ALZHEIMER’S DISEASE: EPIDEMIOLOGY AND RISK FACTORS

Manju Beier, PharmD, FASCP*

ABSTRACT

Alzheimer’s disease (AD) is the most common cause of dementia. It is estimated that 4.5 million Americans have AD. Several risk factors for AD have been identified and others are emerging. By far, age is the greatest risk factor, followed by family history. There are 2 forms of AD: familial (ie, early onset) and sporadic (ie, late onset). Familial cases usually occur before age 60 years and are caused by inheritance of mutations in 1 or more of 3 genes: PS1 (presenilin 1), PS2 (presenilin 2), and APP (amyloid precursor protein). APOE (apolipoprotein E) is the most studied gene that increases risk for AD in both familial and sporadic AD. The ε4 allele of APOE is associated with the highest AD risk, but it is neither necessary nor sufficient for developing AD. It does appear to reduce the age of maximal prevalence of AD in larger studies. This article reviews the current data on other risk factors under investigation (ie, race, hormone therapy in women, and depression), in addition to the role of APOE ε4 in mild cognitive impairment (thought to be a possible precursor of the early stage of AD) and other types of cognitive impairment. This article also discusses the costs of AD from several perspectives (patient, caregiver, society, and the healthcare system), and the limitations and challenges in interpreting cost analyses (in particular, the methods used to calculate the cost of unpaid caregiver time). Attempts to perform cost-effectiveness analyses are fraught with complications that do not currently permit a comparison of drugs used to treat or a firm estimate of cost differences with or without drug treatment. However, these medications, along with drugs used to treat the neuropsychiatric symptoms, play a critical role in managing AD throughout the disease process. (Adv Stud Pharm. 2005;2(4):116-125)

Alzheimer’s disease (AD) is gaining much attention, in part because of several famous persons who have discussed their diagnosis publicly (eg, President Ronald Reagan and Charlton Heston), but also because the “baby boomers” are now entering retirement age, which is the age of risk for this disease. It is estimated that by 2030, the entire baby-boom generation will be older than age 65 years, referred to as the “2030 problem.” Also, as AD is discussed more openly, the ravages of this disease are becoming more apparent to the general public, thus potential patients and family members have a clearer idea of the challenges they will face. The Alzheimer’s Association, in a Gallup poll commissioned by them, indicates that AD is a familiar occurrence; 1 in 10 Americans say they have a family member with AD and 1 in 3 know someone with the disease.

INCIDENCE AND PREVALENCE

Alzheimer’s disease is the most common cause of dementia, accounting for approximately 60% of cases. The Sidebar, titled “Some of the Most Common Forms of Dementia,” lists other common forms of dementia. AD often coexists with vascular dementia (VaD), which can impede diagnosis, particularly because the risk factors for VaD are so common in older persons (dyslipidemia, hypertension, and heart disease). It is estimated that approximately 1 in
10 individuals older than age 65 years and nearly 50% older than age 85 years have AD. In actual numbers, that translates to an estimated 4.5 million persons with AD, based on data from the 2000 US Census. Of these 4.5 million, 7% are 65 to 74 years, 53% are 75 to 84 years, and 40% are 85 years or older. The census data also suggest that by 2050, a 3-fold increase in the prevalence of AD is expected (13.2 million persons).

As will be discussed by Gary M. Levin, PharmD, BCPP, FCCP, later in this monograph, AD can be categorized as mild, moderate, or severe. The current distribution is weighted toward mild disease, as shown in Figure 1, although all patients invariably progress through these stages, ultimately to death. Once diagnosed, persons with AD can live from 8 to 20 years. The survival time is determined by age at diagnosis and the severity of other medical conditions.

### Risk Factors

Several risk factors for AD have clearly been identified and others are emerging. By far, age is the greatest risk factor, followed by family history. Those individuals with a parent or sibling with AD are 2 to 3 times more likely to develop AD, and the likelihood increases with each additional affected family member. However, the exact role that genes play in AD development is not entirely straightforward.

