Incidence of Adverse Treatment Effects in Parkinson's Disease: Evidence From a Large Employer Population

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BACKGROUND

- Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic neurons, which causes reduced dopamine production and a resulting loss of motor function.
- The goal of PD treatment is to correct the shortage of dopamine; treatment is often initiated when symptoms become disabling or disrupt daily activities.
- Currently, levodopa is the most effective drug for controlling PD symptoms and for many years was the preferred agent in newly diagnosed patients.[1]
- Because long-term use of levodopa leads to motor complications (e.g., dyskinesias) that can be difficult to manage, physicians often treat patients with dopamine agonists (e.g., pramipexole and ropinirole) and monoamine oxidase B (MAOB) inhibitors (e.g., rasagiline and selegiline) during the early stages of PD.
- Use of these drugs in early-stage PD may allow levodopa use to be delayed. However, these medications, especially dopamine agonists, have more side effects and do not control symptoms as well as levodopa. Moreover, in the long-term, motor complication rates are the same, regardless of what medication is used first.[2]
- In addition to motor complications, there is increasing recognition of and need for quantification of nonmotor symptoms (e.g., impulse behaviors, nausea, sleep attacks, psychoses) associated with PD and its treatments.[3]

OBJECTIVE

- To evaluate the incidence of adverse effects (AEs) commonly associated with PD and its treatments in a large, real-world population.

METHODS

Study Design

- Retrospective analysis of the MarketScan Commercial Claims and Encounters database, an employer- and health plan–sourced database of inpatient, outpatient, and pharmacy claims for > 30 million lives (2000–2011) throughout the United States (US), including retirees in managed Medicare plans.

Patient Selection Criteria

- ≥ 1 PD diagnosis (ICD-9-CM 332.0) between 2000 and 2011.
- ≥ 30 days exposure to ≥ 1 of the following PD regimens:
  - Levodopa monotherapy (L-dopa)
  - Dopamine agonist monotherapy (DA)
  - Anticholinergic monotherapy (AC)
  - L-dopa+DA
  - MAOB inhibitor monotherapy (MAOB)
  - L-dopa+catechol-O-methyltransferase (COMT) inhibitor (L-dopa+COMT)
  - L-dopa+AC
  - L-dopa+MAOB
  - Amantadine monotherapy (AMTD).
- Patients were grouped into nonmutually exclusive cohorts based on exposure to these regimens during postdiagnosis follow-up, regardless of the first-observed regimen.

