dopamine receptor agonist bromocriptine, and the antiparkinson drug amantadine.³ Psychosis, agitation, and some behavioral disturbances may be treated with antipsychotics. However, because the potential for adverse effects including extrapyramidal symptoms is considerable among the elderly, antipsychotics should be used sparingly in the treatment of Alzheimer's disease.^{1,3} Likewise, benzodiazepines for behavioral symptoms are associated with worsening cognition and falls.³ Of possible benefit in treating behavioral symptoms are the mood stabilizers carbamazepine and valproate, the sedating antidepressant trazodone, the atypical anxiolytic buspirone, and the SSRIs. More research is needed to identify protective factors that can provide prophylaxis, risk reduction, and delay of symptom onset as well as treatments for the cognitive impairment and associated symptoms of Alzheimer's disease.

CONCLUSION

The progressive decline caused by Alzheimer's disease is characterized by cognitive deterioration, mood and behavioral changes, loss of function, and an increasing need for care. Dementia is the paramount feature of Alzheimer's disease, but associated symptoms are likely to include depression, anxiety, irritability, mood lability, sleep disturbance, inappropriate behavior, catastrophic reactions, delusions of persecution, visual hallucinations, or agitation. Ninety percent of Alzheimer's disease diagnoses can be made on the basis of a general medical and psychiatric evaluation.

The costs of Alzheimer's disease are enormous. Alzheimer's imposes emotional and material difficulties on the patient's family, an escalating financial drain on the patient's estate, and a burden on public health. At present, 4 anticholinergic drugs have been approved for the treatment of Alzheimer's disease, but no treatment can prevent or cure the illness. In the interest of delaying onset of

symptoms, researchers are now testing alternative therapies including estrogen replacement (for women), nonsteroidal anti-inflammatory agents, ginkgo biloba, vitamin E, and the selective monoamine oxidase-B inhibitor selegiline. More research is needed into protective factors and efficacious treatments.

Drug names: amantadine (Symmetrel and others), bromocriptine (Parlodel and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), donepezil (Aricept), galantamine (Reminyl), rivastigmine (Exelon), selegiline (Eldepryl and others), tacrine (Cognex), trazodone (Desyrel and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, amantadine, bromocriptine, and selegiline are not approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's disease; bupropion is not approved for the treatment of depression in Alzheimer's disease; buspirone is not approved for the treatment of anxiety in Alzheimer's disease; and carbamazepine, trazodone, and valproate are not approved for the treatment of agitation in Alzheimer's disease.

REFERENCES

1. Small GW, Rabins PV, Barry PP, et al. Diagnosis and treatment of Alzheimer disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997;278:1363-1371
2. Henke CJ, Burchmore MJ. The economic impact of tacrine in the treatment of Alzheimer's disease. *Clin Ther* 1997;19:330-345
3. American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Alzheimer's Disease and Other Dementias of Late Life. *Am J Psychiatry* 1997;154(suppl):1-39
4. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias. *Am J Geriatr Psychiatry* 2000;8:29-34
5. Patterson MB, Bolger JP. Assessment of behavioral symptoms in Alzheimer disease. *Alzheimer Dis Assoc Disord* 1994;8(suppl 3):4-20
6. Rasmusson DX, Brandt J, Steele C, et al. Accuracy of clinical diagnosis of Alzheimer disease and clinical features of patients with non-Alzheimer neuropathology. *Alzheimer Dis Assoc Disord* 1996;10:180-188
7. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921-923
8. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter for diagnosis and evaluation of dementia (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1994;44:2203-2206
9. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 1998;88:1337-1342
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
11. Ernst RL, Hay JW. The US economic and social costs of Alzheimer's disease revisited. *Am J Public Health* 1994;84:1261-1264
12. Schulz R, O'Brien AT, Bookwala J, et al. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist* 1995;35:771-791
13. Leon J, Cheng C-K, Neumann PJ. Alzheimer's disease care: costs and potential savings. *Health Affairs* 1998;17:206-216