Burden of Alzheimer's Disease and Association With Negative Health Outcomes

Daniel C. Malone, RPh, PhD; Trent P. McLaughlin, PhD; Peter M. Wahl, BA; Christopher Leibman, PharmD; H. Michael Arrighi, PhD; Mark J. Cziraky, PharmD; and Lisa M. Mucha, PhD

Objective: To examine the association of Alzheimer's disease (AD) with common chronic conditions, acute care events, and risk of hospitalization.

Study Design: Retrospective matched cohort analysis.

Methods: Community-dwelling subjects with a diagnosis of and/or medication for AD were matched to subjects without AD based on age, sex, and geographic region. Administrative claims from commercially insured health plans for medical and pharmacy services provided from January 1, 2000, to March 31, 2006 (inclusive) were analyzed. The Deyo Charlson Index (DCI) was used to assess the number of chronic conditions. The outcomes of interest were risk of fractures and hospitalization.

Results: Among 5396 persons with AD and a matched cohort of 5396 persons without the condition, subjects with AD were more likely to have a diagnosis for any of the DCI components, had a higher rate of fractures (17.7% vs 7.9%, P <.00) and other urgent medical events (eg, pneumonia 14.0% vs 6.3%, P <.00), and were more likely to be hospitalized (odds ratio = 1.7; 95% confidence interval = 1.5, 1.9). There were significant differences in the medication use between the 2 groups, with the use of psychotics/tranquilizers 9-fold higher among persons with AD.

Conclusion: Persons with AD have higher odds of experiencing a fracture, being hospitalized, and requiring other acute care medical services than those without AD. The disease also is associated with a higher prevalence of common chronic conditions.

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With an aging society, the burden of Alzheimer's disease (AD) is becoming a greater concern for society and especially healthcare payers. Alzheimer's disease is typically characterized by progressive memory loss, confusion, and a variety of other cognitive and functional deficits. Although the exact mechanism of AD is not completely understood, recent studies suggest that the presence of beta-amyloid plaques and deposits combined with tangles, twists, or strands of the protein tau may be responsible for neuronal and cognitive loss.[1,2] In 2007, the number of persons in the United States with AD was estimated to be approximately 5 million, with more than 24 million worldwide.[2,3] The overall prevalence of AD among persons over age 65 years is 5.7%, increasing from approximately 3% for persons age 65 to 70 years to more than 30% for persons age 85 years or older.[4,5]

The estimated lifetime cost of persons with AD has been estimated to be $174,000.[2] In 2005, Medicare spent $91 billion for healthcare for persons with AD, with $21 billion associated with long-term care services.[2] The excess cost burden to managed care organizations of persons with AD has been estimated to be more than $4000 per person per year.[6]

To date, the bulk of the literature on the economic burden of AD has focused on 3 aspects: costs associated with long-term care, informal care costs (ie, the costs associated with loved ones providing around-the-clock care to AD patients living at home), and the incremental impact of AD on the cost of treating other chronic conditions.[4,6,7] This body of literature suggests that direct medical costs are primarily focused on the later stages of the disease (long-term care costs) or are associated with more subtle effects such as poor treatment adherence leading to worse outcomes in other illnesses such as diabetes or hypertension. However, AD can be associated with significant events that directly increase medical expenditures. Previous research has shown AD to be a risk factor for falls in the elderly, and hospitalization rates have been shown to increase with increasing AD severity.[8-11]

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The purpose of this analysis was to expand on these reports by providing a more detailed look at resource use in AD patients, focusing on those who still are living in the community and therefore are theoretically at an earlier

For author information and disclosures, see end of text.

Take-Away Points

Alzheimer's disease is a debilitating condition that affects both community and institutionalized elderly persons.

- Persons with newly diagnosed Alzheimer's disease have a higher prevalence of cardiovascular disease, diabetes, and various other conditions than age- and sex-matched controls.
- The risk of bone fracture is significantly higher among persons with Alzheimer's disease.
- Persons living in the community with Alzheimer's disease are hospitalized more frequently than age- and sex-matched controls.

and less severe stage of disease. Specifically, AD patients and age- and sex-matched peers from a number of managed care plans across the United States were compared with respect to rates of comorbid chronic illness, presence of acute events, pharmacologic treatment, and associated direct medical costs in hopes of providing a broader perspective of the economic impact of AD.

