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Antiparkinson Drug Adherence and Its Association with Health Care Utilization and Economic Outcomes in a Medicare Part D Population

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ABSTRACT

Objectives: We examine the associations of adherence to antiparkinson drugs (APDs) with health care utilization and economic outcomes among patients with Parkinson's disease (PD). **Methods:** By using 2006–2007 Medicare administrative data, we examined 7583 beneficiaries with PD who filled two or more APD prescriptions during 19 months (June 1, 2006, to December 31, 2007) in the Part D program. Two adherence measures— duration of therapy (DOT) and medication possession ratio (MPR)—were assessed. Negative binomial and gamma generalized linear models were used to estimate the rate ratios (RRs) of all-cause health care utilization and expenditures, respectively, conditional upon adherence, adjusting for survival risk, sample selection, and health-seeking behavior. **Results:** Approximately one-fourth of patients with PD had low adherence (MPR < 0.80, 28.7%) or had a short DOT (≤400 days, 23.9%). Increasing adherence to APD therapy was associated with decreased health care utilization and expenditures. For example, compared with patients with low adherence, those with high adherence (MPR = 0.90–1.00) had significantly lower rates of hospitalization (RR = 0.86), emergency room visits (RR = 0.91), skilled nursing facility episodes (RR = 0.67), home health agency episodes (RR = 0.83), physician visits (RR = 0.93), as well as lower total health care expenditures (−$2242), measured over 19 months. Similarly, lower total expenditure (−$6308) was observed in patients with a long DOT versus those with a short DOT. **Conclusions:** In this nationally representative sample, higher adherence to APDs and longer duration of use of APDs were associated with lower all-cause health care utilization and total health care expenditures. Our findings suggest the need for improving medication-taking behaviors among patients with PD to reduce the use of and expenditures for medical resources.

Keywords: antiparkinson drug, expenditures, health care utilization, Medicare, medication adherence.

Introduction

Parkinson's disease (PD), characterized by tremor, rigidity, and bradykinesia, is the second most common neurodegenerative disorder after Alzheimer's disease in the United States [1]. This disease predominantly affects people aged 60 years or older [2]; an estimated 1.6 million Medicare beneficiaries live with PD [3]. PD places substantial economic burden on patients and insurers, and costs society on average $10.8 billion annually [4]. The cost of PD is expected to increase with the aging baby boomers [5,6].

While there is no treatment to cure PD, or proven treatments to slow down its progression, antiparkinson drugs (APDs) are considered the mainstream approach to control motor symptoms [7–9]. Despite the importance of taking APDs regularly and consistently [10–13], evidence regarding adherence to these agents among a representative sample of patients with PD is limited. Studies of APD adherence were clinical-based studies with small sample sizes and short observation periods [14–16]. Although two studies were conducted at the population level [17,18], findings were limited to patients with PD in managed care settings. Higher nonadherence rates were observed in population-based studies (61%–67%) [17,18] compared with clinical studies (12.0%–12.5%) [14–16], due to differences in the study populations and how adherence was measured.

Patient adherence to prescribed APD regimens is critical for optimal motor function, quality of life, and preventing the need for more costly health care services, such as hosplitzation [13]. A study of 3119 patients with PD enrolled in managed care plans during 1997 to 2004 demonstrated that compared with good adherers, poor adherers had more hospitalizations (2.3 vs. 1.8)

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and higher total health care spending ($2383) annually [18]. Despite these findings, this study failed to account for many potential confounders. For example, "healthy-user effect" has been implicated as a source of bias because adherers tend to be healthier or engage in health-seeking behaviors, thereby having lower health care utilization and expenditures [19–22]. Other potential confounders not yet addressed in studies include physician specialty, the frequency of treatment changes (i.e., switching and augmentation), and whether patients live in long-term care (LTC) facilities [13]. To address these gaps, this study aimed to examine the prevalence of APD adherence and the association of adherence with health care utilization and expenditures while controlling for potential confounders among a Medicare Part D population diagnosed with PD. The rationale for this study was to have a better understanding of medication-taking behaviors and their consequences through improving upon previous studies' methodological issues, as well as targeting population generalizable to Medicare Part D beneficiaries. Our generalizable findings intend to assist clinicians and policymakers to appropriately target patients with PD with poor adherence to APDs, and/or readjust clinical practices in the Medicare Part D population with PD.

Methods

Study Design and Data

We conducted a retrospective cross-sectional study by using the 2006–2007 Chronic Care Conditions Data Warehouse data that represent a 5% random sample of Medicare beneficiaries [23]. The Chronic Care Conditions Data Warehouse data include detailed administrative claims for all Medicare Part A (inpatient), B (outpatient), and D (prescription drug event) services. The first 5 months (January 1, 2006, to May 31, 2006) served as baseline; beneficiaries were followed for up to 19 months (June 1, 2006, to December 31, 2007) or until death in 2007. We selected June 1, 2006, as the starting date to observe complete drug data for patients enrolled in the Part D program when it went into effect on January 1, 2006, and for those enrolled as late as May 15, 2006. The conduct of this study was approved by the Institutional Review Board of the University of Maryland Baltimore, Maryland.

