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β2-adrenoreceptor medications and risk of Parkinson disease

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Abstract

Objective—A recent study observed a two-fold greater risk of Parkinson disease (PD) in relation to the β2-adrenoreceptor antagonist propranolol and a markedly lower risk of PD for the β2-adrenoreceptor agonist salbutamol. We examined whether confounding by clinical indication for these medications, i.e. tremor and smoking-related pulmonary conditions, explained these associations.

Methods—In a large, population-based case-control study of United States Medicare beneficiaries in 2009 with diagnosis codes, procedure codes, and prescription data (48,295 incident PD cases, 52,324 controls), we examined the risk of PD in relation to use of selected β antagonists (propranolol, carvedilol, metoprolol), the β2 agonist salbutamol, and other medications used for the same clinical indications (primidone, inhaled corticosteroids). We adjusted for demographics, smoking, and overall use of medical care. We then examined the effect of also adjusting for clinical indication and applying medication exposure lagging.

Results—Propranolol appeared to increase PD risk (odds ratio [OR]=3.62, 95% confidence interval [CI] 3.31–3.96). When we adjusted for tremor or abnormal involuntary movement prior to the PD diagnosis/reference date and lagged propranolol exposure, the association was 0.97 (95% CI 0.80–1.18). Primidone, also used for tremor, was similarly sensitive to this adjustment and lagging. β antagonists not indicated for tremor appeared to reduce PD risk (carvedilol OR=0.77,

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95% CI 0.73–0.81; metoprolol OR=0.94, 95% CI 0.91–0.97) and were insensitive to adjustment for indications and lagging. Neither salbutamol nor inhaled corticosteroids were consistently associated with PD risk.

Interpretation—β2-adrenoreceptor agonists and antagonists do not appear to alter PD risk.

Introduction

Recent tissue culture and animal studies indicate that α-synuclein can be regulated through modulation of the β2-adrenoreceptor.[1] Consistent with these findings, nationwide pharmacy data from Norway suggest that the β2-adrenoreceptor antagonist propranolol markedly increases PD risk, and that the β2-adrenoreceptor agonist salbutamol substantially decreases PD risk.[1] Confirmation of the association between β2 (ant)agonist medications and PD is critical given that neuroprotective clinical trials with β2 agonists are already being considered. We hypothesized that these associations might be due to confounding by the clinical indications for these medications, i.e. tremor (propranolol) and pulmonary conditions that are more common in smokers than non-smokers (salbutamol). Therefore, we examined the association between β2 (ant)agonist medications and PD in a large population-based study while accounting for these factors and lagging medication exposures.

Methods

Study design and participants

We conducted a case-control study within an existing study using Medicare data from the United States (U.S.),[2] following approval from the Centers for Medicare and Medicaid Services, and the Human Research Protection Organization at Washington University School of Medicine. Briefly, all participants were U.S. residents who were age 66–90 years old and relied solely on Medicare for health insurance (Parts A/B) in 2009. For the present analysis, we further required Medicare Part D (pharmacy) coverage and at least one prescription event, i.e. fill of a prescription for any medication. We required at least one prescription fill so that both the lagged and unlagged analyses excluded beneficiaries who had Part D coverage but who had filled no prescriptions. This exclusion was necessary in lagged analyses to restrict to beneficiaries who definitively could have made fills within the respective narrowed exposure window.

Among beneficiaries who met the above criteria, we determined PD status from comprehensive (inpatient, skilled nursing facility, outpatient, physician/carrier, durable medical equipment, and home health care) Part A and B Medicare claims data for 2004–2009. PD cases (n=48,295) had at least one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis code for PD (332 or 332.0) in 2009 and no prior codes for PD, atypical parkinsonism (ICD-9 333.0), or dementia with Lewy bodies (ICD-9 331.82). Controls (n=52,324) were a random sample of beneficiaries who met the same criteria, but without these codes. Together, these beneficiaries represented the 54% of cases and 44% of controls from the original case-control study[2] who had Part D coverage and at least one medication filled under this coverage. This original study included all newly diagnosed PD cases in 2009 who met study criteria and a 0.5% random sample of all non-

cases who met the same criteria.[2] We avoided matching controls to cases so that we could obtain unbiased risk estimates for demographic factors known to be associated with PD. This allowed us to develop a predictive model of PD that could be generalized to other samples and to validate our case identification method.

Assessment of medication use

Using Part D data, we identified ever/never use of propranolol and salbutamol in 2008–2009 prior to PD diagnosis/reference, i.e. date of the first ICD-9 code for PD or randomly assigned date in the same year (2009) for controls. For comparison to propranolol, we also assessed the use of carvedilol and metoprolol. We included these medications to investigate whether there is a consistent association between PD and β2 antagonists, or whether it varies according to extent of use for tremor and β2 selectivity. Like propranolol, carvedilol and metoprolol cross the blood brain barrier[3] and block β2-adrenoreceptors.[4] Metoprolol, however, is primarily a selective β1 antagonist. Carvedilol and metoprolol are alternatives to propranolol for treating hypertension and other cardiovascular disorders, but notably neither typically is used to treat tremor. In addition, we included the anticonvulsant primidone, which, like propranolol, is used to treat tremor[5] but is not known to have β-adrenergic activity. Similarly, for comparison to salbutamol, we also determined use of inhaled corticosteroids. These are used to treat asthma and chronic obstructive pulmonary disease (COPD), the primary indications for salbutamol, but do not have β-adrenergic activity. We included all relevant medications in the respective exposure variable, which we name here according to the international nomenclature standard.[6] For example, we included all albuterol medications as salbutamol because Medicare lists medications in Part D data based upon nomenclature in the U.S.

