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Medication Side Effect Profiles in PD Patients in a Safety-Net Hospital

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Abstract

Background: Compulsive behavior, dyskinesias, motor fluctuations, and hallucinations are common Parkinson's disease (PD) medication side effects. These are yet to be examined in relation to race and level of education. The goal of this analysis was to identify socioeconomic or clinical variables that are associated with compulsive behavior, dyskinesias, motor fluctuations, and hallucinations in patients in a safety-net hospital. **Methods**: A movement disorder patient database containing 452 patients with idiopathic PD was analyzed for differences in PD medication side effects using univariate and multivariate logistic regression analysis. Race, sex, and level of education were evaluated as possible confounders. **Results**: A greater proportion of the patients in this study were Caucasian males. The only variable associated with compulsive behavior was age, with higher age having a protective effect (p = 0.0336). Disease duration (defined as time since the onset of symptoms), diagnosis duration (time since formal diagnosis), and level of education were significantly associated with dyskinesia inunivariate analysis (p =< 0.0001, <0.0001, 0.1236 respectively). However, diagnosis duration was the only variable significantly associated with dyskinesia in multivariate analysis (p = 0.0038), in addition to a borderline significant association when comparing individuals with graduate degree to those who had completed high school education or less (p = 0.0599), with a protective effect of higher education. Disease duration, diagnosis duration, and use of monoamineoxidase inhibitors were also significantly associated with motor fluctuations in the univariate analysis, while only diagnosis duration was significantly associated with motor fluctuations in multivariate analysis (p = 0.0035) with longer diagnosis duration associated with higher risk of motor fluctuations. Age, disease duration, and diagnosis duration were associated with an increased risk of hallucinations

in univariate analysis (p =< 0.0001, <0.0001, <0.0001 respectively), but age and disease duration were the only variables associated with hallucinations in multivariate analysis (p = 0.0009, 0.1196 respectively). Race was not associated with a higher risk of compulsive behavior, dyskinesias, motor fluctuations, or hallucinations. **Conclusion**: Compulsive behavior, dyskinesias, motor fluctuations, and hallucinations in our PD population may be associated with differences in socioeconomic status and access to care, but not with differences in race.

Keywords

Parkinson's Disease, Medication Side Effects, Safety-Net Hospital

1. Introduction

The pharmacological therapy of Parkinson's Disease (PD) is commonly associated with side effects, such as compulsive behavior, dyskinesias, motor fluctuations and hallucinations, which can have a significant impact on the quality of life of the patient [1]. The magnitude of these side effects depends on the duration of treatment, duration of the disease, type of drug, and combination of drugs used [2]. While side effects of antiparkinsonian therapy are mostly related to the use of levodopa (L-dopa), dopamine agonists (DA), monoamine oxidase inhibitors (MAOBI), anticholinergics, amantadine, and catechol-O-methyl transferase inhibitors (COMTI) have also been implicated [3] [4] [5] [6] [7].

A recent study suggests that motor fluctuations and dyskinesias are associated with disease progression rather than the duration of L-dopa therapy [8]. The use of dopamine agonists has been especially associated with compulsive behavior, such as compulsive spending, pathological gambling, or hypersexuality [9] [10] [11]. The incidence of impulse control disorder symptoms has been associated with increased length and early initiation of dopamine replacement therapy [7] [12]. In addition, it is estimated that one-quarter to one-third of PD patients will experience hallucinations [13]. Hallucinations have been associated with L-dopa therapy, older age, and longer duration of the disease [14] [15]. However, they are now perceived to be a result of complex interactions between PD medications and PD pathophysiology [16].

This analysis studies a population of PD patients at Boston Medical Center (BMC), an urban safety-net hospital in Boston, MA and aims to identify socioeconomic or clinical variables that are associated with compulsive behavior, dyskinesias, motor fluctuations, and hallucinations in patients in a safety-net hospital.

2. Methods

2.1. Patients and Location

Patients were recruited from the neurology department at Boston Medical Center

(BMC) in Boston, Massachusetts between 2007 and 2012. Movement disorder specialists at Boston Medical Center evaluated the patients and only those who were diagnosed with idiopathic PD were eligible for this study. The Institutional Review Board (IRB) at BMC gave approval for this research.

