Cost-effectiveness of drug therapies for Alzheimer's disease: A brief review

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Abstract: Alzheimer's disease (AD) is an important and rapidly expanding public health problem. Its large economic burden is a result of its disabling nature, chronicity, and high prevalence in older segments of the population. Current treatments of AD have been criticized for providing insufficient benefit to justify their costs, but variability in assessing both costs and benefits make evaluation of the existing data problematic. Inclusion of the value of caregiver time is a major driver of the determination of cost-effectiveness. Population-based studies and those based on application of economic models to other study outcomes tend to identify greater cost-effectiveness than prospectively collected data. Differences in healthcare economics across countries also limit generalization of specific study findings. The current state of evidence suggests that treatment decisions in AD should be based on assessment of benefit in individual patients rather than broader societal economic factors.

Keywords: Alzheimer disease, cost-effectiveness, healthcare costs, drug therapy

The cost-effectiveness of treatments for Alzheimer's disease (AD) is an important but controversial topic. The importance derives from both the economic and public health perspectives. The prevalence of dementia, a majority of which is attributable to AD, is near 25 million cases worldwide and is expected to double every twenty years, reaching over 80 million cases by 2040 (Ferri et al 2005). Dementia affects up to 10% of the population over age 65 and almost half of those over age 85 (Evans et al 1989), but most estimates peak at about one-third of the over 85 group. Nonetheless, nearly one in 10 adults over age 85 can be expected to develop a new case of dementia each year (Aevarsson and Skoog 1996), and this cohort of the oldest old is the most rapidly growing age segment of the population in the world.

The costs associated with this uniformly disabling condition are immense, estimated at over US$315 billion worldwide in 2005 (Wimo et al 2007). Developed nations account for 73% of the spending, but only 46% of prevalent cases live in those countries. Dementia is third most expensive illness in the US, with dementia-related costs rivaling those for cancer and exceeding diabetes mellitus.

Numerous factors underlie the high costs. By definitions intrinsic to its diagnostic criteria, dementia is disabling; this requires others to provide services to the person with dementia. These services have economic value, in part attributable to reduced workforce productivity among those providing care to family members with dementia. In 2002, the incremental annual cost to US businesses associated with family caregiving for people with AD was $36.5 billion (Koppel 2002). Dementia is also a chronic disease. Average survival after diagnosis exceeds five years, leading to a prolonged period of increasing disability. Finally, individuals with dementia generate 25%–50% higher costs in the care of their other conditions, like heart failure and diabetes, than matched cases without dementia (Hill et al 2002). The changing demographics of society will

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result in much higher numbers of the older adults at higher risk over the next several decades. Cost-effective therapies for AD are therefore a public health priority.

There are several ways of considering cost and benefit of therapeutic approaches. "Cost-effectiveness" centers on the relationship between the resources consumed and specified health-related benefits, and allows comparison between two interventions or between intervening and not intervening on a condition (Neumann et al 2000). Such analyses are not structured to assess whether it is more effective to intervene on one condition in comparison to another. This approach differs from "cost-benefit" analyses, in which the outcome is considered is monetary units, rather than health-oriented issues like length, or quality, of life. Guidelines for cost-effectiveness studies have been developed to improve the usefulness and consistency of the research; those guidelines recommend inclusion of time spent in providing care as an important contributor to costs and emphasize the concept of quality-adjusted life years as a useful measure to incorporate quality of life and survival in a single outcome (Siegel et al 1997).

This article is not intended as a comprehensive, systematic, review of costs and benefits in AD treatment. Rather, it is a brief overview of pertinent issues that complicate the interpretation of reports regarding costs and potential economic benefits of antidementia therapies, highlighting results from analysis of prospectively collected and community usage data, and touching upon different types of analysis and their implications. The reader is directed to recent systematic reviews of economic aspects of cholinesterase inhibitors (Wimo 2004) and memantine (Plosker and Lyseng-Williamson 2005) for more comprehensive discussions of this complicated literature.

Differing perspectives on measuring cost

Despite its potential importance to individuals and society, the cost-effectiveness of antidementia therapy remains controversial. The origins of the controversy lie in difficulties with both measuring cost and assigning value to benefit. A key issue in measuring cost is the perspective of who is conducting or interpreting the measurement. From the viewpoint of an economist, treatment impact on all costs – including things like potential losses of workforce productivity – might be appropriate for inclusion in assessment of the therapy. For a payer of healthcare, whether private insurer or public agency, consideration of only those costs covered by the insured's policy is most important.

