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Motor complications in an incident Parkinson's disease cohort

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ABSTRACT

Background

Levodopa treatment in Parkinson's disease (PD) causes motor fluctuations and dyskinesias, but few data describe their development or severity in unselected incident cohorts.

Methods

We gathered demographic, clinical, treatment, smoking, caffeine, and alcohol data from 183 people with PD from the PINE study, a community-based, incident cohort. With Kaplan-Meier survival analysis and Cox regression modelling we assessed the development, and severity, of dyskinesias and motor fluctuations and which factors independently influenced their onset.

Results

After mean follow-up of 59 months, 39 patients (21.3%) developed motor fluctuations and 52 (28.4%) developed dyskinesias. Kaplan-Meier estimates of the probability of motor fluctuations and dyskinesias after 5 years of dopaminergic treatment were 29.2% (95% confidence interval [CI] 21.5–38.8%) and 37.0% (95% CI 28.5–47.1%) respectively. 19.8% developed motor fluctuations requiring treatment changes but only 4.0% (95% CI 1.5–10.4%) developed dyskinesias requiring treatment changes by five years. Cumulative levodopa dose (Hazard ratio [HR] 1.38 [95% CI 1.19–1.60]), female sex (HR 2.41 [1.19–4.89]), and younger age at diagnosis (HR 1.08 [1.04–1.11]) were independently associated with development of motor fluctuations. Cumulative levodopa dose (HR 1.23 [1.08–1.40]), female sex (HR 2.51 [1.40–4.51]) were independently associated with dyskinesias. In exploratory analyses, moderate caffeine exposure was associated with fewer motor fluctuations, longer symptom duration with more dyskinesias, and tremor at diagnosis with higher rates of both complications.

Conclusions

In this community-based incident PD cohort, severe dyskinesias were rare. Cumulative levodopa dose was the strongest predictor of both dyskinesias and motor fluctuations.

INTRODUCTION

Treatment of Parkinson's disease (PD), especially with levodopa, causes dyskinesias and motor fluctuations. These motor complications are potentially disabling and may adversely affect patients' quality of life.[1-3] A previous review of studies of motor complications estimated that the risk of developing motor fluctuations and dyskinesias were both about 40% after levodopa treatment for 4-6 years.[4] However, most previous studies have been based on unrepresentative samples, with attendant selection biases, such as cohorts from specialist clinics or clinical trials in which younger patients with fewer co-morbidities than the general PD population are often over-represented.[5,6] Only two representative, community-based incidence studies have examined the development of motor complications over time, both of which were small, only reported dyskinesias[7,8] and one was retrospective.[8]

Several risk factors for the development of dyskinesias have been identified, including: younger age at diagnosis, female sex, higher levodopa dose, longer duration of levodopa therapy, and lower body weight,[8-14] but most data come from non-incident or hospital-based studies. By contrast, few predictors of motor fluctuations have been identified but dose and duration on levodopa therapy are most commonly reported.[12,15-18] In addition, nicotine, caffeine and alcohol may protect against the development of PD[19] and there is some inconsistent clinical trial data to suggest caffeine and another adenosine A2A antagonist, may reduce dyskinesia risk.[20,21]

We therefore aimed to (i) describe the development of dyskinesias and motor fluctuations in a prospective, community-based, incident cohort of PD; (ii) assess what factors influence their development; and (iii) describe the development of severe motor complications.

METHODS

Study Design and Participants

We used data from the Parkinsonism Incidence in North-East Scotland (PINE) study, a community-based incidence study of PD and other parkinsonian disorders in Aberdeen and surrounding areas with prospective long-term follow-up.[22,23] Attempts were made to identify all newly diagnosed patients with degenerative or vascular parkinsonism between 2002 and 2004 (pilot phase) and 2006 to 2009 (main study phase) using multiple, overlapping methods for case ascertainment.[23] All patients were asked to consent to long-term annual follow-up with interim appointments as required for clinical management. The study was approved by the Multi-centre Research Ethics Committee for Scotland and conducted with the informed consent of the patients involved.

This analysis was restricted to patients who had a diagnosis of idiopathic PD at death or latest follow-up, made by a consultant neurologist with an interest in movement disorders (CEC) using the UK Brain Bank criteria,[24] insofar as follow-up duration permitted supportive criteria to be applied. 15% of patients with a latest diagnosis of PD had initially had an alternative diagnosis. Patients were excluded if they were not followed-up after baseline or if they had not received dopaminergic treatment. Patients were treated according to the clinical judgement of the treating clinicians.

Data collection and assessment of motor complications

At the baseline (i.e. diagnostic) assessment and at subsequent follow-up appointments, consenting patients were interviewed and examined, and information gathered included patient demographics and clinical characteristics (including the Unified PD Rating Scale [UPDRS]) and details of parkinsonian medication. Data were also gathered on exposure to caffeine, alcohol and smoking at verbal interview, including age at first exposure, average level of exposure before baseline and, if relevant, year exposure stopped. At each annual assessment, patients were asked about their ongoing exposures.

Data on motor complications were gathered from the prospectively acquired records of the examining study physician and from part IV of the UPDRS. In patients who reported motor complications, the month and year of onset were recorded from patient self-report or, in the case of asymptomatic dyskinesias that were seen at the assessment, the date of that assessment. Dyskinesias did not have to be witnessed by a physician to be included, but if they were not seen and the history was doubtful, they were not included. Severe motor complications were defined as those which required changes to parkinsonian treatment after discussion with the patient about their impact.

Analysis

The data were extracted from the PINE database (26th June, 2013), checked and cleaned. The cumulative levodopa only dose and the total levodopa-equivalent dose (LED)[25] (including any dopamine replacement therapy) were calculated up to four years from diagnosis since almost all surviving patients had been followed-up for four years. Levodopa and levodopa-equivalent doses were calculated as levodopa or levodopa-equivalent dose in milligrams multiplied by number of days of treatment and divided by 10^5 to give units equivalent to about 70mg levodopa, on average, a day for 4 years. Cumulative alcohol and caffeine lifetime exposure were divided into tertiles and smoking exposure was categorised as never, low and high because there were large numbers of non-smokers in our cohort. Cups of tea and coffee were assumed to contain 47mg and 62mg of caffeine respectively.[26] Tertiles of cumulative alcohol and caffeine exposure over three years after diagnosis were also calculated to investigate whether ongoing exposure after diagnosis was associated with fewer motor complications.

We performed Kaplan-Meier survival analysis of motor fluctuation-free and dyskinesia-free survival from the start of any dopamine replacement therapy (levodopa, dopamine agonist, MAO-B inhibitor)

with patients censored at death or last follow-up. Survival analyses were also performed with different time baselines to facilitate comparisons with previous studies: i) levodopa initiation; and ii) diagnosis. Cox proportional hazards modelling was performed to assess what factors independently influenced the development of motor complications (using start of dopaminergic treatment as the baseline for survival). Univariable (unadjusted) hazards ratios were firstly calculated for all the variables listed in table 1. There were too many variables to include all in a multivariable model. On the basis of *a priori* evidence we selected four variables to include (irrespective of statistical significance) in the two main Cox regression models (i.e. one predicting motor fluctuations and one dyskinesias): age at diagnosis, sex, motor UPDRS score at baseline and cumulative levodopa dose up to four years from diagnosis. This ensured no fewer than about 10 events per variable in the main models.[27] Additional exploratory analyses were performed to investigate the role of other variables including symptom duration prior to diagnosis, weight, MMSE score at diagnosis, different treatment measures (cumulative levodopa-equivalent dose, starting levodopa within one year of diagnosis) and measures of smoking, alcohol and caffeine exposure. These secondary analyses were performed by creating models with the four pre-specified variables together with each of the additional variables in turn. There were no missing data in the variables used in the main analysis; in the secondary analysis, if missing data were present for a particular variable, these observations were excluded from analyses including that variable. Statistical analyses were performed using SPSS version 21 and Stata version 12.

RESULTS

206 patients with a diagnosis of idiopathic PD at latest follow-up were identified from the PINE database (Figure 1), of which seven declined clinical follow-up, ten died before their first follow-up and six had not received dopaminergic medication by time of data extraction. These patients (mean age 70.8) were not treated because they had mild disease with tremor dominance (N=3), had early

dementia while motor symptoms were still mild (N=1), refused treatment (N=1), or did not tolerate levodopa (N=1). The remaining 183 treated idiopathic PD patients (57.4% male, mean age at diagnosis 71.7 years) were included in the main analyses. The mean duration of follow-up was 59 months (SD 22). 66 patients (36.1%) died during the follow-up. Five patients (2.7%) were lost to clinical follow-up. 128 patients (69.9%) started levodopa within the first year of follow up (median duration to treatment onset 4 months, IQR 0-14 months). Most patients (69.9%) received levodopa in the first year after diagnosis and a further 24 (13.1%) received levodopa within four years of follow-up. The patients who received dopaminergic therapy in the first four years, but not levodopa, were mostly treated with ropinirole (33 patients), pramipexole (17 patients), selegiline (13 patients), COMT inhibitors (2 patients), rasagiline (1 patient), or ergot-derived dopamine agonists (2 patients).

Motor Fluctuations

Motor fluctuations occurred in 39 patients (21.3%) (see table 1 and figure 2A). The majority of these were severe enough to require changes in therapy (25 patients [13.7% of total participants, 64.1% of those with motor fluctuations]). These changes were mostly increased frequency of levodopa dosage or adding controlled release levodopa at night. Kaplan-Meier estimates of probability of developing motor fluctuations at five years, with different baselines for time measurement, are shown in table 3. The factors independently associated with the development of motor fluctuations in the main multivariable model were higher cumulative levodopa dose, female sex, and younger age at diagnosis (Table 1). In secondary analyses the presence of tremor at diagnosis was associated with a higher rate and moderate (though not high) lifetime caffeine intake was associated with a lower rate of motor fluctuations.

