RESEARCH

Comparison of Cholinesterase Inhibitor Utilization Patterns and Associated Health Care Costs in Alzheimer's Disease

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ABSTRACT

BACKGROUND: Sustained treatment with a cholinesterase inhibitor (ChEI) is used in the management of the symptoms of Alzheimer's disease (AD). However, the characteristic declines in learning and memory seen in AD may erode the patient's ability to adhere to medication regimens with or without caregiver support.

OBJECTIVES: To examine differences by type of ChEI in (1) monthly prevalence of use, (2) nonpersistence, (3) switching from the index drug to another ChEI, (4) number of days on therapy, (5) medication possession ratio (MPR), and (6) an estimate of the relationship of these characteristics to total annual health care expenditures.

METHODS: Data were from the MarketScan Medicare Supplemental and Coordination of Benefits 2001-2003 database, which comprised 1.47 million Medicare beneficiaries during this 3-year time period. Inclusion criteria were: (1) aged 65 years or older; (2) at least 1 claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 331.0 for AD in any of 15 diagnosis fields on outpatient claims or any of 2 diagnosis fields on inpatient claims at any time during 18 months of observation; (3) at least 1 pharmacy claim for donepezil, galantamine, or rivastigmine preceded by a 6-month period without a ChEI claim; and (4) at least 12 months of follow-up data, for a minimum 18 months continuous enrollment. Multivariate analyses, including logistic regression and exponential conditional mean models, tested for cohort differences in ChEI utilization, controlling for demographics, region of the country, type of insurer, and the Charlson Comorbidity Index (comorbid diagnoses). Using exponential conditional mean models, we also examined the relationship between utilization characteristics and all-cause (i.e., not specific to AD) health care expenditures for a 12-month period, including inpatient and outpatient (physician) care, laboratory and radiology services, emergency room (ER) use, prescription drugs, and long-term care services (e.g., nursing home care, home health visits) paid by Medicare or private insurance, but excluding long-term care services paid by Medicaid. Expenditure was defined as allowed charge (i.e., the total payment received by the service provider including plan and patient paid amounts.)

RESULTS: More than 70% of the patients who received ChEI therapy and who otherwise met the inclusion criteria were excluded from this study due to the absence of at least 1 claim with a diagnosis for AD. Of the 3,177 patients included in the study, the index ChEI was donepezil for 62.8% of the patients (n=1,994); 17.2% received galantamine (n=546) and 20.1% received rivastigmine (n=637). The total number of days of index therapy dispensed was greater for those starting on donepezil (mean [median, SD] days=226 [263, 115]) compared with rivastigmine (206 [233, 120], $P<0.001$), but was not significantly different compared with galantamine (216 [250, 119], $P=0.085$). Monthly prevalence of use was similar for the 3 drugs until month 5 when a smaller proportion of rivastigmine patients had index medication on hand (65.9%) compared with 72.1% of donepezil patients ($P=0.003$) and 72.7% of galantamine patients ($P=0.012$). At 12 months, the likelihood of receiving the index ChEI was higher for donepezil (61.1%) than for either rivastigmine (50.1%, $P<0.001$) or galantamine (56.4%, $P=0.048$) and was higher for galantamine than for rivastigmine ($P=0.030$). The rate of switching for donepezil patients was significantly lower (14.5%) than the switch rate for rivastigmine patients (21.5%, $P<0.001$) and was similar to the switch rate for galantamine patients (15.0%, $P=0.781$ for donepezil vs. galantamine; $P=0.004$ for galantamine vs. rivastigmine). Rates of nonpersistence, measured as having at least 1 gap in therapy of 30 days or more during the 1-year follow-up, were 63.5% for donepezil, 63.7% for galantamine ($P=0.933$ for donepezil vs. galantamine), and 68.0% for rivastigmine ($P=0.042$ for donepezil vs. rivastigmine). MPRs and total days supply of any ChEI did not significantly differ among the 3 drugs. Results of multivariate models showed that, controlling for index ChEI drug, each additional month of ChEI treatment was associated with a reduction of 1% in total all-cause health care costs. The mean (SD) total all-cause 1-year health care costs for patients initiated on the 3 ChEIs were not significantly different: $12,112 ($16,437) for donepezil, $12,137 ($19,154) for galantamine ($P=0.978$), and $12,853 ($14,543) for rivastigmine ($P=0.278$).

CONCLUSIONS: During the first year following initiation of ChEI therapy, patients initiated on donepezil had a greater days supply of the index medication than did patients initiated on rivastigmine. At 12 months following treatment initiation, the proportion of patients in therapy was higher for donepezil than for either rivastigmine or galantamine and was higher for galantamine than for rivastigmine. Patients treated with either donepezil or galantamine were less likely to switch from the index drug to another ChEI than were patients treated with rivastigmine. All-cause 1-year health care costs for patients initiated on the 3 ChEIs were not significantly different.

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What is already known about this subject

- Previous research with 2000-2001 pharmacy claims only, without confirming diagnosis of AD from medical claims, found that 30.4% of newly treated rivastigmine patients and 31.2% of newly treated donepezil patients discontinued treatment or switched to an alternative drug within 60 days of starting therapy ($P=0.72$). After 12 months of follow-up, 19% of the rivastigmine patients and 23% of the donepezil patients had 80% or more days covered by medication ($P=0.34$).
- Separate research with pharmacy claims and confirming diagnosis of AD from at least 1 medical claim in the MarketScan database in 2000-2002 found the same proportion of patients continued their medication with rivastigmine or donepezil (47%, $P=0.50$). The mean (median) duration of continuous use was 234 days (312) for rivastigmine versus 235 days (315) for donepezil ($P=0.91$).