METHODS

This study used a historical cohort design to examine comorbid conditions and costs among persons with AD and persons without the condition. Administrative claims from commercially insured health plans for medical and pharmacy services provided from January 1, 2000, to March 31, 2006 (inclusive) were analyzed. HealthCore, as a subsidiary of WellPoint Inc, maintains the integrated research database used for the analysis. The data consisted of a deidentified, limited-use data set and were compliant with applicable state and federal laws, including the Health Insurance Portability and Accountability Act, and regulations concerning privacy and security of patient identifiable health information.

Study Population

During the study period, approximately 20.4 million lives were included in the data set, with 2% coming from the mid-Atlantic, 26% from the southeastern, 8% from the central, and 64% from the western United States; 8% were over age 65 years; and approximately 8% of the total population were individuals participating in Medicare Advantage programs.

Two cohorts were identified: persons with AD and persons without AD. Persons with AD were required to have at least 1 medical claim with a diagnosis indicating AD—based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 331.0x—and/or a pharmacy claim for a cholinesterase inhibitor or memantine. (For a list of the specific agents, see **eAppendix A** at **www.ajmc.com**.) Subjects with a diagnosis of alcohol- or drug-induced dementia were excluded, as were subjects with fewer than 24 months of continuous data centered on the first diagnosis or medication claim (index date). The comparison cohort was matched to the AD cohort based on age (± 1 year), sex, and geographic region. Non-AD subjects were assigned an index date that corresponded to that of the matched person with AD. Subjects younger than age 50 years on the index date were excluded from the study. Subjects with AD and no matched non-AD subject were excluded (n = 3027), as were AD patients with prescription claims for acetylcholinesterase inhibitors and/or memantine before their index date (n = 1143).

Comorbid Conditions of Interest

Comorbid conditions were identified based on diagnoses associated with medical encounters. For this study we used the Deyo modification of the Charlson index (DCI).[12] Because dementia is one of the conditions contained in the DCI, we excluded diagnosis codes for dementia from the DCI calculation. We also examined the prevalence of other conditions believed to be commonly associated with AD and/or common medical conditions using *ICD-9-CM* codes (see **eAppendix B** at **www.ajmc.com**).

Acute Events of Interest

Using *ICD-9-CM* codes we evaluated the frequency of infections, injuries, and other acute events occurring during the study period. Fractures were of particular interest because persons with AD are known to be at higher risk of falls. We examined the types of fractures experienced by subjects in both the AD and non-AD groups.

Psychotropic Medication Use

We examined the use of medications that are broadly classified into the therapeutic class of psychotropic medications. For this study psychotropic medications included antiepilepsy therapies, antidepressants, antipsychotics/tranquilizers, anxiolytics/sedatives, hypnotic agents/sleep aids, and narcotic analgesics. These medications were identified via National Drug Code numbers on the pharmacy claims.

Analysis

We compared the summed DCI score for both the 12 months before and the 12 months after the index date. A nonparametric Savage scores test was used to compare DCI comorbidity scores. The prevalence of each of the specific DCI conditions also was evaluated. The McNemar χ^2 test for matched pairs was performed to compare the test and control groups for the presence of individual DCI components and other conditions/comorbidities. Where expected cell counts

Table 1. Characteristics of Study Cohorts[a]

Characteristic	Alzheimer's Disease Cohort (n = 5396)	Non-Alzheimer's Disease Cohort (n = 5396)
Male	2066 (38.3)	2066 (38.3)
Age, y		
Mean (SD)	76.9 (10.2)	76.9 (10.2)
Median (range)	78.7 (50.5-104.4)	78.7 (50.5-104.6)
Age category, y		
50-64	850 (15.8)	850 (15.8)
65-79	2151 (39.9)	2152 (39.9)
≥80	2395 (44.4)	2394 (44.4)
Index claim		
Diagnosis	2142 (39.7)	0 (0.0)
AD medication	3141 (58.2)	0 (0.0)
Both	113 (2.1)	0 (0.0)
AD claims during study period		
0	0 (0.0)	5396 (100.0)
1	1154 (21.4)	0 (0.0)
≥2	4242 (78.6)	0 (0.0)

AD indicates Alzheimer's disease.
[a]Values are number (percentage) unless indicated otherwise.

were <5, Fisher exact *P* values were obtained in the corresponding comparisons. In addition, the presence of conditions considered by the investigators to be clinically relevant to AD was compared between the 2 groups. Because it was hypothesized that fracture diagnoses would be common among the AD cohort, the types of fractures that occurred during the course of the study period were more closely examined to determine whether the incidence differed between skeletal sites. We modeled the risk of any fracture using logistic regression, controlling for comorbid conditions, age, sex, and use of narcotics, antidepressants, anxiolytics/sedatives, antipsychotics, and hypnotics. The prevalence of psychotropic medication use was compared between the groups using the McNemar χ^2 test. Finally, we also evaluated the risk of hospitalization controlling for age, sex, and comorbid conditions.