Table 1. Characteristics of patients who developed motor fluctuations

Characteristics	Patients with fluctuations	Patients without	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)

		N=39	fluctuations N=144		
Age at diagnosis in years, median (IQR)		71 (64-74)	74 (69-80)	0.97 (0.94-0.99)	0.93 (0.90-0.97)
Sex: Female, N (%)		23 (59.0%)	55 (38.2%)	1.80 (0.95-3.40)	2.41 (1.19-4.89)
Weight at diagnosis in kg, median (IQR)		70 (64-84)	73 (62-83)	1.00 (0.98-1.03)	1.02 (0.99-1.05)
Motor UPDRS at diagnosis, median (IQR)		26 (18-36)	24 (15-32)	1.02 (0.99-1.05)	1.00 (0.96-1.03)
MMSE at diagnosis, median (IQR) (N=14 missing)		29 (28-30)	29 (27-29)	1.17 (0.97-1.42)	1.13 (0.90-1.42)
Tremor at diagnosis, N (%)		37 (95.0%)	123 (85.4%)	3.50 (0.84-14.58)	4.80 (1.12-20.72)
Duration between symptom onset and diagnosis in years, median (IQR)		1.17 (0.83—2.00)	1.17 (0.75-2.06)	0.93 (0.75-1.14)	0.89 (0.71-1.13)
Started on Levodopa within 1 year from diagnosis, N (%)		25 (64.1%)	103 (71.5%)	0.91 (0.47-1.76)	0.75 (0.29-1.92)
Cumulative Levodopa dose 4 years from diagnosis, median (IQR)		5.56 (1.40-7.60)	2.56 (0.63-4.38)	1.16 (1.04-1.30)	1.38 (1.19-1.60)
Cumulative LED 4 years from diagnosis, median (IQR)		6.43 (3.37-7.60)	3.28 (1.88-5.08)	1.24 (1.08-1.46)	1.01 (0.76-1.36)
PD Subtype, N (%)					
	PIGD	17 (43.6%)	75 (52.1%)	1	1
	Intermediate	6 (15.4%)	20 (13.9%)	1.33 (0.53-3.38)	2.00 (0.73-5.44)
	Tremor dominant	16 (41.0%)	49 (34.0%)	1.31 (0.66-2.60)	1.59 (0.78-3.28)
Smoking lifetime exposure, N (%)					
Pack years [cigarettes per day / 20 x number of years of exposure]	Never	27 (69.2%)	78 (54.2%)	1	1
	Low (1-18)	6 (15.4%)	37 (47.4%)	0.59 (0.24-1.43)	0.79 (0.32-1.94)
	High (>18)	6 (15.4%)	29 (20.1%)	0.65 (0.27-1.57)	0.74 (0.30-1.85)
Current smokers at diagnosis, N (%)		4 (10.3%)	8 (5.5%)	1.70 (0.60-4.78)	1.40 (0.50-4.00)
Alcohol lifetime exposure, N (%)					
[units of alcohol per week x years of exposure]	Never/Low(<40)	16 (41.0%)	45 (31.3%)	1	1
	Moderate(40-240)	12 (30.8%)	49 (34.0%)	0.73 (0.35-1.56)	0.79 (0.35-1.77)
	High(>240)	11 (28.2%)	50 (34.7%)	0.63 (0.29-1.36)	0.71 (0.30-1.70)
Alcohol 3 years after diagnosis, N (%)					
	Never/Low(<1)	14 (35.9%)	58 (40.3%)	1	1
	Moderate(1-11)	11 (28.2%)	38 (26.4%)	1.19 (0.54-2.62)	1.70 (0.73-3.97)
	High(>11)	14 (35.9%)	48 (33.3%)	1.18 (0.56-2.47)	1.70 (0.79-3.60)
Caffeine lifetime exposure, N (%)					
[weight (in mg) per day x years of exposure]	Never/Low(< 10,600)	17 (43.6%)	44 (30.6%)	1	1
	Moderate (10,600 - 16,400)	13 (33.3%)	48 (33.3%)	0.53 (0.26-1.10)	0.34 (0.15-0.76)
	High (>16,400)	9 (23.1%)	52 (36.1%)	0.50 (0.22-1.12)	0.57 (0.24-1.40)
Caffeine 3 years after diagnosis, N (%)					
	Never/Low (<513)	8 (20.5%)	53 (36.8%)	1	1
	Moderate(513-744)	18 (46.2%)	42 (29.2%)	1.59 (0.68-3.72)	1.58 (0.62-4.06)
	High(>744)	13 (33.3%)	49 (34.0%)	1.10 (0.46-2.67)	1.12 (0.44-2.89)

*****Variables adjusted for the variables in the final multivariable model (age at diagnosis, sex, motor UPDRS at diagnosis, and cumulative levodopa dose 4). Abbreviation: PIGD= postural instability and gait disorder.

Dyskinesias

52 patients (28.4%) developed dyskinesias (see table 2 and figure 2B). At onset, only three patients (1.6% of total participants, 5.8% of those with dyskinesia) rated their dyskinesias as painful and five

(2.7% of total participants, 9.6% of those with dyskinesia) as mildly disabling; the rest were not disabling. Only 8 patients (4.4% of total participants, 15.4% of those with dyskinesia) developed dyskinesias which required treatment changes (such as decrease of levodopa dose or addition of amantadine). The median dyskinesia-free survival time was 85 months. Kaplan-Meier estimates of the probability of developing dyskinesias after five years, with different baselines for time measurement, are shown in table 3. Higher cumulative levodopa dose and female sex were found to be independent risk factors for the development of dyskinesias in the main model (Table 2). In the additional models, symptom duration and the presence of tremor at diagnosis were associated with more dyskinesias and there was a suggestion that higher MMSE score was associated with increased risk.

Table 2. Characteristics of patients who developed dyskinesias

Characteristics		Patients with dyskinesias N=52	Patients without dyskinesias N=131	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Age at diagnosis in years, median (IQR)		73 (70-78)	73 (65-80)	1.02 (0.99-1.05)	1.00 (0.97-1.03)
Sex: Female, N (%)		29 (55.8%)	49 (37.4%)	1.79 (1.03-3.10)	2.51 (1.40-4.51)
Weight at diagnosis in Kg, median (IQR)		67 (60-75)	75 (64-85)	0.97 (0.96-0.99)	0.99 (0.96-1.01)
Motor UPDRS at diagnosis, median (IQR)		29 (19-37)	23 (15-32)	1.03 (1.01-1.06)	1.01 (0.98-1.04)
MMSE at diagnosis, median (IQR) (N=14 missing)		29 (28-29)	29 (27-29)	1.07 (0.94-1.23)	1.17 (1.00-1.36)
Tremor at diagnosis, N (%)		49 (94.2%)	111 (84.7%)	2.82 (0.88-9.07)	3.68 (1.14-11.90)
Duration between symptom onset and diagnosis in years, median (IQR)		1.21 (0.71-2.15)	1.08 (0.75-2.00)	1.19 (1.05-1.35)	1.02 (1.01-1.03)
Started on Levodopa within 1 year from diagnosis, N (%)		41 (78.8%)	87 (66.4%)	2.20 (1.13-4.30)	1.55 (0.65-3.70)
Cumulative Levodopa dose 4 years from diagnosis, median (IQR)		4.48 (2.34-6.90)	2.37 (0.23-4.07)	1.19 (1.08-1.32)	1.23 (1.08-1.40)
Cumulative LED 4 years from diagnosis, median (IQR)		5.87 (3.06-7.10)	3.28 (1.73-4.99)	1.19 (1.06-1.35)	1.00 (0.75-1.30)
PD Subtype, N (%)					
	PIGD	26 (50.0%)	66 (50.4%)	1	1
	Intermediate	6 (11.5%)	20 (15.3%)	0.76 (0.31-1.85)	1.23 (0.50-3.10)
	Tremor dominant	20 (38.5%)	45 (34.3%)	0.96 (0.54-1.73)	1.64 (0.86-3.12)
Smoking lifetime exposure, N (%)					
Pack years [cigarettes per day / 20 x number of years of exposure]	Never	30 (57.7%)	75 (57.3%)	1	1
	Low (1-18)	10 19.2%)	33 (25.2%)	0.95 (0.46-1.95)	1.08 (0.52-2.23)
	High (>18)	12 (23.1%)	23 (17.6%)	1.40 (0.71-2.73)	1.21 (0.60-2.44)
Current smokers at diagnosis, N (%)		4 (8.0%)	8 (6.1%)	0.85 (0.30-2.37)	0.80 (0.30-2.30)
Alcohol lifetime exposure, N (%)					

[units of alcohol per week x years of exposure]	Never/Low(<40)	22 (42.3%)	39 (29.8%)	1	1
	Moderate(40-240)	14 (26.9%)	47 (35.9%)	0.53 (0.27-1.04)	0.63 (0.31-1.30)
	High(>240)	16 (30.8%)	45 (34.4%)	0.66 (0.35-1.30)	0.80 (0.38-1.68)
Alcohol 3 years after diagnosis, N (%)					
	Never/Low(<1)	21 (40.4%)	51 (38.9%)	1	1
	Moderate(1-11)	11 (21.2%)	38 (29.0%)	0.67 (0.32-1.39)	0.90 (0.42-1.92)
	High(>11)	20 (38.5%)	42 (32.1%)	1.09 (0.59-2.01)	1.63 (0.85-3.14)
Caffeine lifetime exposure, N (%)					
[weight (in mg) per day x years of exposure]	Never/Low(< 10,600)	16 (30.7%)	45 (34.4%)	1	1
	Moderate (10,600 - 16,400)	20 (38.5%)	41 (31.3%)	1.26 (0.65-2.43)	0.81 (0.40-1.64)
	High (>16,400)	16 (30.7%)	45 (34.4%)	1.13 (0.56-2.25)	0.80 (0.38-1.67)
Caffeine 3 years after diagnosis, N (%)					
	Never/Low (<513)	11 (21.2%)	50 (38.2%)	1	1
	Moderate(513-744)	20 (38.5%)	40 (30.5%)	1.56 (0.74-3.29)	1.40 (0.64-3.08)
	High(>744)	21 (40.4%)	41 (31.3%)	1.56 (0.75-3.24)	1.37 (0.65-2.87)

*Variables are adjusted for the variables in the final multivariable model (age at diagnosis, sex, motor UPDRS at diagnosis, and cumulative levodopa dose). Abbreviation: PIGD= postural instability and gait disorder.

