Original Article

Impact of Anticholinergic Burden and Clinical-Demographic Characteristics on Incident Dementia in Parkinson Disease

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Abstract

Purpose: Anticholinergic medication use measured via the Anticholinergic Cognitive Burden (ACB) scale has been associated with an increased dementia incidence in older adults but has not been explored specifically for Parkinson disease dementia (PDD). We used adjusted Cox models to estimate the risk of incident PDD associated with demographic factors, clinical characteristics, and time-varying total ACB in a longitudinal, deeply-phenotyped prospective PD cohort. **Major findings:** 56.5% of study participants were taking ACB-scale drugs at enrollment. Increasing age, motor symptom burden and psychosis were associated with PDD risk. Female sex and educational achievement were protective against PDD. ACB categories were not associated with PDD overall, but depression and impulse control disorder were strongly associated with PDD in a subsample with high baseline ACB. **Conclusions:** Patient and clinical factors modify PDD risk. PD drug safety and drug-disease interaction studies may require considering multiple mechanisms and including dose-based, prospectively acquired medication exposure measures.

Keywords

Parkinson disease, anticholinergic burden, cognitive impairment, dementia

Introduction

Individuals diagnosed with Parkinson disease (PD) are at high risk of developing cognitive impairment, with longitudinal data suggesting 75% will have measurable cognitive impairment by the 10th year of living with PD.[1,2] PD dementia (PDD) is the most dreaded long-term outcome of PD. There is a critical need to identify potentially modifiable risk factors for PDD. Exposure to medications with anticholinergic properties has been associated with an

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increased risk of all-cause dementia in older adult populations.[3-9] These medications are frequently used among persons with PD,[10,11] usually for the treatment of nonmotor symptoms of PD (eg, overactive bladder, insomnia, depression, or psychosis), and occasionally for motor symptoms.[10,12,13] A few studies have suggested an increase in dementia risk associated with anticholinergic use in persons living with PD,[14-17] but these studies frequently used retrospective or cross-sectional designs, increasing the potential influence of confounding and bias. The objective of this study was to evaluate risk factors for developing PDD, including sociodemographic and clinical characteristics, with a focus on the association of the Anticholinergic Cognitive Burden (ACB) scale as a potential modifiable factor, using existing data from a deeply-phenotyped longitudinal cohort study of persons with PD.

Methods

Ethical and Institutional Approval

The University of Pennsylvania's Institutional Review Board approved this research (protocol #827738). The National Institutes of Health had no input on the study's conduct or interpretation.

Data Source and Study Population

The National Institute on Aging Penn U19 (NIA U19) Center PD clinical cohort consists of 350+ individuals with PD, recruited from the University of Pennsylvania Parkinson Disease and Movement Disorders Center (PD&MDC) starting in 2007. The PD&MDC has a steady state census of approximately 3000 PD patients with approximately 1200 new patient evaluations annually by eight fellowship-trained academic movement disorders neurologists. NIA U19 Center PD participants receive extensive annual (years 1-5) and biennial (year 6 and beyond) motor, cognitive, and functional assessments.[18] Detailed information and assessments were collected on this cohort, including (1) demographic information, (2) family medical and neurodegenerative disease history, plus assessments of (3) motor signs and PD severity (original Unified Parkinson's Disease Rating Scale [UPDRS],[19] then Movement Disorder Society UPDRS Part III [MDS-UPDRS-III]),[20] (4) cognitive function (Dementia Rating Scale-2 [DRS-2])[1,2] (5) psychiatric symptoms (Cognition/Behavior Questionnaire,[21] and Geriatric Depression Scale [GDS-15]).[22] Over-the-counter and prescription medications were ascertained via participants' self-reports and recorded by study personnel during study visits. The data for this study was queried and extracted on June 6, 2023, and all data were deemed current as of that date. Only participants with a normal DRS-2-measured cognitive function (scores >130) at study enrollment were included for analyses.