There are, in fact, 2 forms of AD: familial (ie, early onset) and sporadic (ie, late onset). Familial cases usually occur before age 60 years and are caused by inheritance of mutations in 1 or more of 3 genes: PS1 (presenilin 1), PS2 (presenilin 2), and APP (amyloid precursor protein). As Jeanne Jackson-Siegel, MD, discusses in her article later in this monograph, all of these genes are involved with production of beta amyloid, a protein that forms plaques in the brain, which are the pathophysiologic hallmark of AD. Those individuals who inherit one of these genes will almost certainly develop AD; family members who do not have one of these genes have the same risk of developing AD as the general population. Familial AD is, in fact, rare. Only approximately 200 family lines in the world carry these mutations.

Sporadic AD usually occurs after age 60 years, mostly in the seventh and eighth decade of life. Inheritance of any genetic risk factors is more complex than with familial AD. APOE (apolipoprotein E) is the most studied gene that increases risk for AD. APOE transports cholesterol and fats throughout the body, thus suggesting that reducing serum cholesterol levels can prevent AD. In fact, early studies appeared to show a reduced risk of AD with statin use. However, subsequent analyses have shown no effect on AD risk with statin use.

### Genetics

The APOE gene has 3 alleles: e2, e3, and e4. e4 is associated with the highest risk of AD, but it is neither necessary nor sufficient for developing the disease.

**Figure 1. Prevalence of Alzheimer’s Disease by Age Group and Severity**

Data show the prevalence of severe, moderate, and mild AD in each of 3 age groups, in a biracial community population from 3 adjacent neighborhoods in Chicago, IL.

AD = Alzheimer’s disease.

Approximately 35% to 50% of people with AD have at least one copy of the *APOE*-e4 allele. Those individuals who are homozygous for *APOE* e4 have an even higher risk of AD, but again homozygosity does not guarantee that AD will develop. Data from the Cache County Study (a large Utah county with 5677 elderly) reveal that, of those identified with dementia, 69% had definite, possible, or probable AD (see Dr. Levine’s article later in this monograph for definitions). The presence of e4 alleles reduced the age of maximum prevalence in those patients with AD from 95 years in patients with no e4 alleles to 87 years in heterozygotes and 73 years in homozygotes.

New efforts are focusing on what may be the earliest stages of AD, or mild cognitive impairment (MCI). The relationship between *APOE* e4 and MCI is not yet clearly defined. The Religious Orders Study is a collaborative study with Rush University Medical Center (and several other US medical centers) and more than 1000 older, religious clergy (nuns, priests, and brothers) who have agreed to medical and psychological evaluation each year and brain donation after death. In this study, 181 participants identified as having MCI (and who had at least 1 follow-up evaluation) were followed for a mean of 5.7 years, during which 43.6% developed AD. The presence of the *APOE* e4 allele nearly doubled the risk of developing AD as compared to age- and education-matched persons who did not have an *APOE* e4 allele (Table 1). However, the authors note that the low impact of education may be because of the overall high levels of education for this cohort, as compared to the levels of other cohorts. By contrast, analysis of *APOE* e4 allele frequency in 232 white non-Hispanic older adults showed no apparent relationship with subjective memory complaints. In a bi-ethnic sample, the impact of *APOE* e4 on age of AD onset was greater in white non-Hispanic individuals compared to white Hispanic individuals, suggesting that the effect may vary with ethnic group.

Another group of cognitively impaired patients have been studied. They are classified as “cognitive impairment, no dementia” (CIND), defined (in this study) as some degree of cognitive impairment on clinical examination and neuropsychological testing, which does not meet the criteria for dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. In this study, *APOE* e4 was a significant risk factor for converting from CIND to AD and was associated with decreased age of AD onset. The adjusted odds ratios (OR) for age, sex, education, and presence of the e4 allele are shown in Table 2. Until the exact rela-

### Table 1. Relative Risk of Incident AD Associated with Possession of an *APOE*-e4 Allele

<table>
<thead>
<tr>
<th>Model terms</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.100</td>
<td>1.060–1.141</td>
</tr>
<tr>
<td>Education</td>
<td>0.992</td>
<td>0.924–1.066</td>
</tr>
<tr>
<td><strong>APOE</strong> e4</td>
<td>1.948</td>
<td>1.196–3.173</td>
</tr>
</tbody>
</table>