Note: *A commentary on the subject of this article appears on pages 462-64 of this issue.*

What this study adds

- 72% (8,151/11,328) patients who otherwise met the study criteria and initiated therapy with 1 of 3 ChEI drugs did not have at least 1 claim with a diagnosis for AD.
- Donepezil patients showed greater continuity of therapy as measured by days on therapy (mean [median, SD] = 226 [263, 115]) than did rivastigmine patients (206 [233, 120], $P<0.001$). Continuity was not significantly greater with donepezil than with galantamine (216 [250, 119], $P=0.085$).
- Monthly prevalence of use was similar for the 3 drugs until month 5 when a smaller proportion of rivastigmine patients had at least 1 claim for the index drug (65.9%) compared with 72.1% of donepezil patients and 72.7% of galantamine patients. At 12 months, the likelihood of receiving the index ChEI was higher for donepezil (61.1%) than for either rivastigmine (50.1%, $P<0.001$) or galantamine (56.4%, $P=0.048$), and was higher for galantamine than for rivastigmine ($P=0.030$).
- Results of multivariate models showed that, controlling for index ChEI drug, each additional month of ChEI treatment was associated with a reduction of 1% in total all-cause health care costs. Mean (SD) total all-cause 1-year health care costs for patients initiated on the 3 ChEIs were not significantly different: $12,112 ($16,437) for donepezil, $12,137 ($19,154) for galantamine ($P=0.978$), and $12,853 ($14,543) for rivastigmine ($P=0.278$).

Sustained treatment with effective doses of cholinesterase inhibitors (ChEI) can aid in the management of mild-to-moderate Alzheimer's disease (AD).[1] Failure to achieve and sustain adequate dose levels has been linked to poor outcomes in various areas of medicine, and the Academy of Managed Care Pharmacy (AMCP) and National Committee for Quality Assurance (NCQA) have recently recommended that suboptimal dosing be considered in monitoring pharmaceutical care in Medicare Part D beneficiaries.[2-5] The probability of reaching and sustaining an approved dose is affected by the complexity and convenience of dosing,[6,7] how the benefit and side-effects of the medication are managed by clinicians,[6] as well as a number of patient and environmental factors, such as the cognitive abilities of the patient,[8,9] availability of caregiver support, and the affordability of the treatment.[6]

The characteristic declines in learning and memory seen in AD may erode the patient's ability to adhere to medication regimens with or without caregiver support. However, the day-to-day responsibility of following a medication schedule often falls to caregivers. The physician also plays a role in patient adherence, not only by providing a medication with an easy dosing regimen[6] but also by stressing the importance of adherence to *both* the patient and caregiver. In addition, the physician must provide a realistic expectation to the patient and caregiver regarding the efficacy and improvement that pharmacologic therapy can provide to the patient.[10] Adherence can be negatively impacted by unrealistic expectations of pharmacologic therapy providing a "cure" to the patient.

The 2 previously published studies of adherence with ChEIs have found no meaningful differences in medication adherence between rivastigmine and donepezil and have focused on selected measures, primarily the time until the first discontinuation of ChEI.[11,12] Previous research with 2000-2001 pharmacy claims only, without confirming a diagnosis of AD from medical claims, found that 30.4% (171/563) of newly treated rivastigmine patients and 31.2% (583/1,871) of newly treated donepezil patients discontinued treatment or switched to an alternative drug within 60 days of starting therapy ($P=0.72$). After 12 months of follow-up, 19% of the rivastigmine patients and 23% of the donepezil patients had 80% or more days covered by medication ($P=0.34$).[12]

Separate research with pharmacy claims and confirming diagnosis of AD from at least 1 medical claim in the MarketScan database in 2000-2002 found that the same proportion of patients continued their medication with rivastigmine or donepezil (47%, $P=0.50$). The mean (median) duration of continuous use was 234 (312) days for rivastigmine versus 235 (315) days for donepezil ($P=0.91$).[11] Although time until first discontinuation is an important adherence measure, other measures that extend beyond the first discontinuation event are helpful to more completely understand ChEI use in AD. In addition, both of these prior studies allowed gaps of up to 60 days to refill a 30-day prescription before considering it discontinued,[11,12] raising the question of whether a shorter, 30-day gap would yield a measure more sensitive to any differences across medications. For example, a patient who is 50% compliant with a 30-day supply of medication will take 60 days to exhaust the medication and have no more than an apparent gap of 30 days in therapy between the fill date and the refill date 60 days later.

The U.S. Food and Drug Administration (FDA) approved donepezil for use in mild-to-moderate dementia of the Alzheimer's type on November 25, 1996; rivastigmine on April 21, 2000; and galantamine on February 28, 2001. The purpose of this study was to compare these ChEIs on established measures of medication adherence in a large national Medicare population. The principal research questions were: (1) Are there differences in measures of medication adherence with these 3 AD drugs and (2) is greater adherence to treatment associated with total Medicare expenditures? Additionally, because of the recent interest in suboptimal dosing in Medicare patients, we also examined the percentage of patients reaching an FDA-approved dose, defined as the recommended dosage as indicated on the package label. Descriptive and multivariate analyses of a retrospective Medicare claims database were used to address the study questions in a cohort of AD patients aged 65 years or older.

Methods

This study was a retrospective administrative claims data analysis of patients newly prescribed a ChEI for AD using medical and pharmacy claims data from the Thomson Medstat MarketScan Medicare database for 1.47 million Medicare beneficiaries for services provided for the time period of January 1, 2001, through December 31, 2003. The MarketScan Medicare database contains the health care experience of individuals with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as coordination of benefits amount or COB) and the employer-paid portion are included in this database. The Medicare Supplemental and COB Database provides detailed cost and utilization data from acute health care treatment in inpatient and outpatient settings. This database includes claims for inpatient and outpatient (physician) care, laboratory and radiology services, emergency room (ER) use, prescription drug fills, and long-term care services (e.g., nursing home care, home health visits) paid by Medicare or private insurance. The database excludes claims for long-term care services paid by Medicaid after exhaustion of Medicare and private insurance benefits.