Sample

Sample selection criteria included 1) having one or more claim with a primary or secondary diagnosis of PD (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 332.0) in each of the years 2006 and 2007; 2) continuously enrolled in Medicare Parts A, B, and a Prescription Drug Plan (PDP) throughout the follow-up period (i.e., June 1, 2006, to December 31, 2007, or death in 2007); and 3) having maintained Parts A and B enrollments throughout baseline. We did not require beneficiaries to maintain PDP enrollment throughout baseline because nearly one-third (31.5%) of our sample was of late enrollees, a group who enrolled in Part D in the early part of 2006 (i.e., January 1, 2006, to May 15, 2006) and thus did not have PDP enrollment in each month of the baseline period. From these 9604 eligible beneficiaries, we excluded patients who died in 2006 (n = 36) to ensure that each patient had at least a 7-month (June 1, 2006, to December 31, 2006) drug observation window, as well as those enrolled in Medicare Advantage/Health Maintenance Organizations because of lack of available medical and drug claims (n = 810), resulting in a sample of 8758 Medicare PDP enrollees with a diagnosis of PD. Of these, 7706 (88%) used at least one APD, assessed through Part D claims. We further limited this sample to those with at least two Part D APD prescriptions filled at different time points (n = 7583) to calculate medication adherence and duration [24,25].

Measures

APD adherence measures

APDs approved by the Food and Drug Administration for the treatment of PD were identified by using National Drug Codes. The six major classes of APDs include dopamine precursors (e.g., levodopa), dopamine agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, and anticholinergic agents [7,8]. We excluded three APDs: rotigotine because of its short U.S. market life [26], apomorphine because of rare use in clinical practice [7,8], and pergolide because of withdrawal on March 29, 2007 [27].

Key independent variables included duration of therapy (DOT) and medication possession ratio (MPR), two adherence measures used to assess different components of medication-taking behaviors. DOT assesses the duration of time, or persistence that a patient is treated with APDs, while MPR assesses how regularly patients take APDs while in their possession [28]. DOT was measured as the number of days between the first and last filled prescription of all APDs and the days' supply of the last fill, date of death, or December 31, 2007, whichever came first [24,25,29]. This DOT measure included a permissible gap of 30 or fewer days between refills to allow for any residual effect of previous APDs and any remaining medications stockpiled. More than two-thirds (73%) of APD prescriptions filled by our sample were a 30 days' supply. For assessing medication adherence, we used a modified MPR, calculated as the total days' supply from all APD classes (numerator) divided by the aggregate DOT of all drug classes (denominator) to avoid overestimation of MPR values for drug classes filled concurrently [30]. The MPR numerator included days' supply carried over from prescriptions filled before June 1, 2006; in the denominator, we excluded Part A–covered hospital and skilled nursing facility (SNF) days because of inability of the data to discern medications taken during these periods [31].

Because DOT and MPR were highly negative skewed (more than half of the patients had DOT $\geq$ 540 days and an MPR of $\geq$0.90), we analyzed these two measures as categorical variables with cutoffs close to quartiles of the respective distribution: short ($\leq$400 days), medium (401–539 days), long (540–578 days), and maximum (579 days) DOT; low ($\leq$0.79), moderate (0.80–0.89), and high (0.90–1.00) MPR. An MPR of greater than 1 was truncated at 1, because it was the result of either early refills or exclusion of Part A–covered days (hospital or SNF) from the denominator of MPR calculation.

Outcomes: All-cause health care utilization and expenditures

Our dependent variables were all-cause health care utilization and expenditures measured over the same time frame as adherence. We assessed the total number of visits/episodes that each patient made to each of the following five settings: hospital, emergency room (ER), SNF, home health agency (HHA), and physician office. Expenditures for Medicare Part A, B, and D services were calculated on the basis of payments from individuals (e.g., deductibles and co-payment) and from Medicare and non-Medicare programs (e.g., Veteran Administration). The costs of Part A, B, and D services were summed to yield total expenditures for each individual.

Covariates

We included an extensive set of covariates in this analysis to control for confounding due to sociodemographic characteristics (age, sex, race, and region), the timing of Part D enrollment (early vs. late), Part D low-income subsidy status, whether seen by

neurologists, LTC stay, disease- and drug-related factors, general health status, and use of preventive services. Early enrollees enrolled in the Part D program before 2006, whereas late enrollees joined between January 1, 2006, and May 15, 2006. Length of LTC stay was measured in number of days for which patients resided in either SNFs using Part A SNF claims or other LTC facilities using Minimum Date Set assessment—a mandatory tool for collecting data on residents in Medicare- or Medicaid-certified nursing homes. We used claims-based *International Classification of Diseases*, *Ninth Revision* diagnoses to assess three disease-related factors: depression (yes/no), cognitive disorders (measured by the presence of three main diagnoses—Alzheimer's disease, dementia, and psychosis) [32,33], and overall comorbidities (measured by hierarchical condition categories [34] excluding the above four diseases).

