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Exploring the neuroprotective potential of immunosuppressants in Parkinson's disease

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ABSTRACT

Introduction: Neuroprotective therapy to slow Parkinson's disease (PD) progression is a critical unmet need. Neuroinflammation likely represents an important pathophysiologic mechanism for disease progression. Medications that target this inflammation, such as immunosuppressants, represent potential disease-modifying therapies for PD. The relation between these medications and PD risk might inform candidate selection.
Methods: We conducted a population-based case-control study using Medicare data from the United States. The study included 207,532 incident PD cases and 975,177 controls from 2016 to 2018, age 67–110. We examined the association between PD risk and immunosuppressant use before PD diagnosis/control selection. We considered 37 immunosuppressants, representing >10 medication classes, in Part D prescription claims. We used logistic regression to estimate the relative risk (RR) and 95 % confidence interval (CI) between each medication and PD, while accounting for age, sex, race/ethnicity, smoking, and healthcare utilization. In sensitivity analyses we applied exposure lagging, restricted to immunosuppressant users, and corrected for multiple comparisons.
Results: Medicare beneficiaries using the calcineurin inhibitor tacrolimus (RR 0.49, CI 0.40–0.60) and mTOR inhibitors everolimus (RR 0.38, CI 0.26–0.56) and sirolimus (RR 0.59, CI 0.37–0.93) had a lower risk of PD compared to those not taking the medication. The TNF inhibitor certolizumab was also associated with lower PD risk (RR 0.54, CI 0.34–0.84). Tacrolimus and everolimus remained significant after Bonferroni correction. Sensitivity analyses otherwise confirmed results for all four medications.
Conclusion: Calcineurin or mTOR inhibition might reduce PD risk. Future studies should examine whether these medications or structurally similar agents might have potential as disease-modifying therapies for PD.

1. Introduction

Parkinson's disease (PD) is a multi-system and multi-symptomatic neurodegenerative disorder for which the pathologic hallmark of PD is loss of nigral neurons and intraneuronal α-synuclein aggregation in Lewy bodies and Lewy neurites. While the pathogenic role of these aggregates is uncertain, neuroinflammation may contribute to the PD pathogenic process [1,2]. Numerous symptomatic therapies for PD exist, but identification of a disease-modifying therapy remains elusive. Given the inevitable disease progression in PD, there is an urgent need to identify disease-modifying therapies.

Recently, several investigators have harnessed the power of large administrative datasets to attempt to screen and identify neuroprotective medications [3–5]. Multiple lines of evidence implicate neuroinflammation in the pathogenesis of PD and progression of other neurodegenerative diseases [6–8]. Immunosuppressants can decrease inflammation, but epidemiologic studies are mixed whether immunosuppressants might reduce PD risk [3–5,9–12]. We used a large, population-based United States (U.S.) Medicare dataset to examine the association between the use of immunosuppressant medications and subsequent risk of PD to identify potential novel disease-modifying medications that could possibly be repurposed as neuroprotective

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therapies.

2. Methods

2.1. Study design

Utilizing Medicare data from 2014 to 2018, we conducted a population-based case-control study of incident PD cases and controls in 2016–2018. To construct the sample of cases and controls and to obtain medical and demographic information, we used the following Medicare data files: Medicare beneficiary summary file, along with Medicare carrier (physician/supplier Part B), outpatient, inpatient, skilled nursing facility, hospice, durable medical equipment, home health care, and Medicare Part D (prescription medication) claims data. The inclusion criteria for both cases and controls required the following in the month of PD diagnosis or control selection: age-eligible for Medicare for ≥2 years (age≥67), age ≤110, Medicare Part A, B, and D coverage, absence of Medicare Part C (Medicare Advantage plan) coverage, and residency in the U.S. (50 states or Washington, D.C.). We applied similar criteria to a previous Medicare-based pharmacoepidemiologic study [9] to ensure a population-based sample with complete medical and pharmacy claims information. After necessarily restricting to beneficiaries age-eligible for Medicare, historically [13] and in the present newer study, the primary exclusions pertained to Part C and Part D coverage, with both types of coverage becoming more common over time. This records-based study was approved by the Washington University School of Medicine and the Barrow Neurological Institute Institutional Review Boards and the Center for Medicare & Medicaid Services (CMS) as exempt from need for consent due to data de-identification.

2.2. Case ascertainment

We determined PD case status from comprehensive (inpatient, skilled nursing facility, outpatient, physician/carrier, durable medical equipment, home health care, and hospice) Part A and B claims. Incident PD cases were defined as having ≥1 International Classification of Diseases (ICD) 9th or 10th Clinical Modification (ICD-9-CM, ICD-10-CM) diagnosis code for PD in 2016–2018 (ICD-10-CM: G20) and no years prior (ICD-10-CM: G20 or ICD-9-CM: 332.0). This approach nearly optimizes sensitivity at 84.4 % while still achieving a specificity of 99.0 % [14]. We excluded those with a history of dementia with Lewy bodies (ICD-9-CM: 331.82; ICD-10-CM: G31.83) or atypical parkinsonism (ICD-9-CM: 333.0; ICD-10-CM: G23.1, G23.2, G23.8, G23.9, or G90.3). Otherwise, we included all incident PD cases who met all study inclusion criteria.