All patients aged 65 years or older with (1) at least 18 months continuous enrollment in the Medicare database; (2) at least 1 medical or hospital (facility) claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for AD (331.0) in any of 15 diagnosis fields on outpatient claims or any of 2 diagnosis fields on inpatient claims; and (3) at least 1 pharmacy claim for a ChEI between July 1, 2001, and December 31, 2002, were included in the study. The first instance of a pharmacy claim for a ChEI determined the patient's index date. Patients were followed for 12 months after their index date period (follow-up period) and were required to have 6 months without a ChEI pharmacy claim prior to the index date (baseline period). Because of the possibility of undercoding for AD among the claims, the diagnosis code that was required for inclusion in the study could have occurred during either the baseline or follow-up period.

Patients were classified into treatment groups based on the ChEI that was prescribed on the index date: (1) donepezil hydrochloride, (2) galantamine hydrobromide, or (3) rivastigmine tartrate. Patients starting on more than 1 ChEI on the index date (n=6) were excluded from the study.

Measures

Five adherence measures were used to assess different problems with medication adherence. These included (1) monthly prevalence of use, (2) nonpersistence, (3) switching, (4) number of days on therapy, and (5) medication possession ratio (MPR).

Monthly prevalence of use was defined as whether the patient had the index drug on hand for at least 1 day during the nth month (e.g., 2, 3, … 12) subsequent to that patient's index prescription. Whether the patient had the drug on hand was measured by calculating the date span covered by each prescription claim (from fill date to depletion date, measured as fill date plus days supply), then assessing which months were included in that date span. This methodology calculated each month discretely so those patients who discontinued and then restarted therapy with the index ChEI during a later month were accounted for during that later month.

Nonpersistence was defined as a gap of 30 days or more in therapy at any time during the 12-month follow-up period. A 30-day gap was used because it has the potential to be a more sensitive measure of discontinuation than the 60 days that was used in prior research. To identify nonpersistence, the days supply for each claim was added to the date of the claim to obtain the last date of drug on hand. If there was no ChEI claim within 30 days following the last date of drug on hand, the patient was considered to be nonpersistent.

Switching. A medication switch was defined as the presence of a different ChEI medication other than the index drug at any point during the follow-up period; the definition did not distinguish between augmentation and switching.

Number of days on therapy and MPR. Replicating prior published studies, we calculated the MPR for patients with at least 1 refill (at least 2 pharmacy claims for the same drug) for the index drug, defined as the number of days of index drug supplied divided by 365 days. The numerator, total days on therapy, was the sum of the values in the days supply field of all pharmacy claims for the entire study period for the index agent.

Two measures of prescription drug fill patterns relative to FDA-approved dose were used. The first was the percentage of each treatment group that reached an FDA-approved dose (according to each product label) within the follow-up period. These doses, per FDA-approved labels, are as follows:

- **Donepezil:** 5 mg per day is the approved effective dose; 5 mg is the starting dose, 1 week titration period.[13] Donepezil is available as 5 mg and 10 mg tablets and as 1 mg per mL solution.
- **Galantamine:** 16 mg-24 mg per day is the approved effective dose; 4 mg twice daily (8 mg per day) is the starting dose, with a minimum 4-week titration period after each dosage change, up to 8 mg twice daily.[14] Galantamine is available as 4 mg, 8 mg, and 12 mg tablets; 8 mg, 16 mg, and 24 mg capsules; and 4 mg per mL solution. Galantamine is administered twice daily, preferably with morning and evening meals.
- **Rivastigmine:** 6 mg-12 mg per day is the approved effective dose, given twice daily in doses of 3 mg to 6 mg. The starting dose is 1.5 mg twice daily with a minimum 2-week titration period after each dosage change, up to 3 mg twice daily. Subsequent increases to 4.5 mg and 6 mg twice daily are recommended in product labeling at a minimum of 2 weeks between dose increases.[15] Rivastigmine is available as 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules; 2 mg per mL solution; and 4.6 mg and 9.5 mg per 24-hour transdermal patch.

The second dosing pattern measure was the number of days between the index date and the date the patient first filled a prescription for an FDA-approved dose. The calculation of the mean time to FDA-approved dose included only those patients who reached an FDA-approved dose. Finally, direct all-cause (i.e., not specific to AD) medical expenditures were evaluated as continuous variables, overall and specific to several categories: ChEI drug cost, other pharmacy cost (excluding ChEI), nonfacility medical costs, and hospital facility costs. Prescription drug claims were identified as claims submitted in National Council for Prescription Drug Programs (NCPDP) format. Hospital/facility-level claims were identified as facility claims that billed for room-and-board services. The remaining claims were considered nonfacility medical costs.

Expenditures were defined as allowed charges: the total payment, including payer and patient share, received by the provider for services. This amount included any deductible, coinsurance, or coordination of benefits payments. All expenditures were adjusted to 2003 dollars using the changes in the Medical Care component of the Consumer Price Index.

Statistical analyses. Descriptive analyses compared key patient characteristics stratified by treatment group. Summary variables on demographics (age, gender, geographic region, insurance type, and relationship of the patient to the employee) and comorbidities were evaluated. Student's *t*-tests and Pearson chi-square tests were used to determine the significance of differences between each group and the reference group (the donepezil group) for each patient characteristic. Analyses reported in this manuscript were specified a priori.

Two methods of multivariate analysis were employed. Logistic regression analyses were used to predict 2 binary-dependent variables: switching and nonpersistence. Exponential conditional mean models were used to predict total days of ChEI therapy. Additionally, in order to determine whether persistent use of ChEIs is associated with a change in health care expenditures, 4 exponential conditional mean models were estimated. In each model, the dependent variable was total all-cause health care expenditure. Each model included a persistence measure and covariates for age, gender, region of the country, managed care plan type, the Charlson comorbidity score, and the index ChEI drug. To determine how total expenditures were associated with different persistence measures, each of the 4 models had a different persistence measure: (1) months persistent on index ChEI, (2) months on the index ChEI without any switches, (3) persistent on the index ChEI for 9 or more months, and (4) the number of days until the first 30-day treatment gap of index ChEI. In the exponential conditional mean models, coefficients, standard errors, and 95% confidence intervals were obtained through a ridge-stabilized Newton-Raphson algorithm to maximize the log-likelihood function with respect to the regression parameters implemented in the SAS GENMOD procedure (SAS Institute, Inc., Cary, NC).