2.2. Data Collection

During the clinical encounter, the clinicians evaluated the patients for history or physical exam elements consistent with compulsive behavior, dyskinesias, motor fluctuations, and hallucinations. This data was collected by the clinician using a standardized clinical characteristics data form and then entered into a de-identified database. The form included sections for demographic and clinical information as well as the medications used by the patient. Demographical information collected included the patients' year of birth, sex, ethnicity, and education level. Clinical information included the self-reported date of symptom onset, date of diagnosis, and the presence or absence of potential disease complications such as compulsive behavior, dyskinesias, motor fluctuations, and hallucinations.

2.3. Data Analysis

The main clinical outcomes of interest in this study were the four major side effects of compulsive behavior, dyskinesia, motor fluctuations, and hallucinations. The clinical variables included disease duration (number of years since the onset of symptoms), diagnosis duration (number of years since the diagnosis of PD as a measure of treatment duration), medication groups (carbidopa-levodopa, COMTI, DAs, MAOI), the total number of medications and total number of medication groups. The covariates of interest included age, gender, race (Caucasian vs. non-Caucasian), education (high school and lower, college or some college, graduate degree).

For evaluation of demographics, sample size, mean and standard deviation were calculated and reported for continuous variables. Frequency and relative frequency are reported for dichotomous and categorical variables (**Table 1**). Then, the clinical variables and covariates were evaluated for their possible association with each of the side effects in a univariate logistic regression model in which the side effect is the dependent and the predictor is the independent variable or covariate. Those predictors with a p-value smaller than 0.2 in the univariate logistic regression models were then evaluated for their adjusted association with the side effect in a multivariate logistic model. A p-value of less than 0.05 was considered statistically significant. Those p-values that were less than 0.2 and less than 0.05 are indicated in **Tables 2-5**.

3. Results

3.1. Analysis of Demographic Data and Confounders

Four hundred and fifty-two (452) patients were included in the analysis. Their

Table 1. Demographic information.

Patient Demographics (Total: 452 patients)	Mean (SD)
Age in years	76.25 (10.66)
Disease Duration (in years)	17.23 (7.57)
Diagnosis Duration (in years)	15.74 (7.51)
Total Number of PD Medications Used	1.73 (1.54)
	Frequency (%)
Sex (Male)	227 (50.22)
Race (Caucasian)	375 (83.33)
College Education or Higher	265 (58.63)
Medication Groups	**Frequency (%)**
Carbidopa-Levodopa	284 (62.83)
COMT Inhibitors	78 (17.47)
Dopamine Agonists	160 (35.40)
MAO Inhibitors	76 (16.81)

Table 2. Compulsive behavior.

Categories	Unadjusted			Multivariate		
	OR	CI	*P*-Value	OR	CI	*P*-Value
Age in years	0.964	0.932 - 0.997	0.0336**	0.964	0.932 - 0.997	0.0336**
Disease Duration (in years)	1.018	0.967 - 1.073	0.4963			
Diagnosis Duration (in years)	1.017	0.967 - 1.070	0.5037			
Gender	1.239	0.587 - 2.617	0.5740			
Race	0.689	0.202 - 2.351	0.5514			
Education						
College	1.636	0.603 - 4.444	0.3340			
Graduate	0.865	0.256 - 2.922	0.8159			
Medication Groups						
Carbidopa-Levodopa	1.123	0.495 - 2.548	0.7809			
COMT Inhibitors	1.265	0.495 - 3.232	0.6229			
Dopamine Agonists	0.800	0.353 - 1.813	0.5929			
MAO Inhibitors	1.309	0.512 - 3.347	0.5736			
Total Number of Medications	1.038	0.814 - 1.324	0.7648			
Total Number of Medication Groups	1.042	0.747 - 1.453	0.8082			

** *P*-Value <0.05, * *P*-Value <0.2.

Table 3. Dyskinesias.