Table 3: Kaplan-Meier probabilities of developing motor fluctuations and dyskinesias after five years from dopaminergic treatment initiation, from levodopa initiation, and from diagnosis.

Baseline for time measurement	Motor fluctuations	Dyskinesias
Any complication		
Starting dopaminergic treatment (N=183)	29.2% (21.5–38.8)	37.0% (28.5–47.1)
Starting levodopa treatment (N=160)	30.6% (22.6–40.7)	43.6% (33.7–54.9)
Diagnosis (N=189)	22.8% (16.7–30.7)	29.6% (22.7–37.8)
Severe complications		
Starting dopaminergic treatment (N=183)	19.8% (13.4–28.8)	4.0% (1.5–10.4)

95% confidence intervals are in parentheses.

Motor fluctuations and dyskinesias

23 patients (12.6%) developed both fluctuations and dyskinesias, of whom 14 had developed dyskinesias first.

DISCUSSION

About 30% of patients with PD developed motor fluctuations and about 37% developed dyskinesias within five years of starting dopaminergic treatment. These were higher risks than described in two other community-based incidence cohorts that examined the development of dyskinesias. A Mayo Clinic series reported that 30% of patients developed dyskinesias by five years of starting levodopa[8] and in another study fewer than 20% of patients developed dyskinesias five years from diagnosis.[7] The reasons for these differences, between similar studies, are unclear. No previous community-based inception studies have reported the frequency of motor fluctuations. We found complications to be less common than several other studies, some of which were older and therefore used higher levodopa doses than are used in current practice.[4,18] Dyskinesias were more common in our cohort than motor fluctuations, similar to some studies[15,28] but not others.[16,12,18] Disabling dyskinesias were rare and, although most patients with motor fluctuations did need changes in treatment, very few (4%) developed dyskinesias necessitating treatment changes. This is lower than one previous incident study in which 17% of patients required treatment changes for dyskinesias within five years of levodopa initiation.[8] That study used patient records between 1976 and 1990 and the lower incidence of severe dyskinesias in our study, could be due to lower levodopa doses used in more recent prescribing practice.

Levodopa exposure has consistently been reported as the strongest risk factor for the development of motor fluctuations and dyskinesias in observational studies,[4,8,16] randomised trials of levodopa versus dopamine agonists[29,30] and randomised trials of different levodopa doses.[31] Previous studies have investigated several measures of levodopa exposure, including the initial average daily dose;[7] average daily LED;[8] or levodopa dose at onset of dyskinesias (or study end in those without dyskinesias).[12] Here we have compared cumulative both levodopa only and levodopa-equivalent doses up to four years and early (within one year of diagnosis) commencement of levodopa. Although these variables were correlated, only cumulative levodopa dose was significantly associated with motor complications when they were entered into a multivariable model together.

This suggests that there is little additional effect of non-levodopa dopaminergic treatments, similar to findings from a recent meta-analysis.[32] It also suggests there is no absolute requirement to avoid early levodopa treatment in PD but, as others have suggested,[12] it is important to use the smallest dose that adequately controls the patient's symptoms throughout the course of PD. The fact that baseline motor severity (UPDRS) was not an independent risk factor for motor complications suggests that the association between cumulative levodopa dose and motor complications is not just due to worse disease severity with greater dopaminergic neuronal loss in those needing more levodopa. This conflicts with one large trial which found that both baseline disease severity and levodopa doses were associated with higher frequency of motor complications.[12] However, evidence that levodopa increases risk of dyskinesias independently of disease severity also comes from randomised clinical trials, in which disease severity is randomly allocated to each arm, and those with higher doses of levodopa[31] or levodopa and entacapone[33] had higher incidence of dyskinesias.

Many previous studies have shown that younger age at onset is associated with more dyskinesias,[9,10] and it was the most powerful predictor in a recent large trial.[12] We found that age at diagnosis did not predict dyskinesias, similar to another community-based incidence study.[7] It may be that, as a community-based incidence study, with proportionally few young-onset patients (4.4% under 50), there was insufficient power to detect an effect of age on dyskinesias.

Duration between symptom onset and diagnosis was found to be an independent risk factor for developing dyskinesias but not motor fluctuations. This result was independent of baseline disease severity and levodopa dose so does not appear to be an effect of those presenting later being treated with higher doses of levodopa. This finding must be interpreted cautiously because it was a secondary analysis and the variable is subject to recall bias but it may suggest that patients with more indolent onset of their PD symptoms may be at a higher risk of developing dyskinesias.

The presence of tremor at diagnosis was associated with higher risk of both motor fluctuations and dyskinesias in the secondary analyses, which contrasts with a previous smaller study.[34] Although consistent for both types of complications, the number without any tremor at baseline in this post-hoc analysis was small so this finding, whilst novel and interesting, requires replication.

Female gender was an independent risk factor for both motor fluctuations and dyskinesias, as previous studies have also shown.[12] The reasons for gender differences in the development of motor complications are unclear. A possible explanation is that lower average weight in females results in higher levodopa doses per body weight, and some previous studies found lower weight was a risk factor for dyskinesias.[35,36] We did not, however, demonstrate an association with baseline weight but changes in weight after diagnosis may be more important in the development of complications. It has also been suggested that females have a reduced genetic protection from a dopamine receptor polymorphism,[11] and hormonal differences may be important, with evidence from animal models of effects of oestrogen on the basal ganglia.[37]

Moderate lifetime caffeine exposure was associated with a reduced risk of developing motor fluctuations in the secondary multivariable analyses but there was no dose-response gradient and, given the large number of associations tested in the secondary analyses, it may well be a false positive. Nevertheless, a clinical trial showed caffeine lowered risk of dyskinesias[20] and a trial of another adenosine A2A antagonist, istradefylline reduced daily OFF time.[21] We did not find smoking or alcohol exposure, either before or after diagnosis to be associated with lower risk of dyskinesias. This is consistent with a previous study which showed smoking was not associated with motor complications.[14] However, we lacked power to identify small effects of these exposures on motor complications.

The principal strengths of this study are its prospective design; the representative sample (attempts were made to identify all patients in the community with a new parkinsonian syndrome); regular reviewed of diagnoses to improve diagnostic accuracy; frequent (at least yearly) clinical review to obtain data on motor complications; very high study retention; and careful statistical analyses. Additionally, cumulative levodopa doses were calculated up to 4 years rather than at complication onset. This is clearly better than comparing levodopa dose at onset of motor complications with levodopa dose at end of study in those without complications as this is confounded by difference in time.

The study has several limitations. Firstly, study size, while not small in terms of previous studies of motor complications, is insufficient to identify weak associations or investigate interactions. Secondly, average follow-up duration was only about five years, so better data may be obtained with longer follow-up. Thirdly, some inaccuracy in defining onset of complications is inevitable. Exact timing of onset of both dyskinesias and motor fluctuations was mostly subject to patient recall, although some patients' dyskinesias were observed at clinic visits before they were noticed by the patients themselves, and were recorded as starting when seen. Thus the time to onset of dyskinesias may be overestimated. Assessment of severity was based on data about changes in therapy, which was derived from comprehensive clinical letter that invariably included reasons for treatment changes so we believe this was a reliable assessment. Fourthly, the secondary analyses must be considered as exploratory as many variables were examined and type I errors are possible. Fifthly, data on caffeine, smoking and alcohol were partly retrospective, only average exposures were used, and we did not gather data on sources of caffeine other than tea and coffee.

In conclusion, we are the first to describe the development of both motor fluctuations and dyskinesias in a representative, community-based, incident cohort of PD. We estimate that 29% and 37% develop motor fluctuations and dyskinesias respectively after 5 years of dopaminergic

treatment. Dyskinesias requiring treatment changes were rare (4% at 5 years), which is lower than previous estimates. Higher cumulative levodopa dose, female sex, and tremor at diagnosis were independent risk factors for both motor complications; moderate lifetime caffeine exposure and younger age for fewer motor fluctuations; and longer pre-diagnosis symptom duration for more dyskinesias. Further work with more patients with longer follow-up would be useful for more detailed analysis of risk factors. Individual-patient-data meta-analysis of existing representative studies would be an efficient way to do this.

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AUTHOR'S ROLES

The authors contributed to the following specific roles in the project and manuscript preparation as indicated:

1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

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FIGURE LEGENDS

Figure 1. Flow chart of patients included in the analysis and initiation of levodopa treatment. FU: Follow-Up. *Patients received only dopamine agonist or MAO-B inhibitors within 4 years of follow-up, except for 5 patients who received treatment after 4 years of follow-up.

Figure 2. Kaplan-Meier estimates of the probability that PD patients on a dopaminergic therapy will be free from (A) motor fluctuations and (B) dyskinesias. In each graph, the blue line represents the development of any motor complication and the red represents the development of severe complications, i.e., those needing changes to treatment.