For informal care costs, individual family members of the person with dementia may value their time differently and have different thresholds of willingness to expend monetary assets. A common example of these differences is the retired spouse of a patient being more willing to invest his or her own time in care (rather than paying for outside services) compared with the employed adult child who is more likely to purchase services in order to preserve employment for reasons of income, noncash tangible benefits like health insurance, and intangibles like self-esteem. Variability in monetary valuation of caregiver time is a crucial, and often ignored, aspect of estimates of cost-effectiveness of AD treatments.

Many spousal caregivers attribute a low value to their time. They may perceive time invested in caring as "given" not "taken," view time in post-retirement life as lacking monetary value, or especially in the case of life-long homemakers, view care provision as part of an ongoing and never-compensated task. In contrast, adult children providing care to AD patients may lose work hours and forego higher income employment opportunities to provide care. These potential losses correlate with the patient's disease severity, and might be reduced by interventions that maintain independence longer (Small et al 2002). Since each of these interested parties – society, insurers, and family members – measure cost differently, it should not be surprising that interpretations of cost-effectiveness vary considerably across the published studies.

Another problem in defining cost is the underrecognition and undercoding of dementia. While epidemiologic studies predict large numbers of dementia cases in the population, insurance claims data suggested that a significant proportion – perhaps 70%–90% – of dementia cases was not being recognized by health insurers because they were not being assigned appropriate diagnostic codes by medical practitioners (Gutterman et al 1999). The historic magnitude of the underrecognition and undercoding problem in the US is illustrated by the study of Callahan and colleagues (1995), which noted that – at a University-based Family Medicine clinic – only 25% of patients found to express moderate and severe levels of cognitive impairment had any notation of the deficits in the medical chart. These figures suggest that many older estimates of the economic burden of dementia care may be falsely low. More recent Medicare claims data identify diagnostic coding rates for dementia that more closely approximate epidemiologic predictions (Hill et al 2002). The availability of approved therapeutic options for AD is likely to contribute to the improve rates of diagnosis.

The problem of defining effectiveness

The second crucial problem in defining cost-effectiveness in dementia is a lack of consensus on what constitutes an

appropriate level of benefit from treatment. To comply with the requirements of regulatory authorities, most early clinical trials focused on cognitive measures and clinicians' global impressions to define efficacy and did not collect direct economic measures. Only more recently have trials been planned and conducted with economic outcomes. Even so, AD clinical trials have been criticized for enrolling populations of "pure" AD patients that do not reflect the typical comorbidities associated with an older population. As a result, incremental benefit in study samples may not generalize to real-world populations. It is also justifiable to assume that families who enroll their loved ones in clinical trials are not representative of the caregiving population as a whole. Other problems with adapting trials results on cognition to economic outcomes are the relatively short duration of clinical trials in comparison to the course of disease, nonlinear progression of AD severity within and across individuals, and limitations in testing cognition in more severely demented individuals.

One of the biggest difficulties in assessing the potential impact of dementia treatments is the determination of benefit in quality of life. Anosognosia (organic unawareness of deficits) is a common symptom in AD, such that many patients become unreliable reporters of their own quality of life. They may literally "not know" that they are impaired, and report their self-perceived quality of life as quite high. This is in distinct contrast their family members' proxy attributions of their quality of life (Naglie et al 2006) and very likely different from their premorbid predictions of quality of life in dementia. Also, the impact of dementia on overall family quality of life is generally not well addressed in dementia, though this is measured in other populations like pediatrics and adults with developmental disabilities. As a result, there has been no well-validated or uniformly accepted measure of quality of life in dementia through most of the modern therapeutic era.