Categories	Unadjusted			Multivariate		
	OR	CI	*P*-Value	OR	CI	*P*-Value
Age in years	1.005	0.988 - 1.023	0.5518			
Disease Duration	1.173	1.128 - 1.220	<0.0001**	0.989	0.861 - 1.135	0.8701
Diagnosis Duration	1.162	1.118 - 1.207	<0.0001**	1.239	1.072 - 1.432	0.0038**
Gender	1.160	0.792 - 1.698	0.4461			
Race	1.071	0.626 - 1.833	0.8027			
Education						
College	1.091	0.669 - 1.776	0.7278	0.876	0.445 - 1.722	0.7000
Graduate	0.650	0.376 - 1.125	0.1236*	0.989	0.861 - 1.135	0.0599*
Medication Groups						
Carbidopa-Levodopa	1.264	0.842 - 1.897	0.2576			
COMT Inhibitors	1.064	0.650 - 1.754	0.7969			
Dopamine Agonists	1.148	0.773 - 1.705	0.4945			
MAO Inhibitors	1.056	0.639 - 1.744	0.8308			
Total Number of Medications	1.036	0.915 - 1.173	0.5786			
Total Number of Medication Groups	1.081	0.915 - 1.278	0.3592			

** *P*-Value < 0.05, * *P*-Value < 0.2.

Table 4. Motor fluctuations.

Categories	Unadjusted			Multivariate		
	OR	CI	*P*-Value	OR	CI	*P*-Value
Age in years	0.999	0.982 - 1.016	0.8954			
Disease Duration	1.140	1.099 - 1.183	<0.0001**	0.934	0.813 - 1.073	0.3353
Diagnosis Duration	1.149	1.106 - 1.193	<0.0001**	1.241	1.074 - 1.434	0.0035**
Gender	1.126	0.774 - 1.637	0.5360			
Race	1.151	0.677 - 1.958	0.6028			
Education						
College	1.189	0.733 - 1.927	0.4837			
Graduate	1.053	0.623 - 1.781	0.8467			
Medication Groups						
Carbidopa-Levodopa	1.071	0.721 - 1.591	0.7328	1.571	0.830 - 2.971	0.1650
COMT Inhibitors	1.041	0.638 - 1.699	0.8728			
Dopamine Agonists	1.010	0.684 - 1.492	0.9583			
MAO Inhibitors	1.753	1.055 - 1.910	0.0301**	1.571	0.830 - 2.971	0.1650
Total Number of Medications	1.002	0.887 - 1.133	0.9738			
Total Number of Medication Groups	1.083	0.918 - 1.277	0.3449			

** *P*-Value < 0.05, * *P*-Value < 0.2.

Table 5. Hallucinations.

Categories	Unadjusted			Multivariate		
	OR	CI	*P*-Value	OR	CI	*P*-Value
Age in years	1.057	1.034 - 1.081	<0.0001**	1.051	1.020 - 1.082	0.0009**
Disease Duration	1.097	1.061 - 1.134	<0.0001**	1.097	0.976 - 1.232	0.1196*
Diagnosis Duration	1.098	1.062 - 1.135	<0.0001**	0.983	0.872 - 1.108	0.7764
Gender	1.127	0.737 - 1.725	0.5809			
Race	0.708	0.376 - 1.334	0.2857			
Education						
College	1.315	0.765 - 2.260	0.3221			
Graduate	0.918	0.499 - 1.689	0.7837			
Medication Groups						
Carbidopa-Levodopa	0.935	0.581 - 1.504	0.7813			
COMT Inhibitors	1.214	0.695 - 2.118	0.4959			
Dopamine Agonists	1.070	0.665 - 1.721	0.7813			
MAO Inhibitors	1.160	0.646 - 2.083	0.6182			
Total Number of Medications	1.025	0.881 - 1.193	0.7473			
Total Number of Medication Groups	1.042	0.885 - 1.270	0.6863			

**P-Value < 0.05, *P-Value < 0.2.

demographics are outlined in Table 1. 51.71% of the patients were male and most of the patients included in the analysis were Caucasian (82.96%), while the remainder were mostly African American, Hispanic, Asian, or mixed race. The mean age was 76 and the mean time since diagnosis of PD was 15.74 years. Among socioeconomic variables, the level of education showed that patients were divided into those who had completed a high school education or less (25.22%), college or some college (34.5%), and those with a graduate degree (24.12%).