Results

The overall sample consisted of 3,177 patients. After stratification by ChEI, the sample sizes were: 1,944 (62.8%) donepezil; 546 (17.2%) galantamine; and 637 (20.1%) rivastigmine. Figure 1 depicts the construction of the final samples. The demographic characteristics of the samples were similar with few statistically significant differences (Table 1).

Compared with donepezil-treated patients, rivastigmine-treated patients were, on average, a few months younger; less likely to reside in the northeastern United States; and more likely to reside in the South. Gender, insurance plan type, and relation to employee were not significantly related to type of ChEI prescribed.

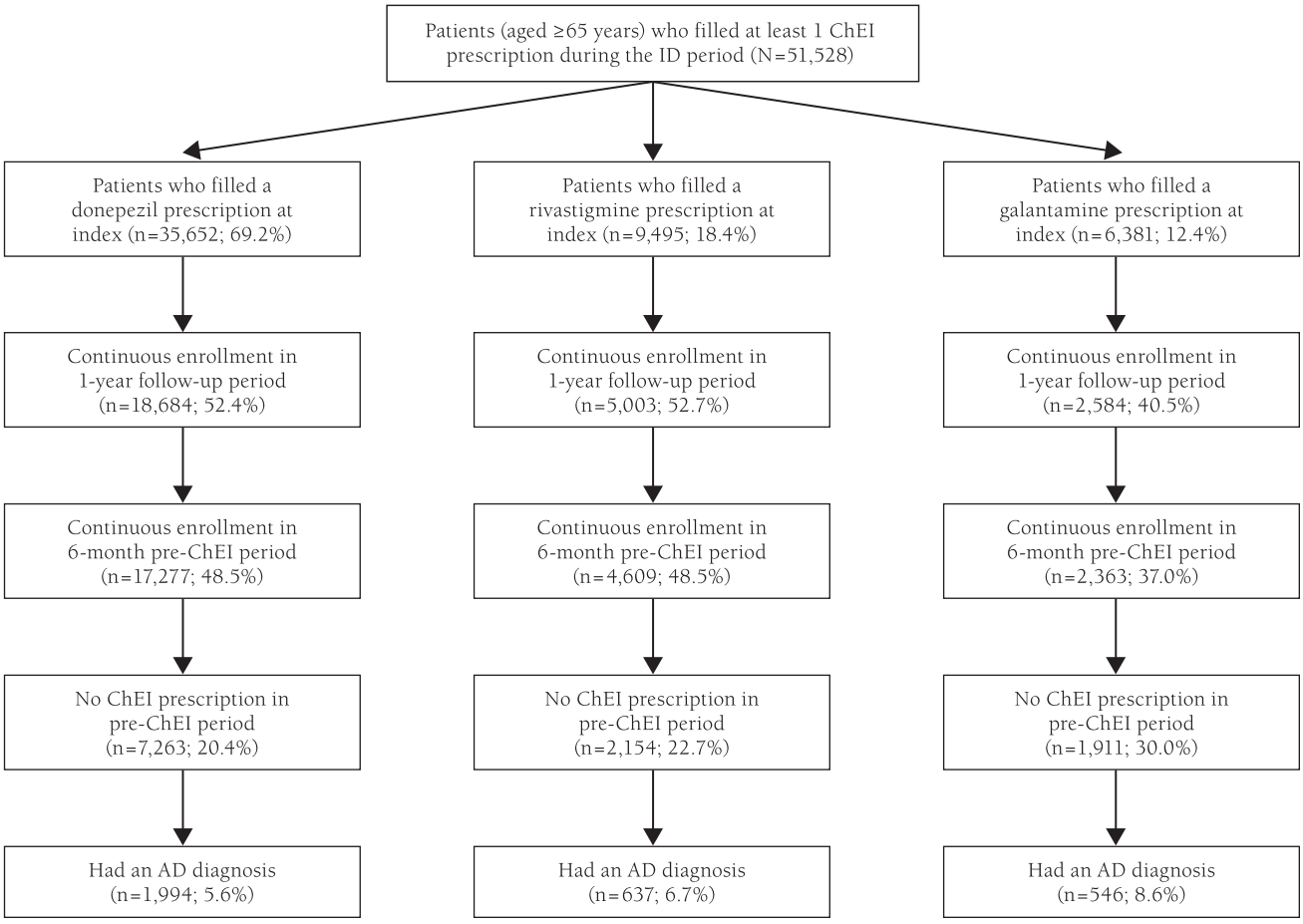
Charlson comorbidity scores showed no significant differences between the study groups in either the baseline or follow-up periods. Rates of comorbid diagnoses making up the Charlson score were also compared across treatment groups with few statistically significant differences (data not shown). Overall, treatment groups were very similar on patient demographic and clinical characteristics.

Adherence

Significant differences were found in some of the duration of therapy measures (Table 2). Mean MPRs did not significantly differ among the 3 study drugs. Donepezil patients showed a significantly lower rate of nonpersistence in the 12-month follow-up period than did rivastigmine patients (63.5% and 68.0%, respectively; $P=0.042$). Nonpersistence rates for donepezil and galantamine (63.7%) were comparable ($P=0.933$), as were nonpersistence rates for galantamine and rivastigmine ($P=0.125$). Donepezil patients showed a significantly lower rate of switching than did rivastigmine patients (14.5% and 21.5%, respectively, $P<0.001$) and a rate similar to that of galantamine patients (15.0%, $P=0.781$ for donepezil vs. galantamine; $P=0.004$ for galantamine vs. rivastigmine). Number of days on index therapy, measured as total days supply of the index medication, was greater for those starting on donepezil (mean [median, SD] days=226 [263, 115]) than for those whose index drug was rivastigmine (206 [233, 120], $P<0.001$), but was not significantly different compared with galantamine (216 [250, 119], $P=0.085$). Total days supply of any ChEI medication (i.e., count of all ChEI therapy days irrespective of drug) did not significantly differ by index medication in any comparison.