Because Part D coverage was unavailable until 2006, we included only the Part D claims data from 2008–2009. We supplemented this information with Part A and B claims data from 2004–2009 to improve our exposure assessment to expand the range of years considered. These data included Healthcare Common Procedure Coding System (HCPCS) codes for the use of salbutamol or inhaled corticosteroids (Supplemental Table 1). For all medications we created variables that took into account the source of the information (Part D pharmacy claims vs. procedure codes from Part A/B claims), the route of delivery, and/or dose.

We calculated dose (mg/day) for the β antagonist medications and primidone. We first determined the daily dose for individual prescription drug events as the product of the medication strength and the quantity dispensed divided by the number of days' supply for the given fill. We then computed the median daily dose across all fills for each medication. For salbutamol we calculated the cumulative number of defined daily doses (DDD) for comparability to the previous study.[1] We calculated this as the product of the medication strength and quantity dispensed divided by the DDD for that given medication.[7, 8]

Assessment of medical conditions and smoking

We used ICD-9 and Current Procedural Terminology (CPT) codes (Supplemental Table 1) from comprehensive claims data from 2004–2009, up to PD diagnosis/reference, to assess

tobacco smoking and the medical conditions of interest, including tremor. We defined tremor as the presence of ≥ 1 ICD-9 code 333.1 (essential and other specified forms of tremor) and/or ≥ 1 ICD-9 code 781.0 (abnormal involuntary movement) prior to PD diagnosis/reference. In our data, ICD-9 781.0 is strongly predictive of PD[2] as well as strongly correlated with ICD-9 333.1, among both PD cases and controls (both $p < 0.0001$).

The claims data include ICD-9 codes for history of tobacco use (V15.82) and tobacco dependence (305.1) and CPT codes for smoking cessation counseling (99406, 99407). Even in combination, these four codes are not sufficiently sensitive to characterize tobacco smoking history accurately.[9, 10] Therefore, we created and validated a smoking variable as the probability of having ever smoked based on sex, race/ethnicity, birth cohort, and > 600 ICD-9 and CPT codes including the above tobacco-specific codes and 17 other medical conditions.[2] We estimated this probability with a logistic regression model that we developed from Behavioral Risk Factor Surveillance System (BRFSS) survey data from a population-based sample of Medicare-aged respondents.[11] We then assigned all beneficiaries with any of the above tobacco-specific codes a probability of 100%, which is the positive predictive value of these codes in Medicare data for having ever smoked.[10] Because of the high positive predictive value, we also used these tobacco-specific codes to identify beneficiaries who definitively had ever smoked. However, these tobacco-specific codes[9, 10] and the medical conditions included in the smoking predictive model do not completely capture smoking histories. Pack-years and time since quitting smoking are inversely associated with PD,[12–14] while nicotine dependence is associated with the development of both asthma[15] and COPD.[16] Therefore, we combined all home oxygen therapy HCPCS codes[17] into a dichotomous oxygen use variable as a potential marker for greater intensity and duration of smoking. Of 21 tobacco-related diagnosis/procedure codes in our previous predictive model of PD,[2] HCPCS codes for oxygen concentrators were the codes most strongly associated with asthma, COPD, and nicotine dependence. In addition, we created a dichotomous variable for any Part D fills for medications specifically used for nicotine dependence (nicotine and/or varenicline).

Statistical analysis

Using Stata,[18] we constructed logistic regression models with PD as the outcome and medications as independent variables to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We adjusted *a priori* for age (continuous), sex, and race/ethnicity (7 categories) in all models. Unless otherwise stated, we also adjusted for smoking (estimated probability of having ever smoked as a continuous variable, ever/never oxygen use, ever/never nicotine/varenicline) and for the number of unique diagnosis codes (continuous). We adjusted for the latter because overall use of medical care might confound PD-medicine associations, given that use of care can confound the association between two medical conditions.[9, 19] We used the number of unique diagnosis codes as a measure of use of care because this measure more fully addresses confounding by use of care than comorbidity indices or the number of inpatient, outpatient, and other physician or provider visits.[9]

Because some residual confounding by indication possibly could remain following adjustment for overall use of care, we also examined the effect of adjusting for the other

medications and for selected medical conditions to further address confounding by indication.[20] These indications included tremor (propranolol and primidone); asthma and COPD (salbutamol); hypertension, myocardial infarction, and heart failure (propranolol, carvedilol, and metoprolol); and epilepsy (primidone). However, because these indications may not always be coded, we also examined the effect of restricting results to beneficiaries with the condition and/or lagging medication exposure by 6, 12, or 18 months. That is, we ignored all fills that occurred in the 6, 12, or 18 months prior to the PD diagnosis or control reference date. In each lagged analysis we excluded beneficiaries without Part D claims by the end of the respective exposure period, and adjusted for the number of unique diagnosis codes for the respective period rather than the entire period. Eighteen months is the maximum lag we could apply within the available two years of Part D data, given that we required at least one prescription to be filled prior to this 18 month lag period.