2.3. Control selection

Eligible controls were Medicare beneficiaries who, at selection, also met the study inclusion criteria and did not have a history of PD, dementia with Lewy bodies, or atypical parkinsonism. Prior to applying the Part D coverage criteria, which was specific for the present pharmacoepidemiologic study, we randomly selected controls 5:1 to cases while frequency matching on the month and year of case diagnosis. We did not match on demographic factors because our large sample size allowed full adjustment for these factors without matching.

2.4. Exposure ascertainment

Using Medicare Part D data from 2014 to 2018, we identified use of immunosuppressants as a binary variable (yes/no for the respective active ingredient, hereafter "medication") any time in this period prior to the PD diagnosis or control selection date. We excluded medications available over the counter and non-systemic formulations (e.g., topical and ophthalmologic) from this analysis. In total, 37 medications across >10 categories of immunosuppressants were available for analysis, i.e., used by > 10 cases and >10 controls (per CMS requirements) in this period: calcineurin inhibitors (tacrolimus and cyclosporine), corticosteroids that can suppress the immune system (prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, hydrocortisone, cortisone, and flunisolide), antimetabolites (hydroxyurea, mercaptopurine, and fluorouracil), dihydrofolate reductase (DHFR) inhibitors (methotrexate), mammalian target of rapamycin (mTOR) inhibitors (everolimus and sirolimus), Janus kinase (JAK) inhibitors (tofacitinib), inosine monophosphate dehydrogenase (IMDH) inhibitors (ribavirin, mycophenolate, azathioprine, and leflunomide), tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab, etanercept, and golimumab), miscellaneous immunosuppressants (hydroxychloroquine, sulfasalazine, mesalamine, interferon, thalidomide, glatiramer, and fingolimod), and biologics (infliximab, secukinumab, tocilizumab, ustekinumab, and rituximab).

2.5. Assessment of covariates

We obtained age, sex, and race/ethnicity as reported in the Medicare beneficiary summary file for the year of diagnosis/selection. We estimated the probability of having ever smoked using a validated algorithm we developed for application in Medicare data to estimate this probability for each individual [15]. We also calculated the number of unique diagnosis codes (before the diagnosis/selection date minus the respective exposure lagging period) for each beneficiary as a measure of healthcare utilization [2].

2.6. Statistical analysis

Using Stata/MP version 17, we constructed a logistic regression model for each medication with PD as the outcome and the medication of interest as the independent variable to calculate the adjusted odds ratio to estimate the relative risk (RR) and 95 % confidence interval (CI). We adjusted *a priori* for age (continuous), sex (male/female), and race/ethnicity (non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, Native American, and other), smoking probability (continuous), and healthcare utilization in all models. We previously demonstrated that the latter is a critical confounder in epidemiology studies of PD [2].

We performed a series of sensitivity analyses to assess resiliency of results. First, we used an alternative metric for healthcare utilization, the number of types of specialists seen [2]. Second, we applied exposure lagging up to the maximum possible, a 3-year lag, in order to address potential effects of the prodromal period on medication use. In these models we adjusted for healthcare utilization metrics calculated up to the lag date, unless specified, and restricted to beneficiaries who had filled a Part D prescription for any medication before that date. Third, we restricted to beneficiaries who had used any of the 37 immunosuppressants, similar to the active comparator design [16], which helps address confounding by indication. We did not simultaneously apply the new user design, as the prodromal period would render this design unable to identify causal associations. We also did not implement propensity score matching to further examine potential for confounding because we encountered positivity assumption violations for several of the medications. Fourth, we attempted to adjust for use of other immunosuppressants used for these same indications in multi-medication models, specifically lasso regression to address multicollinearity. Finally, given the many statistical comparisons, we applied a Bonferroni correction for multiple comparisons.

As complementary exploratory analyses for the medications that demonstrated resiliency in the above sensitivity analyses, we examined the following: 1) dose-response associations, specifically maximum dosage (mg/day) from January 2014 to PD diagnosis/control reference date (2–5 years prior), among cases and controls who ever used the respective medication; and 2) associations between the respective medications and risk of dementia with Lewy bodies or risk of atypical parkinsonism.

3. Results

3.1. Characteristics of beneficiaries

We included 207,532 incident PD cases and 975,177 controls in our study. Demographics of our cases relative to controls were consistent with previous studies (Table 1). PD cases (78.8 years, SD 7.3) were slightly older than controls, (75.8 years, SD 7.4). Proportionally more PD cases than controls were male and White, and cases appeared less likely to have ever smoked.

3.2. Immunosuppressants inversely associated with PD

Numerous immunosuppressants across multiple classes were inversely associated with PD in our primary analysis, as well as with dementia with Lewy bodies (Table 2; Supplemental Table 1). However, in our sensitivity analyses, we found RRs were somewhat sensitive to the length of exposure lagging and to our method of adjustment for healthcare utilization. Results generally stabilized and converged, respectively, regarding these two factors (Table 2), as well as with the results of our active comparator sensitivity analysis (Table 3), at approximately 24 months of exposure lagging. Although our sample size diminished with this 2-year exposure lag, especially with the simultaneous application of the active comparator design, several immunosuppressants remained consistently associated with an approximately 30–50 % lower risk across analyses (Tables 2 and 3). In particular, the calcineurin inhibitor, tacrolimus, was associated with a significantly lower risk of PD, in contrast to cyclosporine in the same medication class, for which no inverse association was suggested. In addition, both mTOR inhibitors we considered, particularly everolimus but also sirolimus, albeit with a wider CI that included unity in our sensitivity analyses, were inversely associated with PD. Finally, the TNF inhibitor certolizumab also was inversely associated with PD consistently. Although used too infrequently to consider in our sensitivity analyses, rituximab was associated with similarly lowered risk. All the above five inversely associated medications remained in lasso regression, with the inverse RRs for tacrolimus and everolimus still particularly marked. Tacrolimus and everolimus also remained significant after Bonferroni correction for multiple comparisons in our primary analysis.