Monthly prevalence of use over the 12-month follow-up period was graphed for each treatment group and is presented in Figure 2. For the first few months after initiation of therapy, prevalence of use among the 3 ChEIs was similar. However, at month 5, prevalence of use for rivastigmine (65.9%) became significantly lower than for donepezil (72.1%, $P=0.003$) and galantamine (72.7%, $P=0.012$). At month 7, prevalence of use for galantamine (63.7%) also became significantly lower than for donepezil (68.9%, $P=0.023$). From months 7 through 12,

FIGURE 1 Patient Selection (from MarketScan Medicare Claims Database of 1.47 Million Members, 2001-2003)



AD=Alzheimer's disease; ChEI=cholinesterase inhibitor; ID period=July 1, 2001, through December 31, 2002; Index=first ChEI claim date during the ID period.

prevalence of use for donepezil was consistently higher than for the other 2 study drugs. The proportion of patients in therapy at the end of the study period (month 12) was higher for donepezil (61.1%) than for either rivastigmine (50.1%, $P<0.001$) or galantamine (56.4%, $P=0.048$) and was higher for galantamine than for rivastigmine ($P=0.030$).

Multivariate regression models further examined treatment group differences while controlling for other factors. Table 3 shows the results of 3 models examining the probability of switching, probability of nonpersistence, and the total days dispensed of the index ChEI. In all 3 models, galantamine and rivastigmine as the index ChEI were independent variables, with donepezil as the reference category.

The results of the logistic model predicting switching showed that younger (compared with older) patients and those starting on rivastigmine (compared with donepezil) were significantly more likely to switch to another ChEI during the 12-month follow-up period. The results of the second logistic model predicting nonpersistence showed that patients who started on rivastigmine were more likely to have a ≥30-day treatment gap than were those initiated on donepezil. No other variables were statistically significant predictors of nonpersistence.

The third model shown in Table 3 is an exponential conditional mean model that estimates total days on the index drug during the 12-month follow-up period. Again, the only significant predictor was initiation of treatment on rivastigmine. Compared

TABLE 1 Characteristics of Population

	Donepezil Patients (N = 1,994)		Galantamine Patients (N = 546)			Rivastigmine Patients (N = 637)		
	Mean	SD	Mean	SD	*P* Value	Mean	SD	*P* Value
Age	79.93	6.24	79.48	6.3	0.133	79.04	6.31	0.002
CCI score: baseline	1.44	1.63	1.44	1.59	0.994	1.47	1.74	0.619
CCI score: follow-up	1.95	1.94	1.88	1.84	0.424	1.94	2.05	0.930
	# Patients	%	# Patients	%	*P* Value	# Patients	%	*P* Value
Gender								
Male	761	38.16%	221	40.48%	0.326	238	37.36%	0.717
Female	1,233	61.84%	325	59.52%	0.326	399	62.64%	0.717
Age group, years								
65-74	392	19.66%	121	22.16%	0.197	162	25.43%	0.003
75-84	1,141	57.22%	312	57.14%	0.974	344	54.00%	0.154
85-94	445	22.32%	105	19.23%	0.121	126	19.78%	0.177
95+	16	0.80%	8	1.47%	0.230	5	0.78%	0.967
Plan type								
Indemnity	1,109	55.62%	312	57.14%	0.525	366	57.46%	0.416
POS	50	2.51%	18	3.30%	0.349	23	3.61%	0.178
PPO	734	36.81%	196	35.90%	0.695	222	34.85%	0.371
Capitated POS	101	5.07%	20	3.66%	0.137	26	4.08%	0.288
Geographic region								
Northeast	373	18.71%	72	13.19%	0.001	74	11.62%	<0.001
North central	694	34.80%	210	38.46%	0.114	231	36.26%	0.502
South	599	30.04%	174	31.87%	0.411	261	40.97%	<0.001
West	325	16.30%	90	16.48%	0.918	71	11.15%	<0.001
Unknown	3	0.15%	0	0.00%	0.083	0	0.00%	0.083
Relation to employee								
Employee	1,588	79.64%	416	76.19%	0.080	487	76.45%	0.086
Spouse	404	20.26%	130	23.81%	0.071	149	23.39%	0.092
Dependent	2	0.10%	0	0.00%	0.157	1	0.16%	0.742

Columns represent the drug that patients received on the index date.
P values for the comparison of the means (Student's t-tests) or percentages (Pearson chi-square tests) of the galantamine and rivastigmine patients with donepezil patients.
CCI = Charlson Comorbidity Index; POS = point of service; PPO = preferred provider organization.

with donepezil-treated patients, those treated with rivastigmine were dispensed significantly fewer days drug supply.

FDA-Approved Dosage

The percentage of patients who reached an FDA-approved dose was significantly higher for donepezil than for the other 2 study drugs (99.1% donepezil, 73.4% galantamine, 78.8% rivastigmine, $P<0.001$, Table 2). This result is largely because the donepezil starting and effective doses are the same (5 mg), while the FDA-approved doses for the other 2 agents are higher than their starting doses, which also means that time is required for titration. Although 5 mg was the starting dose for donepezil, there were a few patients who started below 5 mg, indicating some possible pill splitting of the 5 mg tablets. A higher percentage of rivastigmine patients than galantamine patients reached an FDA-approved dose ($P=0.031$). Among patients who did reach an FDA-approved dose, the mean time to approved dose was significantly shorter for donepezil (mean [SD] days = 1 [13]), than for galantamine (46 [73], $P<0.001$) or rivastigmine (33 [67], $P<0.001$, data not shown).