For pairs of medications with shared indications (propranolol/primidone and salbutamol/inhaled corticosteroids) we also generated more flexible models that allowed us to estimate separate ORs for each medication alone and for both medications together, relative to neither medication. Accordingly, we formally tested for interaction between the two medications in each pair, which we did by introducing the product term between the two medications in a logistic regression model with both main effects terms.

For each β antagonist medication and primidone, we also used logistic regression to examine the association between dose (mg/day) and PD among those who took the respective medication. For these models we considered dose in approximate tertiles. We also considered salbutamol dose in three categories, as defined by the prior study (< 60 DDD, 60–180 DDD, > 180 DDD).[1] For all medications we calculated the p for trend while retaining dose as a continuous measure modeled linearly.

Because of the importance of smoking on the occurrence of most indications for β2 (ant)agonists we repeated all analyses while stratifying by the presence of any tobacco-specific code, i.e. definitive ever smokers[10] vs. other beneficiaries. We also repeated all analyses while focusing on the most certain PD cases (n=17,951), which we defined as cases who had an ICD-9 code for PD from a neurologist or ≥ 3 PD codes in 2009, and had no evidence of secondary parkinsonism, i.e. no ICD-9 code 332.1 and no Part D fills of dopamine antagonist medication in 2008–2009. Otherwise, we included all 48,295 cases and 52,324 controls in all unlagged models, as we obtained demographic data from the Medicare base file for 2009, and we had no missing data other than race/ethnicity for 0.1% cases and 0.1% controls, who we retained in analysis in an “unknown race/ethnicity” category.

We had > 99.9% statistical power to detect ORs ≥ 2.20 or ≤ 0.66, i.e. the same or stronger associations than observed in the earlier study[1] for propranolol and salbutamol, respectively. We hypothesized that these associations would be attenuated by adjustment for the medications’ indications, but we also had 99% power to detect ORs as modest as 1.25 for propranolol and 0.93 for salbutamol. Even in the most restrictive analysis when we simultaneously focused on the most certain PD cases and applied the maximum lag, we had 99% power to detect ORs as modest as 1.65 for propranolol and 0.84 for salbutamol.

Role of the Funding Source

The co-authors were solely responsible for all decisions related to statistical analysis, interpretation of results, and decision to publish.

Results

Participant characteristics

Most cases (85.5%) and controls (83.7%) were non-Hispanic white. On average, cases were 78.6 years old at PD diagnosis, and controls were 76.4 years old on their comparable reference date. PD risk was greater in men and whites, and increased with age (all $p \leq 0.001$). PD risk was lower in relation to smoking (probability of ever smoking, oxygen use, and use of nicotine and/or varenicline). After accounting for these demographic differences and overall use of medical care, there was, as expected, an inverse association between PD and cancer, and a positive association between PD and REM sleep behavior disorder, constipation, anxiety, and depression (all $p \leq 0.001$).

Propranolol and PD

Initially, use of propranolol appeared to be associated with a greater PD risk, regardless of adjustment for smoking and overall use of medical care (Table 1). However, the association weakened substantially when we adjusted for tremor reported prior to PD diagnosis/reference (Table 1), or restricted to beneficiaries with tremor (OR=1.27, 95% CI 1.09–1.48, not in tables). The association also weakened consistently with greater lagging of propranolol exposure (Table 1). When we simultaneously adjusted for tremor and applied the maximum lag of 18 months, the OR attenuated by > 70%, and was close to null. When we focused on the most certain PD cases, lagging and adjustment for tremor had a similar effect on the PD-propranolol OR, and even the 12 month lagged OR was close to null (0.94, 95% CI 0.80–1.11, not in tables).

Adjustment for other β (ant)agonists, primidone, and their indications did not materially change PD-propranolol ORs (not in tables). However, there was some evidence of statistical interaction, specifically antagonism, between propranolol and primidone in relation to PD (Table 2). Accordingly, after adjustment for tremor, in no instance did the point estimate for propranolol and primidone exceed that for primidone alone. This remained true when we focused on the most certain PD cases (Table 2). In exploratory analyses in which we investigated the sensitivity of the overall PD-propranolol association, the magnitude of the OR was affected, but the overall pattern of attenuation that occurred with lagging or tremor adjustment was not. These analyses included adjustment for one dichotomous “any tremor” variable (instead of the two ICD-9 codes separately) or only one of the two ICD-9 codes; lagging the tremor variable(s); and excluding, as in the prior study,[1] users with < 365 DDD of propranolol. We also observed no evidence that PD risk increased with propranolol dose (mg/day) (Table 3).