Data are from 181 participants in the Religious Orders Study at Rush University Medical Center who met criteria for mild cognitive impairment. A proportional hazards model included terms for age, education, and e4 allele. The results show that possession of the e4 allele nearly doubles the risk of developing AD, when controlling for age, sex, and education level. Older age was associated with an increased risk of AD with a 10% increase in risk for each year of age. Educational attainment showed less of an effect in this group, perhaps because of the overall high levels of education in this group overall. *Data from a proportional hazards model stratified for sex.* AD = Alzheimer’s disease; *APOE = apolipoprotein E; CI = confidence interval.* Reprinted with permission from Aggarwal et al.* Neurocase. 2005;11:3-7.*

### Table 2. Role of the *APOE*-e4 Allele in Progression of CIND to AD

<table>
<thead>
<tr>
<th>Progression</th>
<th>Age (for every year increase)</th>
<th>Sex (F:M)</th>
<th>Education (for every year increase)</th>
<th>Presence vs absence of <em>APOE</em>-e4 allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIND → normal (n = 29)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CIND (n = 85)</td>
<td>(1.01–1.09)</td>
<td>(0.77–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIND (n = 68)</td>
<td>(1.08–1.18)</td>
<td>(0.90–0.89)</td>
<td>(0.76–0.89)</td>
<td>(1.48–4.92)</td>
</tr>
<tr>
<td>CIND → VaD</td>
<td>1.11</td>
<td>NS</td>
<td>0.62</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data from a nested case-control study design of the Canadian Study of Health and Aging, a longitudinal cohort (n = 10 263) of aging and cognition. From these data, the positive predictive value of *APOE* e4 for predicting CIND conversion to AD was 0.48 and the negative predictive value was 0.65. *Significant interaction was found between the presence of *APOE*-e4 allele and age, with the presence of the e4 allele causing a decrease in age at onset of dementia. No significant first-degree interactions were found between other factors.* AD = Alzheimer’s disease; *APOE = apolipoprotein E; CIND = cognitive impairment, no dementia; NS = not significant; VaD = vascular dementia.* Reprinted with permission from Hsiung et al.* CMAJ. 2004;171:863-867.*
tion between possession of an ε4 allele and AD is described, genetic testing is not recommended for the general population. Furthermore, for family members of a patient with AD, testing is recommended only after comprehensive genetic counseling.

**Gender and Hormone Therapy**

The role of estrogen and hormone replacement therapy (HRT) in the risk or prevention of AD has become controversial or at least unclear, given the results of the Women's Health Initiative Memory Study (WHIMS).21 Observational studies had suggested that HRT may protect postmenopausal women against AD, but randomized, controlled trials refuted those ideas. Specifically, the WHIMS compared the rates of dementia or cognitive decline in women taking HRT as estrogen-plus-progestin or estrogen-only replacement therapy versus placebo.22 Neither hormone therapy protected against cognitive decline, and they may have even increased the risk.23 Questions arise as to whether the type of hormone therapy (eg, different doses and different sources of estrogen or progestin) or the time at which the therapy is taken (ie, postmenopausal vs perimenopausal) may affect the risk of cognitive decline. Several authors have suggested that both of these factors can affect cognitive outcomes.24-26 Thus, the decision to use any perimenopausal hormone therapy should be based on clinical factors relating to menopause and any patient-specific considerations (eg, history of breast cancer), and not on any possible effect on future cognitive decline.

**Social and Mental Stimulation**

One of the most interesting findings in recent years is the role of social and mental stimulation in predicting risk of future AD. Participants in the Alzheimer's Disease Case Control Study at Case Western Reserve University reported their participation in 26 nonoccupational activities (classified as passive, intellectual, and physical) throughout early (ages 20–39 years) and middle (ages 40–60 years) adulthood. Participants in this analysis included 193 people with possible or probable AD and 358 healthy controls. The results showed that the controls (ie, those individuals not having AD) were more active during mid-life than the cases, in diversity (different types of activities) and intensity (number of hours per month), as shown in Tables 3 and 4. If participation increased from early to middle adulthood, the probability of AD decreased significantly, and those individuals who performed less than the mean value of activities had a 3.85 higher risk of AD than those who performed at least the mean levels (95% confidence interval [CI], 2.65–5.58; \( P < .001 \)). However, it was unclear if the reduction in activities with time became a risk factor for AD, was an early manifestation of the disease, or both.27

### Table 3. Comparison Between Case- and Control-Group Members on Diversity Scores of Nonoccupational Activities

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adjusted Mean*</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive diversity</td>
<td>0.84</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Intellectual diversity</td>
<td>0.44</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Physical diversity</td>
<td>0.42</td>
<td>0.53</td>
<td></td>
</tr>
</tbody>
</table>

\( P \leq .001 \) for all comparisons.