Assignment of quality of life is especially important in economic analyses of treatment effectiveness because of the use of "cost-utility" analyses by payer agencies like the UK's National Health Service (Green et al 2005). The basis of cost-utility analysis is a unit known as the "Quality Adjusted Life Years" (QALYs). The QALY allows incorporation of both patient preferences for different outcomes and reduced long term morbidity and mortality associated with treatment (Neumann et al 2000). It is based on a scale of 1.0 (perfect) to 0.0 (dead). The QALY scale assumes that there is nothing worse than death, but since AD is ranked as one of the most feared illnesses among older adults, this may not be a valid assumption in dementia. There are relatively few data available on the meaningfulness of current QALY estimates for dementia, and even those have been subject to widely different interpretations (Neumann, 2005).

Prospective studies

Although economists often employ statistical and inferential models to assess costs and benefit, clinical medicine is generally more comfortable with directly collected data as evidence. Unfortunately, relatively few studies have collected prospective data on cost-related issues in AD. It is important to note that, even among those that have, many of the cost assignments are estimates based on investigator-assigned valuation of services rather than actual expenditures.

Secondary economic analyses were conducted as part of a standard efficacy trial of donepezil vs placebo of 1-year duration which enrolled mild to moderately impaired AD patients (Mean MMSE = 19). The study was conducted in several northern European countries. Accounting for patient costs alone, there was a net increase in costs of care estimated at US$291 per patient. Reduced use of social services was observed and valued at US$1158, but this was more than offset by the cost of drug and increased use of medical services. Caregiver costs were reduced in all domains except caregiver use of emergency department services, resulting in an average annualized savings of US$1388. The large majority of these savings were attributable to reduced time in direct patient care. The authors concluded that the total cost of care for patients with mild to moderate AD and their caregivers was $1,097 less per patient among the donepezil-treated group (Wimo et al 2003a). Obviously, minor differences in the valuation of caregiver time could exaggerate or eliminate this margin of benefit.

Economic outcomes were also prospectively collected as part of a long-term double-blind placebo controlled trial of donepezil vs placebo among mild and moderately impaired AD patients in the UK (Mean MMSE = 19). This is commonly referred to as the AD2000 study (AD2000, 2004). Despite statistically significant effects in favor of donepezil on cognitive and functional measures, the investigators identified that donepezil treatment was associated with a GB £498 increase in overall costs relative to placebo (exclusive of costs attributable to donepezil and institutionalization). No differences in rates of nursing home placement, behavioral symptoms, or caregiver health outcomes were identified. The authors concluded that "donepezil is not cost-effective" with effectiveness defined as cost neutrality or better, or, as prolonged time to disability. Caregiver time was not included as a variable in the economic analysis because measures of caregiver time input did not differ between treatment groups.

The validity of this exclusion is questionable, however, since numerous other economic measures also did not differ by group and were included in the analysis for cost-effectiveness. Several other factors also limit the interpretation and generalizability of the AD2000 findings. Though intended to provide a closer reflection of typical clinical practice than most trials, this study used an unconventional and complicated methodology that makes comparison to other studies infeasible (Birks 2006). The trial suffered from serious levels of under-enrollment, with less than one-tenth of its intended sample completing one year of treatment. Finally, the study was conducted in a restricted geographical area, the West Midlands of England. It is unknown whether dementia-related health care practices there are representative of other regions or countries. This issue is important because, differences in baseline care practices have influenced other economic analyses (Feldman et al 2004).

Overall costs increase with worsening dementia severity (Langa et al 2001; Small et al 2002; Zhu et al 2006). Therefore, studies of cost-effectiveness in samples with more advanced dementia are justified. A randomized double-blind, placebo controlled trial of donepezil in moderate to severe AD patients conducted at 32 sites (22 Canadian, 6 Australian, 4 French) included prospectively-collected cost data using a "utilization of services" questionnaire and estimates of time spent in caregiving (Feldman et al 2004). As with studies in milder patients, direct patient care costs were not reduced by donepezil therapy, but reductions in caregiver time investment were calculated to provide a societal cost benefit of US$224 over a six month period. The diversity of centers involved in this study proved to be important since baseline cost estimates (and therefore relative value of the intervention) differed significantly by country, which reinforces the possibility that the AD2000 conclusions may not prove generalizable.