Expenditures

Mean (SD) total all-cause 1-year health care costs for patients initiated on the 3 ChEIs were not significantly different: $12,112 ($16,437) for donepezil, $12,137 ($19,154) for galantamine ($P=0.978$), and $12,853 ($14,543) for rivastigmine ($P=0.278$, Table 2). Table 4 shows the coefficients and marginal effects associated with 4 measures of adherence. The marginal effects

represent the increase in mean total all-cause health care expenditures associated with each measure. For example, the marginal effect of each month persistent on the index ChEI shows a decrease of $125.64 (beta=-0.0102 from Table 4 representing 1.02% reduction per month persistent) in expenditures as the number of months on therapy increases without any switching.

In all 4 models, as adherence improved, there was a significant reduction in all-cause health care expenditures, when controlling for other variables. The most sizable decrease was seen in the model that included being persistent on the index ChEI for 9 or more months. Patients who remained on therapy for 9 or more months showed a $617.62 ($P<0.001$) decrease in acute health care expenditures. The adherence level, which measured days not months (number of days to discontinuation), showed that acute health care expenditures decreased by $5.46 for every day the patient remained on therapy.

Discussion

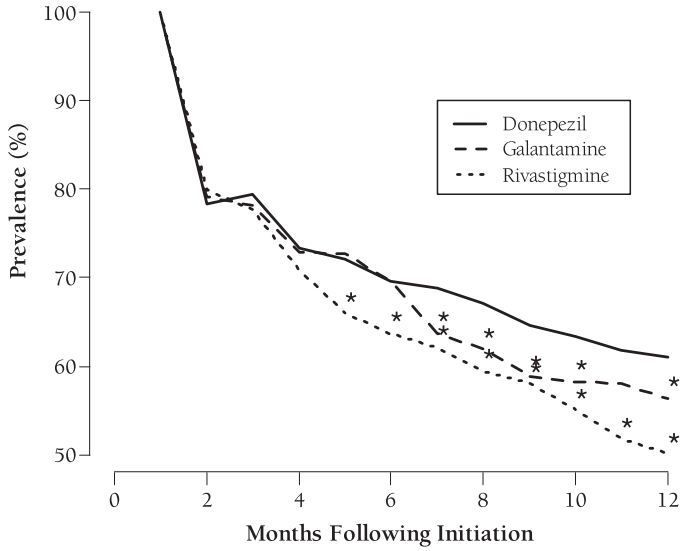
This study found that, during the first year following initiation of ChEI therapy, patients initiated on donepezil had a greater days supply of the index medication than did patients initiated on rivastigmine. Beginning at month 5, following treatment initiation, patients treated with either donepezil or galantamine had a greater prevalence of use than did patients treated with rivastigmine, and beginning at month 7, patients treated with donepezil had greater prevalence of use than did either galantamine-treated or rivastigmine-treated patients. Prevalence of use in month 12 was higher for donepezil than for either galantamine or rivastigmine and higher for galantamine than for rivastigmine.

Patients treated with either donepezil or galantamine were less likely to switch from the index drug to another ChEI than were patients treated initially with rivastigmine. The likelihood of reaching an FDA-approved dose was greater for donepezil than for either galantamine or rivastigmine and was greater for rivastigmine than for galantamine. However, neither MPR for the index drug nor total days supply of ChEI medication (summing all ChEI therapy days irrespective of drug) significantly differed by index medication.

The economic analyses in the present study showed that while it would be assumed that patients who are more persistent would incur more health care expenditures due to greater drug costs, the opposite is true. Patients who were more persistent had lower health care expenditures.

Our results are generally consistent with an earlier study by Mauskopf et al. in finding no difference in adherence between donepezil and rivastigmine in the 60 days following onset of treatment. However, the findings of our analysis of nonpersistence differ from those of Mauskopf et al., who found no meaningful difference between donepezil and rivastigmine patients on that measure. Of patients remaining on therapy for at least 60 days in the Mauskopf et al. study, mean time to discontinuation was 331 days for rivastigmine and 337 days for donepezil. The emergence of adherence differences between ChEI's as early as the fifth month of treatment in the present study may reflect use of a more sensitive definition of treatment discontinuation and differences in the cohorts studied. The present study did not exclude patients with fewer than 60 days of initial ChEI utilization and sampled those with an Alzheimer's diagnosis.[12]

FIGURE 2 Use Prevalence for Index Medication by Month Following Treatment Initiation



*=*Persistence Lower than Donepezil, P<0.05, as determined by a Pearson chi-square test.*

Results of the present study are complementary to those of a similar study using the MarketScan database and an overlapping but older eligibility period by Suh et al.[11] The Suh et al. study did not examine total days of ChEI use and monthly prevalence of use, as did the present study. Like the present study, the Suh et al. study did not find differences in mean days of continuous use between donepezil and rivastigmine. Finally, the results of the present study in a community-dwelling population replicate those seen in a recent publication by Dybicz et al., which showed that those patients living in an institution or nursing home and treated with donepezil reached an effective dose (as defined in FDA-approved product labeling) in less time than did patients treated with the other ChEIs.[16]

The significance of some adherence measures and lack of significance of others indicates the need to include multiple adherence measures in a study. The use of multiple adherence measures is a key feature of this study that makes it distinctive from other ChEI adherence studies. Multiple measures provide a