Activities are classified as passive, intellectual, or physical and are assessed based on diversity of activities within each type and intensity (number of hours per month). Cases are patients with possible or probable Alzheimer's disease.

*Adjusted means take into account covariates (year of birth, education, gender, and income adequacy) in the statistical analyses.

Adapted with permission from Friedland et al. *Proc Natl Acad Sci U S A*. 2001;98:3440-3445.27

### Table 4. Comparison Between Case- and Control-Group Members on Intensity Scores of Nonoccupational Activities

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adjusted Mean*</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive intensity</td>
<td>62.23</td>
<td>68.43</td>
<td></td>
</tr>
<tr>
<td>Intellectual intensity</td>
<td>57.45</td>
<td>67.94</td>
<td></td>
</tr>
<tr>
<td>Physical intensity</td>
<td>31.18</td>
<td>34.50</td>
<td></td>
</tr>
<tr>
<td>Middle adulthood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive intensity</td>
<td>99.33</td>
<td>101.84</td>
<td></td>
</tr>
<tr>
<td>Intellectual intensity</td>
<td>68.15</td>
<td>79.21</td>
<td></td>
</tr>
<tr>
<td>Physical intensity</td>
<td>37.74</td>
<td>41.09</td>
<td></td>
</tr>
</tbody>
</table>

Activities are classified as passive, intellectual, or physical and are assessed based on diversity of activities within each type and intensity (number of hours per month). Cases are patients with possible or probable Alzheimer's disease.

*Adjusted means take into account covariates (year of birth, education, gender, and income adequacy) in the statistical analyses.

Adapted with permission from Friedland et al. *Proc Natl Acad Sci U S A*. 2001;98:3440-3445.27
Lindstrom et al. showed that for each additional daily hour of middle-adulthood television viewing, the risk of AD increased 1.3 times (controlling for year of birth, gender, income, and education). Hall et al. showed that rural residence during childhood can also have a measurable impact on risk for AD, even among those with low education levels (≤6 years). The OR for AD for those individuals with low education and rural residence was 6.5 (95% CI, 2.6–16.7), 0.5 for those with low education and childhood urban residence (95% CI, 0.1–2.9), and 1.5 for those with high education (≥7 years) and childhood rural residence (95% CI, 0.4–5.2) compared to the high education and childhood urban residence group. Scarmeas and Stern reviewed the hypothesis that participation in mentally stimulating activities (eg, higher education) may create a cognitive reserve, which emerges from more efficient cognitive networks developed through mental stimulation. This cognitive reserve may delay onset of AD or permit a greater tolerance for AD pathology.

**RACE**

African Americans are known to have a higher risk of AD than whites, and also possess many of the risk factors for vascular dementia. A report from the Alzheimer's Association indicates that the genetic risk factors for AD seem to be different for African Americans compared to whites, and that the APOE genotype alone does not explain the increased frequency of AD in African Americans. The report also notes that African Americans tend to be diagnosed at a later stage, limiting the effectiveness of any treatments for the disease symptoms, and that the age-specific prevalence of dementia is 14% to 100% higher in African Americans than in whites. Taylor et al. have recorded a marked increase in the number of African Americans with AD, which has nearly doubled from 1991 to 1999. The increase was particularly strong in African-American women, in whom the rate increased by 4.7-fold compared to 2.3-fold for white women. In fact, African Americans had a higher rate of identified AD in 1999 than whites (62.5/1000 vs 40.9/1000), a reversal of rates from 1991 (13.7/1000 vs 16.5/1000), based on Medicare databases. The authors suggested that the causes of this increase are probably multifactorial and may not reflect an increased risk per se of African Americans for AD. During this time period, African Americans had improved access to healthcare and there was increased sensitivity among healthcare practitioners and the general public to AD in African Americans (ie, that its symptoms are not a normal part of aging). Also, changes in ICD-9 coding rules allowed for identification of patients with AD when they also had risk factors for VaD, such as prior stroke, which is more common among African Americans than whites. The authors were unable to estimate rates for Hispanics or Asians because of the small number in their database.