Other β antagonists and PD

When we explored whether there was a consistent, medication-class effect between β antagonists and PD, we observed marked differences depending upon the medication. In

contrast to propranolol, the other β antagonists carvedilol and metoprolol were associated with lower PD risk (Table 1). Moreover, these associations were relatively insensitive to adjustment for tremor and to lagging. Among beneficiaries with tremor, ORs were close to null (1.02, 95% CI 0.85–1.22 for carvedilol; 1.05, 95% CI 0.95–1.16 for metoprolol, not in tables). Similarly, among users of carvedilol or metoprolol, we observed an inverse association between dose (mg/day) and PD risk, which largely disappeared when we restricted to beneficiaries with tremor (Table 3). The associations between PD and both carvedilol and metoprolol were quite similar among those with and without tobacco-specific codes (not in tables).

Primidone and PD

There was a very strong positive association between PD and use of the non-β2-active tremor medication primidone prior to PD diagnosis/reference (Table 1). As for propranolol, this association markedly attenuated with either adjustment for tremor or with exposure lagging. With both adjustment for tremor and 12–18 months of lagging, the OR attenuated by > 90%. With tremor adjustment and at least a 12 month lag, the PD-primidone OR was close to null, both overall (Table 1) and when considering propranolol co-exposure (Table 2). The PD-primidone ORs were sensitive to changes in our method of tremor adjustment similar to the PD-propranolol ORs (not in tables). Among users of primidone there was an inverse association between primidone dose (mg/day) in relation to PD, which was no longer apparent when we focused on beneficiaries with tremor (Table 3).

Salbutamol and inhaled corticosteroids and PD

Use of salbutamol and inhaled corticosteroids and their indications asthma and COPD were each associated with a reduced risk of PD after adjustment for use of care (Table 4). Each of these inverse associations attenuated with adjustment for smoking. This attenuation was clearest for salbutamol and resulted in an OR relatively close to null. This was true overall and when we stratified by presence of a tobacco-specific code. Inhaled corticosteroids remained inversely associated with PD, overall and among those without a tobacco-specific diagnosis or procedure code. When we included salbutamol, inhaled corticosteroids, asthma, COPD, and smoking into a single model, ORs for salbutamol and inhaled corticosteroids further weakened (not in tables). Nonetheless, the latter remained significant, as did the association for asthma, probability of ever smoking, and oxygen use.

The PD-salbutamol association was similar whether we used Medicare Part D (pharmacy) claims or Part A/B claims (HCPCS codes). PD-salbutamol ORs were very sensitive, however, to the route of administration. Only salbutamol via a metered dose inhaler (MDI) was inversely associated with PD (10.5% of cases, 11.2% of controls, OR=0.81, 95% CI 0.77–0.84, not in tables). The inverse association between PD and salbutamol MDIs was very similar when we stratified by tobacco-specific codes or use of inhaled corticosteroids, or restricted to beneficiaries with asthma and/or COPD. Among the most certain PD cases, the OR was 0.75 (95% CI 0.70–0.79, not in tables). However, among salbutamol MDI users, we did not observe a dose-response association with PD risk, either overall or when stratified by smoking (Table 5).

Discussion

In this large population-based study we examined whether β2-adrenoreceptor (ant)agonist medications affect PD risk. Another recent study suggested that the β2 antagonist propranolol increases PD risk and that the β2 agonist salbutamol decreases PD risk.[1] Our results indicate that propranolol does not increase PD risk. Rather, our results suggest that the onset of tremor in the PD prodromal period may lead to propranolol use, and thereby a positive association with PD. We replicated the previous finding of a more than two-fold increased risk of PD with propranolol use, but this risk was completely nullified by adjusting for tremor and lagging propranolol exposure by 18 months. The prior analysis of PD and propranolol also reported an attenuation of the association with 1–2 years of lagging, but their risk estimate remained well above null, despite also attempting to exclude propranolol for tremor. We speculate that in the previous study, propranolol may have been first prescribed for symptomatic tremor control during the prodromal period of PD or even after PD diagnosis, since PD cases were identified by use of levodopa for one year. Our diagnosis date, identified by the first ICD-9 code for PD, occurs earlier in the course of disease; therefore, an 18 month lag might have been more effective in eliminating propranolol used for (uncoded) pre-PD diagnosis tremor. Still, half of our PD cases with a diagnosis of "essential and other specified forms of tremor" first received that code > 18 months before PD diagnosis.[2] Further, prior studies of PD and medical conditions suggest inflation of risk estimates without lagging.[21–23] Thus, additional lagging of propranolol might have yielded risk estimates even closer to those for the β antagonists not used for tremor. Consistent with our conclusion that the relation between propranolol and PD is due to tremor, there was no evidence that PD risk was greater among users of the other common β antagonists we considered, carvedilol and metoprolol. This was true with or without adjustment for tremor or exposure lagging, demonstrating a notable additional inconsistency with the PD-propranolol association. The starkly contrasting results likely occur because carvedilol and metoprolol are not commonly used to treat tremor in the U.S.[24] As such, the only β2 antagonist that appeared possibly to increase PD risk, in our study, was the one most frequently used to treat a postural/action tremor, which commonly occurs in PD. While bidirectional results possibly could arise from pharmacological differences between propranolol and the other two β antagonists, namely β selectivity and ease of crossing the blood brain barrier, the associations were not simply in opposite directions. Rather, risk estimates for propranolol were sensitive in a specific manner that closely paralleled risk estimates for primidone, a tremor medication that does not have β2 activity. In particular, ORs for propranolol and primidone were close to null when we simultaneously adjusted for tremor and applied an 18 month lag. Moreover, after accounting for tremor, there was no evidence that taking both propranolol and primidone was associated with greater PD "risk" than taking primidone alone.