For the four medications with the strongest results and common enough to apply a 2-year lag while restricting to individuals who had received the respective medication, we observed RR point estimates below one for three of the medications when we investigated dose-response associations: RR 0.994 (95 % CI 0.981–1.006) per mg/day of certolizumab (median 14.28 mg); RR 0.830 (95 % CI 0.670–1.026) per mg/day of everolimus (median 10 mg); and RR 0.880 (95 % CI

Table 1
Characteristics of incident Parkinson's disease (PD) cases and controls, U.S. Medicare 2016–2018.

	PD Cases	Controls
	N = 207,532	N = 975,177
	%	%
Sex		
Male	50.7	39.9
Female	49.3	60.1
Age		
Mean (SD)	78.8 (7.3)	75.8 (7.4)
Median (range)	78 (67–109)	74 (67–110)
Race/ethnicity		
Non-Hispanic White	83.9	83.3
Black	5.9	7.1
Hispanic	6.0	5.3
Asian/Pacific Islander	3.2	3.2
Native American	0.3	0.4
Other	0.7	0.7
Smoking index[a] > median	34.0	48.8
Healthcare utilization (number of unique diagnosis codes)[b]		
Mean (SD)	108.4 (67.7)	73.1 (52.6)
Median (range)	97 (0–650)	61 (0–630)

Abbreviations: PD = Parkinson's disease; SD = standard deviation.
[a] Estimated probability of ever smoking tobacco (Faust et al., 2023) divided by the number of unique diagnosis codes (or by one if no codes) (Searles Nielsen et al., 2017).
[b] Prior to PD diagnosis or control reference.

Table 2
Immunosuppressants and Parkinson's disease (PD) risk, U.S. Medicare 2016–2018.

Immunosuppressant (systemic forms only)	PD Cases N = 207,532 n (%)	Controls N = 975,177 n (%)	RR[a]	95 % CI[a]
Calcineurin inhibitors				
Cyclosporine	120 (0.1)	432 (0.04)	0.90	(0.73–1.12)
Tacrolimus	117 (0.1)	688 (0.1)	**0.49**	**(0.40–0.60)**
Corticosteroids				
Prednisone	56,195 (27.1)	244,226 (25.0)	**0.81**	**(0.80–0.82)**
Methylprednisolone	35,308 (17.0)	159,609 (16.4)	**0.83**	**(0.82–0.84)**
Dexamethasone	4348 (2.1)	18,716 (1.9)	**0.83**	**(0.80–0.86)**
Hydrocortisone	817 (0.4)	2381 (0.2)	0.97	(0.89–1.06)
Flunisolide	390 (0.2)	1438 (0.2)	1.01	(0.90–1.14)
Prednisolone	281 (0.1)	1018 (0.1)	0.89	(0.78–1.03)
Triamcinolone	245 (0.1)	526 (0.05)	**1.30**	**(1.11–1.53)**
Cortisone	13 (0.01)	21 (0.002)	2.10	(0.99–4.47)
Antimetabolites				
Fluorouracil	6135 (3.0)	25,974 (2.7)	**0.81**	**(0.79–0.84)**
Hydroxyurea	525 (0.3)	2038 (0.2)	**0.89**	**(0.80–0.98)**
Mercaptopurine	95 (0.1)	490 (0.1)	**0.75**	**(0.60–0.94)**
DHFR inhibitors				
Methotrexate	3152 (1.5)	14,575 (1.5)	**0.86**	**(0.83–0.90)**
mTOR inhibitors				
Everolimus	30 (0.01)	249 (0.03)	**0.38**	**(0.26–0.56)**
Sirolimus	25 (0.01)	107 (0.01)	**0.59**	**(0.37–0.93)**
JAK inhibitors				
Tofacitinib	83 (0.04)	320 (0.03)	0.89	(0.69–1.16)
IMDH inhibitors				
Leflunomide	703 (0.3)	2996 (0.3)	**0.82**	**(0.75–0.90)**
Azathioprine	604 (0.3)	2495 (0.3)	**0.87**	**(0.79–0.96)**
Mycophenolate	391 (0.2)	1568 (0.2)	**0.77**	**(0.68–0.86)**
Ribavirin	92 (0.04)	513 (0.05)	**0.69**	**(0.55–0.87)**
TNF inhibitors				
Adalimumab	322 (0.2)	1466 (0.2)	0.89	(0.78–1.01)
Etanercept	264 (0.1)	1395 (0.1)	**0.79**	**(0.69–0.91)**
Certolizumab	25 (0.01)	148 (0.02)	**0.54**	**(0.34–0.84)**
Golimumab	23 (0.01)	107 (0.01)	0.79	(0.49–1.26)
Biologics				
Ustekinumab	32 (0.02)	175 (0.02)	0.80	(0.54–1.18)
Tocilizumab	27 (0.01)	89 (0.01)	1.01	(0.64–1.59)
Infliximab	20 (0.01)	76 (0.01)	0.88	(0.52–1.50)
Secukinumab	13 (0.01)	74 (0.01)	0.59	(0.31–1.09)
Rituximab	12 (0.01)	64 (0.01)	**0.51**	**(0.26–0.98)**
Miscellaneous				
Hydroxychloroquine	2536 (1.2)	12,378 (1.3)	**0.81**	**(0.77–0.85)**
Mesalamine	1584 (0.8)	6223 (0.6)	**0.89**	**(0.84–0.95)**
Sulfasalazine	960 (0.5)	4278 (0.4)	**0.85**	**(0.79–0.92)**
Glatiramer	154 (0.07)	372 (0.04)	**2.11**	**(1.73–2.58)**
Interferon	151 (0.07)	411 (0.04)	**1.92**	**(1.58–2.34)**
Thalidomide	17 (0.01)	62 (0.01)	0.70	(0.39–1.24)
Fingolimod	12 (0.01)	38 (0.004)	1.94	(0.99–3.80)