**OTHER POSSIBLE RISK FACTORS**

More recently, depression and other factors are also being evaluated for a role in AD onset. Depression is a known, frequent comorbid condition with AD that can sometimes mask diagnosis of AD. The Multi-institutional Research in Alzheimer's Genetic Epidemiology study showed that the presence of depression in a family member of a patient with AD or of depressive symptoms in a patient with AD before AD onset are associated with the development of AD, even in families in which the first depressive symptoms occurred more than 25 years earlier. The OR was highest if depression occurred within 1 year of AD onset (OR 4.57; 95% CI, 2.87–7.31), lower if the depression occurred more than 1 year before AD onset (OR 1.38; 95% CI, 1.03–1.85), but still substantial if the depression first occurred more than 25 years before (OR 1.71; 95% CI, 1.03–2.82).

Two other studies have analyzed multiple risk factors for AD. Lindsay et al. showed that use of non-steroidal anti-inflammatory drugs, wine consumption, coffee consumption, and regular physical activity were associated with a reduced risk of AD, whereas family history of dementia, gender, history of depression, estrogen replacement therapy, head trauma, antiperspirant or antacid use, smoking, high blood pressure, heart disease, or stroke were not associated with AD—conflicting with other reports on some of these risk factors. Similarly, Tyas et al. showed that increased age, fewer years of education, history of migraines (especially in women), and self-reported memory loss at baseline increased the risk of AD, whereas vaccinations and occupational exposure to excessive noise reduced the risk of AD. Clearly, the causes of AD are multifactorial and perhaps interconnected, but healthy diet, regular exercise, normal homocysteine level, and mental stimulation are modifiable risk factors of which benefits extend well beyond reducing the risk of AD.
THE COST OF ALZHEIMER’S DISEASE

Similar to risk factors, the exact cost of AD is difficult to quantify, but it is inherently obvious that AD is a devastating disease that exacts a large financial, emotional, and psychological toll on the patient’s family. The costs of caring for a patient with AD are numerous and varied. They include the cost of drugs to treat the symptoms, hospitalization for falls, specialized home care, ultimately nursing home, hospice care, and cost to caregivers (time, stress, unemployment, and out-of-pocket expenditures). The types of costs change as the disease progresses, as shown in Figure 2. Costs start as mostly unpaid direct care and move quickly to long-term residential care with increasing AD severity. Long-term care costs ultimately constitute the major cost driver for AD. The extent to which the family pays directly for these costs depends on their specific circumstances.

Several studies have been published, using American and other international cohorts, to estimate the cost of AD. Creating an accurate cost-outcome analysis poses several challenges, in part because older studies may have used less accurate diagnostic methods for AD. However, the biggest challenge is to establish a cost or monetary value for unpaid caregiver time. The cost of unpaid care can be estimated by using a replacement wage (ie, the wage that a worker would have to be paid to provide such care if the caregiver was unable). These costs are considered to be direct costs. Caregiver costs can also be calculated using estimated lost wages when a caregiver has to stay home to be with the patient with AD (an indirect cost), but most caregivers are spouses of patients with AD and are usually of retirement age. Lost wages are more applicable to adult children of patients with AD who become the patient’s caregiver.

