Parkinsonism and Related Disorders 21 (2015) 36–41

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Relationships between antiparkinson medication nonadherence, regimen modifications, and healthcare utilization and expenditures

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ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form
13 October 2014
Accepted 21 October 2014

Keywords:
Antiparkinson regimen modifications
Medication nonadherence
Medicare

ABSTRACT

Objectives: To examine 1) the effect of prior antiparkinson drug (APD) nonadherence on subsequent APD regimen modifications; and 2) the influence of modifications on healthcare utilization and costs by patients with Parkinson's disease (PD).
Methods: This retrospective cohort study included 7052 PD patients with ≥2 APD prescriptions who initiated a modification of APD regimens in 2007. Modification was assessed as changing from one APD to another and/or adding a new APD to an existing regimen. Nonadherence was measured using Medication Possession Ratio <0.8. Discrete-time survival analyses were used to estimate the effect of prior non-adherent behavior on initiating APD modifications. Generalized linear models were used to estimate the effect of initiating medication modifications on subsequent 3-month medical use and costs.
Results: Initiation of APD modifications in any given month was higher among patients who were nonadherent to APDs in the preceding month (adjusted hazard ratio [HR] = 1.23), compared to their adherent counterparts. Modifications significantly predicted higher risk of all-cause and PD-related hospitalizations (adjusted relative risk [RR] = 1.22 and 1.83, respectively), home health agency utilization (RR = 1.18 and 1.52), and use of physician services (RR = 1.14 and 1.41), as well as higher total all-cause healthcare expenditures (mean = $1064) in any given 3-month interval.
Conclusions: Prior nonadherence to APDs might influence initiation of APD modification. APD modifications were associated with increased health care utilization and expenditures, with the caveats that indications of modifications and disease severity may still play roles. Prescribers should consider patients' medication adherence when changing APD regimens to lower the costs of medical services.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting older adults. Approximately 1.5 million Americans currently live with PD, with the majority of the cases aged 50 years or older [1]. PD ranks among the top 15 leading causes of death in 2010 [2] and costs patients and insurers about $11 billion annually [3]. The mortality and economic burden of PD are expected to rise as the baby boomer cohort ages. Although there is no cure available for PD, antiparkinson drugs (APDs) are considered the mainstream approach to manage motor symptoms [4–6].

APD therapy regimens are frequently modified in patients with PD. These modifications are made to optimize the beneficial effects on disease symptoms and to improve patient health outcomes [4,5]. Common modifications include dose titration, change in dose frequency, drug switching, and drug augmentation [4,5]. Decisions to modify APD regimens in patients with PD have been challenging for providers because of patients' nonadherence to APD therapy [7–10]. Prior studies have shown a substantial proportion (ranging from 28.7 to 67.0%) of PD patients did not adhere to their

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http://dx.doi.org/10.1016/j.parkreldis.2014.10.021
1353-8020/

medications [11–13]. Medication non-adherence behavior has been a concern due to its potential risk for unnecessary modifications to APD regimens [7,8]. Missing prescribed APDs likely results in poor response to the medications and persistence or worsening of parkinsonism symptoms [8,10]. Based on these clinical features, prescribers may inadvertently make unneeded changes on patients' existing treatment regimens, a practice that may provide no benefits for PD patients [10]. However, the association between non-adherence and modifications to APD regimens has not been addressed in empirical studies among populations with PD.

Even less well understood is the influence of APD regimen modifications on health resource utilization by patients with PD. Therapy modifications may be warranted if patients are not adherent due to lack of drug efficacy and/or emergence of motor or non-motor symptoms [4,5,14]. Such modification strategies may alleviate symptoms and prevent the need for more costly healthcare services, such as hospitalization. On the other hand, if there are no known adverse reasons for non-adherence, patients' symptoms may not be improved and their use and costs of medical service may remain high [7]. To our knowledge, no studies have explored whether medication modifications provide benefits by examining the influence of such changes on medical utilization and costs.

The study aims are two-fold: 1) to investigate the effect of prior adherence to APDs on subsequent initiation of modifications to APD regimens; and 2) to examine the influence of APD regimen modifications on healthcare utilization and expenditures. Our findings will provide empirical evidence concerning APD regimen modifications associated with poor medication-taking behavior and the impact of modifications on health outcomes among PD patients.

2. Methods

2.1. Study design and data

A retrospective cohort study was conducted using 2006–2007 Medicare 5% sample data that include administrative claims for all Medicare Parts A (inpatient), B (outpatient), and D (prescription drug event) services [15]. We assessed patients' medication adherence, regimen modifications, and utilization and expenditure outcomes in each month from January 1, 2007 to December 31, 2007 or death (i.e., follow-up period). The 2006 Medicare data were used to determine prior medication adherence among patients whose first medication modification occurred during early 2007, as well as to measure characteristics at baseline (7/1/2006–12/31/2006). The conduct of this study was approved by the Institutional Review Board of the University of Maryland Baltimore, Maryland.

2.2. Sample

Beneficiaries were included if they: 1) had ≥1 claims with a primary or secondary diagnosis of PD (*International Classification of Diseases*, Ninth Revision, ICD-9-CM codes 332.0) in each of the years 2006 and 2007; 2) were continuously enrolled in Medicare Parts A, B, and D Prescription Drug Plan throughout the baseline and follow-up period; and 3) had two or more APD prescriptions. From these 8426 eligible beneficiaries, we excluded patients who died in 2006 ($n = 36$) due to their missing data at baseline. We also excluded those enrolled in Medicare Advantage/Health Maintenance Organizations due to lack of available medical and drug claims ($n = 810$) for these beneficiaries. Finally, we excluded 528 PD patients who had a history of modified APD regimens in 2006, resulting in a final sample of 7052 PD patients.