Exposure Definition

Because PD is associated with cholinergic deficit, we focused our analyses on anticholinergic medication exposure. There is no gold standard for measuring anticholinergic drug exposure in observational studies. Retrospective measurements commonly use the Anticholinergic Cognitive Burden (ACB) scale,[4,23] which can be derived using the medication list recorded and updated at each study visit by study coordinators for study participants. Medications for each participant were classified using the ACB scale as having a low/possible (ACB = 1), medium (ACB = 2), or high (ACB = 3) ACB (Table S1). A time-varying total ACB was calculated as the sum of ACBs for individual medications at each visit for the duration that the participant was in the study. Considering the necessity of anticholinergic medication use for certain PD symptoms,[23] we created an alternative time-varying total ACB measure that excluded amantadine (ACB = 2), quetiapine (ACB = 3), and trihexyphenidyl (ACB = 3) from the scale.

Outcome Definition

The primary outcome of this study was PDD. The DRS-2, recommended by the MDS for assessing global cognition in PD, was used to diagnose dementia.[24-26] The DRS-2 score consists of 5 subscales in which points are earned for attention, initiation/perseveration, construction, conceptualization, and memory (score range 0-144, with lower scores indicating impairment).[25] Study participants were considered to have PDD if they had dementia based on a DRS score of ≤130.[27-31] Participants were censored upon the earliest occurrence of (1) the study outcome, (2) death, (3) loss to follow-up, or (4) end of dataset.

Covariates

Variable selection for our analytical model was based on literature review, expert opinion, and completeness/availability of data and included the following: age at enrollment, sex, highest education level completed, family history of PD, neuropsychiatric disorders/symptoms (psychosis, anxiety, impulse control disorder [ICD],[21] and depression[22]), motor symptom burden and treatment (UPDRS-III score and total levodopa equivalent daily dose [LEDD][32] estimated from PD medications), and use of other central nervous system (CNS)-acting drugs, that, according to the American Geriatrics Society (AGS) Beers Criteria®[33] (Table S2), may potentially worsen cognitive function. Neuropsychiatric disorders/symptoms, LEDD, and UPDRS-III scores were treated as time-varying,

whereas the remaining variables were measured at study enrollment. Missing values (<2% of selected variables) were imputed based on the last observation carried forward;[34] remaining missing values were excluded during time-varying analyses. Data on the Vascular Risk Factor Questionnaire, Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire, magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) collection via lumbar puncture were not collected for all participants and were excluded.

Statistical Analysis

All analyses were performed using SAS v9.4 and R v4.3.1. We evaluated total ACB categories as a time-varying exposure over follow-up visits for the primary analyses. We first organized the data in a counting process style (i.e., reshaping the data so that each patient had multiple rows containing covariate values across different time intervals), then used Cox proportional hazards models with time-varying covariates[35] to examine the association between demographic and clinical characteristics, anticholinergic medication exposure (based on total ACB categories) and the risk of PDD, adjusting for the remaining covariates. We conducted a similar analysis using the alternative aforementioned time-varying ACB (with medications used to treat PD symptoms removed) as the exposure. We also conducted a post-hoc sensitivity analysis to examine whether there would be an association between time-varying ACB and PDD risk among people with a total ACB of 2+ (indicating at least moderate exposure) at study enrollment.

Results

Baseline characteristics of 384 enrolled participants with PD in our study sample are shown in Table 1. The median age at enrollment was 69 years (interquartile range [IQR] 63-75); over 2/3 were male (66.9%), and most participants had at least a college degree (68%). Depression was reported in about 24.8% of participants, and anxiety in 33.8%. Motor symptom burden at enrollment was mild to moderate, with a median UPDRS-III score of 22 (IQR 14-29). About 75% of participants took at least 5 medications of any kind at baseline, with a median of 7 (IQR 4.5-9) medications and a median LEDD of 600 mg (IQR 300-899.3 mg). More than half of the participants (56.5%) were taking at least 1 medication on the ACB scale upon study entry, and almost 1/3 (30.7%) had a total ACB of 3+ at baseline. The most common medications reported for each ACB category at baseline are shown in Table S3. Moreover, 22.1% of the participants were taking high-risk medications for people with cognitive impairment/dementia from the AGS Beers Criteria® that were not on the ACB scale.