TABLE 2 Key Outcome Measures by Index Agent During 12-Month Follow-Up Period

	A	B	C			
	Donezepil Patients	Galantamine Patients	Rivastigmine Patients	*P* Value A Versus B[a]	*P* Value A Versus C[a]	*P* Value B Versus C[a]
	(n=1,994)	(n=546)	(n=637)			
Total days supply of index medication—mean [SD] median (range)	225.60 [114.65] 263 (1-365)	215.97 [119.30] 250 (3-365)	206.33 [119.95] 233 (2-365)	0.085	<0.001	0.167
Total days supply of any ChEI medication—mean [SD] median (range)	244.27 [105.61] 280 (1-530)	236.32 [113.77] 270 (4-547)	236.26 [110.53] 275 (2-574)	0.142	0.100	0.993
Reached FDA-approved dose, N (%)	1,976 (99.10%)	401 (73.44%)	502 (78.81%)	<0.001	<0.001	0.031
Switched from index agent to another ChEI, N (%)	290 (14.54%)	82 (15.02%)	137 (21.51%)	0.781	<0.001	0.004
Lack of persistence (≥30-day treatment gap on index ChEI), N (%)	1,267 (63.54%)	348 (63.74%)	473 (67.97%)	0.933	0.042	0.125
Medication possession ratio, index ChEI—mean [SD] median (range)	0.74 [0.26] 1 (0-1)	0.74 [0.26] 1 (0-1)	0.71 [0.27] 1 (0-1)	0.614	0.066	0.071
All-Cause Health Care Costs—Mean [SD] Median (Range)						
ChEI drug cost	1,215 [609] 1,344 (1-6,116)	1,212 [758] 1,296 (17-6,796)	1,272 [942] 1,351 (8-9,225)	0.916	0.152	0.220
Other pharmacy cost (excluding ChEI)	2,687 [3,811] 1,986 (0-71,750)	2,996 [4,054] 2,174 (0-53,528)	2,897 [3,279] 2,179 (0-41,029)	0.097	0.177	0.646
Medical cost	4,683 [9,226] 2,228 (0-281,365)	4,388 [6,854] 2,092 (0-64,757)	4,753 [6,983] 2,409 (0-56,793)	0.411	0.839	0.366
Hospital-facility cost	3,527 [10,831] 0 (0-176,786)	3,541 [16,391] 0 (0-349,749)	3,932 [9,976] 0 (0-90,513)	0.985	0.383	0.628
Total all-cause health care cost	12,112 [16,437] 7,052 (128-298,586)	12,137 [19,154] 7,142 (344-358,735)	12,853 [14,543] 7,716 (210-117,254)	0.978	0.278	0.475
Prevalence of Use (% of Patients Who Possessed an Index Medication on Each Month)						
Month 1	100.00%	100.00%	100.00%			
Month 2	78.28%	79.12%	79.91%	0.674	0.385	0.739
Month 3	79.44%	78.21%	77.71%	0.530	0.351	0.837
Month 4	73.32%	72.89%	70.80%	0.842	0.214	0.426
Month 5	72.12%	72.71%	65.93%	0.748	0.003	0.012
Month 6	69.56%	69.60%	63.74%	0.986	0.006	0.033
Month 7	68.86%	63.74%	62.17%	0.023	0.002	0.578
Month 8	67.15%	61.90%	59.50%	0.022	<0.001	0.399
Month 9	64.64%	58.79%	58.08%	0.012	0.003	0.806
Month 10	63.39%	58.24%	55.10%	0.028	<0.001	0.278
Month 11	61.74%	58.06%	51.81%	0.119	<0.001	0.031
Month 12	61.08%	56.41%	50.08%	0.048	<0.001	0.030

[a] *P values are based on Pearson chi-square tests for differences in proportions and Student's t-tests for differences in means.*
ChEI=cholinesterase inhibitor; FDA=U.S. Food and Drug Administration.

more complete characterization of how AD patients use therapies in a real-world setting than would any single measure.

The adherence differences observed in the present study may have both clinical and economic implications. A double-blind trial showed that stopping donepezil after 12 weeks of treatment (6 weeks at 5 mg per day followed by 6 weeks at 10 mg per day) resulted in declines in behavioral and cognitive aspects of the disease.[17] Adherence to ChEIs may delay nursing home placement, thereby reducing burden to public and private entities that manage patient benefit, consistent with the finding in the present study that time on medication was associated with declining total medical expenditures.[18,19] Although the present study assessed the level and types of adherence, it did not address the reasons for nonadherence or whether differences

TABLE 3 *Regression Model Results for Switching, Discontinuation, and Days on Index Therapy*

	Probability of Switch From Index Drug (Logistic Model 1, n=3,177)			Probability of Nonpersistence With Index Drug (Logistic Model 2, n=3,177)			Total Days on Index Therapy (Exponential Conditional Mean Model, n=3,177)		
Parameters	**Odds Ratio**	***P* Value**	**95% Confidence Interval**	**Odds Ratio**	***P* Value**	**95% Confidence Interval**	**Parameter Estimate**	***P* Value**	**95% Confidence Interval**
Intercept							5.6774		5.3616-5.9933
Index drug is galantamine	1.025	0.858	0.785-1.338	1.011	0.911	0.830-1.232	-0.044	0.193	-0.110-0.022
Index drug is rivastigmine	1.573	<0.001	1.251-1.977	1.227	0.036	1.014-1.487	-0.085	0.008	-0.148-0.022
Age	0.979	0.006	0.964-0.994	1.007	0.249	0.995-1.019	-0.003	0.178	-0.007-0.001
Female	1.053	0.611	0.863-1.285	1.110	0.176	0.954-1.290	-0.026	0.310	-0.077-0.024
Region									
Northeast	0.917	0.573	0.679-1.239	1.000	1.000	0.800-1.251	0.054	0.155	-0.021-0.129
North central	0.916	0.489	0.714-1.175	1.053	0.600	0.868-1.277	0.005	0.883	-0.059-0.069
West	1.074	0.654	0.787-1.464	1.124	0.336	0.886-1.426	0.048	0.236	-0.032-0.128
Health Plan									
POS	1.308	0.324	0.767-2.231	1.153	0.546	0.726-1.830	-0.076	0.323	-0.227-0.075
PPO	0.867	0.257	0.677-1.110	0.913	0.341	0.757-1.101	0.016	0.613	-0.046-0.079
Capitated POS	1.023	0.924	0.644-1.624	1.094	0.630	0.759-1.576	0.011	0.861	-0.109-0.131
Charlson score in baseline period	0.968	0.290	0.912-1.028	1.019	0.406	0.974-1.066	-0.007	0.360	-0.022-0.008
Goodness-of-fit statistic	Hosmer & Lemeshow test		Pr>ChiSq=0.659	Hosmer & Lemeshow test		Pr>ChiSq=0.515	Pearson chi-square		Pr>ChiSq=1