Bold is for significant results ($p < 0.05$).
Abbreviations: CI = confidence interval; DHFR = dihydrofolate reductase; IMDH = inosine monophosphate dehydrogenase; JAK = Janus kinase; mTOR = mammalian target of rapamycin; PD = Parkinson's disease; RR = relative risk; TNF = tumor necrosis factor.
[a] Relative risk adjusted for age (continuous), sex, race/ethnicity, smoking, and healthcare utilization.

Table 3
Two-year lagged systemic immunosuppressant exposure and Parkinson's disease (PD) risk, overall and among those using any immunosuppressant, U.S. Medicare 2016–2018.

Immunosuppressant class	Immunosuppressant (systemic forms only)	PD Cases N = 184,164[a] n (%)	Controls N = 816,842[a] n (%)	2-year lagged RR (95 % CI)[a]	2-year lagged active comparator RR (95 % CI)[a,b]
Calcineurin inhibitors	Tacrolimus	79 (0.04)	467 (0.06)	**0.68 (0.53–0.87)**	**0.72 (0.57–0.92)**
	Cyclosporine	76 (0.04)	271 (0.03)	1.11 (0.86–1.44)	1.18 (0.91–1.53)
Corticosteroids	Prednisone	28,187 (15.3)	115,288 (14.1)	**0.90 (0.89–0.91)**	**0.96 (0.94–0.98)**
	Methylprednisolone	16,635 (9.0)	70,397 (8.6)	**0.89 (0.88–0.91)**	**0.95 (0.93–0.97)**
	Dexamethasone	1672 (0.9)	7262 (0.9)	**0.86 (0.81–0.91)**	**0.92 (0.87–0.97)**
	Hydrocortisone	460 (0.3)	1322 (0.2)	**1.23 (1.10–1.38)**	**1.32 (1.18–1.47)**
	Flunisolide	248 (0.13)	826 (0.1)	**1.17 (1.01–1.35)**	**1.26 (1.08–1.45)**
	Prednisolone	111 (0.1)	432 (0.1)	0.93 (0.75–1.15)	1.00 (0.81–1.24)
	Triamcinolone	93 (0.05)	228 (0.03)	1.27 (0.99–1.63)	**1.38 (1.07–1.77)**
	Cortisone[c]	–	–	–	–
Antimetabolites	Fluorouracil	2825 (1.5)	10,726 (1.3)	**0.89 (0.85–0.93)**	**0.94 (0.90–0.98)**
	Hydroxyurea	340 (0.2)	1352 (0.2)	0.93 (0.82–1.05)	1.00 (0.88–1.13)
	Mercaptopurine	76 (0.04)	363 (0.04)	0.91 (0.70–1.17)	0.96 (0.74–1.23)
DHFR inhibitors	Methotrexate	2248 (1.2)	10,108 (1.2)	0.97 (0.92–1.02)	1.03 (0.98–1.08)
mTOR inhibitors	Sirolimus	15 (0.01)	73 (0.01)	0.70 (0.39–1.23)	0.74 (0.42–1.31)
	Everolimus	12 (0.01)	94 (0.01)	**0.48 (0.26–0.90)**	**0.51 (0.28–0.95)**
JAK inhibitors	Tofacitinib	45 (0.02)	138 (0.02)	1.39 (0.98–1.96)	**1.47 (1.04–2.08)**
IMDH inhibitors	Leflunomide	421 (0.2)	1764 (0.2)	0.99 (0.88–1.10)	1.05 (0.94–1.17)
	Azathioprine	382 (0.2)	1674 (0.2)	0.96 (0.85–1.07)	1.01 (0.91–1.14)
	Mycophenolate	229 (0.1)	980 (0.1)	0.88 (0.76–1.02)	0.93 (0.81–1.08)
	Ribavirin	63 (0.03)	306 (0.04)	0.89 (0.68–1.17)	0.95 (0.72–1.26)
TNF inhibitors	Adalimumab	216 (0.1)	977 (0.1)	0.99 (0.86–1.16)	1.05 (0.91–1.22)
	Etanercept	209 (0.1)	1077 (0.1)	0.89 (0.77–1.04)	0.94 (0.81–1.10)
	Certolizumab	17 (0.01)	92 (0.01)	0.67 (0.39–1.15)	0.72 (0.42–1.23)
	Golimumab	14 (0.01)	72 (0.01)	0.92 (0.51–1.65)	0.97 (0.54–1.74)
Biologics	Ustekinumab	18 (0.01)	83 (0.01)	1.05 (0.63–1.76)	1.11 (0.66–1.85)
	Infliximab	13 (0.01)	52 (0.01)	1.05 (0.56–1.98)	1.13 (0.60–2.12)
	Secukinumab[c]	–	–	–	–
	Tocilizumab[c]	–	–	–	–
	Rituximab[c]	–	–	–	–
Miscellaneous	Hydroxychloroquine	1750 (0.95)	8304 (1.02)	**0.94 (0.89–0.99)**	1.00 (0.95–1.06)
	Mesalamine	1085 (0.6)	4131 (0.5)	1.01 (0.95–1.09)	**1.08 (1.01–1.16)**
	Sulfasalazine	627 (0.3)	2666 (0.3)	0.96 (0.88–1.05)	1.02 (0.93–1.12)
	Interferon	126 (0.07)	338 (0.04)	**2.18 (1.77–2.69)**	**2.28 (1.85–2.81)**
	Glatiramer	124 (0.07)	303 (0.04)	**2.34 (1.88–2.89)**	**2.43 (1.96–3.01)**
	Thalidomide	14 (0.01)	38 (0.005)	1.33 (0.70–2.52)	1.44 (0.76–2.73)
	Fingolimod[c]	–	–	–	–