RESULTS

A total of 5396 subjects with AD met all inclusion criteria. A cohort of 5396 matched non-AD subjects also were included in the study. Table 1 displays the demographic characteristics of the 2 cohorts. Overall, 38.3% were male and the mean (SD) age was 76.9 (10.2) years; median age for the sample was 78.7 years. For persons in the AD cohort, more than half (n = 3141, 58.2%) were identified as having AD based on medication use, with few subjects (n = 113, 2.1%) having both an AD diagnosis and a prescription claim for an AD medication on the same date. Also, most AD patients (n = 4242, 78.6%) had 2 or more AD claims during the study period.

As shown in Table 2, the mean (SD) DCI score was 2.1 (2.2) for the AD cohort versus 1.2 (1.8) for the non-AD cohort (*P* <.0001). The prevalence of 12 of the 14 conditions that comprise the DCI was significantly higher in the AD cohort than in the non-AD cohort (*P* <.003). Table 2 also lists other chronic comorbidities occurring in the AD and non-AD cohorts. All of these comorbidities (anxiety, cardiac arrhythmias, cardiomyopathy, depression, dyslipidemia, epilepsy, hypertension, osteoporosis, other nonorganic psychoses, Parkinson's disease) were more frequently identified among those persons in the AD cohort (*P* <.0001). The percentage of patients with at least 1 claim for Parkinson disease was 10-fold higher in the AD cohort than in the non-AD cohort. Epilepsy was 6 times more prevalent, depression was 5 times more prevalent, and anxiety was 3 times more prevalent in the AD cohort than in the non-AD cohort.

Persons with AD were significantly more likely to have diagnoses associated with adverse health outcomes (anemia, respiratory infections, burns, complications of surgical or medical care, complications of diabetes, fractures, malnutrition, open wounds, pneumonia, poisonings, sprains and strains, superficial injuries, and venous thrombosis) compared with persons without AD (*P* <.001) (data not shown). There were no significant

Table 2. Distribution of Chronic Conditions by Study Group[a]

Condition	Alzheimer's Disease Cohort (n = 5396)	Non-Alzheimer's Disease Cohort (n = 5396)	*P*
DCI, mean (SD)			
12-mo period before index date	1.4 (1.7)	0.7 (1.3)	<.0001
12-mo period after index date	1.6 (1.8)	0.9 (1.6)	<.0001
Entire study period	2.1 (2.2)	1.2 (1.8)	<.0001
Specific DCI conditions (24-mo period)			
Myocardial infarction	383 (7.1)	216 (4.0)	<.0001
Congestive heart failure	960 (17.8)	512 (9.5)	<.0001
Peripheral vascular disease	630 (11.7)	348 (6.5)	<.0001
Cerebrovascular disease	2072 (38.4)	672 (12.5)	<.0001
Chronic pulmonary disease	1288 (23.9)	851 (15.8)	<.0001
Rheumatologic disease	226 (4.2)	167 (3.1)	.0029
Peptic ulcer disease	174 (3.2)	109 (2.0)	<.0001
Mild liver disease	42 (0.8)	10 (0.2)	<.0001
Diabetes	1092 (20.2)	746 (13.8)	<.0001
Hemiplegia or paraplegia	98 (1.8)	27 (0.5)	<.0001
Moderate or severe renal disease	253 (4.7)	159 (3.0)	<.0001
Malignancy	873 (16.2)	686 (12.7)	<.0001
Moderate or severe liver disease	15 (0.3)	6 (0.1)	.0784
Metastatic solid tumor	98 (1.8)	92 (1.7)	.7125
Other conditions (24-mo period)			
Anxiety	551 (10.2)	177 (3.3)	<.0001
Cardiac dysrhythmias	1592 (29.5)	934 (17.3)	<.0001
Cardiomyopathy	267 (5.0)	153 (2.8)	<.0001
Depression	1120 (20.8)	251 (4.7)	<.0001
Dyslipidemia	2171 (40.2)	1870 (34.7)	<.0001
Epilepsy	158 (2.9)	20 (0.4)	<.0001
Hypertension	3336 (61.8)	2552 (47.3)	<.0001
Osteoporosis	1317 (24.4)	943 (17.5)	<.0001
Other nonorganic psychoses	549 (10.2)	33 (0.6)	<.0001
Parkinson's disease	460 (8.5)	43 (0.8)	<.0001