Drug-related variables included medication burden (i.e., numbers of distinct medications) and changes in APD regimens (i.e., number of switches and augmentations). Switch was defined as starting a different APD to replace the previous one that was later discontinued without any refills. Augmentation required adding a different APD to an existing drug regimen. To ensure accuracy of occurrences of augmentation, we required that both old and new APDs be refilled at least one time and that refill periods must overlap. General health status was proxied by two measures—whether patients died in 2007 and health care utilization at baseline. We used baseline hospitalizations in expenditure outcome analyses; for each of the five utilization outcomes (hospitalization, ER, SNF, HHA, and physician visits), baseline utilization of the respective medical service was measured. These utilization parameters have been demonstrated to be significantly associated with poor health status [35–37]. The measure of mortality was also used to control for survival bias.

Use of four preventive services (influenza vaccinations, colorectal cancer screening, prostate cancer screening for males only, and mammography screening or pap smears for females only) was measured from June 1, 2006, to December 31, 2007, by using Part B claims data to control for the effect of health-seeking behaviors on medication adherence and outcomes [38]. We selected these four services because 1) they were covered by Medicare before and throughout the study period (2006–2007) and 2) most of the services (including influenza vaccinations, mammograms, and pap smears) were recommended to be performed annually [39]. A yearly prostate-specific antigen testing was encouraged during our study period [40]. Colorectal cancer screening, depending on the type of tool used, was recommended every 10 years (colonoscopy), every 5 years (flexible sigmoidoscopy), or annually (fecal occult blood test) [39]. The frequency of these selected services is higher than that of other nonselected Medicare-covered preventive services (e.g., once per lifetime for pneumococcal vaccine).

Statistical Analyses

Descriptive statistics were presented for sociodemographic and clinical characteristics of the sample overall, and by the MPR categories. We reported crude health care utilization prevalence and rates (per patient-year) and health care expenditures (means and SDs), overall and by DOT and MPR categories. Separate negative binomial generalized linear models (GLMs) with adjustment for covariates and two types of biases were used to estimate rate ratios and 95% confidence intervals for the association of DOT and MPR with utilization rates for all five services. We used gamma GLM to approximate the highly right-skewed distribution of expenditure outcomes [41,42]. We converted the coefficients from the gamma GLM models to marginal effects (i.e., absolute dollar differences) with standard errors and *P* values. When estimating the associations of DOT with utilization and expenditure outcomes, we excluded patients with a maximum DOT (579 days) because only 1% of these patients had hospitalization or SNF utilization. Estimates from this maximum DOT group are likely to be biased because utilization has yet to occur.

Heckman Correction for Sample Selection Bias

To generalize our study results to the entire Medicare Part D population, we corrected for sample selection bias inherent in self-selection into PDP or Medicare-Advantage Prescription Plans [43] by using Heckman's two-stage procedures [44]. In the first stage, a probit model was used to predict the probability of beneficiaries enrolling in a PDP as opposed to Medicare-Advantage Prescription Plans among the entire 2006-2007 5% Chronic Care Conditions Data Warehouse population with evidence of Part D enrollment. Variables in the probit model to predict the PDP enrollment included age, sex, race, residency, death in 2007, and comorbidities. In addition to these factors, we included two variables at the regional ZIP code level: 1) number of different PDP plans available to beneficiaries, derived from 2006 Centers for Medicare & Medicaid Services Medicare Advantage Landscape Source files [45] and 2) percentage of employees offered health insurance, derived from the 2006 Medical Expenditure Panel Survey [46]. From the first-stage probit model, we generated an inverse Mills ratio that represents potential sample selection bias; the inverse Mills ratio was then incorporated into our multivariate regression models in the second stage [44].

All analyses were performed by using PROC GENMOD (SAS version 9.2, SAS Institute, Inc., Cary, NC) and GLM (STATA version 11.1, Stata Corp., College Station, TX).

Results

Our sample of 7583 beneficiaries with PD was predominantly older than 65 years (93.6%), female (59.9%), white (89.3%), and early enrollees (68.5%) (Table 1). More than half (51.1%) were low-income subsidy eligible and more than two in three (69.6%) visited neurologists during the study period. This Medicare PD sample had high comorbidity: 39.0% had a diagnosis of depression, 62.2% were cognitively impaired, and 52.4% had nine or more comorbidities. Their medication burden was substantial, with half (50.0%) using 13 or more medications. Almost half (46.3%) resided in SNFs or other LTC facilities and did not engage in any of the studied preventive services (46.4%). One in 5 (19.4%) had a baseline hospitalization; more than 1 in 10 (13.7%) died during 2007. Approximately a quarter had an MPR of less than 0.8 (28.7% = 2179 of 7583) or a DOT of 400 days or less (23.9%) over the period of 19 months (579 days). Across the three MPR groups, there were statistically significant differences in the majority of the measured characteristics, including age, race, region, early Part D enrollment, low-income subsidy status, whether seen by neurologists, cognitive conditions, comorbidities, change in the APD regimen, LTC stay, use of preventive services, death in 2007, and DOT.

