

The Cost Benefit to Health Plans Of Pharmacotherapy for Alzheimer's Disease

As with other chronic diseases of aging, early diagnosis and pharmacologic therapy may reduce the costs for enrollees with Alzheimer's disease

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ABSTRACT

Treatment of Alzheimer's disease (AD) is a major public health issue, with the potential for significant impact on MCOs. As the number of people affected with AD continues to rise, the importance of this problem will grow as well. This article reviews patient and caregiver outcomes associated with reduced health care costs and their implications for MCOs. Cholinesterase inhibitors (ChEIs) are effective in treating cognitive, functional, and behavioral symptoms for patients with mild to moderate and moderate to severe AD. Treatment with memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to benefit patients with moderate to severe AD. Pharmacoeconomic studies indicate that donepezil and memantine treatment may reduce total costs of care for AD patients and their caregivers, with potential economic benefits to MCOs.

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INTRODUCTION

Neurodegenerative dementing diseases, like Alzheimer's disease (AD), have obvious health consequences for patients. Caregivers also suffer physical, emotional, and financial consequences from the stress and the time requirements of providing care. The impact of neurodegenerative diseases on the patient-caregiver dyad translates into potential adverse financial consequences for MCOs. Increased costs associated with neurodegenerative diseases may be offset, however, by patient care strategies that target reducing the emergence of debilitating symptoms and associated comorbid conditions that emerge in both patients and caregivers.

METHODS

Medline searches were conducted, using *donepezil*, *galantamine*, *rivastigmine*, *acetylcholinesterase inhibitors*, *memantine*, *Alzheimer disease*, *managed care programs*, and *economic* as key words. From these searches, 75 English-language articles addressing economic issues of treatment in AD were identified. Only three of these also included *managed care programs* as a key word. None of these three involved prospective clinical trials. Therefore, the articles involving dou-

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ble-blind placebo controlled trials with economic outcomes were identified from the reference lists and selected for further review.

FINDINGS

Dementia costs in MCOs. According to a recent review, studies of MCO enrollees identified higher total health care costs for patients with dementia than for those without, ranging from 1.5 to 1.9 times higher, even after adjusting for comorbidities. Increased costs can be attributed to hospital visits (Fillit 2004). In one study that compared Medicare MCO enrollees with AD-related dementias ($n=3,934$) to age- and gender-matched controls ($n=19,300$), hospital claims for patients with dementia were nearly twice those of enrollees without dementia (Hill 2002).

Increased resource utilization for patients with dementia has been attributed to inadequate management of comorbidities in this population (Fillit 2004). In patients with AD, the incidence of comorbidities increases with disease progression and 60 percent of patients have three or more comorbid conditions (Doraiswamy 2002). In AD, however, unlike congestive heart failure or diabetes, the high prevalence of comorbidities does not, by itself, account for increased health care costs (Fillit 2004). Cognitive impairment increases the difficulty of complying with medication, diet, and other self-management regimens for these comorbid diseases, contributing to more frequent hospitalization (Fil-

lit 2000a, 2004). Patients with dementia appear less able to identify and report new symptoms early, before the onset of a more serious condition requiring hospital admission (Fillit 2004, Torian 1992). Once hospitalized, patients with AD are prone to events that prolong hospital stays, such as infection or falls and other accidents (Fillit 2000a, 2004; Torian 1992).

Effect on caregivers. The burden of AD falls on caregivers along with patients. The functional decline and behavioral symptoms associated with AD contribute significantly to caregiver burden. Behavioral symptoms add to the burden by increasing caregiver stress and distress (Kaufer 1998, Schulz 1995). This burden appears to contribute to increased rates of poor health outcomes in caregivers, including depression, substance abuse, and illness (Fillit 2000b, Hill 2002, Schulz 1995). Caregiver mental health and well-being often is affected by the burden of providing care to a loved one. Forty-two percent of caregivers attending a memory disorders clinic had probable or definite psychological morbidity as defined by the General Health Questionnaire, which includes measures of psychiatric symptoms, social function, and life satisfaction (Brodaty 1998). Caregivers of patients with dementia may have increased physiologic stress responses, as suggested by the finding that women who care for husbands with AD experience increased cortisol production associated with caregiving events (Davis 2004). A study of 1,222 caregiver-patient dyads found that levels of depression and anxiety among caregivers were not significantly different before or after transfer of a patient from home to the institutional care setting (Schulz 2004).

Caregiver health and MCOs. Improving patient and caregiver outcomes provides the opportunity to reduce costs to MCOs by reducing health care resource utilization (Fillit 2004, Hill 2002) and emergent

morbidity in caregivers (Brodaty 1998).