Figure 1. AE Incidence per 1,000 PYs of PD Regimen Exposure

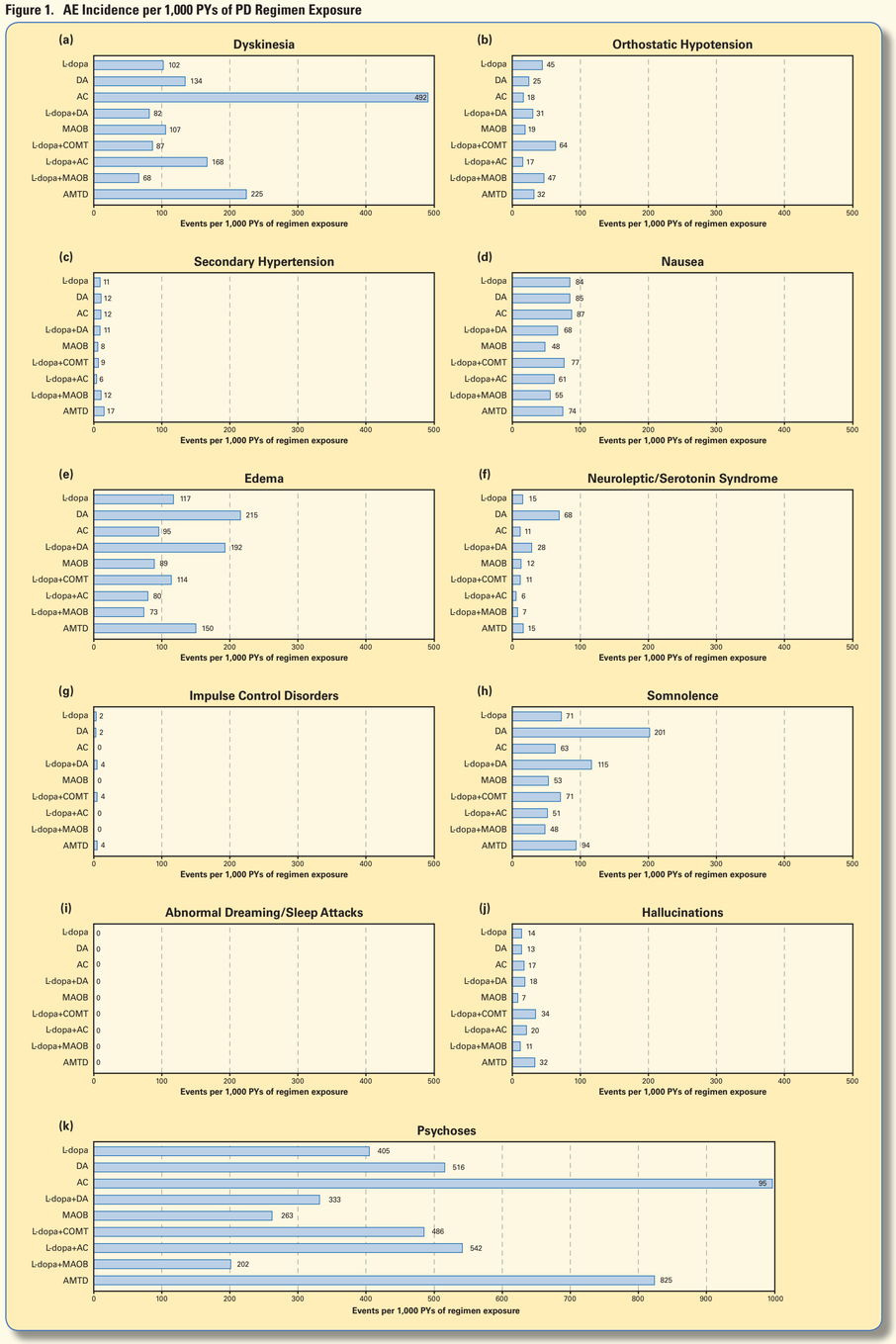

Table 1. Patient Characteristics, by PD Regimen

	Selected Regimen Exposures Observed During Follow-Up (Nonmutually Exclusive)																	
	L-dopa (n = 67,296)		DA (n = 24,357)		AC (n = 4,870)		L-dopa+DA (n = 18,560)		MAOB (n = 6,573)		L-dopa+COMT (n = 8,951)		L-dopa+AC (n = 2,682)		L-dopa+MAOB (n = 6,008)		AMTD (n = 5,483)	
Total PYs of regimen exposure	80,246		18,324		3,314		19,871		3,565		6,965		2,101		4,981		2,383	
Age at first exposure, mean (SD)	74.64	(9.99)	69.13	(11.22)	67.25	(12.31)	70.9	(10.52)	68.46	(11.26)	72.3	(10.14)	70.45	(10.97)	68.45	(10.13)	69.05	(11.16)
Sex (n, %)																		
Male	38,128	56.66	14,071	57.77	2,564	52.65	11,026	59.41	4,070	61.92	5,527	61.75	1,613	60.14	3,798	63.22	3,084	56.25
Geographic region (n, %)																		
Northeast	7,608	11.31	2,340	9.61	543	11.15	2,000	10.78	892	13.57	1,052	11.75	291	10.85	883	14.70	577	10.52
North Central	23,739	35.28	8,679	35.63	1,523	31.27	6,868	37.00	1,885	28.68	3,146	35.15	817	30.46	1,855	30.88	1,864	34.00
South	19,027	28.27	8,606	35.33	1,742	35.77	5,639	30.38	2,222	33.81	2,728	30.48	851	31.73	1,751	29.14	1,850	33.74
West	16,795	24.96	4,670	19.17	1,053	21.62	4,015	21.63	1,565	23.81	2,004	22.39	717	26.73	1,507	25.08	1,184	21.59
Unknown	127	0.19	62	0.25	9	0.18	38	0.20	9	0.14	21	0.23	6	0.22	12	0.20	8	0.15
Payer type (n, %)																		
Commercial	11,146	16.56	8,657	35.54	1,965	40.35	5,510	29.69	2,514	38.25	2,151	24.03	808	30.13	1,667	27.75	1,930	35.20
Medicare managed care	56,150	83.44	15,700	64.46	2,905	59.65	13,050	70.31	4,059	61.75	6,800	75.97	1,874	69.87	4,341	72.25	3,553	64.80
Charlson score, mean (SD)[a]	1.05	(1.73)	1	(1.65)	0.96	(1.67)	0.9	(1.58)	0.68	(1.30)	0.96	(1.60)	0.53	(1.18)	0.71	(1.39)	0.58	(1.35)