We excluded 93 participants with PDD at baseline and four with missing data. Therefore, our Cox proportional hazards regression models included data drawn from 287 participants. The median follow-up duration was 6.0 years (IQR 3.1-8.2), during which 130 participants met our definition of PDD. Adjusted Cox models with total ACB as a time-varying exposure over the follow-up period showed an association between age at enrollment and the risk of PDD development (adjusted hazard ratio [AHR] 1.07, 95% confidence interval [CI] 1.04-1.10), as shown in Table 2. Psychosis and greater UPDRS-III total scores were associated with an increased risk of developing PDD (AHRs 1.81, 95% CI 1.26-2.59, and 1.02, 95% CI 1.01-1.04, respectively). We observed negative associations between higher education levels (college, graduate school) and PDD risk compared to lower education levels (high school or less), with AHRs ranging from 0.34-0.43. Female sex was also associated with a lower risk of PDD (AHR 0.49, 95% CI 0.32-0.74). No association was observed between variables measuring or indicating a family history of PD, anxiety, depression, ICD, LEDD, or the use of other potentially inappropriate medications for persons with cognitive impairment/dementia from the Beers Criteria®. Total ACB was not associated with PDD.

The additional analysis using the alternative time-varying total ACB that excluded three commonly prescribed drugs in PD also showed similar association patterns between covariates and the risk of developing PDD (Table 3). When examining this association among 122 eligible participants with a baseline total ACB of 2+, we mostly observed similar findings (albeit with increased imprecision due to decreased sample size), except that ICD and depression were associated with PDD (Table S4).

Discussion

Preventing or delaying dementia is a priority for persons living with PD. In this study of a single-center sample of individuals enrolled in a natural history study of PDD, we examined whether anticholinergic medication use was associated with PDD. Our findings confirmed known associations between age, sex, motor symptom severity, psychiatric symptom burden, and PDD risk, but we did not detect a significant drug-disease interaction when using a standard anticholinergic drug exposure tool.

We found that age was associated with an increased risk of PDD. Age is an independent risk factor for all forms of dementia, including PDD.[36] In our cohort, female sex appeared to be protective against PDD development. This may be attributed to the selective nature of the cohort, which we believe consisted of female participants with above-average access to subspecialist health care and

Table 1. Characteristics of Participants at Baseline Enrollment Visit (n = 384).

Characteristics	
Age at enrollment in years, median (IQR)	69 (63-75)
Sex, n (%)	
Female	127 (33.1%)
Male	257 (66.9%)
Education level, n (%)	
Post-graduate	151 (39.3%)
College graduate	110 (28.7%)
Some college	73 (19.0%)
Highschool	50 (13.0%)
Family history of PD,[a] n (%)	70 (18.5%)
Disease duration at enrollment in years, median (IQR)	5.0 (2.3-9.0)
Psychosis,[b] n (%)	111 (29.1%)
Anxiety,[b] n (%)	129 (33.8%)
Impulse control disorder,[b] n (%)	72 (18.9%)
Depression,[c] n (%)	95 (24.8%)
UPDRS-III,[a] median (IQR)	22 (14-29)
LEDD in milligrams, median (IQR)	600 (300-899.3)
ACB score, median (IQR)	1 (0-3)
ACB score category, n (%)	
0	167 (43.5%)
1	51 (13.3%)
2	48 (12.5%)
3+	118 (30.7%)
Alternative[d] ACB score, median (IQR)	0 (0-1)
Alternative[d] ACB score category, n (%)	
0	217 (56.5%)
1	72 (18.8%)
2	15 (3.9%)
3+	80 (20.8%)
Other potentially inappropriate medications[e] for persons with cognitive impairment/dementia from 2019 Beers criteria®, n (%)	85 (22.1%)