Table 2 shows prevalence and crude rates of utilization outcomes by DOT and MPR. Lower proportions of hospitalization were observed among long DOT users (58.4%) than among short and medium DOT users (66.4% and 69.0%, respectively), and among high adherers (46.7%) than among low and moderate adherers (56.6% and 56.7%, respectively). Similar patterns were observed with hospitalization rates. Also, patients with long DOT and high MPR had lower utilization of ER, SNF, and HHA than did their less adherent and shorter duration peers. Patients with high MPR also had fewer physician visits than did those with low MPR.

Mean total expenditures were lower in long DOT users ($32,472) than in short DOT users ($54,488), and the same pattern was observed for Part A ($10,497 vs. $33,849) and Part B ($11,062

Table 1 – Distributions of demographic and clinical characteristics among 7583 Medicare Part D Prescription Drug Plan enrollees with Parkinson's disease (PD), and by different MPRs.

Characteristics	Total sample		MPR*						P†
	n	%	Low		Moderate		High		
Patients	7583	100	2179	100	1456	100	3948	100	
Age (y)									<0.001
Mean ± SD, median	77.2 ± 8.9, 78.0		76.5 ± 8.8, 77.0		77.1 ± 9.1, 78.0		77.6 ± 8.9, 79.0		
≤64	488	6.4	139	6.4	89	6.1	260	6.6	
65–74	2074	27.4	673	30.9	426	29.3	975	24.7	
75–84	3492	46.0	979	44.9	653	44.8	1860	47.1	
85+	1529	20.2	388	17.8	288	19.8	853	21.6	
Sex									0.370
Female	4543	59.9	1279	58.7	874	60.0	2390	60.5	
Male	3040	40.1	900	41.3	582	40.0	1558	39.5	
Race									<0.001
White	6775	89.3	1868	85.7	1316	90.4	3591	91.0	
Black	382	5.1	156	7.2	65	4.5	161	4.1	
Other‡	426	5.6	155	7.1	75	5.2	196	5.0	
Region									<0.001
Northeast	1575	20.8	399	18.3	295	20.3	881	22.3	
North Central	2075	27.4	532	24.4	359	24.7	1184	30.0	
South	2847	37.5	913	41.9	583	40.0	1351	34.2	
West	1086	14.3	335	15.4	219	15.0	532	13.5	
Early vs. late enrollees									<0.001
Early enrollees	5192	68.5	1394	64.0	1005	69.0	2793	70.7	
Late enrollees	2391	31.5	785	36.0	451	31.0	1155	29.3	
Low-income subsidy (LIS) status									<0.001
LIS	3873	51.1	1017	46.7	720	49.5	2136	54.1	
Non-LIS	3710	48.9	1162	53.3	736	50.5	1812	45.9	
Seen by neurologists									<0.001
Yes	5280	69.6	1631	74.9	1065	73.1	2584	65.5	
No	2303	30.4	548	25.1	391	26.9	1364	34.5	
Depression§									0.161
Yes	2959	39.0	825	37.9	597	41.0	1537	38.9	
No	4624	61.0	1354	62.1	859	59.0	2411	61.1	
Number of cognitive conditions‖									0.008
Mean ± SD, median	2.0 ± 0.9, 2.0		2.0 ± 0.9, 2.0		2.0 ± 0.9, 2.0		2.0 ± 0.9, 2.0		
0	2865	37.8	850	39.0	531	36.5	1484	37.6	
1	1810	23.9	465	21.3	347	23.8	998	25.3	
2–3	2908	38.3	864	39.7	578	39.7	1466	37.1	
Comorbid conditions									<0.001
Mean ± SD, median	8.8 ± 3.1, 9.0		9.2 ± 3.2, 9.0		9.0 ± 3.2, 9.0		8.6 ± 3.0, 8.0		
1–6	1765	23.3	475	21.8	317	21.8	973	24.6	
7–8	1845	24.3	470	21.6	332	22.8	1043	26.4	
9–10	1786	23.6	494	22.7	358	24.6	934	23.7	
11–22	2187	28.8	740	34.0	449	30.8	998	25.3	
Number of non-PD drugs									0.084
Mean ± SD, median	15.7 ± 8.2, 14.0		15.7 ± 8.2, 14.0		16.2 ± 8.3, 15.0		15.5 ± 8.1, 14.0		
0–7	1811	23.0	525	24.1	329	22.6	957	24.2	
8–12	2048	27.0	574	26.3	359	24.7	1115	28.2	
13–18	1904	25.0	546	25.1	387	26.6	971	24.6	
19–76	1820	25.0	534	24.5	381	26.2	905	22.9	
Change in APD regimen									<0.001
Mean ± SD, median	1.3 ± 0.6, 1.0		1.4 ± 0.7, 1.0		1.4 ± 0.7, 1.0		1.3 ± 0.6, 1.0		
0	5658	75.0	1543	70.8	1054	72.4	3088	78.2	
1	1165	15.4	342	15.7	250	17.2	573	14.5	
2–8	733	9.6	294	13.5	152	10.4	287	7.2	
Length of long-term care stay (mo)									<0.001
Mean ± SD, median	12.7 ± 18.3, 0.0		8.8 ± 15.6, 0.0		12.2 ± 17.8, 0.0		15.0 ± 19.5, 0.0		
0	4072	53.7	1307	60.0	762	52.3	2003	50.7	
1–12	1645	21.7	532	24.4	356	24.5	754	19.1	
13–19	1866	24.6	340	15.6	338	23.2	1191	30.2	
Preventive services use									<0.001