COSTS TO THE HEALTHCARE SYSTEM

For the US healthcare system, the total direct and indirect costs are estimated to be at least $100 billion. For the person with AD, average lifetime costs are estimated at $174 000 (based on 1991 data). The Alzheimer’s Association reports that Medicare costs for beneficiaries with AD are expected to increase 75%, from $91 billion in 2005 to $160 billion in 2010. The Alzheimer’s Association report also suggests that Medicaid expenditures on residential dementia care will increase 14% from $21 billion in 2005 to $24 billion in 2010. Currently, the average cost for nursing home care is $42 000 per year per patient with AD. O’Brien and Caro also showed higher costs of nursing home care for patients with AD compared to other types of dementia (mean annual costs $42 230 vs $40 470, respectively), based on data from the 1995 Massachusetts Medicaid nursing home database. Perhaps much of these costs are due to the severity of disease once patients are placed in a nursing home. In this study, 80% of AD residents were in the top 5 care levels compared to 71% of those individuals with other types of dementia (Figure 3). This translates into an additional 103 hours of care per year for a patient with AD, based on the median number of management minutes per care level. The authors concede that the dollar values may be unique to Massachusetts because the study used Massachusetts Medicaid 1997 per diem rates to determine costs (each state determines its own levels of reimbursement). However, the authors note that Medicaid is responsible for 72% of all nursing home resident days in the United States.

Substantial costs also accrue even before nursing home placement. In a study comparing 3 groups (patients with AD at an ambulatory AD center, patients with AD at an internal medicine practice, and controls, all older than age 65 years), the Medicare costs were highest in the AD center group, but both AD groups had much higher healthcare costs than controls. Mean person annual Medicare costs were
$19,418, $18,753, and $12,085, respectively. Of note, non-AD hospitalizations and length of stay by AD populations were the main cost drivers.46

**Costs to the Patients and Caregivers**

Patients with AD and their caregivers carry the lion’s share of the economic burden of AD, through direct medical costs and the indirect costs of emotional strain and lost social and professional opportunities. According to a report by the Alzheimer’s Association, AD costs American businesses $61 billion per year. Of that, $36.5 billion covers costs related to caregivers (ie, lost productivity, absenteeism, and worker replacement).47 More than 70% of patients with AD live at home, with family and friends providing 75% of their care.48 The remaining expenditures are for paid care, costing an average of $19,000 per year, usually paid out of pocket by families.49 In a recent study of patients with AD in Massachusetts, the cost per patient with AD was $23,436 for informal care and $8064 for formal services (with variations primarily according to the level of assistance needed for instrumental activities of daily living).50

**Cost of Alzheimer’s Disease Medications**

There are currently 5 medications to treat the symptoms of AD, which will be reviewed in detail in Part 2 of this monograph series on AD. Four of these medications (tacrine, donepezil, galantamine, and rivastigmine) are acetylcholinesterase inhibitors, and are approved for treatment of mild to moderate AD. Memantine is a noncompetitive NMDA receptor antagonist, approved for use in moderate to severe AD. Tacrine is not used to any measurable extent because of several limitations related to dosing and hepatotoxicity.

Several cost-outcome analyses have been published, in an effort to determine if the efficacy of these drugs translates into cost effectiveness. However, the study designs vary widely and are of short duration (from which long-term cost data are extrapolated, thus they do not consider the irregular course of the disease), may not use empirical data from the efficacy studies, and do not consider differences or changes in reimbursement systems outside the current system under study.51

For example, pooled data from 2 concurrent randomized controlled trials compared galantamine to placebo (6 months of treatment) in 825 patients with mild to moderate AD. The analysis also compared the time spent assisting patients with their activities of daily living and the time patients could be left unsupervised. In patients with mild AD, galantamine use resulted in 3.5 fewer hours per week required of the caregiver. In patients with moderate AD, caregivers spent 6 hours less each week with the patients taking galantamine. However, nonresident caregivers of patients treated with galantamine were 3 times more likely to say that the patient did not need supervision versus resident caregivers, and there was no difference in the amount of time patients could be left unsupervised between treatment groups as reported by resident caregivers. Thus, the ratio of resident to nonresident caregivers in each treatment group could have affected the results.52

In a study analyzing resource utilization data from a 28-week randomized, controlled trial of memantine (n = 252) versus placebo (n = 166) in patients with moderate to severe AD, memantine use resulted in significantly less caregiver time (51.5 hours less per month; 95% CI, -95.27 to -7.17; P = .02). Total costs, when considered from a societal perspective, decreased by $1089.74/month (nonoverlapping 95% CI for

![Figure 3. Proportion of Nursing Home Residents in Each Management Category by Type of Dementia](image-url)

Data are from a cost-outcome study of nearly 50,000 Massachusetts nursing home residents covered primarily by Medicaid, of whom 8.8% had a diagnosis of AD, and an additional 17.6% had another type of dementia. Significantly more residents with AD were assigned to the more resource-intensive levels of care. AD = Alzheimer’s disease.