Bold is for significant results ($p < 0.05$).
Abbreviations: CI = 95 % confidence interval; DHFR = dihydrofolate reductase; IMDH = inosine monophosphate dehydrogenase; JAK = Janus kinase; mTOR = mammalian target of rapamycin; PD = Parkinson's disease; RR = relative risk; TNF = tumor necrosis factor.
[a] Relative risk adjusted for age, sex, race/ethnicity, probability of ever smoking, and healthcare utilization (count of unique diagnosis codes). Restricted to cases and controls who filled any Part D medication ≥2 years prior to the PD diagnosis/control reference date.
[b] Also restricted to cases and controls who used any immunosuppressant ≥2 years prior to the PD diagnosis/control reference date.
[c] Cannot show due to small numbers (≤10 PD cases or controls).

0.501–1.545) per mg/day of sirolimus (median 1.08 mg). Tacrolimus dosage per day (median 2 mg) was not inversely associated with PD (RR 1.009 (95 % CI 0.942–1.081) per mg per day).

3.3. Immunosuppressants positively associated with PD

Three medications for multiple sclerosis representing three different classes, interferon, glatiramer, and fingolimod, were positively associated with PD. When we included these medications together in a single model all remained associated with PD, although the association for fingolimod attenuated.

3.4. Associations with PD based on immunosuppressant chemical structure

Because three of the four immunosuppressants with the strongest findings shared structural similarity and were used so rarely, we combined these three medications (tacrolimus, sirolimus, and everolimus) in

order to explore consistency of results across demographic factors. Use of any of these three immunosuppressants was associated with a markedly reduced risk of PD, even with a 2-year lag, whether our healthcare utilization adjustment variable was lagged in parallel (RR 0.65, CI 0.53–0.81, $p < 0.0005$) or unlagged (RR 0.47, CI 0.39–0.56, $p < 0.0001$) and we consistently observed a strong inverse association across groups defined by age, sex, race/ethnicity, or smoking index (Supplemental Table 2).

4. Discussion

In this large, population-based Medicare administrative data study, we systematically explored the potential influence of immunosuppressants on PD risk. Our study adds to the existing literature by providing population-based human data to inform repurposing of U.S. Food and Drug Administration (FDA) approved medications for potential PD disease-modifying trials. While neuroprotective therapies for PD have historically been identified in disease-model systems, MPTP and A53T mutant α-synuclein treated mice for example, our study approaches drug identification from human data to inform future model system validation studies and hopefully increase the likelihood of successful clinical trials [17,18]. Some of our key findings represent unique potential disease-modifying mechanisms and many have corresponding model system data that warrant support for further exploration. After adjusting for important covariates, we found consistent associations across multiple categories of immunosuppressants that suggest a potential broader mechanism of action, as well as chemical structure for further examination. Three structurally similar medications across two different classes of immunosuppressants, specifically mTOR inhibitors and calcineurin inhibitors, stood out as being robustly associated with decreased risk of PD. Everolimus is a derivative of the mTOR inhibitor sirolimus. Sirolimus and tacrolimus (and its natural analog, FK506) contain the same FK506 binding protein (FKBP)-binding domain, which provides a chemical basis for the mutual antagonism exerted by these molecules [19]. This structural similarity and its differences from cyclosporin, which was not associated with PD, would merit further examination. While an investigational agent that interacts with the FKPB-receptor was recommended and selected for initial examination for PD in the past [20,21], tacrolimus, sirolimus, and everolimus are structurally more similar to each other than that agent. In addition, one of the stronger findings in our study was that TNF inhibition, especially via certolizumab, was inversely associated with PD risk, consistent with a recent study [22].

One consistent theme in this study is that medications that suppress T-cell activity appeared to reduce risk of developing PD, notably the calcineurin inhibitor, tacrolimus. A recent study using electronic health records of patients aged 60 and older found similar results in that PD is less common among tacrolimus users than comparable controls or cyclosporin users [23]. While the contrasting results for tacrolimus and cyclosporin might suggest a mechanism other than calcineurin inhibition, cyclosporin does not cross the blood-brain barrier as well as tacrolimus, and calcineurin inhibition remains a plausible neuroprotective mechanism [23]. There is substantial evidence from *in vitro* and *in vivo* animal PD models that calcineurin inhibition decreases neuroinflammation [24]. Calcineurin inhibitors prevent calcineurin's serine-threonine phosphatase activity which inhibits the translocation of nuclear factor of activated T-cells family of transcription factors from the cytoplasm to the nucleus of activated T-cells [24]. Tacrolimus also modulates hypertrophic/proliferative responses and proinflammatory cytokine expression in astrocytes and microglia in *vitro*/focal transient brain ischemia [25]. Furthermore, the medication glatiramer acetate induces GA-specific regulatory $CD4^+$ and $CD8^+$ T cells and a TH1–TH2 shift with consecutively increased secretion of anti-inflammatory cytokines [26]. This induction could underlie the positive association between glatiramer and PD, but this association should be interpreted with caution, given that this medication is used to treat multiple sclerosis.

