Comparative Risk 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 the symptoms of PD 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.
- 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.[2]
- Limited data are available from large real-world populations assessing the comparative risk of adverse effects (AEs) across all classes of PD treatments.

OBJECTIVE

- To assess the comparative risk of AEs across common treatment regimens for PD 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 Medicare managed care plans.

Patient Selection

- ≥ 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).
- Mutually exclusive index groups were assigned based on first (index) PD regimen observed.
- Patients had ≥ 6 months preindex plan enrollment.

Figure 1. Adjusted HRs for AE Risk (Reference Group = MAOB)

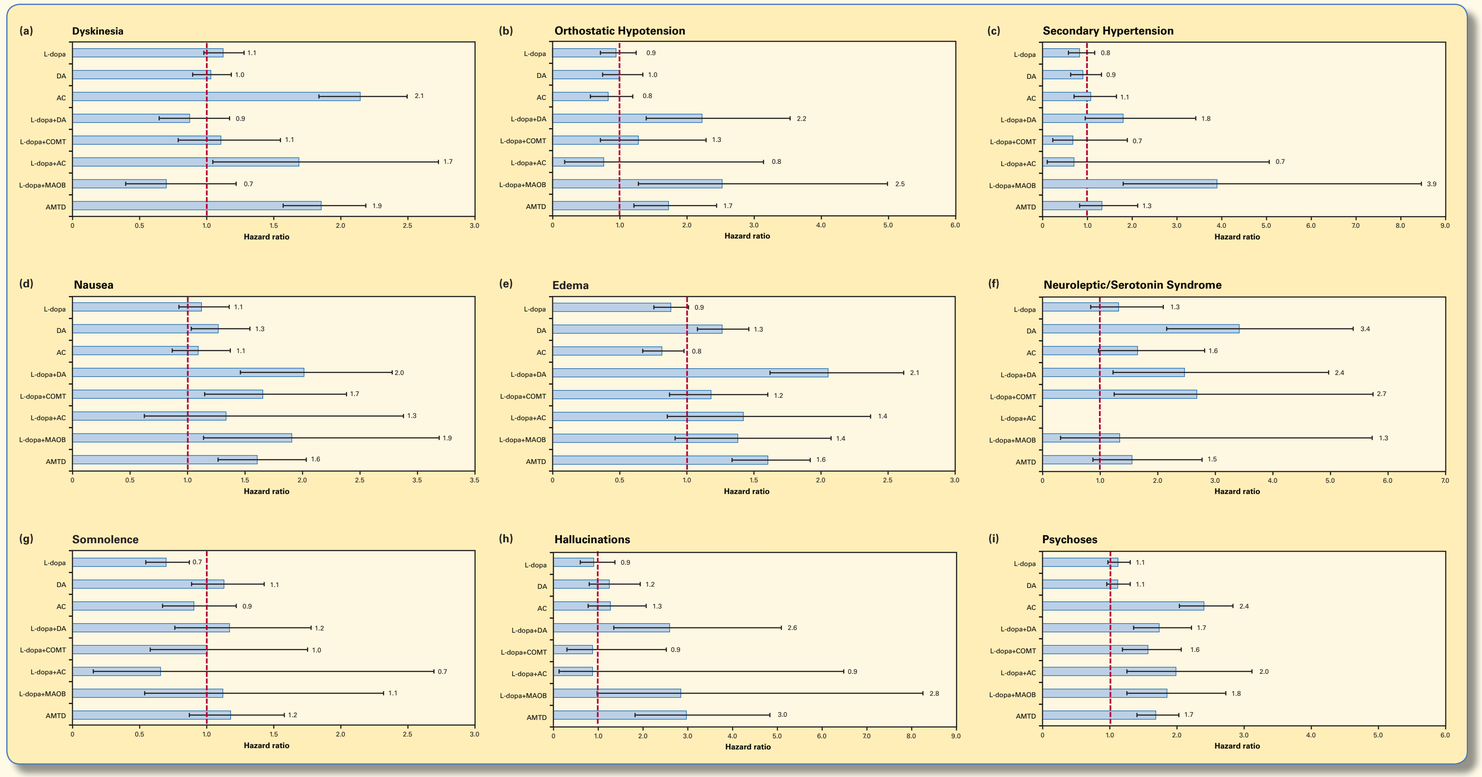

Table 1. Patient Characteristics, by Index PD Regimen

	Index PD Regimen (Mutually Exclusive)																	
	L-dopa (n = 28,249)		DA (n = 7,775)		AC (n = 1,496)		L-dopa+DA (n = 578)		MAOB (n = 1,498)		L-dopa+COMT (n = 343)		L-dopa+AC (n = 106)		L-dopa+MAOB (n = 198)		AMTD (n = 1,409)	
Age at index date, mean (SD)	75.95	(9.72)	67.97	(11.28)	65.90	(12.41)	69.22	(11.44)	66.34	(11.32)	72.93	(10.91)	72.64	(10.75)	69.41	(10.28)	69.07	(11.18)
Sex (n, %)																		
Male	16,251	57.53	4,514	58.06	719	48.06	346	59.86	944	63.02	213	62.10	59	55.66	119	60.10	806	57.20
Geographic region (n, %)																		
Northeast	3,093	10.95	649	8.35	166	11.10	56	9.69	232	15.49	24	7.00	11	10.38	33	16.67	131	9.30
North Central	10,530	37.28	2,836	36.48	495	33.09	247	42.73	356	23.77	121	35.28	34	32.08	45	22.73	552	39.18
South	7,978	28.24	3,014	38.77	542	36.23	155	26.82	533	35.58	123	35.86	28	26.42	78	39.39	477	33.85
West	6,617	23.42	1,262	16.23	289	19.32	117	20.24	374	24.97	75	21.87	32	30.19	39	19.70	248	17.60
Unknown	31	0.11	14	0.18	4	0.27	3	0.52	3	0.20	—	—	1	0.94	3	1.52	1	0.07
Payer type (n, %)																		
Commercial	5,155	18.25	3,732	48.00	772	51.60	269	46.54	819	54.67	106	30.90	32	30.19	90	45.45	592	42.02
Medicare managed care	23,094	81.75	4,043	52.00	724	48.40	309	53.46	679	45.33	237	69.10	74	69.81	108	54.55	817	57.98
Charlson score, mean (SD)[a]	1.23	(1.71)	0.99	(1.51)	1.03	(1.67)	1.04	(1.72)	0.62	(1.10)	1.13	(1.72)	0.97	(1.60)	0.89	(1.49)	0.92	(1.43)

[a] Charlson score based on diagnoses observed over 6 months before the index date.

Study Measures