With less direct effect on MCOs, but of importance to the overall economic burden of AD, improved clinical outcomes also may have a positive effect on the indirect cost of caregiver productivity. In a study of 1,715 caregivers of patients with AD, caregiver productivity decreased as AD severity increased; measures of lost productivity included missed workdays and hours per week providing care. The authors suggest that costs may be reduced by a treatment that increases the time patients with AD remain in less severe stages of the disease (Small 2002).

Rationale for treatment. There is a perception among health care providers that current treatments for AD are relatively ineffective and that, at most, they can prolong the course to inevitable death without improving patient quality of life (Boise 1999, Wilkinson 2004). This view, however, neglects the fact that many age-related illnesses are routinely treated with little expectation of immediate clinical improvement. For instance, the objective behind the aggressive treatment of diabetes mellitus and hypertension is reducing risk for, or delaying, the debilitating complications from these diseases (Geldmacher 2004). Similarly, delaying functional decline and reducing behavioral symptoms in AD holds the potential for sustaining function and quality of life for patients with AD.

Pharmacologic options. The cholinesterase inhibitor (ChEI) class of drugs has proven effective for treating the cognitive, functional, and behavioral symptoms of patients with mild to moderate AD (Doody 2001). More recently, the U.S. Food and Drug Administration approved memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of moderate to severe AD. Table 1, page 46 summarizes published prospective, randomized, placebo-controlled clinical trial data

for pharmacologic agents in patients with mild to moderate AD and in those with moderate to severe AD.

Studies in mild to moderate AD. ChEIs provide significant treatment benefits for patients with mild to moderate AD. Six-month randomized, placebo-controlled studies of donepezil showed improved cognition and stabilized function compared with baseline values (Burns 1999, Rogers 1998). Donepezil also improved behavioral symptoms compared with baseline during a 6-month period (Holmes 2004).

One-year randomized, placebo-controlled studies showed that donepezil provided significant long-term cognitive and functional benefits in mild to moderate AD. During the studies, cognition was either improved (Mohs 2001) or stabilized (Winblad 2001) in patients treated with donepezil compared with baseline values. Although mean functional ability declined compared with baseline after 1 year of treatment, patients treated with donepezil had significantly less decline than those who received placebo (Winblad 2001). Also, a greater proportion of patients maintained daily function on donepezil compared with placebo (Mohs 2001).

No difference was seen in behavioral symptoms in patients treated with donepezil versus placebo in one of these studies (Winblad 2001). Yet the authors noted a general absence of baseline and emergent behavioral symptoms in this population of patients with mild to moderate AD. The duration of benefit is unknown, but a randomized, placebo-controlled study in the United Kingdom, sponsored by the National Health Service, showed that patients who received long-term donepezil treatment had cognitive and functional outcomes superior to placebo for at least 2 years (AD2000 2004).

In randomized, placebo-controlled studies lasting up to 6 months, the ChEI galantamine showed improved

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cognition and stabilized function compared with baseline values (Raskind 2000, Tariot 2000, Wilcock 2000). In a 5-month study, behavioral symptoms were stabilized compared with baseline values for patients treated with galantamine (Tariot 2000). Similarly, a 3-month open-label study showed improved behavioral symptoms compared with baseline for patients treated with galantamine (Monsch 2004).

Six-month randomized, placebo-controlled studies of the ChEI rivastigmine showed either improved

(Rosler 1999) or stabilized (Corey-Bloom 1998) cognition. In these studies, function was not statistically different from placebo but declined or was stabilized for patients treated with rivastigmine compared with baseline values (Corey-Bloom 1998, Rosler 1999).

A 2004 review of available data on rivastigmine concluded that the agent can improve psychotic and nonpsychotic symptoms associated with AD. A meta-analysis of three 6-month trials of patients with mild to moderate AD determined that rivastigmine

may improve or prevent disruptive behavioral and psychological symptoms of dementia significantly more effectively than placebo (Finkel 2004).

Studies in moderate to severe AD.

To date, prospective studies in advanced AD have been reported only for the ChEIs donepezil and rivastigmine and the NMDA-receptor antagonist memantine. A 6-month randomized, placebo-controlled study of donepezil treatment in these patients suggested that the benefits of donepezil treatment extend beyond

TABLE 1 Summary of pharmacotherapeutic outcomes in prospective randomized, placebo-controlled studies