Memantine was approved for use in the European Union in 2002 and in US in 2003; it is indicated for use in moderate and severe stages of dementia. Cost data regarding its usage were prospectively collected at 30 US trial sites, using the Resource Utilization in Dementia instrument, as part of a 7-month double-blind placebo-controlled trial of moderate-to-severely impaired AD patients (Mean MMSE = 11) (Wimo et al 2003b). As with studies of donepezil, individual patient costs were not reduced by treatment, but the valuation assigned to caregiver time led the authors to conclude that memantine therapy was associated with a reduction in societal costs of ~US$1090 per month. This is a much larger cost benefit compared to other studies. The difference is attributable to using Bureau of Labor statistics that provide for hourly rates of US$9.18–$23.65 depending on factors like age and gender of the caregiver. In contrast, the caregiver time was valued at only US$4.36/hour in the study of donepezil in moderate and severe patients (Feldman et al 2004).

Population studies

Only a few studies have examined the impact of antidementia drugs on healthcare costs in clinical practice settings. In an early study of this type, a longitudinal survey of caregivers of patients with AD reported direct medical expenses in 108 patients receiving donepezil over 6 months of care and compared them with costs of care among 268 control patients matched on demographic and clinical variables (Small et al 1998). No significant differences were found in mean direct medical expenses between groups. Although patients receiving donepezil had higher expenditures for prescription drugs, a nonsignificant trend toward a reduced rate of institutionalization (10% placebo vs 5% donepezil) offset the effects increased drug costs.

Subsequently, the effects of donepezil on the costs of AD in a managed care organization were examined in a two-year study (Fillit et al 1999). Costs attributable to medical care and prescriptions were assessed in 70 individuals with dementia before and after they were prescribed donepezil. Although treatment was associated with decreased costs of medical care, overall costs were increased by ~US$2.11/day, attributable to the cost of prescription medications.

Hill and colleagues (2002) examined health care costs in 204 patients with AD and related dementias who were receiving donepezil and 204 matched controls. After controlling for age, sex, comorbid conditions, pharmacy benefit status, and complications of dementia, mean costs per year of medical services and prescription drugs were found to be ~US$3900 lower in the donepezil group. Reduced expenditures were most apparent in lower use of inpatient hospital and postacute skilled nursing facility (SNF) services, but were partially offset by the higher prescription-drug costs in donepezil-treated patients. Briefer treatment duration (<9 months) was associated with lesser benefit (~US$3600).

Another managed care study examined costs in 1366 patients with AD and related disorders and 13660 controls (Fillit et al 2002). Among more mildly impaired AD patients, 35% received a cholinesterase inhibitor drug (donepezil in all but one patient). Use of a cholinesterase inhibitor was associated with an annualized cost savings of US$2408. Unfortunately, no statistical analysis of this figure is reported, so its meaningfulness can not be interpreted.

More recently, healthcare costs in association with donepezil were assessed in a managed Medicare setting (Lu et al 2005). Cost data from 229 donepezil-treated patients were compared with data from 458 dementia patients who had never been treated using a regression analysis to estimate the impact of donepezil treatment on healthcare costs and utilization over one year of follow up. The groups were matched for age, sex, number of comorbid conditions, and complications of severe dementia. The mean costs of medical services per year in the donepezil group were ~US$2500 less than those in the control group. Significantly lower hospital and skilled nursing facility costs in the treated group were partially offset by US$1241 higher costs associated with higher prescription medication, physician office and outpatient hospital expenditures. Patients receiving donepezil had less use of much more expensive inpatient services and a higher number of physician's office visits (11 vs 8 visits) compared with controls, suggesting a more cost-effective use of healthcare resources in the treated group. Caution is warranted in interpreting these case-control findings, however, since the social and family environment of patients receiving prescription medication for dementia is likely to differ from those not being similarly treated, and the cost effects may simply be correlates of overall family function.

Modeling studies of cost-effectiveness

Space precludes a detailed review of all claims of cost-benefit related to treatment with antidementia drugs based on economic modeling, but there are common themes among them. Most have been sponsored by manufacturers of therapeutic agents and most have reported positive results, which raises the possibility of publication bias in the available studies. Prior to the emergence of prospective pharmacoeconomic data since 2003, economic implications of AD therapies were typically imputed on the basis increased direct costs of care associated with higher levels of severity. Some older economic models did not identify higher total costs of care in more severely affected patients, as it appeared that costs shifted from being informal and caregiver-borne, to formal and institutionally-borne. However, more recent data suggests dramatic increases in both direct and indirect costs with disease progression (Langa et al 2001; Zhu et al 2006).