Motor complications in an incident Parkinson's disease cohort

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ABSTRACT

Background

Levodopa treatment in Parkinson's disease (PD) causes motor fluctuations and dyskinesias, but few data describe their development or severity in unselected incident cohorts.

Methods

We gathered ~~data on~~ demographic~~s~~, clinical ~~details~~, ~~drug~~ treatment~~, and~~ smoking, caffeine, and alcohol data ~~history~~ from 183 people with PD from the PINE study, a community-based, incident cohort. With Kaplan-Meier survival analysis and Cox regression modelling we assessed the development, and severity, of dyskinesias and motor fluctuations and which factors independently influenced their onset.

Results

After mean follow-up of 59 months, 39 patients (21.3%) developed motor fluctuations and 52 (28.4%) developed dyskinesias ~~after mean 59 months (SD)~~. Kaplan-Meier estimates of the probability of motor fluctuations and dyskinesias after 5 years of dopaminergic treatment ~~was~~ were 29.2% (95% confidence interval [CI] 21.5–38.8%) and ~~of dyskinesias was~~ 37.0% (95% CI 28.5–47.1%) respectively. 19.8% developed motor fluctuations requiring treatment changes but only 4.0% (95% CI 1.5–10.4%) developed dyskinesias requiring treatment changes by five years. Cumulative levodopa dose (Hazard ratio [HR] 1.38 [95% CI 1.19–1.60]), female sex (HR 2.41 [1.19–4.89]), and~~, and~~ younger age at diagnosis (HR 1.08 [1.04–1.11]) ~~,~~ were independently associated with development of motor fluctuations. Cumulative levodopa dose (HR 1.23 [1.08–1.40]), ~~and~~ female sex (HR 2.51 [1.40–4.51]) were independently associated with dyskinesias. In ~~secondary~~ exploratory analyses, moderate caffeine exposure was associated with ~~lower rates of~~fewer motor fluctuations, longer symptom duration with more dyskinesias, and tremor at diagnosis with higher rates of both complications.

Conclusions

In this community-based incident PD cohort, severe dyskinesias were rare. Cumulative levodopa dose was the strongest predictor of both dyskinesias and motor fluctuations.

INTRODUCTION

Treatment of Parkinson's disease (PD), especially with levodopa, ~~is associated with the development~~causes ~~of motor complications, namely~~ dyskinesias and motor fluctuations. These motor complications are ~~common and~~ potentially disabling ~~consequences of chronic levodopa therapy~~ and may adversely affect patients' quality of life.[1-3]

~~Ahlskog and Muenter reviewed~~ A previous review of studies of ~~dyskinesias and~~ motor ~~fluctuations~~complications ~~and~~ estimated that the risk of developing motor fluctuations and dyskinesias were both about 40% after levodopa treatment for 4-6 years.[4] However, most previous studies have been based on unrepresentative samples, with attendant selection biases, such as cohorts ~~derived~~ from specialist clinics ~~cohorts~~or clinical trials in which younger ~~onset~~ patients with fewer co-morbidities than the general PD population are often over-represented.[5] ~~or from clinical trials in which trial participants again tend to be~~are, ~~on average, younger than the general PD population with fewer co-morbidities.~~[6] Only two representative, community-based incidence studies have examined the development of motor complications over time, both of which were small, only reported dyskinesias[7,8] and one was retrospective.[8] ~~The latter showed that whilst dyskinesias were common (30%) at five years, most were mild and only 17% required treatment adjustment.~~[8]

Several risk factors for the development of dyskinesias have been identified, including: younger age at ~~PD~~ diagnosis, female sex, higher levodopa dose, longer duration of levodopa therapy, and lower body weight~~.~~,[8-14] ~~The two previous community based incident cohorts both found that higher initial levodopa dose was an independent risk factor for developing dyskinesias, whereas only one[8] found age at diagnosis to be an independent risk factor~~but most data come from non-incident or hospital-based studies. By contrast, ~~relatively~~ few ~~data on~~ predictors of motor fluctuations ~~are available~~have been identified but dose and duration on levodopa therapy are most commonly reported.[12,15-18] In

addition, ~~cigarette smoking~~nicotine, caffeine and alcohol may protect against the development of PD[19] and there is ~~also~~ some inconsistent clinical trial data~~evidence from clinical trials~~ to suggest ~~that~~ caffeine and another adenosine A2A antagonist, may reduce dyskinesia~~the~~ risk ~~of developing motor complications~~.[20,21]

We therefore aimed to (i) describe the development of dyskinesias and motor fluctuations in a prospective, community-based, incident cohort of ~~treated~~ PD; (ii) assess what factors influence their development; and (iii) describe the development of severe ~~dyskinesias and~~ motor ~~fluctuations~~complications.

METHODS

Study Design and Participants

We used data from the Parkinsonism Incidence in North-East Scotland (PINE) study, a community-based incidence study of PD and other parkinsonian~~sm~~ disorders in Aberdeen and surrounding areas with prospective long-term follow-up.[22,23] Attempts were made to identify all newly diagnosed patients with degenerative or vascular parkinsonism between 2002 and 2004 (pilot phase) and 2006 to 2009 (main study phase) using multiple, overlapping methods for case ascertainment.[23] All patients were asked to consent to long-term annual follow-up with interim appointments as required for clinical management. The ~~PINE~~ study was approved by the Multi-centre Research Ethics Committee for Scotland and ~~was~~ conducted with the informed consent of the patients involved.

This analysis was restricted to patients who had a diagnosis of idiopathic PD at death or latest follow-up, made by a consultant neurologist with an interest in movement disorders (CEC) using the UK Brain Bank criteria,[24] insofar as follow-up duration permitted ~~the~~ supportive criteria to be applied. 15% of patients with a latest diagnosis of PD had initially had an alternative diagnosis.

Patients were excluded if they were not followed-up after baseline or if they had not received dopaminergic treatment. ~~The study size was determined by the number of incident patients in the study period. Treatment was initiated and managed~~Patients were treated according to the clinical judgement of the treating clinicians.

Data collection and assessment of motor complications

At the baseline (i.e. diagnostic) assessment and at subsequent follow-up appointments, consenting patients ~~who had consented~~ were interviewed and examined, and information gathered included patient demographics and clinical characteristics (including the Unified PD Rating Scale [UPDRS]) and detains of parkinsonian medication. Data were also gathered on exposure to caffeine, alcohol and smoking at verbal interview, including age at first exposure, average level of exposure before baseline and, if relevant, year exposure stopped. At each annual assessment, patients were asked about their ongoing exposures.

Data on motor complications were gathered from the prospectively acquired records of the examining study physician and from part IV of the UPDRS. In patients who reported motor complications, the month and year of onset were recorded from patient self-report or, in the case of asymptomatic dyskinesias that were seen at the assessment, the date of that assessment.~~(which were based on clinical history and examination and included date of onset) and from part IV of the UPDRS.~~ Dyskinesias did not have to be witnessed by a physician to be included, but if they were not seen and the history was doubtful, they were not included. Severe motor complications were defined as those which required~~ing~~ changes to parkinsonian~~in~~ treatment after discussion with the patient about their impact.

Analysis

The data were extracted from the PINE database (26th June, 2013), checked and cleaned. ~~Medication histories were updated each year, from which we calculated t~~The cumulative levodopa only dose and the total levodopa-equivalent dose (LED)[25] (including any dopamine replacement therapy) were calculated up to four years from diagnosis since almost all surviving patients had been followed-up for four years. Levodopa and levodopa-equivalent doses were calculated as levodopa or levodopa-equivalent dose in milligrams multiplied by number of days of treatment and divided by 10^5 to give units equivalent to about 70mg levodopa, on average, a day for 4 years. ~~Measures of cumulative lifetime exposure at baseline for caffeine, alcohol and smoking were calculated.~~ Cumulative ~~A~~alcohol and caffeine lifetime exposure ~~was~~ were divided into tertiles and smoking exposure was categorised as never, low and high because there were large numbers of non-smokers in our cohort. ~~Weight of caffeine was calculated on the basis of a c~~Cups of tea and coffee were assumed to contain~~ing~~ 47mg and 62mg of caffeine respectively~~and a cup of coffee containing 62mg~~.[26] ~~Measures~~ Tertiles of cumulative alcohol and caffeine exposure ~~to caffeine and alcohol~~ over three years after diagnosis were also calculated to investigate whether ongoing exposure after diagnosis was associated with fewer motor complications ~~and divided into tertiles; this was not calculated for smoking as there were too few current smokers in the study~~.

We performed Kaplan-Meier survival analysis of motor fluctuation-free and dyskinesia-free survival from the start of any dopamine replacement therapy (levodopa, dopamine agonist, MAO-B inhibitor) with patients censored at death or last follow-up. Survival analyses were also performed with different time baselines to facilitate comparisons with previous studies: i) levodopa initiation; and ii) diagnosis. Cox proportional hazards modelling was performed to assess what factors independently influenced the development of motor complications ~~from the onset of dopaminergic therapy~~ (using start of dopaminergic treatment as the baseline for survival). Univariable (unadjusted) hazards ratios were firstly calculated for all the variables listed in table 1. There were too many variables to include all in a multivariable model. On the basis of *a priori* evidence we selected four variables to include

(irrespective of statistical significance) in the two main Cox regression models (i.e., one ~~for the development of~~ predicting motor fluctuations and one ~~for~~ dyskinesias): age at diagnosis, sex, motor UPDRS score at baseline and cumulative levodopa dose up to four years from diagnosis. This ensured ~~that there was~~ no fewer than about 10 events per variable in the main models.[27] Additional exploratory analyses were performed to investigate the role of other variables including symptom duration prior to diagnosis, weight, MMSE score at diagnosis, different treatment measures ~~of levodopa exposure~~ (cumulative levodopa-equivalent dose, starting levodopa within one year of diagnosis) and measures of smoking, alcohol and caffeine exposure. These secondary analyses were performed by creating models with the four pre-specified variables together with each of the additional variables in turn. There were no missing data in the variables used in the main analysis; in the secondary analysis, if missing data were present for a particular variable, these observations were excluded from analyses including that variable. Statistical analyses were performed using SPSS version 21 and Stata version 12.