Mild to moderate Alzheimer's disease					
	Outcome*			Parameters	
	Cognition	Function	Behavior	Study length	Baseline MMSE
Donepezil studies					
Rogers 1998	Improved [†]	Stabilized [†]		6 months	10–26
Burns 1999	Improved [†]	Stabilized [†]		6 months	10–26
Holmes 2004			Improved [†]	6 months	10–27
Winblad 2001	Stabilized [‡]	Slowed decline [†]	NS	1 year	10–26
Mohs 2001	Improved [†]	Slowed decline [†]		1 year	12–20
AD2000 Collaborative Study Group 2004	Slowed decline [‡]	Slowed decline [‡]	Stabilized, NS [‡]	2 years	10–26
Rivastigmine studies					
Corey-Bloom 1998	Stabilized [†]	Slowed decline [†]		6 months	10–26
Rosler 1999	Improved [†]	Stabilized [†]		6 months	10–26
Galantamine studies					
Raskind 2000	Improved [†]	Stabilized [†]		6 months	11–24
Tariot 2000	Improved [†]	Stabilized [†]	Stabilized [‡]	5 months	10–22
Wilcock 2000	Improved [†]	Stabilized [†]		6 months	11–24
Advanced Alzheimer's disease					
	Outcome*			Conditions	
	Cognition	Function	Behavior	Study length	Baseline MMSE
Donepezil study					
Feldman 2001	Improved [‡]	Stabilized [†]	Improved [‡]	6 months	5–17
Rivastigmine study[§]					
Karaman 2005	Improved [†]	Stabilized [‡]		1 year	≤14
Memantine study					
Reisberg 2003	Slowed decline [†]	Slowed decline [†]	NS [‡]	7 months	3–14
Memantine add-on study					
Tariot 2004	Improved [†]	Stabilized [‡]	Stabilized [‡]	6 months	5–14

* Intent-to-treat data relative to baseline values for maximally effective dose; all outcomes are statistically different from placebo unless otherwise indicated.

[†] Primary efficacy measure.

[‡] Secondary efficacy measure.

[§] Patients with "advanced moderate" Alzheimer's disease.

MMSE=Mini-Mental State Examination, NS=not statistically different from placebo.

mild to moderate AD. Donepezil treatment improved cognition and behavioral symptoms while stabilizing function compared with baseline values in this patient population (Feldman 2001).

In a 1-year open-label trial, rivastigmine improved neuropsychiatric and behavioral symptoms compared with baseline in patients with probable AD in an advanced moderate stage; though these results suggest a beneficial behavioral effect for rivastigmine, they are subject to the limitations of the open-label design (Aupperle 2004). A small (N=44) 1-year placebo-controlled, randomized study of patients having "advanced moderate" AD (Mini-Mental State Examination) found that rivastigmine improved cognition and produced significantly better outcomes than placebo for cognitive and functional parameters (Karaman 2005).

In a 7-month randomized, placebo-controlled study of patients with moderate to severe AD, treatment with memantine produced significantly better outcomes than placebo on several measures of cognition and function. Nevertheless, both the memantine and placebo groups exhibited a decline in cognition and function relative to baseline. In other words, drug treatment helped slow deterioration relative to placebo but did not stabilize the patients' condition. No treatment benefit was observed for the behav-

ioral symptoms of AD in this study (Reisberg 2003).

In one 6-month randomized, placebo-controlled study, patients receiving memantine treatment adjunctive to long-term donepezil therapy (mean duration: 2.4 to 2.5 years donepezil treatment at baseline) had improved cognition, stabilized function, and stabilized behavioral symptoms (Tariot 2004). Outcomes in these domains were significantly better in patients treated with memantine plus donepezil than in patients taking donepezil plus placebo.

These studies suggest that ChEI therapy may continue to benefit patients in the advanced stages of disease and that memantine treatment is an appropriate adjunctive therapy in advanced AD. Both ChEI monotherapy and memantine add-on therapy may improve the outcomes for patients with later-stage AD.

Comparative efficacy of treatment

Evaluation of clinical studies of ChEIs has shown a relatively small number of patients needed to treat (NNT) for one additional patient to benefit. One recent meta-analysis assessed NNT for "global response" (defined as a rating of patients as improved on various global assessments). The NNT was 8 for patients treated with donepezil and 22 for patients treated with galantamine (Lanctot 2003). Application of the NNT

method to a published 1-year study (Mohs 2001) on functional decline has shown that for patients treated with donepezil, the NNT to prevent ADL loss during 1 year was five. Similarly, the NNT for donepezil to delay nursing home placement for 1 year was 6 (Geldmacher 2004, Lopez 2002). In contrast, the NNT for other chronic conditions affecting the elderly can be much higher; for example, with antihypertensives, 29 to 86 patients must be treated for 5 years to prevent 1 major cardiovascular event (Lanctot 2003).