Reference category for index drug is donepezil.
Reference category for region is South.
Reference category for health plan is indemnity plan.
POS=point of service; PPO=preferred provider organization.

in total medical expenditures were attributable to aspects of the disease, such as severity of cognitive or functional impairment. Additionally, even though adherence measures were generally better for patients treated with donepezil than for those treated with rivastigmine, those adherence differences did not translate into cost differences; total 1-year all-cause health care costs did not significantly differ among the index ChEI medication cohorts.

Limitations

The use of a retrospective claims-based database for this study allowed for a large sample of patients who used ChEIs from across the United States but also involves limitations that need to be considered when interpreting the findings. First, this study was not a randomized controlled trial, and we cannot rule out sample biases that might account for the differences observed across treatment groups. Although treatment groups were similar in key characteristics, we could not evaluate the potential influence of some factors, such as degree and type of cognitive, functional, and behavioral impairment, because this information is not available in our data. Second, the database's regional distribution did not represent that of the overall U.S. population.

Third, while the number of months of persistence and the rate of discontinuation can be measured, we cannot determine the reason for discontinuation or the contribution of efficacy, safety, tolerability, or other factors to the differences that were observed. Nor can we determine from the claims database the extent to which patients actually used the medication that was dispensed by the pharmacy. Because of this, our definition of discontinuation and the permissible gap in refill dates may have included some patients with low levels of ongoing compliance (less than 50%) who had, in fact, not discontinued their ChEI. We did not examine the effects of longer or shorter permissible gaps on our results.

Fourth, in addition to the absence of clinical information for these patients, rivastigmine was not approved by the FDA until late February 2001, not marketed until sometime thereafter, and was, therefore, not available for clinical use during the entire

TABLE 4 Beta and Marginal Effect of Persistence on Total All-Cause Health Care Expenditures for 12-Month Follow-Up

	Total Medical Expenditures	
	Beta	Marginal Effect
Months persistent on any ChEI (exponential conditional mean model; Deviance=2,658.15)	-0.0086[a]	-$105.68
Months persistent on the index ChEI without any switches (exponential conditional mean model; Deviance=2,657.27)	-0.0102[b]	-$125.64
Persistent on the index ChEI for ≥9 months ChEI (exponential conditional mean model; Deviance=2,654.86)	-0.0949[c]	-$617.62
Number of days to first 30-day treatment gap with ChEI (exponential conditional mean model; Deviance=2,650.16)	-0.0004[d]	-$5.46

[a] *P=0.025*
[b] *P=0.013*
[c] *P=0.002*
[d] *P<0.001*

All models included the persistence measures shown plus covariates: age, gender, region, plan type, Charlson Comorbidity Index score, and index ChEI drug. In all models, n=3,177 and degrees of freedom for model deviance tests were 3,164.
ChEI=cholinesterase inhibitor.

3-year period of claims that was used in this study. This later approval date may account for some of the difference in loss of patient cases when the exclusion criterion for no prior ChEI use was applied for the pre-treatment period; 58% of donezepil cases were excluded versus 53% of rivastigimine cases and 19% of the galantamine cases.

Fifth, the use of ChEI drugs was poorly associated with a diagnosis of AD. After application of the other exclusion criteria, such as continuous enrollment and no prior use of a ChEI drug, the requirement for at least 1 medical or hospital-facility claim with a diagnosis of AD resulted in the exclusion of 72.5% of donepezil patients, 71.4% of galantamine patients, and 70.4% of rivastigmine patients.

Sixth, rivastigmine is approved for mild-to-moderate dementia associated with Parkinson's disease. We used selection criteria that included at least 1 medical or hospital-facility claim with a diagnosis code of 331.0 for AD but did not exclude patients with a diagnosis of Parkinson's disease (ICD-9-CD code 332.xx). However, the dosing and use of rivastigmine for either indication are the same. Finally, we did not have data on long-term care costs that were paid by Medicaid after exhaustion of Medicare and private coverage benefits and, therefore, could not assess the relationship between ChEI use and long-term care utilization and cost.

Conclusions

The results of this study showed some significant differences in adherence measures among the donepezil, galantamine, and rivastigmine groups. Prevalence of use with the initial ChEI at 12 months was higher for donepezil than for either rivastigmine or galantamine and higher for galantamine than for rivastigmine. The likelihood of reaching an approved dose before stopping treatment was greater for donepezil than for either galantamine or rivastigmine and was greater for rivastigmine than for galantamine. No difference was observed in either MPR, the commonly used measure of how consistently a patient takes medication as prescribed within a treatment episode, or total days of ChEI therapy; these findings suggest that utilization differences between ChEIs are primarily related to switching medications. Economic analyses found that reductions in acute health care expenditures correlate with ChEI adherence; however, all-cause health care costs were not significantly related to choice of initial ChEI medication.

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DISCLOSURES

This research was sponsored by Pfizer, Inc., and 3 of the authors (Brian Cuffel, Thomas McRae, and Megan del Valle) are employees of Pfizer, Inc. Cuffel was primarily responsible for the study concept and design, with assistance from Mark and Mucha. Wang performed the majority of the data collection, with assistance from Mucha. Data interpretation was performed primarily by Mucha with assistance from Wang and McRae. Mucha performed the majority of the writing of the original manuscript, with assistance primarily from del Valle. Cuffel performed the majority of the revision, with assistance from McRae, Mark, and del Valle.

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