RESULTS

2~~11~~206 patients with a diagnosis of idiopathic PD at latest follow-up were identified from the PINE database (Figure 1), of which ~~11~~ seven ~~had~~ declined clinical follow-up, ~~a further~~ ten ~~had~~ died before their first follow-up and ~~eight~~six had not received ~~any~~ dopaminergic medication by time of data extraction. These patients (mean age 70.8) were not treated because they had mild disease with tremor dominance (N=3), had early dementia while motor symptoms were still mild (N=1), refused treatment (N=1), or did not tolerate levodopa (N=1). The remaining 183 treated idiopathic PD patients (57.4% male, mean age at diagnosis 71.7 years) were included in the main analyses. The mean duration of follow-up was 59 months (SD 22). 66 patients (36.1%) died during the follow-up. Five patients (2.7%) were lost to clinical follow-up. 128 patients (69.9%) started levodopa within the first year of follow up (median duration to treatment onset 4 months, IQR 0-14 months). Most

patients (69.9%) received levodopa in the first year after diagnosis and a further 24 (13.1%) received levodopa within four years of follow-up. The patients who received dopaminergic therapy in the first four years, but not levodopa, were mostly treated with ropinirole (33 patients), pramipexole (17 patients), selegiline (13 patients), COMT inhibitors (2 patients), rasagiline (1 patient), or ergot-derived dopamine agonists (2 patients).

Motor Fluctuations

Motor fluctuations occurred in 39 patients (21.3%) ~~by the time of data extraction~~ (see table 1 and figure 2A). The majority of these were severe enough to require changes in therapy (25 patients [13.7% of total participants, 64.1% of those with motor fluctuations]). These changes were mostly increased frequency of levodopa dosage or adding ~~a~~ controlled release levodopa at night. Kaplan-Meier estimates of probability of developing motor fluctuations at five years, with different baselines for time measurement, are shown in table 3. ~~After five years on therapy the Kaplan-Meier estimate of the probability of developing any motor fluctuations was 29.2% (95% CI 21.5–38.8%) and of developing severe motor fluctuations was 19.8% (95% CI 13.4–28.8%) (Figure 2A). In the 160 patients treated with levodopa, probability of developing any motor fluctuation five years from levodopa initiation was 30.6% (95% CI 22.6–40.7%). In 191 patients (including eight untreated patients) the probability of developing motor fluctuations five years from diagnosis was 23.4% (95% CI 16.6–30.4%).~~ The factors independently associated with the development of motor fluctuations in the main multivariable model were higher cumulative levodopa dose ~~over the four follow-up years since baseline~~, female sex, and younger age at diagnosis (Table 1). In ~~the~~ secondary analyses the presence of tremor at diagnosis was associated with a higher rate and moderate (though not high) lifetime caffeine intake was associated with a lower rate of motor fluctuations. ~~None of the other variables was significantly associated in multivariable analyses.~~

Table 1. Characteristics of patients who developed motor fluctuations

Characteristics		Patients with ~~MF~~ fluctuations N=39	Patients without ~~MF~~ fluctuations N=144	Unadjusted HR (95% CI)	Adjusted HR*~~†~~ (95% CI)
Age at diagnosis in years, median (IQR)		71 (64-74)	74 (69-80)	0.97 (0.94-0.99)	0.93 (0.90-0.97)
Sex: Female, N (%)		23 (59.0%)	55 (38.2%)	1.80 (0.95-3.40)	2.41 (1.19-4.89)
Weight at diagnosis in kg, median (IQR)		70 (64-84)	73 (62-83)	1.00 (0.98-1.03)	1.02 (0.99-1.05)
Motor UPDRS at diagnosis, median (IQR)		26 (18-36)	24 (15-32)	1.02 (0.99-1.05)	1.00 (0.96-1.03)
MMSE at diagnosis, median (IQR) (N=14 missing)		29 (28-30)	29 (27-29)	1.17 (0.97-1.42)	1.13 (0.90-1.42)
Tremor at diagnosis, N (%)		37 (95.0%)	123 (85.4%)	3.50 (0.84-14.58)	4.80 (1.12-20.72)
Duration between symptom onset and diagnosis in years, median (IQR)		1.17 (0.83—2.00)	1.17 (0.75-2.06)	0.93 (0.75-1.14)	0.89 (0.71-1.13)
Started on Levodopa within 1 year from diagnosis, N (%)		25 (64.1%)	103 (71.5%)	0.91 (0.47-1.76)	0.75 (0.29-1.92)
Cumulative Levodopa dose 4 years from diagnosis, median (IQR)		5.56 (1.40-7.60)	2.56 (0.63-4.38)	1.16 (1.04-1.30)	1.38 (1.19-1.60)
Cumulative LED~~*~~ 4 years from diagnosis, median (IQR)		6.43 (3.37-7.60)	3.28 (1.88-5.08)	1.24 (1.08-1.46)	1.01 (0.76-1.36)
PD Subtype, N (%)					
	PIGD	17 (43.6%)	75 (52.1%)	1	1
	Intermediate	6 (15.4%)	20 (13.9%)	1.33 (0.53-3.38)	2.00 (0.73-5.44)
	Tremor dominant	16 (41.0%)	49 (34.0%)	1.31 (0.66-2.60)	1.59 (0.78-3.28)
Smoking lifetime exposure, N (%)					
Pack years [cigarettes per day / 20 x number of years of exposure]	Never	27 (69.2%)	78 (54.2%)	1	1
	Low (1-18)	6 (15.4%)	37 (47.4%)	0.59 (0.24-1.43)	0.79 (0.32-1.94)
	High (>18)	6 (15.4%)	29 (20.1%)	0.65 (0.27-1.57)	0.74 (0.30-1.85)
Current smokers at diagnosis, N (%)		4 (10.3%)	8 (5.5%)	1.70 (0.60-4.78)	1.40 (0.50-4.00)
Alcohol lifetime exposure, N (%)					
[units of alcohol per week x years of exposure]	Never/Low(<40)	16 (41.0%)	45 (31.3%)	1	1
	Moderate(40-240)	12 (30.8%)	49 (34.0%)	0.73 (0.35-1.56)	0.79 (0.35-1.77)
	High(>240)	11 (28.2%)	50 (34.7%)	0.63 (0.29-1.36)	0.71 (0.30-1.70)
Alcohol 3 years after diagnosis, N (%)					
	Never/Low(<1)	14 (35.9%)	58 (40.3%)	1	1
	Moderate(1-11)	11 (28.2%)	38 (26.4%)	1.19 (0.54-2.62)	1.70 (0.73-3.97)
	High(>11)	14 (35.9%)	48 (33.3%)	1.18 (0.56-2.47)	1.70 (0.79-3.60)
Caffeine lifetime exposure, N (%)					
[weight (in mg) per day x years of exposure]	Never/Low(< 10,600)	17 (43.6%)	44 (30.6%)	1	1
	Moderate (10,600 - 16,400)	13 (33.3%)	48 (33.3%)	0.53 (0.26-1.10)	0.34 (0.15-0.76)
	High (>16,400)	9 (23.1%)	52 (36.1%)	0.50 (0.22-1.12)	0.57 (0.24-1.40)
Caffeine 3 years after diagnosis, N (%)					
	Never/Low (<513)	8 (20.5%)	53 (36.8%)	1	1
	Moderate(513-744)	18 (46.2%)	42 (29.2%)	1.59 (0.68-3.72)	1.58 (0.62-4.06)
	High(>744)	13 (33.3%)	49 (34.0%)	1.10 (0.46-2.67)	1.12 (0.44-2.89)

*~~Cumulative levodopa-equivalent dose (LED) up to 4 years from diagnosis (mg l~~Levodopa-equivalent dose ~~(mg) x number of days of treatment x 10^{-5}; one unit is equivalent~~equals about ~~to 70mg levodopa on average a day for 4 years). †~~Variables adjusted for the variables in the final multivariable model (age at diagnosis, sex, motor UPDRS at diagnosis, and c~~C~~umulative l~~L~~evodopa dose 4~~ years from diagnosis~~). Abbreviation~~s~~: ~~HR=hazards ratio; IQR=interquartile range;~~; PIGD= postural instability and gait disorder~~; MF=motor fluctuations~~.

Dyskinesias

52 patients (28.4%) ~~had~~ developed dyskinesias ~~by the time of data extraction~~ (see table 2 and figure 2B). At onset, only three patients (1.6% of total participants, 5.8% of those with dyskinesia) rated their dyskinesias as painful and five (2.7% of total participants, 9.6% of those with dyskinesia) as mildly disabling; the rest were not disabling. Only 8 patients (4.4% of total participants, 15.4% of those with dyskinesia) developed dyskinesias which required treatment changes (such as decrease of levodopa dose or addition of amantadine). The median dyskinesia-free survival time ~~to onset of dyskinesias~~ was 85 months. ~~After five years on therapy the~~ Kaplan-Meier estimates of the probability of developing dyskinesias after five years, with different baselines for time measurement, are shown in table 3. ~~was 37.0% (95% CI 28.5–47.1%) and of developing severe dyskinesias was 4.0% (95% CI 1.5–10.4%) (Figure 2B). The median time to onset of dyskinesias was 85 months. In the 160 patients treated with levodopa, probability of developing any dyskinesia five years from levodopa initiation was 43.6% (95% CI 33.7–54.9). In 191 patients (including eight untreated patients) the probability of developing dyskinesias five years from diagnosis was 29.3% (95% CI 22.5–37.6%).~~ Higher cumulative levodopa dose ~~at 4 years from diagnosis~~ and~~,~~ female sex were found to be independent risk factors for the development of dyskinesias in the main ~~multivariable~~ model (Table 2). In the additional models, symptom duration and the presence of tremor at diagnosis ~~was~~ were associated with ~~higher rates of~~more dyskinesias and there was a suggestion that higher MMSE score was associated with increased risk.

