Utilization of Antihypertensives, Antidepressants, Antipsychotics, and Hormones in Alzheimer Disease

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Abstract: This study explores the longitudinal relationship between patient characteristics and use of 4 drug classes (antihypertensives, antidepressants, antipsychotics, and hormones) that showed significant changes in use rates over time in patients with Alzheimer disease. Patient/caregiver-reported prescription medication usage was categorized by drug class for 201 patients from the Predictors Study. Patient characteristics included use of cholinesterase inhibitors and/or memantine, function, cognition, living situation, baseline age, and sex. Assessment interval, year of study entry, and site were controlled for. Before adjusting for covariates, useage increased for antihypertensives (47.8% to 62.2%), antipsychotics (3.5% to 27.0%), and antidepressants (32.3% to 40.5%); use of hormones decreased (19.4% to 5.4%). After controlling for patient characteristics, effects of time on the use of antidepressants were no longer significant. Antihypertensive use was associated with poorer functioning, concurrent use of memantine, and older age. Antipsychotic use was associated with poorer functioning and poorer cognition. Antidepressant use was associated with younger age, poorer functioning, and concurrent use of cholinesterase inhibitors and memantine. Hormone use was associated with being female and younger age. Findings suggest accurate modeling of the Alzheimer disease treatment paradigm for certain subgroups of patients should include antihypertensives and antipsychotics in addition to cholinesterase inhibitors and memantine.

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Pharmacy costs account for nearly one-third of costs for medicare beneficiaries with Alzheimer disease (AD),[1] and these costs are persistent from year to year.[2] However, there is little literature documenting patterns of prescription medication use among patients with AD.

In an earlier report, we examined patterns of cholinesterase inhibitors and memantine use over time in a large cohort of patients with AD enrolled in the Predictors Study at 3 US academic AD centers.[3] In this follow-up study, we aim to expand our understanding of resource utilization in AD as applied to other pharmaceutical interventions. We examined (1) patterns of utilization in 4 drug classes (ie, antihypertensives, antidepressants, antipsychotics, and hormones) that showed significant changes in use rates in our 6-year study period and (2) the longitudinal relationships between patient characteristics and drug use. Our study design allows for substantially longer term analysis than can generally be conducted in clinical trials. Clinical information included in the Predictors Study also allows for more detailed examination of the relationship between medication use and patient characteristics than would be possible with insurance claims data. As the prevalence rates of AD continue to rise, understanding patterns of medication use will help inform appropriate policy and care decisions.

METHODS

Sample

The sample was drawn from the Predictors 2 cohort, consisting of patients recruited from Columbia University Medical Center, Johns Hopkins School of Medicine, and Massachusetts General Hospital. The study was approved by each local institutional review board. The inclusion/exclusion criteria are fully described elsewhere.[4,5] Briefly, subjects met Diagnostic and Statistical Manual of Mental Disorders-III-R criteria for primary degenerative dementia of the Alzheimer type and National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD. Enrollment required a modified Mini-Mental State Examination score ≥ 30, equivalent to approximately ≥ 16 on the Folstein Mini-Mental State Examination (MMSE).[6,7] Clinical

diagnosis of AD has been confirmed in 93% of those patients with postmortem evaluation.[8] Patient recruitment began in 1997. After the baseline interview, patients were followed annually. Study recruitment was staggered: 3.0% (n = 6) entered the study in 1997, 8.5% (n = 17) in 1998, 8.0% (n = 16) in 1999, 26.9% (n = 54) in 2000, 24.4% (n = 49) in 2001, 13.4% (n = 27) in 2002, 10.0% (n = 20) in 2003, and 6.0% (n = 12) in 2004 or later. For data used in this analysis, 17 patients had one assessment (8.5%), 41 had 2 (20.4%), 32 had 3 (15.9%), 36 had 4 (17.9%), 33 had 5 (16.4%), and 42 had 6 or more assessments (20.9%). Median follow-up for the cohort was 4 years. Patients who did not respond at a particular visit could respond at a subsequent visit. The analysis sample consisted of 785 observations from 201 patients.

Measures

Medication Use

Detailed descriptions of both prescription and over-the-counter medications were reported by patients and informants. A neurologist who specializes in dementia (N.S.) categorized all 429 unique prescription medications reported in the data into the following 18 categories: anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs, antihistamines, prostate anticholinergic, antihyperlipidemics, antidiabetics, antihypertensives, antiepileptics, antipsychotics, antiemetics, neuroleptics, stimulants, antiparkinsonians, antidepressants, benzodiazepines, narcotics, hormones, and other prescription medications. A complete list of medications by category is available upon request from the authors. For each drug category, we constructed a dichotomous variable indicating whether a patient reported using any medications in that category since the last visit. We focused on drug classes instead of individual drugs because access to specific drugs may vary depending on insurance coverage and physician preference. Because an earlier analysis showed significant changes in use rates over time in 4 of the 18 drug classes (ie, antihypertensives, antidepressants, antipsychotics, and hormones) and stable or low frequency of use in the other 14 drug classes,[3] we focus on these 4 drug classes in this study.