Thus, ChEI treatment may improve outcomes for a large fraction of patients with AD, significantly reducing the burden on caregivers and MCO costs associated with complications of functional decline (e.g., malnutrition, incontinence) or emergence of difficult behaviors (which may require pharmacotherapy, emergency treatment, or hospitalization). Table 2 compares the NNT for ChEIs and other pharmacologic agents used to treat chronic conditions in the elderly.

Social and economic benefits of pharmacologic treatment. Reducing the amount of time caregivers spend assisting patients with ADL may reduce the stress caused by the behavioral symptoms of AD (Fillit 1999a, Sano 2003). For example, caregivers of patients with moderate to severe AD treated with donepezil reported spending 6 fewer hours per week as-

TABLE 2 Comparison of number-needed-to-treat (NNT) analyses for dementia and other common conditions in the elderly

Drug	Outcome prevented	Treatment duration (years)	NNT
Alendronate (Cummings 1998)	Hip fracture	4	15
Statins (LaRosa 1999)	Myocardial infarction (MI)	4	28
ACE inhibitors (AIRE 1993)	Death in congestive heart failure	1	18
Antihypertensives (meta-analysis) (Lanctot 2003)	Major event (MI, stroke, or death)	5	29-86
Cholinesterase inhibitors (meta-analysis) (Lanctot 2003)	Global decline	≤1	12
Donepezil (Mohs 2001)*	Loss in activities of daily living	1	5
Donepezil (Lopez 2002)*	Nursing home placement	1	6

ACE=angiotensin-converting enzyme.

*GELDMACHER 2004 calculated/reported these NNTs.

sisting with ADL after 6 months of treatment (Feldman 2003). Similarly, caregivers of patients with mild to moderate AD treated with galantamine reported spending 3.7 fewer hours per week assisting with ADL after 6 months of treatment (Sano 2003). These reductions in the time needed to assist patients with ADL probably result from preserved functional ability during ChEI therapy. Analysis of clinical data for rivastigmine, using a hazard model to calculate the caregiving time saved, projected a reduction of 690.4 caregiving hours over the course of 2 years for patients with mild AD at baseline (Marin 2003).

Treatment with donepezil also was associated with reduced caregiver distress for AD patients with prominent neuropsychiatric symptoms (Holmes 2004). Distress increased significantly when, in this double-blinded withdrawal of therapy trial, donepezil treatment was stopped. Reducing the

demands on caregivers will allow them respite, potentially improving the quality of care they provide or reducing caregiving-related morbidities.

Choice of agent may affect caregiver and prescriber satisfaction with treatment. In 3-month head-to-head studies (Jones 2004, Wilkinson 2002), caregivers of patients with mild to moderate AD reported greater overall satisfaction (including tolerability and physician contact for side effects) and ease of use for donepezil treatment compared with galantamine treatment or rivastigmine treatment.

In the first of these studies, 92.2 percent of patients treated with donepezil remained on the maximum dose (10 mg, once daily) at the study's end, compared with 71.4 percent of patients treated with galantamine (12 mg, twice daily) (Jones 2004).

Similarly, at the second study's end,

87.5 percent of donepezil-treated patients remained on the maximally effective dose (10 mg, once daily) compared with 47.3 percent of patients treated with rivastigmine (maximum: 6 mg, twice daily) (Wilkinson 2002).

Interpretation of these results must be tempered, however, by a 1-year study comparing galantamine and donepezil. That study found a comparable proportion of patients remained on the maximum recommended dose for each drug by study's end: 71.1 percent of patients taking galantamine and 69.2 percent of patients taking donepezil remained on the maximum recommended dose (12 mg twice daily and 10 mg once daily, respectively) (Wilcock 2003).

Dosing, efficacy, and tolerability. Regression analysis of multiple studies has shown that sustaining a higher dose of donepezil (10 mg, as opposed to 5 mg, total daily dose) and rivastigmine (6 mg to 12 mg, total daily dose vs. 1 mg to 4 mg, total daily dose) produced beneficial effects on cognitive tests; such benefits were not seen over a range of high, medium, or low doses of galantamine (16 mg to 36 mg, total daily dose) (Ritchie 2004). Higher doses of galantamine and rivastigmine were associated with higher dropout rates. With donepezil, analysis indicated a possible association between higher doses and increased dropouts, but not to the extent of the other two drugs (Ritchie 2004). These results suggest MCOs that include pharmacy benefits may need to evaluate formulary inclusions and monitor prescribing patterns to maximize effectiveness of AD treatment.