Assumptions about costs of care as they relate to measures of severity have been generated by analysis of caregiver reported service use in small samples. Among the most commonly cited is the study by Ernst and colleagues (1997), which used a cohort of 64 patients to estimate costs associated with specific cognitive test scores and used that information to predict the economic consequences of maintaining or improving cognition. The predicted economic impact of a theoretical treatment was greatest in the moderately impaired patients, rather than mild or end-stage patients. The report provides an example of a person with a MMSE of 7; if treatment could prevent cognitive decline for 1 year, cost savings would be ~US$3700 (in 1997 dollars). Sustaining a two point increase in MMSE in the same patient would predict an annual cost savings of ~US$7100 (Ernst et al 1997). Subsequent studies have mapped cognitive results from double-blind placebo-controlled trials of anti-dementia drugs onto this model to estimate cost-savings with available therapeutic agents (Hauber et al 2000). More recent studies suggest that daily function is a better predictor of costs than cognition (Wolstenholme et al 2002; Zhu 2006). Numerous studies of cholinesterase inhibitors and memantine have shown relative preservation of functional capacity in comparison to placebo, which might be predicted to reduce costs. However, among studies with statistically significant advantages on functional ratings among the treated cohort, prospectively collected pharmacoeconomic data have not shown predicted levels of direct cost savings (Wimo et al 2003a, 2003b; AD2000 2004; Feldman et al 2004).

Another common approach to modeling cost savings with treatment is the use of statistical models that estimate costs avoided by delaying transition to more severe levels of impairment or dependency (Stewart et al 1998; Ward et al 2003; Jones et al 2004). These approaches are supported by a double-blind placebo controlled trial of donepezil that showed a higher likelihood of maintaining daily function in the treated group over one year (Mohs et al 2000), but is not supported by the AD2000 trial, which showed no effect of donepezil treatment on time to increased disability (AD2000 2004). A key issue in the interpretation of the economics associated with "delayed-transition" models is whether the patient is dependent, ie, requires full time care, while residing in community settings. If all patients residing in community settings are considered "nondependent," as was done in formulating policy on payment for antidementia drugs in the UK, then the potential to discern economic effects of treatment is minimized (Neumann et al 2005). Clearly, better consensus on defining dependency in dementia and associated health utility estimates that influence the calculation of QALYs is required.

A relatively understudied component of the economic consequences of the antidementia drugs is their impact on behavioral disturbances intrinsic to the disease. Behavioral symptoms

like agitation, aggression, and psychosis are major drivers of cost in community dwelling dementia patients (Herrmann et al 2006), as well as a critical factor in the economically important decision to institutionalize. While there are indications that cholinesterase inhibitors can reduce, or delay the emergence of behavioral symptoms, either alone (Trinh et al 2003) or in conjunction with memantine (Cummings et al 2006), no cost-benefit analyses of this effect appear to have been published.

In summary, modeling studies generally support the potential for cost-effectiveness of existing antidementia therapies. However, their underlying assumptions may not be accurate for the treated population. More research is required to understand how they can be effectively and objectively applied, and whether they will better map onto prospectively observed outcomes.

Summary

Numerous studies employing different methodologies have been undertaken to explore the potential value of antidementia therapies. Despite their common use in many countries, definitive evidence of cost benefits has not emerged. The calculation of health utilities, which determine cost-effectiveness, remains fraught with lack of consensus and idiosyncratic interpretations of existing data (Neumann 2005). Furthermore, in the absence of a better understanding of how to measure quality of life issues among people with dementia and their caregivers, the theoretical basis of QALY-based measurements is doubtful in this patient population.

Prospective trials suggest but do not confirm benefits at the family and societal levels and argue against direct individual cost benefits to the patient. In contrast, population based studies suggest reduced costs of care to insurers among patients treated with cholinesterase inhibitors. It is likely that family and social factors predisposing to better overall care contribute to positive outcomes observed in the managed care settings. Published studies that model costs and savings tend to appear the most favorable toward antidementia treatments, but are subject to several levels of bias in design, interpretation, and publication. The current state of the available data is perhaps best summarized by the Cochrane Library review of cholinesterase inhibitors for dementia, which states that, "it would be inappropriate for any provider of healthcare to make a decision regarding the availability of (antidementia drugs) for patients based on these economic models (Birks 2006).