Patient Clinical and Demographic Characteristics

Data on clinical characteristics of the patients were recorded at each visit. Disease progression was characterized by transition from milder stages of dementia to more severe stages, measured by MMSE.[6] Higher MMSE scores indicate better cognition. Blessed Dementia Rating Scale (BDRS) Parts I (Instrumental Activities of Daily Living) and II (Basic Activities of Daily Living) were used to assess patients' functional capacity.[9] Higher BDRS scores indicate worse functioning. At baseline, demographic characteristics (eg, age, ethnicity, sex, and education) were recorded. Information on living arrangements was collected at each visit, dichotomized as living at home or in a long-term care facility (ie, retirement home, assisted living facility, or nursing home).

Analysis

We used random effects logistic regression models to examine the effects of patient characteristics on utilization rates of antihypertensives, antidepressants, antipsychotics, and hormones over time. The random effects logistic regression framework allows an exploration of the combination of fixed effects that are common to all individuals in the population or common to groups of individuals and random effects that indicate individual level variations. The fixed effects parameters are interpreted as average effects of each explanatory variable on the dependent variables. The random effects parameters are interpreted as deviations from the mean for each individual and, therefore, model the magnitude of unobserved heterogeneity.

In our estimation model, we included time as measured in years following baseline (year 0). The coefficient on year estimates average linear trend in the dependent variable over time. An odds ratio (OR) greater than 1 on the coefficient on time indicates increasing likelihood of use over time. We included a year squared term in the model to estimate whether the rate of change over time was constant. The year squared term was not statistically significant in any of the models, and, therefore, was dropped.

All clinical variables and living arrangement were entered in our estimation model as time-variant covariates. Age at baseline and sex were entered as time-invariant covariates. Because the sample was overwhelmingly white (93%), we did not include race as an explanatory variable. In addition, we controlled for concurrent use of cholinesterase inhibitors and memantine and year of study entry in the regression models. We also controlled for possible differences in use patterns by region by including study site as a covariate. Because patients' psychiatric symptoms and extrapyramidal signs did not significantly affect use of any of the drug classes we examined here, we excluded these variables from our final models. All analyses were performed using Stata 9.0.[10]

RESULTS

Patient Characteristics

At baseline, patients' average age was 76 years (SD = 8.1), 61% were female, 93% were White, and 84% lived at home (Table 1). Patients were well educated, with an average of 14 years of schooling (SD = 3.1). Average MMSE was 22.0 (SD = 3.5) and average BDRS was 4.8 (SD = 2.5). Psychotic symptoms (34%) and extrapyramidal

TABLE 1. Baseline Characteristics (N=201)

	Baseline Characteristics Mean (SD)
Female (%)	61.2
Baseline age	76.3 (8.1)
Live at home (%)	84.0
Functional capacity, BDRS	4.8 (2.5)
Folstein MMSE	22.0 (3.5)
Extrapyramidal signs (%)	15.5
Psychotic symptoms (%)	33.8
Charlson comorbidity index	1.5 (1.1)
Site (%)	
Columbia	46.2
Johns Hopkins	25.4
Massachusetts general	28.4
Year of entry into study	2001 (1.9)

BDRS indicates Blessed Dementia Rating Scale; MMSE, Mini-Mental State Examination.

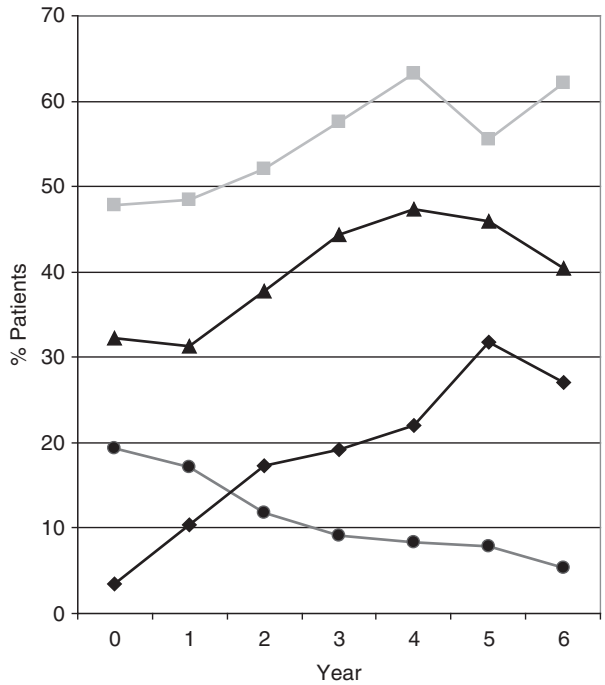

FIGURE 1. Utilization rates of antihypertensives, antidepressants, antipsychotics, and hormone over time, ▲ indicates antidepressants; ■, antihypertensives; ◆ antipsychotics, ●, hormones.

signs (16%) were common. On average, patients had 1.5 comorbidities (SD = 1.1), with 15% with none, 43% with 1, 26% with 2, and 16% with 3 or more comorbidities. The most prevalent comorbidities at baseline were hypertension (35.5%), diabetes (10.7%), myocardial infarction (6.6%), congestive heart failure (4.6%), and chronic obstructive pulmonary disease (4.6%).