Costs of care. Improved patient outcomes may translate into reduced economic burden for patients and caregivers. In an economic evaluation of a 1-year study, the total cost of care for patients with mild to moderate AD and their caregivers was \$1,097 less for patients treated with donepezil than for patients receiving placebo. Most of these savings came

TABLE 3 Cost savings per patient for 1 year of donepezil therapy in mild to moderate Alzheimer's disease

Source	Cost savings with donepezil treatment vs. placebo (U.S. \$*)
Direct patient costs	
Donepezil (study medication)	(\$1,280)
Patient hospitalization	(\$216)
Patient emergency room	(\$23)
Patient health care professionals	\$5
Patient concomitant medications	0
Patient social services	\$1,158
Patient accommodation (living arrangement)	\$65
Total patient	(\$291)
Caregiver costs	
Caregiver hospitalization	\$145
Caregiver emergency room	(\$11)
Caregiver health care professionals	\$216
Caregiver medications	\$5
Caregiver patient care time	\$1,018
Caregiver missed work	\$15
Total caregiver	\$1,388
Net cost savings	\$1,097

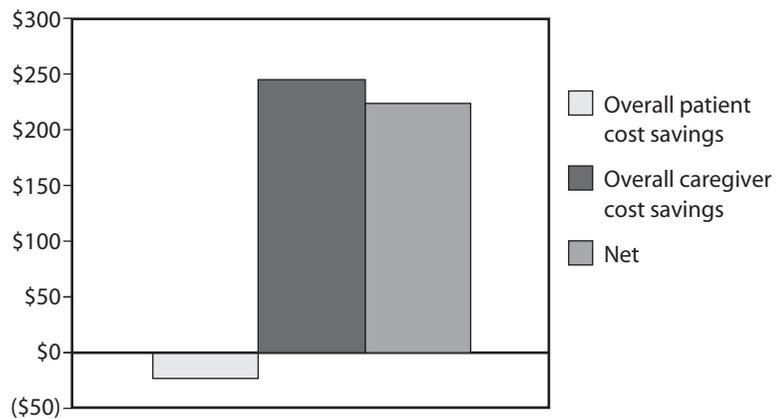
* Calculated as placebo group cost minus donepezil group cost over 12 months of study.
SOURCE: WIMO 2003A

from reductions in the time caregivers spent assisting patients with daily functioning, caregiver hospitalizations, and caregiver visits to physicians (Table 3). Total patient and caregiver cost savings during 1 year for donepezil vs. placebo in the treatment of mild to moderate AD were \$291 and \$1,388, respectively. Likewise, in another pharmacoeconomic study, total societal cost per patient was \$224 less for those with moderate to severe AD who had received donepezil for 6 months. Much of this savings came from reductions in the time caregivers spent assisting patients (Figure). Given that they are based on assigning a value to caregiver time, these economic advantages do not translate directly to cost savings for MCOs. Nevertheless, direct patient costs, exclusive of donepezil prescription cost, were lower among patients who took donepezil, with savings reported for health care professionals, physician services, acute-care hospital, and residential care among other variables; as a result, the difference in total patient costs was only \$23 when donepezil cost was included (Feldman 2004).

Modeling studies suggest that treatment with rivastigmine and galantamine also may result in cost savings (Hauber 2000a,b; Lyseng-Williamson 2002; Migliaccio-Walle 2003). A long-term head-to-head study of patients treated with either galantamine or donepezil found that both groups maintained baseline levels of daily functioning for 9 months; more caregivers of patients treated with galantamine reported maintenance or improvement in burden than did caregivers of patients treated with donepezil (Wilcock 2003). The lack of direct economic analysis in this study makes it difficult to translate the benefits of treatment into cost savings, however.

The nature of the health care economy also affects the analysis of cost-benefit from treatment of AD. For

FIGURE Comparison of patient and caregiver cost savings associated with 24 weeks' donepezil treatment



SOURCE: FELDMAN 2004

example, a long-term, placebo-controlled trial of donepezil reported no significant difference in costs under the UK National Health Service for patients in the placebo or treatment group (AD2000 2004). The study design limits the interpretation, however, because diagnosis was not standardized, treatment was interrupted, and there was insufficient enrollment to analyze cost outcomes in a valid manner. Even if formal costs are unchanged by treatment, it is reasonable to anticipate that maintaining patient daily function at baseline levels for an extended time would at least delay additional time and energy burdens on the caregiver.

In a 7-month study of patients with moderate to severe AD treated with memantine, caregiver burden was assessed by the Resource Utilization in Dementia instrument, which also measured disease-related economics through structured caregiver interviews (Reisberg 2003).

In that study, caregivers of patients treated with memantine reported spending 45.8 fewer hours per month with patients compared with caregivers of patients receiving placebo ($P=.01$). Economic analysis showed that patients treated with memantine had \$1,090 lower total monthly costs

from a societal perspective than patients receiving placebo ($P=.01$). As seen with other studies, the main source of this savings was reduced caregiver costs. Nevertheless, from a patient perspective, direct medical costs were higher in the memantine group than in the placebo group (Wimo 2003b).