Table 2. Characteristics of patients who developed dyskinesias

Characteristics	Patients with dyskinesias N=52	Patients without dyskinesias N=131	Unadjusted HR (95% CI)	Adjusted HR~~*‡~~ (95% CI)
Age at diagnosis in years, median (IQR)	73 (70-78)	73 (65-80)	1.02 (0.99-1.05)	1.00 (0.97-1.03)
Sex: Female, N (%)	29 (55.8%)	49 (37.4%)	1.79 (1.03-3.10)	2.51 (1.40-4.51)
Weight at diagnosis in Kg, median (IQR)	67 (60-75)	75 (64-85)	0.97 (0.96-0.99)	0.99 (0.96-1.01)

Motor UPDRS at diagnosis, median (IQR)		29 (19-37)	23 (15-32)	1.03 (1.01-1.06)	1.01 (0.98-1.04)
MMSE at diagnosis, median (IQR) (N=14 missing)		29 (28-29)	29 (27-29)	1.07 (0.94-1.23)	1.17 (1.00-1.36)
Tremor at diagnosis, N (%)		49 (94.2%)	111 (84.7%)	2.82 (0.88-9.07)	3.68 (1.14-11.90)
Duration between symptom onset and diagnosis in years, median (IQR)		1.21 (0.71-2.15)	1.08 (0.75-2.00)	1.19 (1.05-1.35)	1.02 (1.01-1.03)
Started on Levodopa within 1 year from diagnosis, N (%)		41 (78.8%)	87 (66.4%)	2.20 (1.13-4.30)	1.55 (0.65-3.70)
Cumulative Levodopa dose 4 years from diagnosis, median (IQR)		4.48 (2.34-6.90)	2.37 (0.23-4.07)	1.19 (1.08-1.32)	1.23 (1.08-1.40)
Cumulative LED* 4 years from diagnosis, median (IQR)		5.87 (3.06-7.10)	3.28 (1.73-4.99)	1.19 (1.06-1.35)	1.00 (0.75-1.30)
PD Subtype, N (%)					
	PIGD	26 (50.0%)	66 (50.4%)	1	1
	Intermediate	6 (11.5%)	20 (15.3%)	0.76 (0.31-1.85)	1.23 (0.50-3.10)
	Tremor dominant	20 (38.5%)	45 (34.3%)	0.96 (0.54-1.73)	1.64 (0.86-3.12)
Smoking lifetime exposure, N (%)					
Pack years [cigarettes per day / 20 x number of years of exposure]	Never	30 (57.7%)	75 (57.3%)	1	1
	Low (1-18)	10 19.2%)	33 (25.2%)	0.95 (0.46-1.95)	1.08 (0.52-2.23)
	High (>18)	12 (23.1%)	23 (17.6%)	1.40 (0.71-2.73)	1.21 (0.60-2.44)
Current smokers at diagnosis, N (%)		4 (8.0%)	8 (6.1%)	0.85 (0.30-2.37)	0.80 (0.30-2.30)
Alcohol lifetime exposure, N (%)					
[units of alcohol per week x years of exposure]	Never/Low(<40)	22 (42.3%)	39 (29.8%)	1	1
	Moderate(40-240)	14 (26.9%)	47 (35.9%)	0.53 (0.27-1.04)	0.63 (0.31-1.30)
	High(>240)	16 (30.8%)	45 (34.4%)	0.66 (0.35-1.30)	0.80 (0.38-1.68)
Alcohol 3 years after diagnosis, N (%)					
	Never/Low(<1)	21 (40.4%)	51 (38.9%)	1	1
	Moderate(1-11)	11 (21.2%)	38 (29.0%)	0.67 (0.32-1.39)	0.90 (0.42-1.92)
	High(>11)	20 (38.5%)	42 (32.1%)	1.09 (0.59-2.01)	1.63 (0.85-3.14)
Caffeine lifetime exposure, N (%)					
[weight (in mg) per day x years of exposure]	Never/Low(< 10,600)	16 (30.7%)	45 (34.4%)	1	1
	Moderate (10,600 - 16,400)	20 (38.5%)	41 (31.3%)	1.26 (0.65-2.43)	0.81 (0.40-1.64)
	High (>16,400)	16 (30.7%)	45 (34.4%)	1.13 (0.56-2.25)	0.80 (0.38-1.67)
Caffeine 3 years after diagnosis, N (%)					
	Never/Low (<513)	11 (21.2%)	50 (38.2%)	1	1
	Moderate(513-744)	20 (38.5%)	40 (30.5%)	1.56 (0.74-3.29)	1.40 (0.64-3.08)
	High(>744)	21 (40.4%)	41 (31.3%)	1.56 (0.75-3.24)	1.37 (0.65-2.87)

*~~Cumulative levodopa-equivalent dose (LED) up to 4 years from diagnosis (mg lLevodopa-equivalent dose x number of days of treatment x 10^{-5}; one unit is equivalent to 70mg levodopa on average a day for 4 years).~~ ‡Variables are adjusted for the variables in the final multivariable model (age at diagnosis, sex, motor UPDRS at diagnosis, and cCumulative lLevodopa dose ~~4 years from diagnosis~~). Abbreviation~~s~~: ~~-~~PIGD= postural instability and gait disorder.

Table 3: Kaplan-Meier probabilities of developing motor fluctuations and dyskinesias after five years from dopaminergic treatment initiation, from levodopa initiation, and from diagnosis.

Baseline for time measurement	Motor fluctuations	Dyskinesias
Any complication		

Starting dopaminergic treatment (N=183)	29.2% (21.5–38.8)	37.0% (28.5–47.1)
Starting levodopa treatment (N=160)	30.6% (22.6–40.7)	43.6% (33.7–54.9)
Diagnosis (N=-189)	23.42.8% (16.67–30.47)	29.-36% (22.57–37.68)
Severe complications		
19.8% (13.4–28.8)		
4.0% (1.5–10.4)		
Starting dopaminergic treatment (N=183)	19.8% (13.4–28.8)	4.0% (1.5–10.4)

95% confidence intervals are in parentheses.

Motor fluctuations and dyskinesias

23 patients (12.6%) had developed both fluctuations and dyskinesias by the time of data extraction, of whom 14 had developed dyskinesias first.

DISCUSSION

We have estimated that aAbout 30% of patients with PD developed motor fluctuations and about 37% developed dyskinesias within five years of starting dopaminergic treatment. These were higher risks than described in two other community-based incidence cohorts that examined the development of dyskinesias. A Mayo Clinic series from the Mayo Clinic, between 1976 and 1990 reported that 30% of patients developed dyskinesias of any severity were present in 30% of patients by five years of starting levodopa[8] and in an incident cohort in Cambridge, UK,another study- fewer than 20% of patients developed dyskinesias five years from diagnosis.[7] The reasons for these differences, between similar studies, are unclear. No previous community-based inception studies have reported the frequency of motor fluctuations. We found complications to be less common than several other studies, some of which were older and therefore used higher levodopa doses than are is used in current practice.[4,18] Dyskinesias were more common in our cohort than motor fluctuations, similar to some studies[15,28] but not others.[16,12,18] Disabling dyskinesias were rare and, although the majority ofmost patients with motor fluctuations did have need changes in treatment, due to their development, only a small minorityvery few (4%) developed dyskinesias necessitating treatment

changes ~~in treatment (4% at 5 years)~~. This is lower than one previous incident study in which ~~reported that~~ 17% of patients required treatment changes ~~developed~~ for dyskinesias ~~that required treatment changes by~~ within five years of levodopa ~~treatment with~~initiation ~~levodopa~~.[8] That study used patient records between 1976 and 1990 and the ~~difference in~~lower incidence of severe dyskinesias in our study, could ~~also~~ be due to lower levodopa doses used in more recent prescribing practice.

Levodopa exposure has consistently been reported as the strongest risk factor for the development of motor fluctuations and dyskinesias in observational studies,[4,8,16] randomised trials of levodopa versus dopamine agonists[29,30] and randomised trials of different levodopa doses.[31] Previous studies have investigated several measures of levodopa exposure, including the initial average daily dose;[7] average daily LED;[8] or levodopa dose at onset of dyskinesias (or ~~end of~~ study end in those without dyskinesias).[12] Here we have compared cumulative both levodopa only and~~,~~ levodopa-equivalent doses up to four years and early (within one year of diagnosis) commencement of levodopa. Although these variables were correlated, only cumulative levodopa dose was significantly associated with motor complications when they were entered into a multivariable model together. This suggests that there is little additional effect of non-levodopa dopaminergic treatments, ~~which is~~ similar to findings from a recent meta-analysis.[32] It also suggests there is no absolute requirement to avoid early levodopa treatment in PD but, as others have suggested,[12] it is important to use the smallest dose that adequately controls the patient's symptoms throughout the course of PD. The fact that baseline motor severity (UPDRS) was not an independent risk factor for motor complications suggests that the association between cumulative levodopa dose and motor complications is not just due to worse disease severity with greater dopaminergic neuronal loss in those needing more levodopa.~~It can also be argued that levodopa dose is a proxy for disease severity, so that those with more aggressive disease are both more likely to get motor complications and to receive more levodopa. However, Oour data showed that baseline motor was not an~~

~~independent risk factor, although we may have been underpowered to detect this, which suggests this finding is not confounded by disease severity. This is in By contrast to~~ This conflicts with one large trial which found that both baseline disease severity and levodopa doses were associated with higher frequency of motor complications.[12] However, e~~E~~vidence that levodopa increases risk of dyskinesias independently of disease severity also comes from randomised clinical trials, in which disease severity is randomly allocated to each arm, and those with higher doses of levodopa[31] or levodopa and entacapone[33] had higher incidence of dyskinesias.