2.3. APD regimen modifications

Six therapeutic classes of APDs approved by the Food and Drug Administration for the treatment of PD were examined: 1) dopamine precursors; 2) dopamine agonists; 3) monoamine oxidase B inhibitors; 4) catechol-O-methyltransferase inhibitors; 5), amantadine; and 6) anticholinergic agents [4,5]. We excluded three APDs: rotigotine (due to its short U.S. market life) [16], apomorphine (due to rare use in clinical practice) [4,5], and pergolide (due to market withdrawal on March 29, 2007) [17]. We measured the initiation of APD regimen modifications, defined as the first record of APD switching and/or augmentation in 2007. Switching was defined for each patient prescribed a new APD to replace a previously-prescribed APD later discontinued without refill [11]. Augmentation was measured for each patient to whom a different APD was added to an existing regimen [11]. To ensure accuracy of occurrences of augmentation, we required both the existing and new APD be refilled at least once and that the refill periods must overlap.

2.4. Adherence to APDs

To assess adherence to APD regimens, we employed the modified Medication Possession Ratio (MPR), calculated as the total days' supply from all APD classes (numerator) divided by the aggregate duration of all medication classes (denominator) [18]. Adherence was measured for each patient for each month from as early as October 2006 to December 2007, the month of death, or the first documented modification to APD regimens, whichever came first. Monthly adherence values during 2006 were used to predict the initiation of medication modification during January to March 2007. In the denominator, we excluded Part A-covered hospital and skilled nursing facility days due to the lack of prescription claims data to discern APD use [19]. Level of adherence was further dichotomized as adherent (MPR $\geq$ 0.8) or non-adherent (MPR $<$ 0.8). The cutoff point of 0.8 for adherence measure is commonly used in previous APD studies [12,13,20].

2.5. Outcome measures—healthcare utilization and expenditures

All-cause and PD-related healthcare utilization were assessed as binary variables (yes/no) at three month intervals from 2007 Medicare Parts A and B claims data. The 3-month interval was used to increase the likelihood of observing utilization outcomes following medication modifications. Utilization outcomes included: 1) hospitalizations; 2) emergency department visits; 3) home health agency episodes; and 4) office-based physician visits. PD-related utilization was defined as any medical claims of PD (ICD-9-CM 332.0) in the primary or secondary diagnosis position.

All-cause expenditures measured at 3-month intervals included total payments from individuals (e.g., deductibles and co-payments), Medicare, and non-Medicare programs (e.g., Veterans Administration). We calculated all-cause expenditures for Medicare Parts A, B, and D services, and then summed these three services to yield total expenditures for each individual. PD-related expenditures were not assessed due to the challenge of differentiating expenses contributed to specific diseases in Medicare claims data.

2.6. Covariates

Covariates measured at baseline included: sociodemographics (age, sex, race, and region), Part D enrollment, Part D low-income subsidy status, whether seen by neurologists, medication burden, disease-related characteristics, use of preventive health services, and baseline hospitalizations (yes/no). Early enrollees enrolled in the Part D program before 2006, whereas late enrollees joined between 1/1/2006 and 5/15/2006. A prior study has indicated that the early enrollees tended to adhere to their medications compared to the late enrollees [11]. Length of long-term care stay was measured during the study period in number of days for which patients resided in either skilled nursing facilities using Part A data or other long-term care facilities using Minimum Date Set [21]. In our study, less than 1% of PD patients lived in nursing homes throughout the entire study period, with the vast majority of the sample spending some time (i.e., ≥1 day) in facilities. Thus, all nursing home patients were included for maximizing our sample size and optimizing the generalizability of our findings.

Medication burden was calculated as the total number of distinct medications (other than APDs) utilized by the patient. We used claims-based ICD-9 diagnoses to ascertain depression status (yes/no), cognitive disorders (measured by the presence of three main diagnoses—Alzheimer's disease, dementia, and psychosis) [22], and overall comorbidities (measured by Hierarchical Condition Categories [23], excluding depression, cognitive disorders, and PD). Using Part B claims data, we measured four preventive services—influenza vaccinations, colorectal cancer screening, prostate cancer screening for males only, and mammography screening or pap smears for females only—to control for the effect of healthy behaviors on medication adherence and outcomes [24].

2.7. Statistical analyses

Descriptive statistics were presented for sociodemographic and clinical characteristics of the sample overall, and by whether patients initiated modifications to APD regimens. To address temporality between medication adherence and modification, we examined the effect of prior 1-month APD adherence on the initiation of APD regimen modifications in the current month. To test the robustness of the relationship between medication adherence and modification, we conducted sensitivity analyses by using prior 2- or 3-month adherence values. Because both adherence and modification were assessed in person-months, discrete-time survival analysis with a complementary log–log link was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of APD regimen modifications. This approach is more flexible and efficient than standard Cox survival models in handling interval-censored data [25].

To assess the effect of initiating APD regimen modifications on healthcare utilization and expenditures in the following 3 months, we used binomial and gamma generalized linear models [26], respectively, adjusting for baseline covariates and medication adherence in the month before regimen modifications. We used generalized estimating equation method to account for the intercorrelation among repeated measured outcomes within each patient. In these analyses, we excluded 58 patients who had insufficient observation period (<3 months) for outcomes, resulting in a total sample of 6994 PD patients. Relative ratio (RRs) and their 95% CIs