Another key finding in our study is that mTOR inhibitors were associated with a lower risk of PD. With two years of lagging, sirolimus demonstrated an RR point estimate similar to tacrolimus. Several studies demonstrate that mTOR, a serine/threonine kinase, has implications on autophagy, cell differentiation, and cell survival [2,27]. A serine/threonine kinase, mTOR operates through two distinct complexes (mTORC1 and mTORC2), each with unique protein compositions and sensitivities to rapamycin [28], the natural analog of sirolimus. Rapamycin protects neurons from death in both cellular and animal toxin models of PD [27,29]. This protective action may be attributable to reduced aggregation of α-synuclein [30] or to blocked translation of RTP801/REDD1/Ddit4, a protein that is induced in cell and animal models of PD and in affected neurons of PD patients and that causes neuron death by leading to dephosphorylation of the survival kinase Akt [27,29]. Although PD model systems have historically been poorly predictive of success in human trials, the evidence from our large population-based human study provides compelling converging evidence that this mechanism may be relevant for PD in humans.

We acknowledge several limitations to this study. Because Medicare is only universally available to Americans upon turning age 65, we were unable to include younger PD patients or to determine if beneficiaries used immunosuppressants prior to becoming eligible for Medicare. Similarly, we were limited to data for the 2 to 5-year period immediately before diagnosis, which impacted the length of our exposure lag. With that said, most of the medications studied are taken long term, providing confidence in our exposure assessment. Nonetheless some of these medications are used by relatively few people, which limited power, especially for our sensitivity analyses and dose-response analyses. In these dose-response analyses, we conservatively restricted to the small percentage of individuals who used the respective medication, and of note, the results for everolimus and sirolimus were consistent with a possible protective effect but not significant. We also note that prior to application of exposure lagging and the active comparator design, most medications across many classes of immunosuppressants appeared to lower the risk of PD. While these multiple mechanisms may converge on common pathways, it is possible that the underlying diseases treated with these medications might explain the apparently neuroprotective effect. These conditions include several types of cancer and organ transplant (Table 4), which might be associated with smoking. However, we adjusted for a validated indicator of smoking [15] and the immunosuppressants we investigated are used for a variety of indications, which suggests that the use of the medications, not the primary indication, might partially explain our findings, although it is difficult to rule out residual confounding by smoking. Another caveat is that our study assumes that beneficiaries are diagnosed accurately and that codes are entered correctly. Given the likely high specificity of our method of PD ascertainment [14], we anticipate minimal impact on risk estimates [31]. In addition, we have consistently demonstrated that the demographics and well-established disease associations in Medicare beneficiaries replicates the epidemiologic literature on PD [13]. Finally, while our study is population-based and generalizable to older individuals with specific types of Medicare coverage, we were unable to include other age-eligible Medicare beneficiaries. Insofar as they only differ with regard to demographics, our findings likely extend to these individuals as well because we confirmed that our main finding remained strong across all demographic factors we considered.

In summary, this large pharmacoepidemiology study identified several potential neuroprotective medications that could be repurposed for neuroprotective clinical trials and might suggest target mechanisms or chemical structures for further development as well, namely mTOR inhibitors, *anti*-TNF therapy, and possibly calcineurin inhibitors, several of which modulate peripheral T-cell activity and perhaps microglia. As these medications are all FDA-approved and have known safety profiles, advancing one or more of these medications into clinical trials would be highly efficient.

Table 4
Mechanism of action and FDA approved indication of selected immunosuppressant medications.

Immunosuppressant	Mechanism of Action	FDA Approved Indication
Calcineurin inhibitors		
Tacrolimus	Inhibits calcineurin, a calcium- and calmodulin-dependent phosphatase.	Prophylaxis of organ rejection in liver, kidney, lung, and heart transplant
Cyclosporine	Inhibits production and release of several cytokines including interleukin II, which inhibits interleukin II-induced activation of resting T-lymphocytes	Organ transplant rejection prophylaxis, liver, kidney, lung, and heart transplant; and psoriasis
mTOR inhibitors		
Everolimus	Binds to FKBP-12, an intracellular protein, to form a complex that inhibits activation of mTOR serine-threonine kinase. This inhibition suppresses cytokine mediated T-cell proliferation, halting progression from the G1 to the S phase of the cell cycle Everolimus reduces protein synthesis and cell proliferation	Advanced hormone receptor-positive HER2-negative breast cancer; prophylaxis of allograft rejection in liver transplantation; metastatic or unresectable progressive pancreatic neuroendocrine tumors; progressive, well-differentiated, nonfunctional gastrointestinal or lung neuroendocrine tumors; advanced renal cell cancer; prophylaxis of organ rejection in renal transplant; partial-onset seizures associated with tuberous sclerosis complex; angiomyolipoma; subependymal giant cell astrocytoma
Sirolimus	Sirolimus inhibits T-lymphocyte activation and proliferation in response to antigenic and cytokine stimulation and inhibits antibody production Everolimus also reduces angiogenesis by inhibiting vascular endothelial growth factor and hypoxia-inducible factor expression	Organ rejection prophylaxis renal transplants

Abbreviations: FDA = United States Food and Drug Administration; FKBP-12 = FK506 binding protein 12; mTOR = mechanistic target of rapamycin.

