Increased Risk of Falls and Fractures in Patients With Psychosis and Parkinson's Disease

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BACKGROUND

- Psychosis is a common complication of Parkinson's disease (PD), particularly at advanced stages of the disease, with a prevalence up to 75%[1]
- Both PD and PD-related psychosis (PDP) have been separately implicated as risk factors for falls and fractures due to cognitive and motor impairment.[2,3]
- Whether the risk of falls and fractures is higher in patients with PDP compared with patients with PD has not been established.

DISCLOSURES

JF, JBL, JB, and MSA are employees of RTI Health Solutions. MER was an employee of RTI Health Solutions at the time this work was performed. CD, MET, and GD are employees of ACADIA Pharmaceuticals. This study was conducted by RTI Health Solutions with funding from ACADIA Pharmaceuticals.

OBJECTIVES

- To understand whether the risk of falls and fractures differed between patients with PDP and patients who have PD without psychosis at a similar disease stage and to estimate the absolute risks of falls and fractures among patients with PDP and among those with PD without psychosis

METHODS

Data Sources and Population

- This study was conducted using the MarketScan (IBM Watson Health) Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases.
- The study population consisted of all adults in MarketScan aged 40 years or older with a recorded diagnosis of PD occurring between January 1, 2008, and June 30, 2018, with at least 6 months of continuous enrollment before PD diagnosis date, although gaps in enrollment of ≤ 7 days were permitted.
- Patients with a PD diagnosis without psychosis were followed from the first identified PD diagnosis date during the study period (**PD cohort**).
- Patients were excluded from the PD cohort if one of the following exclusion criteria occurred at any point before the qualifying PD diagnosis date:
  - Diagnosis of psychosis
  - Dispensing of an atypical antipsychotic prescription or haloperidol
  - Diagnosis of bipolar disorder, schizophrenic disorders, or Huntington's disease, which are usually treated with antipsychotics
  - Diagnosis of secondary PD, including drug-induced PD, vascular PD, or essential tremor and dementia
  - Diagnosis of a pathologic fracture that may have resulted from conditions such as cancer, infection, osteomalacia, and Paget's disease
- Psychosis was identified on or after the PD diagnosis date. After a noted psychosis diagnosis, patients were included in the **PDP cohort**.
- Patients were excluded from the PDP cohort if one of the following exclusion criteria occurred at any point before the qualifying psychosis diagnosis date:
  - Prior dispensing of an atypical antipsychotic prescription or haloperidol
  - Diagnosis of bipolar disorder, schizophrenic disorders, or Huntington's disease, which are usually treated with antipsychotics
  - Diagnosis of secondary PD, including drug-induced PD, vascular PD, or essential tremor and dementia
  - Diagnosis code for a pathologic fracture that may have resulted from conditions such as cancer, infection, osteomalacia, and Paget's disease
- To more directly compare the rates of falls and fractures between patients with PDP and those with PD without psychosis, we matched patients with PDP to patients with PD without psychosis at similar points in their disease trajectories using a sequential propensity score matching approach (Figure 1).

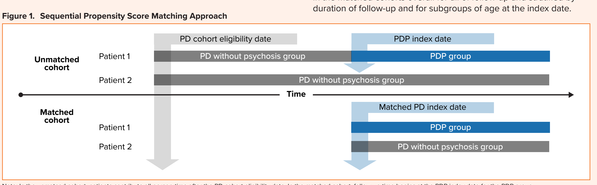
Variables

- Outcomes included the following[4]:
  - Falls (identified from diagnosis coding)
  - Fractures (identified from diagnosis coding coupled with a procedure code for a fracture repair)
    - Site-specific fractures of interest (femur, hip, pelvis, upper limb, vertebral)
  - Composite falls and/or fractures
- Covariates included patient demographics, frailty indicators, fall/fracture risk factors, comorbidities, comedication use, and health care utilization

Statistical Approach

- Descriptive statistics were used to compare baseline characteristics between the groups of patients with and without psychosis, both in the unmatched and matched cohorts.
- Within the unmatched and propensity-matched cohorts, we estimated crude incidence rates (IRs) for composite falls/fracture, falls, and fractures for the PD and PDP cohorts.
- IRs and incidence rate ratios (IRR) of each outcome were estimated in the matched cohorts overall for all of follow-up and stratified by duration of follow-up and for subgroups of age at the index date.