Practical considerations

There is a troubling undertone in discussions about cost and effectiveness regarding treatments for AD. Advocates and critics alike seem to ignore the roles of the patient/family unit and the physician in the decision-making process regarding whether treatment is providing a meaningful benefit. It is inappropriate to make treatment decisions in the clinical setting on the "treat all" vs "treat none" (Clarke 2004) dichotomy implied by the question, "Are antidementia therapies cost-effective?"

Existing data indicate that families are able to identify and report individualized goals for dementia intervention (Rockwood et al 2002) and that physicians acknowledge that there are treatment outcomes not detected by standard instruments (Rockwood et al 2004). In light of this, and the fact that most patients seek care for symptomatic illnesses to relieve suffering rather than reduce costs, it seems appropriate to make individualized treatment decisions based on the patient/family's needs and goals, and monitor the success of treatment in achieving them. If treatment creates intolerable adverse effects, or fails to deliver satisfactory levels of efficacy, discontinuation would be warranted (and likely cost-effective). In contrast, if the patient is doing discernibly well, relative to expectation, and the family is satisfied with the situation, then continuing the therapy would seem appropriate on clinical grounds alone. AD is a devastating and depersonalizing illness, and there is reasonable evidence available that treatment can blunt its effects in many patients. At the current state of knowledge, careful clinical decision-making in collaboration with the patient and family – rather than isolated consideration of murky economic factors – appears to be the most prudent and compassionate course of action to determine treatment strategies for the patient with dementia.

References

[AD2000] AD2000 Collaborative Group. 2004. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): Randomised double-blind trial. *Lancet*, 363:2105–15.

Aevarsson O, Skoog I. 1996. A population-based study on the incidence of dementia disorders between 85 and 88 years of age. *J Am Geriatr Soc,* 44:1455–60.

Birks J. 2006. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*, 1:CD005593.

Callahan CM, Hendrie HC, Tierney WM. 1995. Documentation and evaluation of cognitive impairment in elderly primary care patients. *Ann Intern Med,* 122:422–9.

Clarke N. 2004. AD2000 design and conclusions [Letter]. *Lancet,* 364:1215–16.

Cummings JL, Schneider E, Tariot PN, et al. 2006. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology,* 67:57–63.

Evans DA, Funkenstein HH, Albert MS, et al. 1989. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA,* 262:2551–6.

Feldman H, Gauthier S, Hecker J, et al. 2004. Economic evaluation of donepezil in moderate to severe Alzheimer disease. *Neurology,* 63:644–50.

Ferri C, Prince M, Brayne C, et al. 2005. Global prevalence of dementia: a Delphi consensus study. *Lancet,* 366:2112–17.

Fillit H, Gutterman EM, Lewis B. 1999. Donepezil use in managed Medicare: Effect on health care costs and utilization. *Clin Ther,* 21:2173–85.

Fillit H, Hill JW, Futterman R. 2002. Health care utilization and costs of Alzheimer's disease: The role of co-morbid conditions, disease stage, and pharmacotherapy. *Fam Med*, 34:528–35.

Gutterman E, Markowitz J, Lewis B, et al. 1999. Cost of Alzheimer's disease and related dementia in managed-Medicare. *J Am Geriatr Soc,* 47:1065–71.

Green C, Picot J, Loveman E, et al. 2005. Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. *Pharmacoeconomics*, 23:1271–82.

Hauber AB, Gnanasakthy A, Snyder EH, et al. 2000. Potential savings in the cost of caring for Alzheimer's disease: Treatment with rivastigmine. *Pharmacoeconomics*, 17:351–60.

Herrmann N, Lanctot KL, Sambrook R, et al. 2006. The contribution of neuropsychiatric symptoms to the cost of dementia care. *Int J Geriatr Psychiatry*, 21:972–6.

Hill JW, Futterman R, Duttagupta S, et al. 2002. Alzheimer's disease and related dementias increase costs of comorbidities in managed Medicare. *Neurology*, 58:62–70.

Hill JW, Futterman R, Mastey V, et al. 2002. The effect of donepezil therapy on health costs in a Medicare managed care plan. *Manag Care Interface,* 15:63–70.