Our results for salbutamol and inhaled corticosteroids offer additional evidence that the previously reported associations for both propranolol and salbutamol on PD risk are not causal. When we examined whether the β2 agonist salbutamol decreased PD risk, we did confirm an inverse association prior to adjustment for smoking. However, the overall PD-salbutamol OR was close to null after adjusting for smoking. Any remaining association was

restricted to MDIs, and that association was weak relative to the earlier study,[1] which observed a 44% reduced risk of PD with salbutamol use more generally. On the other hand, we expected that the relative risk of PD in relation to salbutamol would be attenuated in our analysis, given that we assessed exposure with fewer years of medication data, and adjusted for smoking, whereas the earlier study did not. Smoking is associated with a markedly lower risk of PD,[12–14] and smoking-related pulmonary conditions are important indications for salbutamol. Furthermore, we observed an independent inverse association between inhaled corticosteroids and PD, and this association was stronger than that for salbutamol, unless we restricted to MDIs, which suggests that salbutamol was used chronically. However, even then, the PD-salbutamol OR was weaker than the association between PD and oxygen use. Taken together, this suggests that the modest inverse association between salbutamol inhalers and PD that we observed was not due to a specific medication-class. Inhaled corticosteroids do not have β2 activity, which suggests that β2 agonism is not the cause of the inverse PD-salbutamol association.

While our results strongly call into question whether β2 (ant)agonists affect PD risk, we acknowledge some limitations of our analyses. First, the weak but significant inverse associations for some of the medications used for asthma, COPD, and cardiovascular disorders including hypertension may indicate residual confounding by smoking. Any inverse association between PD and both salbutamol and inhaled corticosteroids disappeared when we restricted to definitive smokers, which also suggests residual confounding by smoking. Our primary smoking variable was a probabilistic determination of “ever smoking” that does not account for recentness, duration, or intensity of smoking. Still, “ever smoking” is strongly related to PD in our and other[14] studies, so adjusting for this component remains a strength. In addition, we adjusted for nicotine dependence medications and oxygen use, which appeared to serve, in part, as cumulative measures of smoking. Second, we lagged medication exposures up to 18 months prior to PD diagnosis/reference, but a longer lag would have been ideal. Nonetheless, our case ascertainment method allowed us to identify PD patients earlier than the previous study, so we effectively were able to lag exposure further into the prodromal period of PD than that study.[1] Thus, even a modest lag addressed confounding by tremor for a sufficient portion of the prodromal PD period to correct the PD-propranolol risk estimate substantially. Another potential limitation is that our case ascertainment method presumably includes some “cases” who were mistakenly coded as having PD, but instead have other conditions such as essential tremor. Notably, however, our conclusions were strengthened when we restricted the PD-propranolol risk estimates to the most certain cases. Finally, we note that the pharmacologic effects of both β2 agonists and antagonists potentially complicate the interpretation of our risk estimates. For example, β2 agonists can cause tremor, so it is possible that cases in the prodromal period would tend to avoid these medications, which would bias the PD-salbutamol association downward. At the same time, the risk estimates for metoprolol and carvedilol could be biased downward, as well. Metoprolol (and hence perhaps carvedilol) may treat tremor as well as propranolol,[25] and so suppression of tremor might mask early PD, leading to delayed PD ascertainment. This may explain the inverse associations we observed between PD and these medications, given that results did not differ by smoking and that those inverse associations disappeared when we restricted results to beneficiaries with tremor.

Given the many complexities inherent in an analysis of β2 (ant)agonist medications and PD, we cannot completely rule out the possibility that there could be some effect of these medications, but it is clear that if any effect exists it is much smaller than previously reported. Epidemiologic studies with even greater ability to adjust for smoking and to lag medication exposures will be required to confirm that β2 (ant)agonists do not affect PD risk. In the meantime, our results suggest that a PD neuroprotective clinical trial with β2 agonists may not be warranted. In addition, altering use of β2 (ant)agonist medications in an attempt to affect PD risk or PD progression must be balanced against the possibility that β2 agonists might increase tremor in PD patients and that avoidance of β antagonists might increase mortality related to cardiovascular disease. These conditions are much more common than PD, and the potential negative public health impact of reducing the use of β antagonists could be substantial, without benefit on PD risk or progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

β-adrenoreceptor Antagonists and Primidone in Relation to Parkinson Disease, by Medication Exposure Lagging and Adjustment for Tremor