[a]Missing 6/384 (1.56%).
[b]Missing 2/384 (0.52%).
[c]Missing 1/384 (0.26%).
[d]Score excluded 3 drugs: amantadine, quetiapine, and trihexyphenidyl.
[e]Medications included in 2019 Beers Criteria® but not listed in ACB scale.
ACB: anticholinergic cognitive burden; IQR: interquartile range; LEDD: levodopa equivalent daily dose; PD: Parkinson disease; UPDRS-III: Unified Parkinson's Disease Rating Scale Part III.

better management of risk factors for other types of dementia. Prior studies have found that males living with PD tend to have worse cognitive abilities[37,38] and have a higher rate of PDD.[39] Although some studies found no association between sex and PDD after adjustment for potential confounding factors such as age, history of dementia, smoking, and number of siblings,[40,41] a meta-analysis reported that male sex is a risk factor for PDD before confounding adjustment.[42] These findings collectively support the hypothesis that the relationship between biological sex and dementia may differ across dementia types. While Alzheimer's disease is consistently more prevalent in women,[43-45] the development of PDD appears to follow a different pattern, suggesting that much more remains to be understood about the role of biological sex in PDD. Our finding that higher levels of education were protective against dementia was also consistent with previous literature, not only among PD patients[42] but also in the general population,[46-50] with a more consistent association occurring when the years of education reflected cognitive capacity.[49]

Higher UPDRS-III scores were associated with an increased risk of developing PDD in our cohort, consistent with prior studies of PDD risk.[1,42,51] We did not observe

Table 2. Associations Between Participants' Characteristics and Risk of Developing PDD (n = 287).

Characteristics	Adjusted[a] HR (95% CI)	*P*-value
Age at enrollment	**1.07 (1.04-1.10)**	**<0.001**
Education level		
High school or less	REF	REF
Some college	**0.41 (0.20-0.85)**	**0.017**
4 years of college	**0.34 (0.17-0.67)**	**0.002**
Post-graduate	**0.43 (0.23-0.82)**	**0.009**
Disease duration at enrollment	1.02 (0.98-1.07)	0.3
Female sex	**0.49 (0.32-0.74)**	**<0.001**
Family history of PD	1.06 (0.69-1.64)	0.8
Psychosis	**1.81 (1.26-2.59)**	**0.001**
Anxiety	1.04 (0.71-1.53)	0.8
Impulse control disorder	1.12 (0.71-1.76)	0.6
Depression	1.26 (0.81-1.96)	0.3
UPDRS-III total	**1.02 (1.01-1.04)**	**0.003**
LEDD categories		
0-300 mg	REF	REF
300-600 mg	0.95 (0.58-1.56)	0.8
600-900 mg	1.15 (0.66-2.03)	0.6
900-1200 mg	0.91 (0.46-1.81)	0.8
>1200 mg	1.65 (0.86-3.15)	0.13
Other potentially inappropriate medications for persons with cognitive impairment/dementia from 2019 Beers criteria®	1.01 (0.64-1.57)	>0.9
Time-varying ACB categories		
0	REF	REF
1	1.19 (0.69-2.06)	0.5
2	0.75 (0.39-1.45)	0.4
3+	1.03 (0.67-1.58)	0.9

[a]Adjusted for remaining covariates.
ACB: anticholinergic cognitive burden; HR: hazard ratio; CI: confidence interval; LEDD: levodopa equivalent daily dose; PD: Parkinson disease, PDD: Parkinson disease dementia; UPDRS-III: Unified Parkinson's Disease Rating Scale Part III. Bolded values indicate statistical significance.

that increasing LEDD is associated with PDD, which may reflect the clinical practice of reducing levodopa as PD progresses and drug response declines. Antiparkinsonian medications can have harmful effects on cognition depending on striatal basal dopamine levels and tend to cause more intolerable adverse effects without sustained motor benefit at advanced stages.[52,53]