Figure 1. Sequential Propensity Score Matching Approach

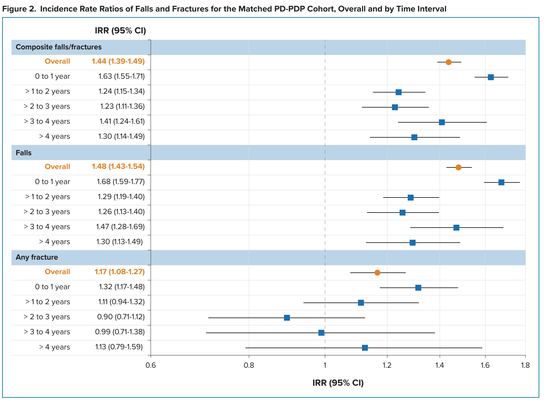


Note: In the unmatched cohort, patients contribute all person-time after the PD cohort eligibility date. In the matched cohort, follow-up time begins at the PDP index date for the PDP group or a matched PD index date.

RESULTS

- We identified 154,841 patients with PD in total before matching.
  - 154,339 had PD without psychosis (33 patients had a composite fall and/or fracture before the index date that resulted in the patient not contributing time at risk, leaving 154,306 patients in the analysis).
  - 12,132 patients received a diagnosis of psychosis on or after the PD diagnosis date and were included in the PDP group (5 patients had a composite fall and/or fracture before the index date that resulted in the patient not contributing time at risk, leaving 12,127 patients in the analysis).
- Patients in the PDP group were generally sicker than those in the PD without psychosis group, as evidenced by higher rates of comorbidities, frailty indicators, health care utilization, and risk factors associated with falls and fractures than those in the PD without psychosis group (Table 1).
- The IR for composite falls and/or fractures in patients with PD was 11.41 events per 100 person-years (95% confidence interval [CI], 11.29-11.53). Most of the events in both groups were falls. The IR of composite falls and/or fractures among patients with PDP was 29.03 per 100 person-years (95% CI, 28.27-29.81) (Table 2).
- After matching, 24,144 (15.6%) patients with PD without psychosis and 12,077 (99.6%) with PDP were retained (Table 2). Within the matched groups, patients with PDP had higher incidences of composite falls and/or fractures than those without psychosis (IRR = 1.44; 95% CI, 1.39-1.49). The increased rate was noted separately for falls, for any fractures, and within specific types of fracture, including pelvis and hip fractures.
- When stratified by follow-up time, the highest IRR was observed in the period of up to 1 year after the index date for all outcomes (Figure 2). While the IRRs observed in later periods of follow-up for the composite falls/fractures outcome and falls alone were lower than in the 0- to 1-year interval, they were still consistently increased above the null.

Figure 2. Incidence Rate Ratios of Falls and Fractures for the Matched PD-PDP Cohort, Overall and by Time Interval



Note: In the unmatched cohort, patients contribute all person-time after the PD cohort eligibility date. In the matched cohort, follow-up time begins at the PDP index date for the PDP group or a matched PD index date.

Table 1. Selected Descriptive Characteristics Present in at Least 10% of Patients With PDP and Patients With PD Without Psychosis, Before Matching of Patients With PDP

Demographic	Overall[a] (N = 154,841)	PD Without Psychosis[b] (n = 154,339)	PDP (n = 12,132)
Age at index, mean (SD)	72.2 (11.56)	72.2 (11.56)	78.1 (9.24)
Sex, female, n (%)	61,658 (39.8)	61,472 (39.8)	4,773 (39.3)
Frailty indicators, n (%)			
Ambulance/life support	33,006 (21.3)	32,820 (21.3)	7,073 (58.3)
Arthritis	71,362 (46.1)	71,103 (46.1)	8,427 (69.5)
Bladder dysfunction	23,040 (14.9)	22,940 (14.9)	4,038 (33.3)
Cancer screening	42,339 (27.3)	42,244 (27.4)	3,570 (29.4)
Dementia	41,702 (26.9)	41,463 (26.9)	7,416 (61.1)
Difficulty walking	44,696 (28.9)	44,514 (28.8)	7,067 (58.3)
Heart failure	24,723 (16.0)	24,604 (15.9)	4,201 (34.6)
Lipid abnormality	73,850 (47.7)	73,598 (47.7)	7,461 (61.5)
Sepsis	24,953 (16.1)	24,854 (16.1)	4,229 (34.9)
Stroke/brain injury	20,013 (12.9)	19,901 (12.9)	4,015 (33.1)
Vertigo	26,662 (17.2)	26,529 (17.2)	4,038 (33.3)
Weakness	21,935 (14.2)	21,824 (14.1)	4,346 (35.8)
Components of Charlson Comorbidity Index, n (%)			
Chronic obstructive pulmonary disease	25,905 (16.7)	25,796 (16.7)	3,481 (28.7)
Diabetes mellitus	37,095 (24.0)	36,947 (23.9)	3,971 (32.7)
Peripheral vascular disease	26,450 (17.1)	26,318 (17.1)	4,179 (34.4)
Tumor	20,755 (13.4)	20,678 (13.4)	2,486 (20.5)
Other risk factors of falls or fractures, n (%)			
Delirium	22,233 (14.4)	22,061 (14.3)	6,031 (49.7)
Depression	25,705 (16.6)	25,584 (16.6)	4,211 (34.7)
Malnutrition	11,980 (7.7)	11,910 (7.7)	2,545 (21.0)
Orthostatic hypotension	5,431 (3.5)	5,399 (3.5)	1,482 (12.2)
Osteoporosis	13,835 (8.9)	13,776 (8.9)	1,886 (15.5)
Concomitant medications,[d] n (%)			
Anticholinesterase inhibitors	11,821 (7.6)	11,762 (7.6)	2,084 (17.2)
Antidepressants	37,076 (23.9)	36,965 (24.0)	3,871 (31.9)
Benzodiazepines	24,398 (15.8)	24,327 (15.8)	2,394 (19.7)
Diuretics	34,042 (22.0)	33,943 (22.0)	3,124 (25.8)
PD drugs[e]	80,564 (52.0)	80,441 (52.1)	6,672 (55.0)
Health care utilization, mean (SD)[f]			
Number of hospitalizations	0.2 (0.47)	0.2 (0.47)	0.5 (0.72)
Number of emergency department visits	0.5 (1.07)	0.5 (1.07)	1.3 (1.69)