Of the 452 patients enrolled in this study, 284 used carbidopa-levodopa, 160 used DAs, 78 used COMTI, 76 used MAOBI.

In this sample, 30 (6.64%) patients had demonstrated compulsive behavior, 184 (40.71%) suffered from dyskinesia, 227 (50.22%) experienced motor fluctuations, and 122 (27.00%) experienced hallucinations.

3.2. Analysis of Clinical Outcomes

Tables 2-5 demonstrate the results of the multivariate logistic regression analysis. As seen in Table 2, the only variable significantly associated with compulsive behavior was age (OR (95%CI) = 0.964 (0.932, 0.997), $p = 0.0336$) with a protective effect for higher age. Disease duration, diagnosis duration and level of education were significantly associated with dyskinesia in the univariate analysis

(Table 3). However in the multivariate analysis, only diagnosis duration was significantly associated with dyskinesia (OR (95% CI) = 1.239 (1.072, 1.432), p = 0.0038) with longer diagnosis duration associated with higher risk. There was a borderline significant association when comparing individuals with graduate degree tothose who had completed high school education or less (OR (95% CI) = 0.989 (0.861, 1.135), p = 0.0599) with a protective effect of higher education. Disease duration, diagnosis duration, and use of MAOBI medications were also significantly associated with motor fluctuations in the univariate analysis (Table 4) while only diagnosis duration was significantly associated to motor fluctuations in the multivariate analysis (OR (95% CI) = 1.241 (1.074, 1.434), p = 0.0035) with longer diagnosis duration associated with higher risk of motor fluctuations. Hallucinations were associated with age, disease duration, and diagnosis duration on univariate analysis, but only with age (OR (95%CI) 1.051 (1.020, 1.082), p = 0.0009) and disease duration (OR (95%CI) 1.097 (0.976, 1.232), p = 0.1196) in the multivariate analysis (Table 5) with higher age and longer disease duration associated with higher risk. In our study, race was not associated with a higher risk of compulsive behavior, dyskinesia, motor fluctuations, or hallucinations.

4. Discussion

Previous studies have suggested that the use of PD medications, in particular DAs and to a lesser extent L-dopa, are associated with the development of compulsive behavior in the general population [7] [14]. The behavior was related to younger age, but was not related to any of the medication groups, duration of the disease, or duration of diagnosis. Other studies have suggested that compulsive behavior in PD patients is under-recognized and undermanaged by clinicians [12]. In addition, patients may underreport symptoms of compulsive behavior due to embarrassment, unawareness, or because they do not associate these behaviors with PD medications. All things considered, the fact that the patients in our cohort were more likely to have compulsive behavior if they were younger is consistent with the current literature.

In our cohort, dyskinesias were not associated with any specific medication groups, but they were associated with the time since diagnosis and were less likely to occur in patients with a graduate degree. A study in 2006 estimated that the 5-year risk of L-dopa induced dyskinesias was 50% in patients with disease onset between 50 - 59 years and 16% in those with onset after 70 years [17]. Given that the mean age in our population was 76 and the mean duration of diagnosis was 17 years, we can infer that a majority of the patients had a disease onset of close to 59. In our cohort, 41% of the patients had dyskinesias. Among these patients 64% were on L-dopa, 37% on DAs, 9% on COMT inhibitors, and 22.5% on MAOIs. The sum of percentages exceeds 100%, because some patients were on multiple medications at the same time. Among the patients who were not using L-dopa, it is possible that they had used L-dopa in the past, had undergone