[a] Charlson score based on diagnoses observed over a period of up to 6 months before first regimen exposure.

Study Measures

- Patients were followed on AEs defined by ICD-9-CM diagnoses (table of diagnosis codes available upon request) over all observed regimen exposures.
- Patient characteristics (demographics and comorbidities) were measured at initiation of each regimen to which patients had exposure.

Statistical Analyses

- All analyses were descriptive and exploratory in nature; no formal hypotheses were tested.

RESULTS

- In total, 87,373 patients were identified for inclusion (mean [SD] age 72.8 [10.9] years; 56.8% male) (Table 1).
- L-dopa was the largest cumulative exposure (80,246 person-years [PYs]), followed by L-dopa+DA (19,871 PYs) and DA (18,324 PYs).
- Dyskinesia incidence varied by treatment, ranging from 68/1,000 PYs for L-dopa+MAOB to 492/1,000 PYs for AC (Figure 1a).
- Orthostatic hypotension was higher in five of the seven dopamine-containing regimens (64, 47, 45, 31, 25 per 1,000 PYs for L-dopa+COMT, L-dopa+MOAB, L-dopa, L-dopa+DA, and DA, respectively) compared with two of the nondopaminergic regimens (18 and 32 per 1,000 PYs for AC and AMTD, respectively) (Figure 1b).
- Edema incidence was highest during DA (215/1,000 PYs) and L-dopa+DA (192/1,000 PYs) exposures (Figure 1e).
- Somnolence was highest, by far, during DA exposure (201 per 1,000 PYs) (Figure 1h).
- Incidence of psychoses was high for all regimens (range, 202/1,000 PYs for L-dopa+MAOB to 3,500/1,000 PYs for AC) (Figure 1k).
- Abnormal dreaming/sleep attacks and impulse control disorders were not observed, indicating a possible lack of coding for these conditions in routine practice (Figure 1g, Figure 1i).

LIMITATIONS

- We were unable to observe the actual medication-taking behaviors of patients included in the study after prescriptions were filled; therefore, PD regimen exposures in our study represent only prescription acquisition.
- It is not possible in claims data to explicitly link AEs to treatment without additional clinical information. However, because AEs were assessed during known periods of PD drug exposure, such uncertainty may be reduced.
- Our study population primarily consisted of patients in Medicare managed care plans and, therefore, may not be representative of the general Medicare population in the US.
- It is unclear if the associated medications caused the adverse effects or whether they were initiated to limit the side effects of another drug; that is, initiation of treatment because the doctor did not want to worsen side effects by increasing the dose of the offending drug or would be allowed to decrease the dose of the offending drug by adding a new therapy.

CONCLUSIONS

- AE incidence during PD treatment exposure varies by specific regimen.
- Some AEs, such as orthostatic hypotension, appear to be lower in nondopaminergic monotherapies.

FUNDING

This study was funded by Merck Sharp & Dohme Corp.

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Presented at: ISPOR 18th Annual International Meeting
May 18-22, 2013
New Orleans, LA, United States