Jones RW, McCrone P, Guilhaume C. 2004. Cost effectiveness of memantine in Alzheimer's disease. An analysis based on a probabilistic Markov model from a UK perspective. *Drugs Aging*, 21:607–20.

Koppel R. 2002. Alzheimer's Disease: The Costs to U.S. Businesses in 2002 [online]. Alzheimer's Association: Chicago, IL. Accessed December 1, 2006. URL: http://www.alz.org/Downloads/062602ADCosts.pdf.

Langa KM, Chernew ME, Kabeto MU, et al. 2001. National estimates of the quantity and cost of informal caregiving for the elderly with dementia. *J Gen Intern Med,* 16:770–8.

Lu S, Hill J, Fillit H. 2005. Impact of donepezil use in routine clinical practice on health care costs in patients with Alzheimer's disease and related dementias enrolled in a large Medicare managed care plan: A case-control study. *Am J Geriatr Pharmacother*, 3:92–102.

Mohs RC, Doody RS, Morris JC, et al. 2001. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology*, 57:481–8.

Naglie G, Tomlinson G, Tamsey C, et al. 2006. Utility-based quality of life measures in Alzheimer's disease. *J Quality Life*, 15:631–43.

Neumann PJ, Goldie SJ, Weinstein MC. 2000. Preference based measures in economic evaluation in health care. *Ann Rev Public Health,* 21:587–611.

Neumann PJ. 2005. Health utilities in Alzheimer's disease and implications for cost-effectiveness analysis. *Pharmacoeconomics*, 23:437–541.

Plosker GL. Lyseng-Williamson KA. 2005. Memantine: a pharmacoeconomic review of its use in moderate-to-severe Alzheimer's disease. *Pharmacoeconomics*, 23:193–206.

Rockwood K, Graham JE, Fay S. 2002. Goal setting and attainment in Alzheimer's disease patients treated with donepezil. *J Neurol Neurosurg Psychiatry*, 73:500–7.

Rockwood K, Black SE, Robillard A, et al. 2004. Potential treatment effects of donepezil not detected in Alzheimer's disease clinical trials: a physician survey. *Int J Geriatr Psychiatry*, 19:954–60.

Siegel JE, Torrance GW, Russell LB, et al. 1997. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost effectiveness in Health and Medicine. *Pharmacoeconomics*, 11:159–68.

Small GW, Donahue JA, Brooks RL. 1998. An economic evaluation of donepezil in the treatment of Alzheimer's disease. *Clin Ther,* 20:838–50.

Small GW, McDonnell DD, Brooks RL, et al. 2002. The impact of symptom severity on the cost of Alzheimer's disease. *J Am Geriatr Soc*, 50:321–7.

Stewart A, Phillips R, Dempsey G. 1998. Pharmacotherapy for people with Alzheimer's disease: A Markov-cycle evaluation of five years therapy using donepezil. *Int J Geriatric Psychiatry,* 13:445–53.

Trinh NH, Hoblyn J, Mohanty S, et al. 2003. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA*, 289:210–16.

Ward A, Caro JJ, Getsios D, et al. 2003. Assessment of health economics in Alzheimer's disease (AHEAD): treatment with galantamine in the UK. *Int J Geriatric Psychiatry*, 18:740–7.

Wimo A, Winblad B, Engedal K, et al. 2003a. An economic evaluation of donepezil in mild to moderate Alzheimer's disease: Results of a 1-year, double-blind, randomized trial. *Dement Geriatr Cogn Disord*, 15:44–54.

Wimo A, Winblad B, Stoffler A, et al. 2003b. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics*, 21:327–40.

Wimo A. 2004. Cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease: a review with methodological considerations. *Drugs Aging*, 21:279–95.

Wimo A, Winblad B, Jönsson L. 2007. An estimate of the total worldwide societal costs of dementia in 2005. *Alzheimer Dement,* 3:81–91

Wolstenholme J, Fenn P, Gray A, et al. 2002. Estimating the relationship between disease progression and cost of care in dementia. *Br J Psychiatry*, 181:36–42.

Zhu CW, Scarmeas N, Torgan R, et al. 2006. Longitudinal study of effects of patient characteristics on direct costs in Alzheimer disease. *Neurology*, 61:997–1005.