deep brain stimulation (DBS), or that other medications such as DAs, antipsychotics, or anticholinergics were responsible for the dyskinesias [18] [19] [20]. While the exact mechanism is still under investigation, it is suspected that DA and DBS may induce dyskinesias due to maladaptive mechanisms related to dopaminergic and glutaminergic systems [20]. In our cohort, 40% of the patients who were using L-dopa therapy had dyskinesia. Some studies suggest that the incidence of L-dopa induced dyskinesias may be close to 40% [9]. While the incidence of L-dopa induced dyskinesias varies between studies, this finding was consistent with the literature. In addition, our study found that a graduate degree had a protective effect in the development of dyskinesias, suggesting that level of education may influence their incidence. A previous study showed that patients who did not complete college had more severe disease and were less likely to use newer dopaminergic agents compared to those that had completed college [12]. Our findings may add to that study that higher educational level may be protective against the development of dyskinesias. This may be because of differences in the medications used or because patients with higher education may be more medically optimized.

Fifty percent of the patients in the study had motor fluctuations. Previous studies had estimated the prevalence of motor fluctuations to be closer to 40% [21] [22]. Motor fluctuations were associated with a longer duration of the disease consistent with current literature [22]. In our population, motor fluctuations were associated with the use of MAOBI.

Several studies have demonstrated that dopaminergic medications influence hallucinations in PD and that they are associated with increased age and longer disease duration [23] [24] [25]. In this present study, hallucinations were associated with increased age and longer disease duration, which is consistent with the current literature. This could be explained by the fact that older individuals and those who have had PD for a longer time may have more progressed disease or have been receiving dopaminergic therapy for a longer period of time. In our study, hallucinations were not associated with any medication group, L-dopa and DAs being of special interest. This may be because hallucinations may not be a purely dopaminergic adverse event. Previous studies have found that there is no dose-effect relationship between the use of dopaminergic agents and development of hallucinations [24]. In fact, two prospective studies and one retrospective study showed no association between use of L-dopa or DAs and development of hallucinations [15] [26] [27]. In addition, a study by Goetz *et al.* in 1998 showed that there was no simple relationship between the development of visual hallucinations and high plasma levels of L-dopa or sudden changes in plasma levels [28]. This does not rule out a role by dopaminergic therapy in the development of hallucinations, but suggests that its role may be facilitating or even triggering hallucinations in individuals who were already predisposed.

In our study, race was not associated with a higher risk of compulsive behavior, dyskinesias, motor fluctuations, or hallucinations. Racial differences in the incidence of complications of PD, especially compulsive behavior, dyskinesias,

motor fluctuations, and hallucinations have not been specifically studied. A previous study found that the incidence of Parkinson's disease was higher among Hispanics, followed by non-Hispanic whites, Asians, and Blacks [29], however, these differences may not carry over when studying complications of PD. In fact, our study suggests that the risk of developing these complications may be more associated with disease duration and diagnosis duration rather than with race. A possible explanation is that while there are racial differences in the incidence of PD and access to treatment, the progression of the disease and response to treatment does not vary significantly by race [30]. Future studies are needed to investigate the racial differences in the incidence of complications of PD.

This was a cross-sectional study with limited information on temporality, impacting conclusions about causality. We did not have access to data regarding the dosage of medications and the duration they had been taken for, making us unable to evaluate dose-response associations. The data on disease duration was collected by asking the patients about the start of their symptoms, which might be subject to recall inaccuracy and recall bias. Studies have shown that non-motor symptoms of PD can manifest up to 10 years before formal diagnosis is made [31] [32]. In our cohort, the difference between the mean disease duration and diagnosis duration was only 1.5 years, suggesting that it is disease management after diagnosis that affects the clinical manifestations. These data are all from one academic medical center and may not be generalizable to the population of all PD patients. Future directions for this analysis would include an analysis of socioeconomic status and medication adherence to further illustrate some of the findings of this present study.

5. Conclusion

Compulsive behavior was associated with younger age, but not use of L-dopa. Dyskinesias were not associated with any medication group, but were associated with a longer time since diagnosis. In addition, patients with a graduate degree were less likely to have dyskinesias. Motor fluctuations were associated with longer duration of disease and use of MAOBI. Hallucinations were not associated with L-dopa. In conclusion, our study suggests that compulsive behavior, dyskinesias, motor fluctuations, and hallucinations in our PD population may be associated with differences in socioeconomic status and access to care, but not with differences in race.

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