treatment difference, -$1954.90 to -$224.58; P = .01), with the biggest differences seen as reduced total caregiver costs ($823.77/month; P = .03) and direct nonmedical costs ($430.84/month; P = .07) with memantine treatment. Patient direct medical costs were higher primarily because of the cost of the drug, with a trend toward lower direct nonmedical costs.59

It is also important to consider the perspective of the cost study—society, caregiver, managed care plan, or nursing home. For example, patients who are on the border of being institutionalized may require much more home care to delay institutionalization, thus increasing caregiver costs, but they may require the least intensive care once admitted, thus lowering nursing home costs.59 At this time, it is not yet possible to say whether one drug is more cost effective than another because of the specific conditions of cost analyses and the lack of direct, head-to-head comparisons.59 A frequent quandary of cost-outcome studies with AD treatments is that the drugs may prevent institutionalization but as a result increase caregiver burden. However, experience tells us that drugs that can prolong patient functioning and cognition ease not only caregiver time requirements with the patient but, more importantly, caregiver emotional and psychological burden and, for the patient, can increase the time during which they can put their affairs in order.

As the disease progresses, patients with AD often experience neuropsychiatric symptoms. These symptoms will be discussed in more detail in Part 2 of this monograph series, but they are present in most patients with AD.56-58 The most frequent neuropsychiatric symptoms include apathy, depression, agitation/aggression, and wandering.56-58 These symptoms contribute greatly to caregiver stress and burden, diminished quality of life for patient and caregiver, excess patient morbidity, and cost of illness. One study suggests that these symptoms account for 33% of the primary caregiver’s hours of unpaid care, in addition to their normal activities and duties as caregiver for a patient with AD.59 A recent study looked at costs of dealing with neuropsychiatric symptoms after accounting for severity of cognitive impairment and comorbid medical conditions in 128 patients with AD. Those patients with more severe or frequent neuropsychiatric symptoms incurred higher costs than those patients with less severe or frequent symptoms, and the costs were caused predominantly by significantly increased caregiver time and higher long-term care costs. The authors caution that these costs represent an average response for a cohort, not an individual patient, because the progression of disease and its symptoms is not linear.59-60 Neuropsychiatric symptoms can wax and wane throughout the course of the disease.51,62 Beeri et al found that management of behavioral and neuropsychiatric symptoms account for approximately 30% of the total annual cost of AD, of which more than 25% accounts for indirect annual costs and more than 35% for the total direct annual costs.59

As will be reviewed in Part 3 of this monograph series, drugs are not the only intervention for treating AD symptoms, especially as the disease progresses. Treatments using other strategies, such as exercise, sensory stimulation, relaxation, and use of music or audiovisual stimulation, play an important role in optimizing quality of life for the patient with AD. The costs of these treatments must also be considered, as they are administered by nursing home medical staff or family members. Also, for the caregiver, other services are available, such as respite care, foster care, support groups, transportation, meal delivery, and part-time in-home care.

**Conclusions**

Alzheimer’s disease is becoming a more frequent topic of discussion among the general public, creating an awareness for earlier detection and best strategies for loved ones once the disease manifests. With the large baby-boomer population preparing to retire, the number of patients with AD in the United States is expected to increase substantially. Several risk factors have been identified for sporadic AD (the most common form), some of which are modifiable (eg, serum cholesterol levels, exercise, and mental stimulation activities). The costs of AD are difficult to quantify but several studies are offering a general sense of cost. The direct medical care costs can be staggering, particularly because some portion of them often have to be paid out of pocket by the patient or their family/caregivers. Studies are also showing that the costs extend well beyond direct medical care for the patient with AD, inflicting extraordinary caregiver burden as disease progresses. Because this type of care is unpaid, it is difficult to put a price tag on it. Attempts to perform cost-effectiveness analyses are fraught with complications that do not currently permit a comparison of drugs or a firm estimate of cost differences with or without drug treatment. However, the drugs, along with drugs to treat the neuropsychiatric symptoms, play a critical role in managing AD throughout the disease process.
REFERENCES


2. 1991 Gallup survey of 1015 individuals (as reported by reference 3).