Table 1 – *continued*

Characteristics	Total sample		MPR*				P†
	n	%	Low		Moderate	High	
0	3516	46.4	904	41.5	661	45.4	1951	49.4	
1	2934	38.7	929	42.6	559	38.4	1446	36.6	
2–3	1133	14.9	346	15.9	236	16.2	551	14.0	
Death in 2007									0.015
Yes	1037	13.7	262	12.0	196	13.5	579	14.7	
No	6546	86.3	1917	88.0	1260	86.5	3369	85.3	
Hospitalizations at baseline¶									0.787
Yes	1471	19.4	429	19.7	288	19.8	754	19.1	
No	6112	80.6	1750	80.3	1168	80.2	3194	80.9	
Duration of therapy (d)									<0.001
Mean ± SD, median	472 ± 137, 536		428 ± 142, 469		490 ± 113, 536		489 ± 137, 563		
Short (≤400)	1813	23.9	763	35.0	257	17.7	793	20.1	
Medium (401–539)	2061	27.2	767	35.2	490	33.7	804	20.4	
Long (540–578)	2019	26.6	457	21.0	456	31.3	1106	28.0	
Maximum (579)	1690	22.3	192	8.8	253	17.4	1245	31.5	

APD, antiparkinson drugs; *ICD-9*, *International Classification of Diseases, Ninth Revision*; MPR, medication possession ratio.

* Low MPR was defined as <0.80, moderate MPR, 0.80–0.89, and high MPR, 0.90–1.00.

† Statistical significance was tested with chi-squared tests.

‡ Other included Hispanic, Asian, the natives of North America, and individuals with other or unknown races and ethnicities.

§ *ICD-9* codes used to define depression: 296.2x, 296.3x, 300.4, 309.1, and 311.

‖ *ICD-9* codes used to define cognitive conditions: Alzheimer's disease (331.0), dementia (290.1-290.4, 294.1, 294.8, 331.1-331.2, 331.7, and 797), and psychosis (293.81, 293.82, 298.0, 298.1, 298.4, 298.8, 298.9, 297.1, 368.16, and 780.1).

¶ Baseline = January 1, 2006, to May 31, 2006.

vs. $13,367) expenditures (Table 3). Part D expenditures, however, were higher in long DOT users ($10,913) than in short DOT users ($7,272). Similar expenditure findings were found in high adherers relative to those with low and moderate MPR.

Unadjusted results showed significant inverse associations of DOT and MPR with all-cause health care utilization outcomes in general (Table 2). After adjustment for covariates and sample selection bias, a significantly lower hospitalization rate was seen for patients with a medium (rate ratio = 0.83; 95% confidence interval = 0.79–0.88; $P < 0.001$) and long (rate ratio = 0.74; 95% confidence interval = 0.69–0.78; $P < 0.001$) DOT than for patients with a short DOT. Also, significantly fewer ER visits and SNF episodes were observed among the long DOT groups than among the short DOT group. We also noted significantly lower utilization rates for all five health care services for high adherers, although not for moderate adherers, than for low adherers.

After multivariate adjustment, significantly lower total health care expenditures were exhibited in long DOT users (−$6,308, $P < 0.001$) than in short DOT users (Table 4). Total expenditure reductions for patients with long DOT were driven by their significant decreases in Part A (−$10,095, $P < 0.001$) expenditures. Also, patients with high adherence to APDs had significantly lower expenditures in total (−$2,242, $P < 0.01$), Part A (−$6,941, $P < 0.001$), and Part B (−$848, $P < 0.01$) services, but higher Part D spending ($3,068, $P < 0.001$) than did patients with low adherence.

Discussion

With a nationally representative sample of Medicare Part D enrollees with PD, our data showed that more than two-thirds had good adherence to APDs (i.e., an MPR of ≥80%) and had a treatment duration of at least 13 months over a 19-month period. The percentage of good adherers (72.7%) in our PD sample of Medicare Part D beneficiaries was higher than that in previous studies in managed care populations with PD (ranging from 33.0% to 53.5%) [11,17,18]. This variation in adherence estimates may also result from the different designation of PD. We defined patients with PD by using a method of flagging *International Classification of Diseases, Ninth Revision, Clinical Modification* 332.0 codes in two consecutive years. This approach has a high sensitivity of 89.2% and a moderate-to-high positive predictive value of 79.4% in identifying true PD patients, compared with medical chart review [47]. In contrast, other studies of APD adherence identified patients with PD by using diagnostic codes not specific to PD (332.1 [secondary parkinsonism], 333.0 [other degenerative diseases of the basal ganglia], or 333.1 [tremor]), in addition to 332.0 [11,17,18]. The use of these four codes jointly had shown an unsatisfactory sensitivity (18.7%) in detecting patients with PD as compared with medical chart view [48]. In addition, APDs are effective treatment for patients with confirmatory PD diagnosis [7–9] but not for patients without PD (e.g., those with secondary parkinsonism or tremor) [7,8]. Taken together, our chosen approach, compared with that used by previous studies, is likely to identify a sample with a greater proportion of true PD cases who have a higher likelihood of taking APD treatment to control parkinsonism symptoms. Accordingly, the APD adherence estimate observed from our PD sample differed from that of previous studies. Also, our PD enrollees had similar high adherence rates as Part D enrollees with other chronic diseases [49].