The benefits of maintaining treatment are apparent in improved patient outcomes and lower projected health care costs for patients and their caregivers. It is important to note that substantial portions of these cost savings will not translate to fiscal benefits for MCOs because they come from reductions in the time that caregivers spend assisting patients. Nonetheless, small but significant daily respites can reduce caregiver burden and have the potential to reduce costs of providing health care for caregivers. These issues warrant prospective controlled studies in the MCO setting.

Managed care costs. In a study of managed care claims, patients with AD and related dementias were hospitalized 2.5 times more often than patients who did not have dementia (Hill 2002). Patients with AD were significantly more likely to be admitted to a major health center than el-

derly subjects without AD (Albert 1999).

Other studies have suggested that patients with dementia may utilize physicians' office services somewhat less than patients without dementia (Fillit 2000a, Hill 2002).

Together, these studies suggest that many patients with dementia may not seek, or do not receive, routine outpatient or preventive care for potentially serious health conditions. A possibility also exists that AD may cause comorbidities, apart from dementia, or that persons with AD may be prone to other health problems based on an undefined association. If routine care is not an integral part of a disease management strategy for dementia, then costly comorbid conditions may go unnoticed until emergency care or hospitalization is required.

MCOs could lower their costs by helping to reduce excess resource utilization by AD patients (Fillit 1999b, 1999c, 2000b; Hepburn 2001). By educating both physicians and caregivers, MCOs can promote disease management strategies that include improved health maintenance for patients with dementia. Regular assessments allow physicians to screen for emerging comorbid conditions and to assess caregivers for burden-related secondary health issues. A disease management strategy that fosters patient independence and manages risk offers the potential to offset more costly interventions for dementia symptoms and emerging comorbidity (Fillit 2002, Gutterman 1999, Rice 2001). Implementation of these efforts likely will necessitate a change in the knowledge base and practice of physicians who are reticent to diagnose dementia due to the perceived difficulties of caring for patients with this disease.

A more prospective approach to dementia recognition and treatment holds potential to improve the quality and reduce the costs of care. Treatment with ChEIs and/or memantine

may reduce the need for other pharmacologic agents. For example, patients receiving donepezil therapy were less likely to require antidepressants, antipsychotics, and antianxiety drugs or sedative hypnotics than patients not receiving ChEI therapy (Small 1998).

Treatment-related behavioral improvements also may reduce costs. In one study, patients with active, problematic behavioral AD symptoms were shown to incur annual direct costs between \$10,670 and \$16,141 higher than those without these behavioral symptoms. According to the authors, behavioral symptoms may be independent predictors of direct costs in AD; treatment of behavioral symptoms with ChEIs and other adjunctive medications (e.g., neuroleptics, selective serotonin reuptake inhibitors) therefore may help to decrease the cost of care (Murman 2002).

MCOs with agreements to pay for nursing home care with skilled staff may be able to delay or avert a portion of this costly expense by including recommendations for ChEI therapy in their disease management strategy for patients with AD. One case-control study indicated a six-fold reduction in risk for nursing home placement in association with ChEI treatment (Lopez 2002).

This effect was supported by an observational study showing a delay of 21.4 months to the first dementia-related nursing home placement and a delay of 17.5 months to permanent nursing home placement for patients receiving long-term donepezil treatment compared with patients who received limited treatment (Geldmacher 2003).

The recent randomized, placebo-controlled U.K. study did not identify a significant difference in institutionalization between the placebo and donepezil groups at 3 years, but too few patients remained to reliably report outcomes related to nursing home placement (AD2000 2004).

CONCLUSION

Unmet patient and caregiver needs increase costs to MCOs because a loss of patient independence complicates disease management and increases caregiver burden. Patients with AD who receive early diagnosis, persistent pharmacologic treatment, and routine care can maintain their independence longer, potentially reducing or delaying increases in health care costs for themselves and their caregivers. ChEI therapy and adjunctive memantine therapy are effective treatments for the cognitive, functional, and behavioral symptoms of AD. Although these treatments are not curative, they offer the opportunity to delay decline and reduce emergent behavioral disturbances associated with AD.

Disease management strategies that include early diagnosis of AD and early pharmacologic treatment, routine screening for comorbid conditions, and provisions for managing the expectations and health of caregivers potentially will reduce unnecessary emergency department and physician visits as well as hospitalizations. As with other chronic diseases of aging, like dyslipidemia and hypertension, movement toward routine recognition and comprehensive care including appropriate pharmacologic treatment and prospective management — rather than emergency intervention — may reduce the cost of providing health care for MCO enrollees with AD and their caregivers.