DCI indicates Deyo Charlson Index.
[a]Values are number (percentage) unless indicated otherwise.

differences with respect to diagnoses associated with dislocations or diabetes with ophthalmic manifestations.

Subjects with AD were significantly more likely to have a diagnosis for a fracture than subjects without AD. Specifically, 955 (17.7%) subjects in the AD group had at least 1 fracture, compared with 428 (7.9%) in the non-AD cohort (P <.001). The most common fracture type in both groups was fracture of the neck of the femur (5.3% of the AD cohort and 1.4% of the non-AD cohort, P <.01). Vertebral fractures also were relatively common (3.3% of AD cohort vs 1.2% of non-AD cohort, P <.01), as were a number of other fracture types in the AD cohort (Table 3).

A logistic regression analysis was conducted to evaluate predictors of a fracture (Table 4). The adjusted odds ratio for the presence of a fracture was 1.9 (95% confidence interval = 1.6, 2.1) for persons with AD compared with persons without the condition, after controlling for comorbid conditions and patient characteristics. Other signification characteristics that were associated with higher odds ratios for a fracture included being female; older age; diagnosis of osteoporosis, congestive

Table 3. Distribution of Most Common Fractures by Study Group[a]

ICD-9-CM Code	Description	No. (%) Alzheimer's Disease Cohort (n = 5396)	No. (%) Non-Alzheimer's Disease Cohort (n = 5396)
800-829	Any fracture—unique patient count	955 (17.7)	428 (7.9)
Specific fracture types[b]			
820	Fracture of neck of femur	284 (5.3)	76 (1.4)
805	Fracture of vertebral column without mention of spinal cord injury	179 (3.3)	64 (1.2)
807	Fracture of rib(s), sternum, larynx, and trachea	107 (2.0)	46 (0.9)
812	Fracture of humerus	98 (1.8)	40 (0.7)
813	Fracture of radius and ulna	92 (1.7)	54 (1.0)
821	Fracture of other and unspecified parts of femur	86 (1.6)	25 (0.5)
808	Fracture of pelvis	78 (1.4)	25 (0.5)
825	Fracture of 1 or more tarsal and metatarsal bones[c]	65 (1.2)	43 (0.8)
824	Fracture of ankle	57 (1.1)	22 (0.4)
814	Fracture of carpal bone(s)[d]	41 (0.8)	21 (0.4)
823	Fracture of tibia and fibula	41 (0.8)	15 (0.3)

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification.*
[a]All comparisons were statistically significant at $P < .01$ except as noted.
[b]Percentage of total cohort (n = 5396); percentages may sum to more than 100% because some patients had multiple fracture types.
[c]$P = .03$.
[d]$P = .01$.

Table 4. Multivariate Logistic Regression for Presence of Any Fracture Claim

Characteristic or Condition	Referent	Odds Ratio	95% Confidence Interval	*P*
AD cohort	Control group	1.856	1.615, 2.133	<.0001
Age	—	1.041	1.033, 1.048	<.0001
Male	Female	0.633	0.548, 0.733	<.0001
Osteoporosis	No disease	2.957	2.595, 3.369	<.0001
DCI component				
Myocardial infarction	No disease	1.099	0.868, 1.392	.4334
Congestive heart failure	No disease	1.290	1.095, 1.519	.0023
Peripheral vascular disease	No disease	1.138	0.945, 1.371	.1734
Cerebrovascular disease	No disease	1.276	1.112, 1.463	.0005
Chronic pulmonary disease	No disease	1.316	1.143, 1.516	.0001
Rheumatologic disease	No disease	1.202	0.923, 1.565	.1722
Peptic ulcer disease	No disease	1.043	0.752, 1.446	.8020
Mild liver disease	No disease	2.434	1.247, 4.752	.0091
Diabetes	No disease	1.090	0.932, 1.276	.2795
Hemiplegia or paraplegia	No disease	1.081	0.676, 1.728	.7446
Moderate/severe renal disease	No disease	1.299	0.992, 1.700	.0571
Malignancy	No disease	0.989	0.832, 1.176	.9007
Moderate/severe liver disease	No disease	3.244	1.127, 9.336	.0291
Metastatic solid tumor	No disease	1.321	0.890, 1.962	.1675
Narcotic analgesic use	No use	2.699	2.368, 3.077	<.0001
Antidepressant use	No use	1.195	1.038, 1.375	.0130
Anxiolytic/sedative use	No use	0.948	0.818, 1.098	.4724
Antipsychotic use	No use	1.164	0.979, 1.384	.0846
Hypnotic use	No use	1.144	0.970, 1.348	.1092