CRediT authorship contribution statement

Huiam M. Mubarak: Writing – review & editing, Writing – original draft, Investigation. **Brad A. Racette:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization. **Jordan A. Killion:** Writing – review & editing, Validation, Supervision, Formal analysis, Data curation. **Irene M. Faust:** Writing – review & editing, Validation, Formal analysis, Data curation. **Osvaldo J. Laurido-Soto:** Writing – review & editing, Data curation. **Sai Anmisha Doddamreddy:** Data curation, Formal analysis, Writing – review & editing. **Susan Searles Nielsen:** Writing – review & editing, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

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References

[1] K. Maiese, Targeting molecules to medicine with mTOR, autophagy and neurodegenerative disorders, Br. J. Clin. Pharmacol. 82 (2016) 1245–1266, https://doi.org/10.1111/bcp.12804.
[2] A. Gross, B.A. Racette, A. Camacho-Soto, U. Dube, S. Searles Nielsen, Use of medical care biases associations between Parkinson disease and other medical conditions, Neurology 90 (2018) e2155–e2165, https://doi.org/10.1212/WNL.0000000000005678.
[3] Y. Song, B.A. Racette, A. Camacho-Soto, S. Searles Nielsen, Biologic targets of prescription medications and risk of neurodegenerative disease in United States Medicare beneficiaries, PLoS One 18 (2023) e0285011, https://doi.org/10.1371/journal.pone.0285011.
[4] M. Koponen, A. Paakinaho, J. Lin, S. Hartikainen, A.M. Tolppanen, Identification of drugs associated with lower risk of Parkinson's disease using a systematic screening approach in a nationwide nested case-control study, Clin. Epidemiol. 14 (2022) 1217–1227, https://doi.org/10.2147/CLEP.S381289.
[5] J. Romanowska, K. Bjornevik, M. Cortese, J.A. Tuominen, M. Solheim, A. Abolpour Mofrad, J. Igland, C.R. Scherzer, T. Riise, Association between use of any of the drugs prescribed in Norway and the subsequent risk of Parkinson disease: a drug-wide association study, Neurology 101 (2023) e2068–e2077, https://doi.org/10.1212/wnl.0000000000207899.
[6] E.C. Hirsch, T. Breidert, E. Rousselet, S. Hunot, A. Hartmann, P.P. Michel, The role of glial reaction and inflammation in Parkinson's disease, Ann. N. Y. Acad. Sci. 991 (2003) 214–228, https://doi.org/10.1111/j.1749-6632.2003.tb07478.x.
[7] H.J. Lee, J.E. Suk, C. Patrick, E.J. Bae, J.H. Cho, S. Rho, D. Hwang, E. Masliah, S. J. Lee, Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies, J. Biol. Chem. 285 (2010) 9262–9272, https://doi.org/10.1074/jbc.M109.081125.
[8] Y. Ouchi, E. Yoshikawa, Y. Sekine, M. Futatsubashi, T. Kanno, T. Ogusu, T. Torizuka, Microglial activation and dopamine terminal loss in early Parkinson's disease, Ann. Neurol. 57 (2005) 168–175, https://doi.org/10.1002/ana.20338.
[9] B.A. Racette, A. Gross, S.M. Vouri, A. Camacho-Soto, A.W. Willis, S. Searles Nielsen, Immunosuppressants and risk of Parkinson disease, Annals of clinical and translational neurology 5 (2018) 870–875, https://doi.org/10.1002/acn3.580.
[10] A. Paakinaho, M. Koponen, M. Tiihonen, M. Kauppi, S. Hartikainen, A. M. Tolppanen, Disease-modifying antirheumatic drugs and risk of Parkinson disease: nested case-control study of people with rheumatoid arthritis, Neurology 98 (2022) e1273–e1281, https://doi.org/10.1212/WNL.0000000000013303.
[11] U.H. Ju, F.C. Liu, C.S. Lin, W.Y. Huang, T.Y. Lin, C.H. Shen, Y.C. Chou, C.L. Lin, K. T. Lin, C.H. Kao, C.H. Chen, T.Y. Yang, Risk of Parkinson disease in Sjogren syndrome administered ineffective immunosuppressant therapies: a nationwide population-based study, Medicine (Baltim.) 98 (2019) e14984, https://doi.org/10.1097/MD.0000000000014984.
[12] A. Camacho-Soto, A. Gross, S. Searles Nielsen, N. Dey, B.A. Racette, Inflammatory bowel disease and risk of Parkinson's disease in Medicare beneficiaries, Park. Relat. Disord. 50 (2018) 23–28, https://doi.org/10.1016/j.parkreldis.2018.02.008.

[13] S. Searles Nielsen, M.N. Warden, A. Camacho-Soto, A.W. Willis, B.A. Wright, B. A. Racette, A predictive model to identify Parkinson disease from administrative claims data, Neurology 89 (2017) 1448–1456, https://doi.org/10.1212/WNL.0000000000004536.