Figure 1 shows changes in utilization rates of antihypertensives, antidepressants, antipsychotics, and hormones during the study period. Tests for trend over time showed significant increases in utilization rates of antihypertensives (47.8% to 62.2%), antidepressants (32.3% to 40.5%), and antipsychotics (3.5% to 27.0%), and decreases in hormone use (19.4% to 5.4%; all P values for trend over time < 0.001).

Multivariate Results on the Relationship Between Patient Characteristics and Medication Use

We used random effects logistic regression models to examine the relationships between patient characteristics and utilization of antihypertensives, antidepressants, antipsychotics, and hormones. After controlling for patient demographic and clinical characteristics, use of antihypertensives (OR = 1.217, $P < 0.05$) and antipsychotics increased (OR = 1.883, $P < 0.001$), use of hormones decreased (OR = 0.636, $P < 0.01$), and the effects of time on use of antidepressants were no longer significant (Table 2). For both antihypertensives and antipsychotics, the rate of increase in utilization slowed over time (OR = 0.984 and 0.963, respectively, both $P < 0.05$).

After controlling for time and other covariates, different demographic and clinical characteristics were associated with use of different medication classes. Specifically, poorer functioning (OR = 1.229, $P < 0.01$), concurrent use of memantine (OR = 2.725, $P < 0.05$), and older age (OR = 1.061, $P < 0.05$) were associated with higher likelihood of antihypertensive use. Younger age (OR = 0.922, $P < 0.05$), poorer functioning (OR = 1.432, $P < 0.001$), and concurrent use of cholinesterase inhibitors (OR = 2.417, $P < 0.05$) and memantine (OR = 2.483, $P < 0.05$) were associated with higher likelihood of antidepressant use. Poorer functioning (OR = 1.328, $P < 0.01$) and poorer cognition (OR = 0.835, $P < 0.001$) were associated with higher likelihood of antipsychotic use. Being female (OR = 7.280, $P < 0.001$) and younger age

TABLE 2. Random Effects Model of Antihypertensives, Antidepressants, Antipsychotics, and Hormone Use Over Time

	Antihypertensives OR (SE)	Antidepressants OR (SE)	Antipsychotics OR (SE)	Hormones OR (SE)
Interval	1.217 (0.163)*	1.062 (0.145)	1.883 (0.448)***	0.636 (0.115)**
Interval squared	0.984 (0.012)*	0.997 (0.013)	0.963 (0.020)*	1.025 (0.019)
Functional capacity, BDRS	1.229 (0.103)**	1.432 (0.124)***	1.328 (0.162)**	1.036 (0.112)
Cognition, Folstein MMSE	1.056 (0.039)	1.027 (0.037)	0.835 (0.042)***	0.973 (0.045)
Concurrent use of cholinesterase inhibitors	1.294 (0.628)	2.417 (1.256)*	1.285 (0.925)	0.870 (0.524)
Concurrent use of memantine	2.725 (1.501)*	2.483 (1.361)*	0.915 (0.688)	0.737 (0.597)
Baseline age	1.061 (0.039)*	0.922 (0.033)**	0.963 (0.042)	0.902 (0.037)**
Female	0.846 (0.494)	1.203 (0.684)	1.958 (1.402)	7.280 (5.010)***
Live at home	0.440 (0.245)	0.812 (0.463)	0.314 (0.237)	0.798 (0.540)
Site†				
Johns Hopkins	0.394 (0.286)	2.261 (1.583)	1.088 (0.943)	4.767 (3.837)*
Massachusetts general	0.818 (0.562)	1.936 (1.304)	0.216 (0.183)*	2.570 (1.994)
Year of entry into study	0.984 (0.160)	0.876 (0.139)	0.877 (0.188)	0.957 (0.176)
AIC	625.67	606.39	305.27	372.58
BIC	687.60	668.31	367.20	434.50
Log likelihood	−298.84	−289.19	−138.64	−172.29

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
†Reference site = Columbia.
AIC indicates akaike information criterion; BIC, Bayesian information criterion; BDRS, Blessed Dementia Rating Scale; MMSE, Mini-Mental Status Examination; OR, odds ratios.