AD indicates Alzheimer's disease; DCI, Deyo Charlson Index.

Table 5. Factors Associated With Being Hospitalized During the Study Period

Characteristic or Condition	Referent	Odds Ratio	95% Confidence Interval	*P*
AD cohort	Control group	1.678	1.511, 1.864	<.0001
Age	Unit increase	1.020	1.015, 1.025	<.0001
Male	Female	0.860	0.777, 0.952	.0037
DCI component				
Myocardial infarction	No disease	3.043	2.496, 3.710	<.0001
Congestive heart failure	No disease	3.257	2.851, 3.720	<.0001
Peripheral vascular disease	No disease	1.509	1.293, 1.761	<.0001
Cerebrovascular disease	No disease	1.909	1.714, 2.125	<.0001
Chronic pulmonary disease	No disease	1.805	1.612, 2.022	<.0001
Rheumatologic disease	No disease	1.459	1.157, 1.841	.0014
Peptic ulcer disease	No disease	2.952	2.255, 3.863	<.0001
Mild liver disease	No disease	1.217	0.620, 2.386	.5685
Diabetes	No disease	1.566	1.388, 1.767	<.0001
Hemiplegia or paraplegia	No disease	5.606	3.463, 9.077	<.0001
Moderate/severe renal disease	No disease	1.849	1.457, 2.346	<.0001
Malignancy	No disease	1.592	1.394, 1.817	<.0001
Moderate/severe liver disease	No disease	5.106	1.686, 15.463	.0039
Metastatic solid tumor	No disease	2.442	1.753, 3.403	<.0001
AIDS	No disease	5.38	0.989, 29.253	.0514

AD indicates Alzheimer's disease; DCI, Deyo Charlson Index.

heart failure, cerebrovascular disease, or liver disease; and use of narcotic or antidepressant medications.

Of the 5396 subjects in the AD cohort, 1338 (24.8%) had at least 1 acute care inpatient stay. Among the non-AD group, 638 (11.8%) subjects had at least 1 hospitalization. We examined factors that were significantly associated with hospitalization (Table 5). All independent predictors, except for presence of mild liver disease and AIDS, were associated with higher odds ratios for being hospitalized. After adjusting for these other conditions, having AD was associated with an odds ratio of 1.68 (95% CI = 1.51, 1.86) for being hospitalized during the study period.

DISCUSSION

The primary findings of this study demonstrate the substantial burden that AD places on those unfortunate enough to be afflicted with the condition. This study found that persons with AD have an increased number of chronic comorbidities, experience more negative health events including falls and infections, receive more psychotropic medications, and are more likely to be hospitalized than an age-, sex-, and geographic region–matched cohort of subjects without AD. Taken separately, these findings are not new. However, this study is the first known analysis of these factors performed simultaneously, in a population with what might be considered relatively early AD (ie, patients who remain in the community), wherein AD is an independent contributor to morbidity.