This study also demonstrated clinical and economic benefits of persistent and regular APD use. Longer DOT and higher adherence were significantly associated with lower utilization of acute (hospital and ER) and chronic (SNF and HHA) services for any cause, while incurring no change or a decrease in routine office-based physician care. Also, optimal APD-taking behaviors were associated with a significant reduction in total health expenditures. Although patients with longer DOT and higher MPR had higher Part D medication expenditures, this increase was more than offset by cost savings from reduced spending on Part A and B services. This observation suggests that significant

Table 2 – Descriptive statistics (prevalence and rate) and relative risks of all-cause health care utilization by APDs' adherence measures.

Medication measures	Total sample	Prevalence (%)	Person-years	Crude rate*	Unadjusted RR (95% CI)	Adjusted†,‡ RR (95% CI)
Hospitalizations						
DOT§ (d)						
Short	1813	66.4	2072	1.40	1.00	1.00
Medium	2061	69.0	2968	1.16	0.77 (0.71–0.83)‖	0.83 (0.79–0.88)‖
Long	2019	58.4	3297	0.69	0.44 (0.41–0.48)‖	0.74 (0.69–0.78)‖
MPR¶						
Low	2179	56.6	3332	0.93	1.00	1.00
Moderate	1456	56.7	2235	0.85	0.92 (0.84–1.01)	1.02 (0.96–1.08)
High	3948	46.7	5989	0.62	0.68 (0.63–0.74)‖	0.86 (0.81–0.90)‖
Emergency room visits						
DOT§ (d)						
Short	1813	73.9	2072	1.81	1.00	1.00
Medium	2061	75.0	2968	1.55	0.80 (0.74–0.86)‖	0.88 (0.83–0.93)‖
Long	2019	64.9	3297	1.10	0.57 (0.52–0.61)‖	0.87 (0.81–0.92)‖
MPR¶						
Low	2179	67.6	3332	1.34	1.00	1.00
Moderate	1456	65.7	2235	1.21	0.90 (0.83–0.98)#	0.95 (0.88–1.02)
High	3948	59.4	5989	1.01	0.76 (0.71–0.81)‖	0.91 (0.86–0.96)‖
SNF episodes						
DOT§ (d)						
Short	1813	41.2	2072	1.52	1.00	1.00
Medium	2061	48.3	2968	1.39	0.85 (0.77–0.94)‖	0.94 (0.86–1.03)
Long	2019	14.4	3297	0.20	0.12 (0.10–0.13)‖	0.20 (0.18–0.23)‖
MPR¶						
Low	2179	31.7	3332	0.86	1.00	1.00
Moderate	1456	33.6	2235	0.86	0.99 (0.86–1.13)	1.19 (1.07–1.13)‖
High	3948	24.3	5989	0.52	0.62 (0.55–0.69)‖	0.67 (0.61–0.73)‖
Home health agency episodes						
DOT§ (d)						
Short	1813	34.8	2072	0.67	1.00	1.00
Medium	2061	37.0	2968	0.67	0.93 (0.83–1.04)	1.12 (1.02–1.23)#
Long	2019	32.3	3297	0.55	0.74 (0.66–0.83)‖	1.01 (0.91–1.12)
MPR¶						
Low	2179	37.8	3332	0.65	1.00	1.00
Moderate	1456	31.7	2235	0.54	0.83 (0.73–0.93)**	0.91 (0.83–1.00)
High	3948	24.7	5989	0.42	0.65 (0.59–0.71)‖	0.83 (0.76–0.89)‖
Office-based physician visits						
DOT§ (d)						
Short	1813	90.2	2072	12.60	1.00	1.00
Medium	2061	92.8	2968	12.95	1.04 (0.97–1.11)	1.04 (0.97–1.11)
Long	2019	95.2	3297	14.82	1.12 (1.05–1.20)‖	1.12 (1.05–1.20)‖
MPR¶						
Low	2179	94.9	3332	15.24	1.00	1.00
Moderate	1456	92.7	2235	13.67	0.90 (0.83–0.96)**	0.94 (0.90–0.99)#
High	3948	90.8	5989	11.91	0.78 (0.74–0.83)‖	0.93 (0.89–0.97)‖

APD, antiparkinson drugs; CI, confidence interval; DOT, duration of therapy; IMR, inverse Miller's ratio; LTC, long-term care; MPR, medication possession ratio; RR, rate ratio; SNF, skilled nursing facility.

* Rate was calculated as utilization events per patient-year over 1.6 y (19 mo).