	Age-sex-race-adjusted OR (95% CI)[a]			
	No lag	6 months	12 months	18 months
Cases, n[b]	48,295	46,430	43,095	19,122
Controls, n[b]	52,324	50,518	46,341	21,286
Propranolol				
Cases, %	4.4	3.6	2.9	2.4
Controls, %	1.3	1.3	1.2	1.1
Adjusted for age/sex/race only[a]	3.54 (3.24–3.86)	2.97 (2.70–3.26)	2.63 (2.37–2.92)	2.16 (1.84–2.54)
Basic model[c]	3.62 (3.31–3.96)	3.04 (2.76–3.34)	2.70 (2.44–3.00)	2.24 (1.90–2.64)
Also adjusted for tremor[c,d]	1.41 (1.27–1.56)	1.20 (1.07–1.34)	1.11 (0.98–1.25)	0.97 (0.80–1.18)
Carvedilol				
Cases, %	6.9	5.8	4.7	4.1
Controls, %	6.1	5.3	4.4	3.6
Adjusted for age/sex/race only[a]	1.10 (1.04–1.16)	1.06 (1.00–1.12)	1.04 (0.97–1.11)	1.07 (0.97–1.19)
Basic model[c]	0.77 (0.73–0.81)	0.79 (0.74–0.83)	0.79 (0.74–0.84)	0.82 (0.74–0.92)
Also adjusted for tremor[c,d]	0.83 (0.78–0.87)	0.84 (0.79–0.90)	0.85 (0.79–0.91)	0.88 (0.78–0.98)
Metoprolol				
Cases, %	26.3	24.0	20.8	19.0
Controls, %	22.6	21.2	19.1	17.8
Adjusted for age/sex/race only[a]	1.17 (1.14–1.21)	1.12 (1.09–1.16)	1.07 (1.03–1.10)	1.05 (1.00–1.11)
Basic model[c]	0.94 (0.91–0.97)	0.95 (0.92–0.98)	0.93 (0.90–0.96)	0.93 (0.88–0.98)
Also adjusted for tremor[c,d]	0.94 (0.91–0.97)	0.95 (0.92–0.99)	0.94 (0.91–0.98)	0.94 (0.89–0.99)
Primidone				
Cases, %	3.9	2.9	2.2	1.7
Controls, %	0.4	0.4	0.3	0.2
Adjusted for age/sex/race only[a]	10.8 (9.32–12.5)	8.92 (7.61–10.5)	7.84 (6.54–9.40)	7.21 (5.35–9.73)
Basic model[c]	9.68 (8.35–11.2)	8.06 (6.87–9.46)	7.10 (5.91–8.52)	6.72 (4.97–9.09)
Also adjusted for tremor[c,d]	1.76 (1.48–2.08)	1.27 (1.06–1.53)	0.99 (0.80–1.23)	0.96 (0.68–1.36)

[a] Adjusted for age (two linear splines), sex, and race (and ethnicity, in 7 categories).

[b] Excludes cases and controls from the original study[2] who had no Part D coverage in 2008–2009 or with Part D coverage but no medication fills in the respective time period prior to diagnosis/reference.

[c] Adjusted for age, sex, race, probability of ever smoking (continuous, 0 to 1), oxygen use,[17] use of nicotine and/or varenicline, and overall use of medical care (number of unique ICD-9 codes, continuous)[2] in 2004–2009 prior to diagnosis/reference or the specified number of months prior if lagged.

[d] Also adjusted for presence of tremor (Supplemental Table 1) prior to PD diagnosis/control reference.

PD=Parkinson disease; ICD-9=International Classification of Disease, Ninth Revision, Clinical Modification; OR=odds ratio; CI=confidence interval

Table 2.

Propranolol, Primidone, and Parkinson Disease, by Medication Exposure Lagging, Adjustment for Tremor, and Certainty of Parkinson Disease Diagnosis

	% Cases	% Controls	Age-sex-race-adjusted OR (95% CI)[a]		
			Adjusted for age/sex/race only[a]	Basic model[a,b]	Also adjusted for tremor[a,b]
No Lag					
All cases (n=48,295)[c]					
All controls (n=52,324)[c]					
No tremor medication	92.5	98.3	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Propranolol only	3.6	1.3	3.14 (2.86–3.44)	3.24 (2.95–3.56)	1.44 (1.29–1.60)
Primidone only	3.1	0.3	10.7 (9.08–12.6)	9.45 (8.01–11.1)	1.91 (1.59–2.29)
Both	0.8	0.1	12.9 (9.21–18.2)	12.3 (8.71–17.3)	1.40 (0.96–2.04)
Interaction p-value[e]			p<0.001	p<0.001	p=0.002
Most certain cases (n=17,951)[c,d]					
All controls (n=52,324)[c]					
No tremor medication	91.6	98.3	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Propranolol only	3.9	1.3	3.53 (3.16–3.94)	3.54 (3.17–3.96)	1.34 (1.17–1.53)
Primidone only	3.4	0.3	11.8 (9.89–14.1)	11.2 (9.34–13.3)	1.74 (1.41–2.14)
Both	1.0	0.1	16.4 (11.4–23.5)	15.2 (10.6–21.9)	1.39 (0.93–2.09)
Interaction p-value[e]			p<0.001	p<0.001	p=0.03
12 month lag[f]					
All cases (n=43,095)[c]					
All controls (n=46,341)[c]					
No tremor medication	95.2	98.6	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Propranolol only	2.6	1.1	2.42 (2.18–2.69)	2.50 (2.24–2.78)	1.12 (0.99–1.27)
Primidone only	1.9	0.3	7.63 (6.28–9.28)	6.81 (5.60–8.29)	1.02 (0.81–1.27)
Both	0.4	0.04	10.2 (6.24–16.7)	9.94 (6.06–16.3)	0.90 (0.53–1.55)
Interaction p-value[e]			p=0.03	p=0.05	p=0.45
Most certain cases (n=15,642)[c,d]					
All controls (n=46,341)[c]					
No tremor medication	94.8	98.6	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Propranolol only	2.7	1.1	2.63 (2.30–3.00)	2.63 (2.31–3.01)	0.96 (0.81–1.13)
Primidone only	2.1	0.3	8.19 (6.60–10.2)	7.93 (6.38–9.86)	0.90 (0.69–1.17)
Both	0.4	0.04	11.8 (6.93–20.1)	11.1 (6.52–19.0)	0.67 (0.37–1.19)
Interaction p-value[e]			p=0.04	p=0.04	p=0.44