Our deeply-phenotyped cohort allowed us to examine a number of psychiatric nonmotor symptoms. Psychosis was associated with an increased risk for PDD in our cohort. Visual hallucinations[1,42,54,55] or psychosis[56-58] have been previously described as risk factors for developing PDD, and psychosis and dementia often co-exist.[59,60] Depression[61-63] and anxiety[64] have been consistently linked to dementia risk in the general adult population. The data on mood or ICD and cognitive decline in the PD population, however, have been mixed. One natural history study reported that persons with PD and depression were nearly twice as likely to be diagnosed with mild cognitive impairment within four years.[65,66] Using a more precise cognitive instrument, we found depression (measured using the GDS-15) was associated with PDD in the subsample of NIA U19 Center's participants with a higher ACB at enrollment. Anxiety has been reported as a risk factor for cognitive impairment, verbal memory impairment,[67] and longitudinal decline in verbal and visual learning performance among PD patients.[68] However, we did not observe an association between anxiety (measured using the Cognition/Behavior Questionnaire) and PDD risk. Some studies have found that PD patients with ICD have deficiencies in cognitive tasks localizing to frontal regions and visual-spatial planning;[69] others have reported no between-group differences in working memory tasks,[69,70] but prior studies have not found a relationship between ICD and PDD.[71] As with depression, we found an association between ICD and PDD risk only in persons with greater baseline ACB. Taken together, these data highlight the complex roles psychiatric symptoms and

Table 3. Associations Between Participants' Characteristics and Development of PDD Using Alternative[a] ACB Categories (n = 287).

Characteristics	Adjusted[b] HR (95% CI)	*P*-value
Age at enrollment	**1.07 (1.04-1.10)**	**<0.001**
Education level		
High school or less	REF	REF
Some college	**0.45 (0.22-0.92)**	**0.029**
4 years of college	**0.36 (0.19-0.71)**	**0.003**
Post-graduate	**0.45 (0.24-0.85)**	**0.014**
Disease duration at enrollment	1.02 (0.98-1.06)	0.4
Female sex	**0.49 (0.32-0.74)**	**<0.001**
Family history of PD	1.05 (0.68-1.62)	0.8
Psychosis	**1.81 (1.26-2.59)**	**0.001**
Anxiety	1.05 (0.72-1.54)	0.8
Impulse control disorder	1.16 (0.74-1.83)	0.5
Depression	1.25 (0.81-1.94)	0.3
UPDRS-III total	**1.03 (1.01-1.04)**	**0.002**
LEDD categories		
0-300 mg	REF	REF
300-600 mg	0.96 (0.59-1.57)	0.9
600-900 mg	1.20 (0.68-2.11)	0.5
900-1200 mg	0.91 (0.46-1.80)	0.8
>1200 mg	1.56 (0.83-2.95)	0.2
Other potentially inappropriate medications for persons with cognitive impairment/dementia from 2019 Beers criteria®	1.00 (0.64-1.55)	>0.9
Time-varying alternative[a] ACB categories		
0	REF	REF
1	1.21 (0.77-1.91)	0.4
2	0.70 (0.30-1.65)	0.4
3+	0.88 (0.56-1.39)	0.6

[a]Scale excluding 3 drugs: amantadine, quetiapine, and trihexyphenidyl.
[b]Adjusted for remaining covariates.
ACB: anticholinergic cognitive burden; HR: hazard ratio; CI: confidence interval; LEDD: levodopa equivalent daily dose; PD: Parkinson disease, PDD: Parkinson disease dementia; UPDRS-III: Unified Parkinson's Disease Rating Scale Part III. Bolded values indicate statistical significance.

disorders play in the propagation, recognition, and measurement of cognitive decline in persons living with PD.