(OR = 0.902, $P < 0.01$) were associated with higher likelihood of hormone use.

DISCUSSION

The purpose of this study was to examine the patterns of medication usage in a cohort of patients with AD and provide information on the clinical and demographic characteristics of patients that are associated with use of specific classes of drugs. We found that after controlling for demographic and clinical characteristics, use of antihypertensives and antipsychotics increased, whereas use of hormones decreased over time. Use of antidepressants also increased over time, but the trend over time was no longer significant after controlling for patient characteristics. These findings suggest that pharmacological treatment for AD changes with disease duration, and may include antihypertensives and antipsychotics, in addition to the use of cholinesterase inhibitors and memantine.

The increasing rates of antihypertensive use over time may be related to several factors. Rates of hypertension increase with increasing age.[11,12] In this study, baseline age was predictive of antihypertensive use. In a sensitivity analysis, we additionally controlled for number of comorbidities, measured by the Charlson Comorbidity Index. As expected, number of comorbidities was associated with increasing antihypertensive use, but did not substantively affect coefficient estimates. There is some evidence that hypertension may be a risk factor for dementia,[13] but the effect of antihypertensive treatment on cognition is ambiguous.[13–15] In this study, there was no association between cognition and antihypertensive use. Rather, lower functional ability and memantine use were associated with antihypertensive use, suggesting higher utilization in more clinically severe patients.

Use of antipsychotics significantly increased over time in this cohort, and was associated with worse cognition and functioning, suggesting that antipsychotics are more likely to be used in clinically severe patients. Antipsychotics may be prescribed for various reasons, including hallucination, delusion, aggression, agitation, irritability, wandering, poor sleep, or occasionally depressive symptoms.[16] However, our results did not show an association between psychotic symptoms and antipsychotic use, suggesting that patients may have responded to the medications.

The finding of worse cognition and functioning being associated with higher likelihood of antipsychotic use is in accordance with previous findings from the Predictors Study that both delusions and hallucinations[17] and disruptive behavioral symptoms[18] were associated with increased risk for cognitive and functional decline. Further analyses may help elucidate if use of antipsychotics in this cohort is related to other disruptive behavioral symptoms that are common in AD, including agitation, aggression, disinhibition, irritability, and wandering.[19] Alternatively, the association between antipsychotic use and worse cognition and functioning may be due to antipsychotics exacerbating cognitive and functional impairments. Of note, data from the Predictors Study were collected before the US Food and Drug Administration public health advisory against the use of antipsychotics in elderly dementia patients owing to increased risks for stroke and overall mortality.[20–22]

Although unadjusted trends show increasing use of antidepressants over time, this trend disappeared after controlling for patients' characteristics. An earlier study using the Predictors data showed that depression in AD patients neither increased nor persisted over time.[23] Another study investigating the course of depression in these patients reported that the prevalence of depression was stable (~40%) during the first 3 years and significantly decreased during the fourth (28%) and fifth (24%) years of follow up.[24] A lack of significant increases of antidepressant use over time seems to follow the course of depressive symptoms previously described in this cohort. Several patient and clinical factors were associated with antidepressant use, including younger age, poorer functioning, and cholinesterase inhibitors and memantine use. Consistent with previous reports of decline in functioning, but not in cognition preceding the first episode of depressive symptoms in patients with probable AD,[24] the association between poorer functional status and more antidepressant use found in our analysis may also reflect an effect of depressive mood on functional skills.

As expected, hormone use was more common in females (27.6% among females compared with 6.4% among males at baseline). Although early observational studies suggested that postmenopausal hormone treatment may improve cognitive function, more recent data indicate a lack of protective effect and possibly even a detrimental effect for primary prevention.[25–27] Similarly, effects of hormone replacement therapy in course and prognosis after AD onset have been equally disappointing.[28] Decreasing hormone use may reflect increased awareness of such lack of efficacy of hormone therapy. Despite adjusting for year of study entry and intervals, residual confounding effects may still remain.

In this study, we provide a detailed examination of utilization of different classes of prescription medications. Because medication use was reported for 6-month intervals, we were unable to account for medication changes in < 6 months. In addition, patients were selected from tertiary care university hospitals and specialized AD centers and represent a nonrandom sample of those affected by the disease in the population. Patients in our sample also were predominantly White and highly educated. Caution is needed in generalizing the results of this study to patients of other ethnicities, patients at lower education and income levels, and to community AD patients. On the other hand, because patients were selected from specialized AD centers, careful clinical diagnosis of AD and evaluations permitted more reliable and complete data and more accurate coefficient estimates. All classes of medications were evaluated in detail by experienced neurologists. Because patients were recruited at early disease stages and followed for long periods of time, analyses are not compressed in time and the cohort describes the full range of progression. Longer term effects are, therefore, more easily interpreted and strengthen the confidence in our findings.

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