[a]Adjusted for age, sex, and race as in Table 1.

[b]Also adjusted for smoking, oxygen, nicotine/varenicline, use of care, and if stated above tremor, as in Table 1.

[c] Excludes cases and controls from the original study[2] as in Table 1.

[d] PD cases diagnosed by a neurologist and/or with ≥ 3 PD diagnosis codes in 2009; and without atypical parkinsonism, dementia with Lewy bodies, or secondary parkinsonism.

[e] All interaction odds ratio point estimates were < 1.0.

[f] Twelve months is the maximum possible lag when simultaneously considering propranolol and primidone because too few controls used both medications > 18 months prior to their reference date.

Abbreviations as in Table 1

Table 3.

β-adrenoreceptor Antagonists and Primidone Dose[a] in Relation to Parkinson Disease, among Part D Beneficiaries Using the Medication, Overall and Restricted to Beneficiaries with Tremor

	All Medication Users			Medication Users with Tremor		
Dose (mg/day)[a]	**% Cases**	**% Controls**	**OR (95% CI)[b]**	**% Cases**	**% Controls**	**OR (95% CI)[b]**
Propranolol	n=2115	n=705		n=1632	n=208	
<40	25.8	21.7	1.0 (Reference)	24.9	21.2	1.0 (Reference)
40 – <80	34.5	31.9	0.94 (0.74–1.20)	35.2	31.3	0.98 (0.65–1.48)
≥80	39.7	46.4	0.79 (0.63–0.99)	39.9	47.6	0.74 (0.51–1.09)
p for trend[b,c]			p=0.67			p=0.42
Carvedilol	n=3335	n=3197		n=936	n=148	
<12.5	29.0	24.5	1.0 (Reference)	28.2	26.4	1.0 (Reference)
12.5 – <25	32.1	29.5	0.94 (0.82–1.08)	33.2	29.1	1.06 (0.66–1.69)
≥25	38.9	46.0	0.76 (0.67–0.86)	38.6	44.6	0.74 (0.48–1.14)
p for trend[b,c]			p<0.001			p=0.12
Metoprolol	n=12,724	n=11,849		n=4091	n=624	
<50	26.9	22.8	1.0 (Reference)	26.3	26.8	1.0 (Reference)
50	37.5	37.9	0.89 (0.83–0.96)	38.7	38.5	1.04 (0.84–1.29)
>50	35.6	39.3	0.84 (0.79–0.90)	35.0	34.8	1.04 (0.83–1.29)
p for trend[b,c]			p<0.001			p=0.86
Primidone	n=1869	n=203		n=1730	n=166	
<75	33.9	29.6	1.0 (Reference)	33.0	31.9	1.0 (Reference)
75 – <150	27.4	23.2	1.03 (0.69–1.53)	27.6	23.5	1.14 (0.74–1.75)
≥150	38.7	47.3	0.72 (0.51–1.01)	39.4	44.6	0.86 (0.59–1.25)
p for trend[b,c]			p=0.005			p=0.34

[a] Median daily dose (mg/day) categorized by approximate tertiles among users.

[b] Adjusted for age, sex, race, smoking, oxygen, nicotine/varenicline, and use of care as in Table 1.

[c] Based on dose as a continuous measure.

Abbreviations as in Table 1

Table 4.

Salbutamol, Inhaled Corticosteroids, Their Indications, and Smoking in Relation to Parkinson Disease, Overall and by Presence of Tobacco-Specific Diagnosis or Procedure Codes[a]