Several studies have reported an association of the use of anticholinergic medications with the risk of all-cause dementia,[3-9,14-17] We hypothesize that a greater risk of cognitive impairment from central cholinergic blockade is possible in the PD population (as compared with the general older adult population) due to PD related loss of cholinergic neurons. Cholinergic degeneration begins in the prodromal phase of PD, contributing to cognitive and gait dysfunction and eventually to freezing and dementia.[72] We did not observe an association between higher total ACB categories and incident PDD. Exposure misclassification is a potentially strong reason for our findings. There are no standard pharmacologic assays to detect anticholinergic activity in the CNS, despite the availability of serum anticholinergic assays.[73-76] Imaging-based biomarkers for anticholinergic activity have not been developed, even though anticholinergic use was associated with cortical and ventricular abnormalities (as well as cognitive decline) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Indiana Memory and Aging Study (IMAS) cohorts.[77] Without standardized biological tools, multiple scales to assess anticholinergic burden via application to existing data have been developed, including the widely used ACB scale. However, the scales have low to moderate concordance between them, and medications are often inconsistently included in one scale but not another.[23] The available anticholinergic exposure measures were also not developed in populations with underlying cholinergic deficits, as found in PD. Ceiling effects in the PD population may be observed, with toxicity occurring at a lower anticholinergic level than captured by current scales. Of note, the anticholinergic effect on cognition (AEC) score[78] also accounts for the central anticholinergic effects of anticholinergic

medications based on literature reviews of their ability to cross the blood-brain barrier, which could make it more relevant for future research in this population. However, there remains limited *in vivo* data on these effects, particularly concerning drug-drug interactions and the evolving pharmacokinetic and pharmacodynamic properties in older adults. Our findings underscore the need for biological tools to assess central anticholinergic activity or for the development and validation of pharmacoepidemiology tools for PD research that consider critical factors such as dosing, CNS penetration, and drug-drug interactions, allowing characterization of the pharmacological exposome for use in randomized controlled trials and observational cohort studies.

Strengths of our study include a well-phenotyped cohort that had longitudinal assessments. Several weaknesses should be considered in the interpretation of these findings. Data on genes and health behaviors (eg, APOE-ε4, exercise) associated with dementia risk, as well as comorbidities (e.g., cardiovascular, cerebrovascular, or metabolic diseases), were not readily available or routinely collected as aforementioned (partly due to the COVID-19 pandemic). Moreover, medication data were collected by study personnel based on participants' self-reports, and we did not have information on the duration of exposure to anticholinergic or other potentially inappropriate medications prior to study enrollment, nor on medication doses. As a result, we were unable to assess cumulative anticholinergic doses, which may introduce potential residual confounding. Our small sample only included people from 1 clinical center, where most patients cared for were White, highly educated, and had above-average income; thus, our findings are not generalizable to the average older adult population with PD. We used DRS-2 scores as a proxy for dementia diagnosis; our score cut-off was conservative as compared with other studies,[27-31] resulting in potential outcome misclassification.

Conclusions

In this single-center sample of individuals with PD, we found that older age, psychosis, and greater motor symptom burden were positively associated with the risk of PDD development, aligning with previous studies that have identified these factors as predictors for dementia. Alternatively, we observe that female sex and higher education level were protective against PDD. While we did not see an association between ACB and PDD risk, this finding should be interpreted cautiously. Careful weighing of known anticholinergic medication risks vs. benefits should still be applied in this vulnerable patient population, which is usually also elderly, and deprescribing opportunities should be implemented whenever possible. New pharmacological exposome research tools are needed to understand the potential CNS effects of anticholinergics on PD cognitive function and clinical trajectory.

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Declaration of Conflicting Interest

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Ethical Statement

Ethical Approval

The University of Pennsylvania's Institutional Review Board approved this research (protocol #827738). The National Institutes of Health had no input on the study's conduct or interpretation.

Informed Consent

Consent was approved for all participants enrolled in the National Institute on Aging Penn U19 (NIA U19) awarded as Dr. Allison W. Willis, Center Parkinson disease (PD) clinical cohort.

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Supplemental Material

Supplemental material for this article is available online.

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