SD = standard deviation.

Note: All characteristics were assessed during the entire look-back period unless otherwise stated. Patients could contribute to both PD and PDP groups.

[a] All patients were evaluated on their PD cohort eligibility date.

[b] Patients who did not have a psychosis diagnosis on or before their PD cohort eligibility date.

[c] Patients who met the criteria to enter the PDP cohort; evaluated on their first psychosis diagnosis date.

[d] Assessed in a look-back period of up to 1 year before the corresponding cohort entry/eligibility date.

[e] Composed of levodopa-carbidopa, anticholinergics, dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors.

[f] Assessed in the 6 months before the corresponding cohort entry/eligibility date.

Table 2. Incidence Rates and Incidence Rate Ratios of Falls and Fractures for the Matched PD-PDP Cohort[a]

Outcome	Group	No. of Patients	No. of Events	No. of Person-Years	IR (95% CI) per 100 Person-Years	IRR (95% CI)
Unmatched cohort						
Composite falls/fractures	PDP	12,127	5,453	18,783	29.03 (28.27-29.81)	NA
	PD[b]	154,306	36,341	318,488	11.41 (11.29-11.53)	NA
Matched cohort						
Composite falls/fractures	PDP	12,077	5,434	18,735	29.00 (28.24-29.79)	1.44 (1.39-1.49)
	PD[b]	24,144	7,497	37,211	20.15 (19.69-20.61)	Reference
Falls	PDP	12,078	4,859	18,746	25.92 (25.20-26.66)	1.48 (1.43-1.54)
	PD[b]	24,147	6,512	37,230	17.49 (17.07-17.92)	Reference
Any fracture	PDP	12,081	941	18,823	5.00 (4.68-5.33)	1.17 (1.08-1.27)
	PD[b]	24,156	1,597	37,324	4.28 (4.07-4.49)	Reference

[a] Patients who met the criteria for the PDP cohort were evaluated on their psychosis diagnosis date and were matched; patients with PD without psychosis who were selected for the matched cohort were evaluated on the date of the matched PD diagnosis.

[b] Patients with PD without psychosis.

DISCUSSION

- Patients within this study were older and had more comorbidities, more frailty indicators, and more antipsychotic use at the time of PDP diagnosis than at the time of the initially identified PD diagnosis.
- Based on the results in the unmatched PD and PDP cohorts, higher risk for composite falls and/or fractures in patients with PDP compared with patients with PD without psychosis may be attributed to age, disease trajectory, comorbidities, medication use, or a sudden change in disease symptomology.
  - In the matched PD and PDP cohort analysis, these variables were accounted for in the design and analysis to the extent possible using diagnoses, procedures, and medication dispensing in claims data. After accounting for other risk factors, psychosis appears to be an independent risk factor contributing to the risk of falls and fractures.
- Potential limitations of this study arise from the use of coded insurance billing information rather than clinical data, which may introduce the potential for missing or misclassified study variables, including the following:
  - Not all falls may be medically attended, and thus falls identified with diagnosis codes likely represent a subset of all falls, and perhaps only more severe events.
  - Similarly, not all fractures may require repair, and thus only a subset of the more severe events would be represented by our case algorithm; fractures among frail individuals with limited life expectancy may be less likely to be repaired.
  - Prescription claims for medications indicate that a prescription has been dispensed by a pharmacy, but it may not reflect actual exposure to medications and use by the patient.

CONCLUSIONS

- The present study suggests a modest but precise and consistent higher risk of falls and fractures in patients with PDP compared with patients with PD.

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