[14] D.A. Butt, K. Tu, J. Young, D. Green, M. Wang, N. Ivers, L. Jaakkimainen, R. Lam, M. Guttman, A validation study of administrative data algorithms to identify patients with Parkinsonism with prevalence and incidence trends, Neuroepidemiology 43 (2014) 28–37, https://doi.org/10.1159/000365590.

[15] I. Faust, M. Warden, A. Camacho-Soto, B.A. Racette, S. Searles Nielsen, A predictive algorithm to identify ever smoking in medical claims-based epidemiologic studies, Ann. Epidemiol. 85 (2023) 59–67.e6, https://doi.org/10.1016/j.annepidem.2023.04.019.

[16] R. Sendor, T. Sturmer, Core concepts in pharmacoepidemiology: confounding by indication and the role of active comparators, Pharmacoepidemiol. Drug Saf. 31 (2022) 261–269, https://doi.org/10.1002/pds.5407.

[17] F.L. Pagan, M.L. Hebron, B. Wilmarth, Y. Torres-Yaghi, A. Lawler, E.E. Mundel, N. Yusuf, N.J. Starr, M. Anjum, J. Arellano, H.H. Howard, W. Shi, S. Mulki, T. Kurd-Misto, S. Matar, X. Liu, J. Ahn, C. Moussa, Nilotinib effects on safety, tolerability, and potential biomarkers in Parkinson disease: a phase 2 randomized clinical trial, JAMA Neurol. 77 (2019) 309–317, https://doi.org/10.1001/jamaneurol.2019.4200.

[18] M.L. Hebron, I. Lonskaya, C.E. Moussa, Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of α-synuclein in Parkinson's disease models, Hum. Mol. Genet. 22 (2013) 3315–3328, https://doi.org/10.1093/hmg/ddt192.

[19] A. Giordano, Molecular basis of different outcomes for drug-eluting stents that release sirolimus or tacrolimus, Curr. Opin. Drug Discov. Dev 13 (2010) 159–168.

[20] B.M. Ravina, S.C. Fagan, R.G. Hart, C.A. Hovinga, D.D. Murphy, T.M. Dawson, J. R. Marler, Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment, Neurology 60 (2003) 1234–1240, https://doi.org/10.1212/01.wnl.0000058760.13152.1a.

[21] NINDS NET-PD Investigators, A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease, Neurology 68 (2007) 20–28, https://doi.org/10.1212/01.wnl.0000250355.28474.8e.

[22] I. Peter, M. Dubinsky, S. Bressman, A. Park, C. Lu, N. Chen, A. Wang, Anti-tumor necrosis factor therapy and incidence of Parkinson disease among patients with inflammatory bowel disease, JAMA Neurol. 75 (2018) 939–946, https://doi.org/10.1001/jamaneurol.2018.0605.

[23] J.D. Silva, D.C. Jupiter, G. Taglialatela, Reduced prevalence of Parkinson's disease in patients prescribed calcineurin inhibitors, J. Parkinsons Dis. 14 (2024) 533–543, https://doi.org/10.3233/JPD-230313.

[24] M.M. Osman, D. Lulic, L. Glover, C.E. Stahl, T. Lau, H. van Loveren, C. V. Borlongan, Cyclosporine-A as a neuroprotective agent against stroke: its translation from laboratory research to clinical application, Neuropeptides 45 (2011) 359–368, https://doi.org/10.1016/j.npep.2011.04.002.

[25] B. Kaminska, K. Gaweda-Walerych, M. Zawadzka, Molecular mechanisms of neuroprotective action of immunosuppressants–facts and hypotheses, J. Cell Mol. Med. 8 (2004) 45–58, https://doi.org/10.1111/j.1582-4934.2004.tb00259.x.

[26] T. Ziemssen, W. Schrempf, Glatiramer acetate: mechanisms of action in multiple sclerosis, Int. Rev. Neurobiol. 79 (2007) 537–570, https://doi.org/10.1016/s0074-7742(07)79024-4.

[27] C. Malagelada, Z.H. Jin, V. Jackson-Lewis, S. Przedborski, L.A. Greene, Rapamycin protects against neuron death in in vitro and in vivo models of Parkinson's disease, J. Neurosci. 30 (2010) 1166–1175, https://doi.org/10.1523/jneurosci.3944-09.2010.

[28] T. Xu, D. Sun, Y. Chen, L. Ouyang, Targeting mTOR for fighting diseases: a revisited review of mTOR inhibitors, Eur. J. Med. Chem. 199 (2020) 112391, https://doi.org/10.1016/j.ejmech.2020.112391.

[29] C. Malagelada, Z.H. Jin, L.A. Greene, RTP801 is induced in Parkinson's disease and mediates neuron death by inhibiting Akt phosphorylation/activation, J. Neurosci. 28 (2008) 14363–14371, https://doi.org/10.1523/jneurosci.3928-08.2008.

[30] Y. Sugimoto, T. Takasaki, R. Yamada, R. Kurosaki, T. Yamane, R. Sugiura, Rapamycin abrogates aggregation of human alpha-synuclein expressed in fission yeast via an autophagy-independent mechanism, Gene Cell. 30 (2025) e13185, https://doi.org/10.1111/gtc.13185.

[31] H. Brenner, D.A. Savitz, The effects of sensitivity and specificity of case selection on validity, sample size, precision, and power in hospital-based case-control studies, Am. J. Epidemiol. 132 (1990) 181–192, https://doi.org/10.1093/oxfordjournals.aje.a115630.