- Patients were followed on AEs defined by ICD-9-CM diagnoses (table of diagnosis codes available upon request) from index until AE or earliest of the following: new regimen start, plan disenrollment, or end of the database.
- Patient characteristics (demographics and comorbidities) were measured at the index date.

Statistical Analyses

- Patient characteristics were descriptively analyzed with mean and median values for continuous variables and frequency distributions for categorical variables.
- Cox models were estimated for each AE, with covariates for index regimen (reference: MAOB), demographics, and preindex comorbidities and AEs.

RESULTS

- In total, 41,652 patients met the inclusion criteria (mean [SD] age: 73.4 [11.0] years; 57.5% male). (Table 1).
- AC, L-dopa+AC, and AMTD had increased dyskinesia risk relative to MAOB: hazard ratio (HR) (95% confidence interval [CI]): 2.1 (1.8-2.5), 1.7 (1.1-2.7), and 1.9 (1.6-2.2), respectively (Figure 1a).
- L-dopa+DA and L-dopa+MAOB had increased risk of orthostatic hypotension relative to MAOB: HR (CI): 2.2 (1.4-3.5) and 2.5 (1.3-5.0), respectively (Figure 1b).
- L-dopa+DA had the highest edema risk relative to MAOB: HR (CI): 2.1 (1.6-2.6) (Figure 1e).
- L-dopa+DA and AMTD had increased risk of hallucinations relative to MAOB: HR (CI): 2.6 (1.3-5.1) and 3.0 (1.8-4.8), respectively (Figure 1h).
- For 6 of 9 AEs examined, L-dopa+DA had significantly ($P < 0.05$) increased risk relative to MAOB; in 4 of these (orthostatic hypotension, edema, nausea, hallucinations), L-dopa+DA had the highest or second highest HR relative to MAOB among all regimens examined.

LIMITATIONS

- We did not have data on clinical symptoms or other patient characteristics (e.g., race, income status) that may affect both the propensity to initiate specific PD regimens and AE risk.
- Although our study used multivariate Cox regression to control for as many observed confounders as possible, the nonrandomized nature of our study design requires that all associations between treatments and AE risk be interpreted with caution.
- 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.

CONCLUSIONS

- Treatments with high dopaminergic levels (e.g., L-dopa+DA) generally had higher risk of AEs than MAOB monotherapy.
- However, other dopaminergic and nondopaminergic regimens also had higher risk of AEs than MAOB.
- These findings highlight practical challenges presented by current PD treatments.

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