The results of our study are supported by others who also have found a higher prevalence of chronic conditions in persons with AD. Recently, Joyce et al found a higher prevalence of diabetes, hypertension, acute myocardial infarction, coronary artery disease, cerebrovascular diseases, and peripheral vascular diseases in persons with AD compared with a matched cohort of persons without AD.[13] More specifically, the mean (SD) DCI score among persons with AD was 1.7 (1.9), compared with 1.2 (1.7) for persons without AD. Those findings are similar to ours; in our study the DCI was 2.1 (2.2) and 1.2 (1.8) for persons with and without AD, respectively. Similar results have been found in other studies.[6]

Other research also documented the excess burden of comorbidities in persons with AD. Hill et al found that persons with AD have a higher prevalence of cerebrovascular disease (39% vs 10%), congestive heart failure (30% vs 14%), chronic pulmonary disease (25% vs 20%), diabetes (22% vs 16%), peripheral vascular disease (16% vs 9%), myocardial infarction (13% vs 5%), and renal disease (8% vs 3%) compared with age- and sex-matched controls.[6]

The high rate of fractures and other acute events among persons with AD is striking. Our study found that persons with AD had an increased risk of 86% for a fracture, with most occurrences being hip fractures (ie, neck of femur, pelvis). Previous studies have noted a 3-fold higher risk of falls among persons with AD, though the majority of these studies focused on nursing home populations.[8,9,14-16] Weller and Schatzker reported an increased risk of 78% (95% CI = 1.01, 3.14) for hip fractures for persons with AD.[9] Other studies have reported similar odds ratios for risk of hip factures.[17-20] In a 3-year cohort study of 157 persons with Alzheimer-type dementia, 50% of the subjects fell or became unable to walk.[14] Fifteen percent of the subjects experienced a fracture, most commonly of the hip. These findings parallel the results from our study, which reports a fracture rate of 17.7%. As these events were identified via medical claims (ie, the patients were treated at a physician's office, clinic, or hospital), it is also possible that the rates reported here are an underestimation of the true rate, as some patients may not have sought treatment.

We also found higher rates of contusions, sprains/strains, superficial injury, and open wounds, which may be indicative of falls. Recent research has highlighted that persons with AD have disturbances in cognitive function that affects gait function and movement.[10] Persons with dementia have a shorter step, lower gait speed, greater step-to-step variability, and larger sway than persons without AD.[21,22] More importantly, falls in the elderly have been linked to higher mortality rates.[15]

It has been established that use of certain psychoactive medications increases the risk of falls and hip fractures among the general elderly population.[23-27] Use of benzodiazepines is a known risk factor for falls among the elderly.[23-25] Use of 3 or more psychoactive medications also has been linked to an increased risk of falling.[26]

Our study found that persons with AD were significantly more likely to be hospitalized—even after controlling for patient demographics and other chronic conditions. Hospitalization and long-term care contribute to higher direct medical care costs among persons with AD. Joyce and colleagues found that total healthcare costs for AD patients were 5 times greater than those for a matched cohort.[13] The major cost driver in that analysis was inpatient care costs, accounting for 76% of average annual expenditures. Similar results have been reported by Fillit and colleagues.[28]

This study has several limitations. Administrative claims do not capture disease events and episodes in which treatment is not sought or in which treatment is delivered by a provider not within the health plan. It is possible that differences between AD and non-AD groups are due to factors not considered or available within claims databases. However, a thorough and broad inclusion of relevant demographic and clinical characteristics was done in our multivariate analyses in the attempt to control for differences between groups. Miscoding and misdiagnosis does occur in administrative data sets like the one used in this analysis. In addition, administrative data provide no information on the severity of disease. Finally, these patients are not representative of Medicare beneficiaries because the study sample included only Medicare Advantage enrollees.

CONCLUSIONS

This study documents the high burden of AD and also highlights the risk among AD patients for acute events such as falls, injuries, infections, and poisonings. Persons with AD are at significant risk of hospitalization and fractures, with approximately 1 in 6 having a fracture claim and 1 in 4 being hospitalized for some period of time during the 12-month study period. Although further research will be required to better understand the relationship between AD severity and risk of these high-cost medical events, the high rate of psychotropic medication use in this population suggests a potential target for intervention.

Author Affiliations: From the College of Pharmacy (DCM), University of Arizona, Tucson, AZ; Elan Pharmaceuticals (TPM, CL, HMA), San Francisco, CA; Healthcore, Inc (PMW, MJC), Wilmington, DE; and Wyeth Research (LMM), Collegeville, PA.

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The sponsor contributed the study design and methods. All data for the study were retained by HealthCore, Inc and all analyses were conducted by HealthCore, Inc. The sponsor contributed comments to the manuscript but final editing and wording was left to the discretion of the corresponding author.

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Address correspondence to: Daniel C. Malone, RPh, PhD, College of Pharmacy, University of Arizona, PO Box 210202, Tucson, AZ 85721-0202. E-mail: malone@pharmacy.arizona.edu.

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