			Age-sex-race-adjusted OR (95% CI)[b]		
	% Cases	% Controls	Adjusted for age/sex/race only[b]	Also adjusted for use of care[b,c]	Also adjusted for use of care and smoking (basic model)[b,c,d]
All beneficiaries with Part D data	n=48,295	n=52,324			
Salbutamol	19.7	16.3	1.29 (1.25–1.33)	0.89 (0.86–0.92)	0.97 (0.93–1.01)
Inhaled corticosteroids	9.9	9.2	1.13 (1.08–1.18)	0.80 (0.76–0.84)	0.88 (0.84–0.92)
Asthma	20.3	17.3	1.27 (1.23–1.31)	0.85 (0.82–0.88)	0.89 (0.86–0.93)
COPD	33.4	26.7	1.34 (1.30–1.37)	0.89 (0.86–0.91)	0.95 (0.92–0.98)
Smoking: Ever smoked[e]	N/A	N/A	1.36 (1.30–1.43)	0.69 (0.66–0.73)	0.72 (0.68–0.76)
Oxygen	8.9	7.2	1.24 (1.18–1.30)	0.75 (0.71–0.79)	0.78 (0.74–0.82)
Nicotine/varenicline	0.6	0.7	1.03 (0.88–1.21)	0.84 (0.71–0.99)	1.00 (0.84–1.18)
No tobacco-specific codes	n=38,965	n=42,674			
Salbutamol	16.2	13.0	1.29 (1.24–1.34)	0.91 (0.87–0.95)	0.96 (0.91–1.00)
Inhaled corticosteroids	7.5	7.1	1.10 (1.04–1.16)	0.79 (0.75–0.84)	0.84 (0.79–0.89)
Asthma	17.8	15.3	1.24 (1.19–1.29)	0.84 (0.81–0.88)	0.88 (0.84–0.92)
COPD	28.4	22.0	1.33 (1.29–1.38)	0.90 (0.87–0.94)	0.93 (0.90–0.97)
Smoking: Ever smoked[e]	N/A	N/A	3.61 (3.18–4.09)	0.56 (0.49–0.64)	0.58 (0.51–0.67)
Oxygen	6.5	5.0	1.26 (1.18–1.34)	0.76 (0.71–0.81)	0.77 (0.72–0.82)
Nicotine/varenicline	0.1	0.1	--[f]	--[f]	--[f]
Any tobacco-specific code(s)	n=9,330	n=9,650			
Salbutamol	34.7	31.1	1.23 (1.16–1.31)	0.92 (0.86–0.99)	0.99 (0.92–1.07)
Inhaled corticosteroids	19.8	18.7	1.13 (1.05–1.21)	0.89 (0.82–0.96)	0.96 (0.88–1.04)
Asthma	30.5	26.1	1.31 (1.23–1.40)	0.91 (0.85–0.98)	0.96 (0.89–1.03)
COPD	54.2	47.5	1.32 (1.24–1.40)	0.94 (0.88–1.00)	0.99 (0.92–1.05)
Smoking: Ever smoked[e]	N/A	N/A	N/A	N/A	N/A
Oxygen	18.9	16.9	1.15 (1.06–1.24)	0.80 (0.74–0.87)	0.80 (0.74–0.87)
Nicotine/varenicline	2.5	3.5	0.85 (0.72–1.01)	0.85 (0.71–1.01)	0.87 (0.73–1.04)

[a] All were determined from Medicare Part A/B diagnosis or procedure codes from 2004–2009 (Supplemental Table 1) and/or Part D pharmacy data from 2008–2009 prior to PD diagnosis/control reference.

[b] Adjusted for age, sex, and race as in Table 1.

[c] Also adjusted for the number of unique ICD-9 codes as in Table 1.

[d] Also adjusted for ever smoking, oxygen, and nicotine/varenicline as in Table 1. For ORs between PD and each indicator of smoking, adjustment was for the remaining indicator(s).

[e] Probability of ever smoking (continuous, 0 to 1; 1 if any tobacco-specific code). Therefore, no percentages for "ever smoked" are shown, and among those with any tobacco-specific code(s) we could not obtain ORs for or adjust for "ever smoked."

[f] Not estimated due to small numbers and the unexpected lack of a tobacco-specific code.

CPT=Current Procedural Terminology; HCPCS=Healthcare Common Procedure Coding System; COPD=chronic obstructive pulmonary disease; and other abbreviations as in Table 1

Table 5.

Salbutamol Dose and Parkinson Disease among Users of Salbutamol Inhalers,[a] Overall and by Presence of Tobacco-Specific Diagnosis or Procedure Codes[b]

	All users of salbutamol inhalers			No tobacco-specific codes[b]			Any tobacco-specific code(s)[b]		
Dose (DDD)[a]	% Cases n=5089	% Controls n=5858	OR (95% CI)[c]	% Cases n=3221	% Controls n=3714	OR (95% CI)[c]	% Cases n=1868	% Controls n=2144	OR (95% CI)[c]
<60	50.5	50.4	1.0 (Reference)	54.9	54.6	1.0 (Reference)	42.9	43.1	1.0 (Reference)
60–180	22.8	20.6	1.09 (0.99–1.21)	22.1	20.5	1.05 (0.93–1.20)	24.0	20.8	1.17 (0.99–1.39)
>180	26.7	29.0	0.98 (0.89–1.08)	23.0	24.8	0.95 (0.84–1.08)	33.0	36.1	1.01 (0.87–1.18)
p for trend[c,d]			p=0.80			p=0.90			p=0.97

[a]Defined daily dose (DDD) categorized as in Mittal et al. 2017,[1] among beneficiaries who used a salbutamol metered dose inhaler, with or without an adaptor, determined from Part D data described in Table 4.

[b]Determined from Part A/B data described in Table 4.

[c]Adjusted for age, sex, race, smoking, oxygen, nicotine/varenicline, and use of care as in Table 1.

[d]Based on DDD as a continuous measure.

DDD=defined daily dose; and other abbreviations as in Table 1