† Adjusted variables included demographic characteristics (age, sex, race, and residency), low-income subsidy status (yes/no), early/late Part D enrolment, whether seen by neurologists, depression (yes/no), number of cognitive conditions, comorbidities, drug burden, changes in APD therapy, preventive services use, LTC stay, utilization outcome of interest at baseline (January 1, 2006, to May 31, 2006), and IMR. IMR was statistically significant ($P < 0.05$) in all five utilization outcome models, suggesting the presence of sample selection bias.

‡ The length of LTC stay was controlled in all models, but not for SNF outcome models because of a high correction between LTC stay and SNF utilization.

§ Short DOT was defined as ≤400 d, medium DOT, 401–539 d, and long DOT, 540–578 d.

‖ $P < 0.001$.

¶ Low MPR was defined as <0.80, moderate MPR, 0.80–0.89, high MPR, 0.90–0.99, and optimal MPR, 1.00

# $P < 0.05$.

** $P < 0.01$.

Table 3 – Mean and SD of health care expenditures by antiparkinson drugs' adherence measures.

Medication measures	Total expenditures	Part A expenditures	Part B expenditures	Part D expenditures
Total sample	40,471 ± 38,838	19,216 ± 29,968	11,264 ± 12,624	9,991 ± 10,401
DOT* (d)				
Short	54,488 ± 51,937	33,849 ± 41,331	13,367 ± 16,156	7,272 ± 9,131
Medium	52,782 ± 40,819	29,458 ± 30,634	13,103 ± 12,347	10,221 ± 10,788
Long	32,472 ± 23,397	10,497 ± 14,146	11,062 ± 11,937	10,913 ± 8,086
MPR†				
Low	45,867 ± 44,582	24,727 ± 34,910	12,889 ± 14,842	8,251 ± 6,937
Moderate	43,417 ± 38,643	21,603 ± 30,392	11,838 ± 12,226	9,976 ± 7,966
High	36,407 ± 34,850	15,294 ± 26,036	10,155 ± 11,255	10,957 ± 12,460

DOT, duration of therapy; MPR, medication possession ratio.
* Short DOT was defined as ≤400 d, medium DOT, 401–539 d, and long DOT, 540–578 d.
† Low MPR was defined as <0.80, moderate MPR, 0.80–0.89, and high MPR, 0.90–1.00

reductions in health care utilization and expenditures could be achieved by improved duration of use and adherence to APDs. It is worth noting that 70% (723 of 1037) of the patients who died in 2007 were classified as short DOT users. These deceased patients who incurred no further costs after death might have skewed cost estimates of the short DOT group toward having lower health care cost. Despite this artifact of lower health care costs in the short DOT group, their expenditures were observed to be higher than those of medium and long DOT groups. Our findings remained unchanged even after the exclusion of all deceased patients from analysis (e.g., marginal effect for total expenditure = –$7,895, long vs. short DOT groups, $P < 0.001$; data not shown).

Our study measured patients' medication-taking behaviors from two domains— DOT and adherence. These two measures yielded similar patterns, attesting to the robustness of our findings. From a clinical perspective, medication adherence may affect all-cause health care utilization and expenditures through two pathways. First, improved APD adherence alleviates PD symptoms and maintains motor function. Second, patients with improved APD adherence may follow the same healthy

Table 4 – Unadjusted and adjusted* association of DOT and medication adherence with all-cause health care expenditures.

Adherence measures	Total expenditures		Part A expenditures		Part B expenditures		Part D expenditures	
	Marginal effect ($)	Standard error	Marginal effect ($)	Standard error	Marginal effect ($)	Standard error	Marginal effect ($)	Standard error
DOT† (d)								
Unadjusted								
Short (referent)	0.00		0.00		0.00		0.00	
Medium	−1,738	1,517	−4,424‡	1,183	−265	467	2,951‡	320
Long	−22,048‡	1,328	−23,386‡	1,022	−2,305‡	464	3,643‡	280
Adjusted								
Short (referent)	0.00		0.00		0.00		0.00	
Medium	−940	1,177	−3,110§	1,352	−63	376	2,444‡	326
Long	−6,308‡	1,266	−10,095‡	1,431	−350	444	3,749‡	348
MPR‖								
Unadjusted								
Low (referent)	0.00		0.00		0.00		0.00	
Moderate	−2,451	1,392	−3,124¶	1,092	−1,051§	451	1,724‡	256
High	−9,461‡	1,104	−9,433‡	855	−2,734‡	365	2,706‡	248
Adjusted								
Low (referent)	0.00		0.00		0.00		0.00	
Moderate	85	948	−2,935	1,539	−439	343	1,483‡	211
High	−2,242¶	790	−6,941‡	1,307	−848†	292	3,068‡	241

DOT, duration of therapy; IMR, inverse Miller's ratio; MPR, medication possession ratio.
* Adjusted variables included demographic characteristics (age, sex, race, and residency), low-income subsidy status, early/late Part D enrolment, whether seen by neurologists, depression, number of cognitive conditions, comorbidities, drug burden, changes in antiparkinson drugs therapy, preventive service use, long-term care stay, death in 2007, all-cause hospitalizations at baseline (January 1, 2006, to May 31, 2006), and IMR. IMR was statistically significant ($P < 0.05$) in all four expenditure outcome models, suggesting the presence of sample selection bias.
† Short DOT was defined as ≤400 d, medium DOT, 401–539 days, and long DOT, 540–578 d.
‡ $P < 0.001$.
§ $P < 0.05$.
‖ Low MPR was defined as < 0.80, moderate MPR, 0.80–0.89, and high MPR, 0.90–1.00.
¶ $P < 0.01$.

behavior pattern by adhering to drug therapy for other chronic conditions. This "healthy behavior" effect, manifested as cross-over adherence from one therapeutic class as a predictor of improved adherence to other therapeutic classes used for other comorbidities, has been demonstrated in separate studies focusing on patients with osteoporosis and depression [50,51].