REFERENCES

- AD2000 Collaborative Group: Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): Randomised double-blind trial. *Lancet*. 2004;363:2105–2115.
- AIRE. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet*. 1993; 342:821–828.
- Albert SM, Costa R, Merchant C, et al.

- Hospitalization and Alzheimer's disease: Results from a community-based study. *J Gerontol A Biol Sci Med Sci*. 1999;54A:M267–M271.
- Aupperle PM, Koumaras B, Chen M, et al. Long-term effects of rivastigmine treatment on neuropsychiatric and behavioral disturbances in nursing home residents with moderate to severe Alzheimer's disease: Results of a 52-week open-label study. *Curr Med Res Opin*. 2004;20:1605–1612.
- Boise L, Camicioli R, Morgan DL, et al. Diagnosing dementia: Perspectives of primary care physicians. *Gerontologist*. 1999;39:457–464.
- Brodady H, Luscombe G. Psychological morbidity in caregivers is associated with depression in patients with dementia. *Alzheimer Dis Assoc Disord*. 1998;12:62–70.
- Burns A, Rossor M, Hecker J, et al. The effects of donepezil in Alzheimer's disease — results from a multinational trial. *Dement Geriatr Cogn Disord*. 1999;10:237–244.
- Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. *JAMA*. 1998;280:2077–2082.
- Corey-Bloom J, Anand R, Veach J, for the ENA 713 B352 Study Group: A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol*. 1998;1:55–65.
- Davis LL, Weaver M, Zamrini E, et al. Biopsychological markers of distress in informal caregivers. *Biol Res Nurs*. 2004;6:90–99.
- Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1154–1166.
- Doraiswamy PM, Leon J, Cummings JL, et al. Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 2002;57A:M173–M177.
- Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease [published erratum appears in *Neurology*. 2001;57(11):2153]. *Neurology*. 2001;57:613–620.
- Feldman H, Gauthier S, Hecker J, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease. *Neurology*. 2004;53:644–650.
- Feldman H, Gauthier S, Hecker J, et al. Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. *J Am Geriatr Soc*. 2003;51:737–744.
- Fillit H, Knopman D, Cummings J, Appel F. Opportunities for improving managed care for individuals with dementia: Part I—the issues. *Am J Manag Care*. 1999a;5:309–315.
- Fillit H. Care management: improving the quality of managed care for patients with mild to moderate Alzheimer's disease. *Drug Benefit Trends*. 1999b;11:6BH–11BH.
- Fillit H, Knopman D, Cummings J, et al. Opportunities for improving managed care for individuals with dementia: Part 2—a framework for care. *Am J Manag Care*. 1999c;5:317–324.
- Fillit HM. The pharmacoeconomics of Alzheimer's disease. *Am J Manag Care*. 2000a;6:S1139–S1144.
- Fillit H, Cummings J. Practice guidelines for the diagnosis and treatment of Alzheimer's disease in a managed care setting: Part II—Pharmacologic therapy. *Manag Care Interface*. 2000b;13:51–56.
- Fillit H, Hill J, Futterman R. Health care utilization and costs of Alzheimer's disease: The role of co-morbid conditions, disease stage, and pharmacotherapy. *Fam Med*. 2002;34:528–535.
- Fillit H, Hill J. The economic benefits of acetylcholinesterase inhibitors for patients with Alzheimer disease and associated dementias. *Alzheimer Dis Assoc Disord*. 2004;18(suppl 1):S24–S29.
- Finkel SI. Effects of rivastigmine on behavioral and psychological symptoms of dementia in Alzheimer's disease. *Clin Ther*. 2004;26:980–990.
- Geldmacher DS. Donepezil (Aricept) for treatment of Alzheimer's disease and other dementing conditions. *Expert Rev Neurotherapeutics*. 2004;4:5–16.
- Geldmacher DS, Provenzano G, McRae T, et al. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc*. 2003;51:937–944.
- Gutterman EM, Markowitz JS, Lewis B, Fillit HM. Cost of Alzheimer's disease and related dementia in managed-Medicare. *J Am Geriatr Soc*. 1999;47:1065–1071.
- Hauber AB, Gnanasakthy A, Mauskopf JA. Savings in the cost of caring for patients with Alzheimer's disease in Canada: An analysis of treatment with rivastigmine. *Clin Ther*. 2000a;22:439–451.
- Hauber AB, Gnanasakthy A, Snyder EH, et al. Potential savings in the cost of caring for Alzheimer's disease. Treatment with rivastigmine. *Pharmacoeconomics*. 2000b;17:351–360.
- Hepburn KW, Tornatore J, Center B, Ostwald SW. Dementia family caregiver training: Affecting beliefs about caregiving and caregiver outcomes. *J Am Geriatr Soc*. 2001;49:450–457.
- Hill JW, Futterman R, Duttgupta S, et al. Alzheimer's disease and related dementias increase costs of comorbidities in managed Medicare. *Neurology*. 2002;58:62–70.
- Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology*. 2004;63:214–219.
- Jones RW, Soininen H, Hager K, et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *Int J Geriatr Psychiatry*. 2004;19:58–67.
- Karaman Y, Erdogan F, Koseoglu E, et al. A 12-month study of the efficacy of rivastigmine in patients with advanced moderate Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2005;19:51–56.
- Kaufert DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: The Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc*. 1998;46:210–215.
- Lancot KL, Herrmann N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: A meta-analysis. *CMAJ*. 2003;169:557–564.
- LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340–2346.
- Lopez OL, Becker JT, Wisniewski S, et al. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2002;72:310–314.
- Lyseng-Williamson KA, Plosker GL. Galantamine. A pharmacoeconomic review of its use in Alzheimer's disease. *Pharmacoeconomics*. 2002;20:919–942.
- Marin D, Amaya K, Casciano R, et al. Impact of rivastigmine on costs and on time spent in caregiving for families