Many previous studies have shown ~~a relationship between~~that younger age at ~~PD~~ onset ~~and developing motor complications~~is associated with more~~, in particular~~ dyskinesias,[9,10] and it was the most powerful predictor in a recent large trial.[12] We found that age at diagnosis ~~is an independent risk factor for developing motor fluctuations, but not~~did not predict dyskinesias~~. This latter~~, similar to ~~finding supports results from~~ another community-based incidence study ~~that showed that age at baseline was not a risk factor for dyskinesias~~.[7] It may be that, as a community-based incidence study, with proportionally few young-onset patients (4.4% under 50), there was insufficient power to detect an effect of age on dyskinesias.

Duration between symptom onset and diagnosis was found to be an independent risk factor for developing dyskinesias but not motor fluctuations. This result was independent of baseline disease severity and levodopa dose so does not appear to be an effect of those presenting later being treated with higher doses of levodopa. This finding must be interpreted cautiously because it was a secondary analysis and the variable is subject to recall bias but it may suggest~~s~~ that patients ~~that~~ with more indolent onset of their PD symptoms may be at a higher risk of developing dyskinesias.

The presence of tremor at diagnosis was associated with higher risk of both motor fluctuations and dyskinesias in the secondary analyses, which contrasts with a previous smaller study.[34] Although ~~this~~

~~was~~ consistent for both types of complications, the number without any tremor at baseline ~~was small and the~~in this post-hoc analysis was ~~not pre-specified~~small so this finding~~. This result~~, whilst novel and interesting, ~~needs to be~~requires replicat~~ed~~ion ~~in other studies~~.

Female gender was an independent risk factor for both motor fluctuations and dyskinesias, as previous studies have also shown.[12] The reasons for ~~these~~ gender differences in the development of motor complications are unclear. A possible explanation is that ~~the~~ lower average weight in females results in higher levodopa doses per body weight, and some previous studies found lower weight was a risk factor for dyskinesias.[35~~7~~,36~~8~~] We did not, however, demonstrate an association with baseline weight but changes in weight after diagnosis may be more important in the development of complications. It has also been suggested that females have a reduced genetic protection from a dopamine receptor polymorphism,[11] and hormonal differences may be important, with evidence from animal models of effects of oestrogen on the basal ganglia.[37~~90~~]

Moderate lifetime caffeine exposure was associated with a reduced risk of developing motor fluctuations in the secondary multivariable analyses but there was no dose-response gradient and, given the large number of associations tested in the secondary analyses, it may well be a false positive. Nevertheless, ~~Observational data from~~ a clinical trial showed caffeine ~~was associated with a~~ lower~~ed~~ risk of dyskinesias[20] and a ~~clinical~~ trial of another adenosine A2A antagonist, i~~t~~stradefylline reduced daily OFF time.[21] ~~Moderate lifetime caffeine exposure was associated with a reduced risk of developing motor fluctuations in the secondary multivariable analyses but there was no dose-response gradient and, given the large number of associations tested in the secondary analyses, it may well be a false positive. Similarly, w~~We did not find ~~caffeine,~~ smoking or alcohol exposure, either before or after diagnosis to be associated with lower risk of dyskinesias. This is ~~in line~~consistent with a previous study which showed smoking was not associated with motor complications.[14] However, we ~~did not have~~lacked power to identify ~~a~~ small effect~~s~~ of these

exposures on motor complications~~; data was collected retrospectively for pre-diagnostic exposure; and there were very few current smokers in the cohort~~.

The principal strengths of this study are its prospective design; the representative sample (attempts were made ~~i~~to identify all patients in the community with a new ~~diagnosis of PD~~parkinsonian syndrome); ~~that diagnoses were~~ regular~~ly~~ reviewed of diagnoses to ~~achieve high~~ improve diagnostic accuracy; ~~that patients were reviewed clinically~~frequent (at least yearly) clinical review to obtain data on motor complications; very high study retention; and careful statistical analyses. Additionally, cumulative levodopa doses were calculated up to 4 years rather than at complication onset. This is clearly better than comparing levodopa dose at onset of motor complications with levodopa dose at end of study in those without complications as this is confounded by difference in time.

The study has several limitations. Firstly, study size, while not small in terms of previous studies of ~~the development of~~ motor complications, is ~~not large enough~~insufficient to identify weak associations or investigate interactions. Secondly, average follow-up duration was only about five years, so better data may be obtained with longer follow-up. Thirdly, ~~cumulative levodopa doses were calculated up to 4 years and not at complication onset. However, identifying a time-point for control comparisons would be difficult if this was done and th~~This is clearly better than comparing levodopa dose at onset of motor complications with levodopa dose at end of study in those without complications as this is clearly confounded by difference in time. ~~Fourthly,~~ some inaccuracy in defining onset of complications is inevitable. Exact timing of onset of both dyskinesias and motor fluctuations was mostly subject to patient recall, although some patients' dyskinesias were observed at clinic visits before they were noticed by the patients themselves, and were recorded as starting when seen. Thus the time to onset of dyskinesias may be overestimated. Assessment of severity was based on data about changes in therapy, which was derived from comprehensive clinical letter that invariably included reasons for treatment changes so we believe this was a reliable assessment.

Fourthly, the secondary analyses must be considered as exploratory as many variables were ~~included~~ examined and ~~the associations identified may therefore be~~type I errors are possible ~~false positives~~. Fifthly, data on caffeine, smoking and alcohol were partly retrospective, only average exposures were used, and we did not gather data on sources of caffeine other than tea and coffee.

In conclusion, we are the first to describe the development of both motor fluctuations and dyskinesias in a representative, community-based, incident cohort of PD. We estimate that 29% and 37% develop motor fluctuations and dyskinesias respectively after 5 years of dopaminergic treatment. Dyskinesias requiring treatment changes were rare (4% at 5 years), which is lower than previous estimates. ~~Female sex, H~~higher cumulative levodopa dose, female sex, and tremor at diagnosis were independent risk factors for both motor complications; ~~and~~ moderate lifetime caffeine exposure and younger age ~~with~~for fewer motor fluctuations; and longer pre-diagnosis symptom duration for more dyskinesias. Further work with more patients with longer follow-up would be useful ~~to obtain~~for more detailed analysis of ~~the~~ risk factors ~~associated with development of motor complications~~. Individual-patient-data meta-analysis of existing representative studies would be an efficient way to do this.

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AUTHOR'S ROLES

The authors contributed to the following specific roles in the project and manuscript preparation as indicated:

1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

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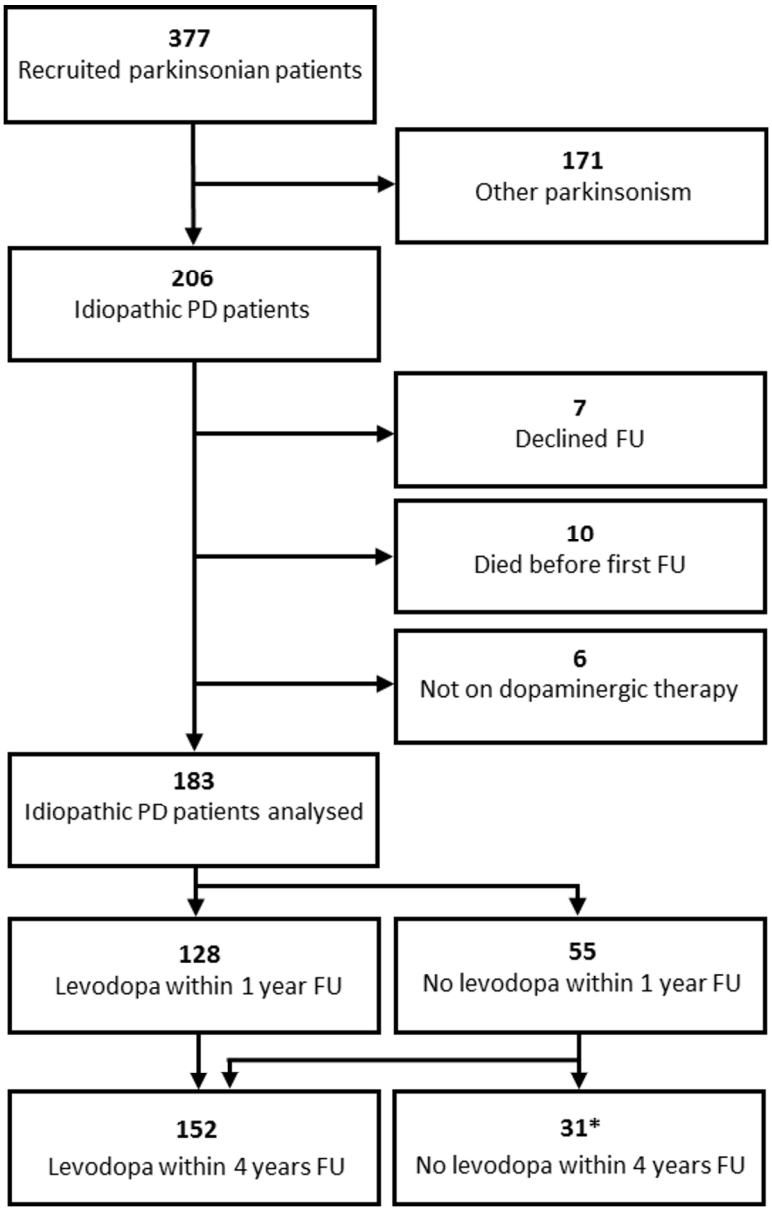
FIGURE LEGENDS

Figure 1. Flow chart of patients included in the analysis and initiation of levodopa treatment. FU: Follow-Up. *Patients received only dopamine agonist or MAO-B inhibitors within 4 years of follow-up, except for 5 patients who received treatment after 4 years of follow-up.