Our study analyzed DOT and MPR as categorical variables in an attempt to provide more nuanced and informative insights on DOT and MPR distributions, as well as to elucidate the nature of the relationships between categorical measures of DOT and MPR and outcomes. The cutoffs used for DOT and MPR groups, however, do not necessarily reflect clinical outcomes. Also, to our knowledge, there is no consensus on the clinically meaningful threshold of duration of adherence to APDs, although an MPR of 0.8 or more has been commonly used in previous APD studies [14,16–18]. In addition, we measured medication adherence during a refill interval, rather than a fixed time period. The fixed period likely results in an artificially inflated time period by including days when APDs were not much in need for patients with early-stage PD with mild motor symptoms, or days when APDs became unwanted because of their ineffectiveness in the advanced stage of PD. To avoid a possible inflation in the treatment period, we used the refill interval, a period during which APDs were prescribed and refilled for symptom control, to provide accurate estimates of adherence to APDs.

Our study is among the first examining a wide spectrum of utilization outcomes, from routine physician care, acute care, to chronic care, using patients with PD. Also, through correction of sample selection bias, we were able to generalize our findings to Medicare Part D enrollees with PD, although not to beneficiaries who did not enroll in Part D. The non-Part D group, most of whom are beneficiaries with drug creditable plans, tended to be healthier, than Part D enrollees [52]. Thus, when applied to non-Part D enrollees, our finding should be interpreted cautiously. Nevertheless, our population-level, generalizable data are useful for health insurers (e.g., Centers for Medicare & Medicaid Services) in planning interventions to reduce a wide range of preventable procedures, and to further generate health care cost savings.

Several limitations of this study should be noted. First, administrative claims do not have information on general health status and PD severity. We addressed the limitation of general health status for PD by controlling for mortality and baseline utilization in regression models. Furthermore, we conducted a post hoc analysis by using institutionalized status as a proxy of PD severity [53]. The analysis showed similar findings between patients with and without LTC stay (data not shown), suggesting that the confounding effect from PD severity might be minimal. Second, there is no direct measure of cognitive status in administrative claims. We were able, however, to measure the presence of dementia, Alzheimer's disease, and psychosis to define cognitive function, as suggested in previous studies [33,54,55]. Third, prescription claims data do not detail drug response and tolerability. We proxied these factors by using the occurrences of medication switching and/or augmentations based on clinical observations that changes in APDs often occur among patients with poorer response or tolerance to these drugs [7,56]. Fourth, we excluded days of Part A–covered hospital and SNF services from DOT calculation, and this might have led to overestimation of the association of DOT with hospitalizations and SNFs. Nevertheless, the potential effect may be limited because only a small proportion of Part A–covered days was excluded from the total follow-up days (1.2% = 45,388 of 3,802,527 for hospital days; 2.2% = 82,312 of 3,802,527 for SNF days; data now shown). Last, we were unable to account for other potential confounders, such as education and income levels, patients' beliefs on APD use, or surgical intervention with deep brain stimulation (DBS) because of administrative data limitations. Patients with PD with high level of education, high income, and strong beliefs on medication use tended to adhere to the medications [16,57], but might have lower health care utilization and/or medical expenditures than do their counterparts. Thus, the omission of these variables might have attenuated the magnitude of associations observed. Patients with PD who underwent DBS (vs. those without) might have higher utilization and medical costs resulting from the surgical procedure and postoperative care. While these surgery patients tended to be less dependent on APDs [58], their tendency to adhere to the medications was unknown. Thus, omitting DBS in our analyses could have either attenuated or augmented our findings.

Despite our cross-sectional design that cannot assess causality, our study provides significant evidence that improved adherence can potentially reduce health care outcomes. Our next step is to apply these criteria over a longer period by using longitudinal data to confirm causal relationships between medication use and outcomes in a Medicare population. In addition, it is crucial to understand the effect of Part D policies, such as Medication Therapy Management and benefit design, on patients' medication-taking behaviors, and consequent effects on health outcomes and spending in this population.

In conclusion, more than two-thirds of beneficiaries with PD are persistent and adherent with APDs. Higher adherence and longer duration of APD medications were associated with lower utilization of acute and chronic care, as well as lower expenditures for total, Part A, and Part B services. This study provided population-based evidence to clinicians and policymakers regarding the importance of improving medication duration and adherence to APDs among patients with PD. Interventions designed to enhance medication-taking behaviors for patients with PD are needed to avoid health care utilization and generate medical savings.

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