- of patients with Alzheimer's disease. *Int Psychogeriatr*. 2003;15:385-398.
- Migliaccio-Walle K, Getsios D, Caro JJ, et al. Economic evaluation of galantamine in the treatment of mild to moderate Alzheimer's disease in the United States. *Clin Ther*. 2003;25:1806-1825.
- Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients [published erratum appears in *Neurology*. 2001;57:1942]. *Neurology*. 2001;57:481-488.
- Monsch A, Giannakopoulos P, on behalf of the GAL-SUI-1 Study Group. Effects of galantamine on behavioural and psychological disturbances and caregiver burden in patients with Alzheimer's disease. *Curr Med Res Opin*. 2004;20:931-938.
- Murman DL, Chen Q, Powell MC, et al. The incremental direct costs associated with behavioral symptoms in AD. *Neurology*. 2002;59:1721-1729.
- Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. *Neurology*. 2000;54:2261-2268.
- Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341.
- Rice DP, Fillit HM, Max W, et al. Prevalence, costs, and treatment of Alzheimer's disease and related dementia: A managed care perspective. *Am J Manag Care*. 2001;7:809-818.
- Ritchie CW, Ames D, Clayton T, Lai R: Metaanalysis of randomized trials of the efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer disease. *Am J Geriatr Psychiatry*. 2004;12:358-369.
- Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998;50:136-145.
- Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomised controlled trial [published erratum appears in *BMJ*. 2001;322:1456]. *BMJ*. 1999;318:633-638.
- Sano M, Wilcock GK, Van Baelen B, Kavanagh S. The effects of galantamine treatment on caregiver time in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2003;18:942-950.
- Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: Prevalence, correlates, and causes. *Gerontologist*. 1995;35:771-791.
- Schulz R, Belle SH, Czaja SJ, et al. Long-term care placement of dementia patients and caregiver health and well-being. *JAMA*. 2004;292:961-967.
- Small GW, Donohue JA, Brooks RL. An economic evaluation of donepezil in the treatment of Alzheimer's disease. *Clin Ther*. 1998;20:838-850.
- Small GW, McDonnell DD, Brooks RL, Papadopoulos G. The impact of symptom severity on the cost of Alzheimer's disease. *J Am Geriatr Soc*. 2002;50:321-327.
- Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology*. 2000;54:2269-2276.
- Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: A randomized controlled trial. *JAMA*. 2004;291:317-324.
- Torian L, Davidson E, Fulop G, et al. The effect of dementia on acute care in a geriatric medical unit. *Int Psychogeriatr*. 1992;4:231-239.
- Wilcock GK, Lilienfeld S, Gaens E, on behalf of the Galantamine International-1 Study Group: Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: Multicentre randomised controlled trial [published erratum appears in *BMJ*. 2001;322:405]. *BMJ*. 2000;321:1445-1449.
- Wilcock G, Howe I, Coles H, et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs Aging*. 2003;20:777-789.
- Wilkinson DG, Passmore AP, Bullock R, et al. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *Int J Clin Pract*. 2002;56:441-446.
- Wilkinson D, Stave C, Keohane D, Vincenzino O. The role of general practitioners in the diagnosis and treatment of Alzheimer's disease: A multinational survey. *J Int Med Res*. 2004;32:149-159.
- Wimo A, Winblad B, Engedal K, et al. 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*. 2003a;15:44-54.
- Wimo A, Winblad B, Stoffler A, et al. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics*. 2003b;21:327-340.
- Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001;57:489-495.