Figure 2. Kaplan-Meier estimates of the probability that PD patients on a dopaminergic therapy will be free from (A) motor fluctuations and (B) dyskinesias. ~~-~~In each graph, the blue line represents the development of any motor complication and the red represents the development of severe complications, i.e., those ~~necessitating~~ needing changes to treatment.



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Title: Motor complications in an incident Parkinson's disease cohort

Manuscript ID: EJoN-15-0093 Author(s): Scott, Nicholas; Macleod, Angus; Counsell, Carl

We would like to thank the reviewers for their helpful comments and include a detailed reply to individual comments, in red, below.

Reviewer: 1

COMMENTS TO AUTHOR(S)

The present investigation drwas its major strength from its cohort based, incident-case methods. The theme is suitable for EJN and of clinical relevance, as it adresses one of the major concerns when manging tretment options for Parkinsons Disease Patients. There are, however, one point that deserve better explanation. The authors should be more precise regarding the type of dopaminergic tretament other than levo-dopa. How many patientes were on ropinierol, comt inhibitors, parmaipexeole and son on.

Response to Reviewer: 1

We have inserted the following explanation into the text (page 7, lines 4-7):

"The patients who received dopaminergic therapy in the first four years, but not levodopa, were mostly treated with ropinirole (33 patients), pramipexole (17 patients), selegiline (13 patients), COMT inhibitors (2 patients), rasagiline (1 patient), or ergot-derived dopamine agonists (2 patients)."

Reviewer: 2

COMMENTS TO AUTHOR(S)

1. Did the authors collect information on the time between clinical onset of disease and diagnosis?

This information was collected but not analysed. In response to the reviewer's comment we have performed unadjusted and adjusted analysis of time between clinical onset and diagnosis. Longer duration between symptom onset and diagnosis was independently associated with risk of dyskinesias. The following changes have therefore been made:

Inserted into the Abstract (p. 2, lines 22-23): "longer symptom duration"

Inserted into the Methods (p.6, lines 9-10): "symptom duration prior to diagnosis,"

Inserted into Results Tables 1 (p.8) and 2 (p.9).

Inserted into Discussion (p.12, lines 15-20): "Duration between symptom onset and diagnosis was found to be an independent risk factor for developing dyskinesias but not motor fluctuations. This result was independent of baseline disease severity and levodopa dose so does not appear to be an effect of those presenting later being treated with higher doses of levodopa. This finding must be interpreted cautiously because it was a secondary analysis and the variable is subject to recall bias

but it may suggest that patients with more indolent onset of their PD symptoms may be at a higher risk of developing dyskinesias."

Inserted into Discussion (p.17, line 14): "and longer pre-diagnosis symptom duration for more dyskinesias"

2. What was the percentage of change of diagnosis from baseline over follow up in this cohort?

We have inserted the following comment into text to add this information Methods (p.4 line 13-14):

"15% of patients with a latest diagnosis of PD had initially had an alternative diagnosis."

3. How reliable was the assessment of severe motor complication; onset of dyskinesias and motor fluctuations?

We have added the following sentences into the Discussion (p.14 lines 7-13) to discuss the potential limitation of inaccuracies, particularly in identifying the timing of onset of these complications.

"Thirdly, some inaccuracy in defining onset of complications is inevitable. Exact timing of onset of both dyskinesias and motor fluctuations was mostly subject to patient recall, although some patients' dyskinesias were observed at clinic visits before they were noticed by the patients themselves, and were recorded as starting when seen. Thus the time to onset of dyskinesias may be overestimated. Assessment of severity was based on data about changes in therapy, which was derived from comprehensive clinical letter that invariably included reasons for treatment changes so we believe this was a reliable assessment."

4. It would be interesting to know why eight patients did not start levo-dopa or any dopaminergic agent. Were they different from the others?

We have checked the case record for these patients and added the relevant data to the text. While doing this, we have discovered an error in the flow chart relating only to patients not included in the main analysis. We have updated figure 1 with the correct data. Those who were not treated were probably more likely to be tremor dominant in their presentation, but we have not made a formal comparison due to low numbers in this group. Their ages were similar. We have added the following reasons for patients not starting treatment into the Results section (p.6 , lines 22-25):

"These patients (mean age 70.8) were not treated because they had mild disease with tremor dominance (N=3), had early dementia while motor symptoms were still mild (N=1), refused treatment (N=1), or did not tolerate levodopa (N=1)."

5. What was the median duration of folow-up?

The median Follow-Up 60 months, IQR (48 months – 72 months). As this was very similar to the mean duration of follow-up (59 months, SD 22 months), which is stated in the text (page 7) we have not added the median follow-up to the manuscript.

6. Did the authors distinguish in the analyses tremor dominant from akinetic phenotype with gait disturbances? This is of course different from presence of tremor at onset.

We have added this data into the Results Tables 1 (p.8) and 2 (p.9). There was no significant effect of PD subtype on the risk of developing either motor fluctuations or dyskinesias.

6. The authors should develop more the discussion on sex differences.

We have expanded this section of the discussion, so that it now reads (p.13, lines 1-9):

"Female gender was an independent risk factor for both motor fluctuations and dyskinesias, as previous studies have also shown.[12] The reasons for gender differences in the development of motor complications are unclear. A possible explanation is that lower average weight in females results in higher levodopa doses per body weight, and some previous studies found lower weight was a risk factor for dyskinesias.[35,36] We did not, however, demonstrate an association with baseline weight but changes in weight after diagnosis may be more important in the development of complications. It has also been suggested that females have a reduced genetic protection from a dopamine receptor polymorphism,[11] and hormonal differences may be important, with evidence from animal models of effects of oestrogen on the basal ganglia.[37]"

Table 1. Characteristics of patients who developed motor fluctuations

Characteristics		Patients with fluctuations N=39	Patients without fluctuations N=144	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Age at diagnosis in years, median (IQR)		71 (64-74)	74 (69-80)	0.97 (0.94-0.99)	0.93 (0.90-0.97)
Sex: Female, N (%)		23 (59.0%)	55 (38.2%)	1.80 (0.95-3.40)	2.41 (1.19-4.89)
Weight at diagnosis in kg, median (IQR)		70 (64-84)	73 (62-83)	1.00 (0.98-1.03)	1.02 (0.99-1.05)
Motor UPDRS at diagnosis, median (IQR)		26 (18-36)	24 (15-32)	1.02 (0.99-1.05)	1.00 (0.96-1.03)
MMSE at diagnosis, median (IQR) (N=14 missing)		29 (28-30)	29 (27-29)	1.17 (0.97-1.42)	1.13 (0.90-1.42)
Tremor at diagnosis, N (%)		37 (95.0%)	123 (85.4%)	3.50 (0.84-14.58)	4.80 (1.12-20.72)
Duration between symptom onset and diagnosis in years, median (IQR)		1.17 (0.83—2.00)	1.17 (0.75-2.06)	0.93 (0.75-1.14)	0.89 (0.71-1.13)
Started on Levodopa within 1 year from diagnosis, N (%)		25 (64.1%)	103 (71.5%)	0.91 (0.47-1.76)	0.75 (0.29-1.92)
Cumulative Levodopa dose 4 years from diagnosis, median (IQR)		5.56 (1.40-7.60)	2.56 (0.63-4.38)	1.16 (1.04-1.30)	1.38 (1.19-1.60)
Cumulative LED 4 years from diagnosis, median (IQR)		6.43 (3.37-7.60)	3.28 (1.88-5.08)	1.24 (1.08-1.46)	1.01 (0.76-1.36)
PD Subtype, N (%)					
	PIGD	17 (43.6%)	75 (52.1%)	1	1
	Intermediate	6 (15.4%)	20 (13.9%)	1.33 (0.53-3.38)	2.00 (0.73-5.44)
	Tremor dominant	16 (41.0%)	49 (34.0%)	1.31 (0.66-2.60)	1.59 (0.78-3.28)
Smoking lifetime exposure, N (%)					
Pack years [cigarettes per day / 20 x number of years of exposure]	Never	27 (69.2%)	78 (54.2%)	1	1
	Low (1-18)	6 (15.4%)	37 (47.4%)	0.59 (0.24-1.43)	0.79 (0.32-1.94)
	High (>18)	6 (15.4%)	29 (20.1%)	0.65 (0.27-1.57)	0.74 (0.30-1.85)
Current smokers at diagnosis, N (%)		4 (10.3%)	8 (5.5%)	1.70 (0.60-4.78)	1.40 (0.50-4.00)
Alcohol lifetime exposure, N (%)					
[units of alcohol per week x years of exposure]	Never/Low(<40)	16 (41.0%)	45 (31.3%)	1	1
	Moderate(40-240)	12 (30.8%)	49 (34.0%)	0.73 (0.35-1.56)	0.79 (0.35-1.77)
	High(>240)	11 (28.2%)	50 (34.7%)	0.63 (0.29-1.36)	0.71 (0.30-1.70)
Alcohol 3 years after diagnosis, N (%)					
	Never/Low(<1)	14 (35.9%)	58 (40.3%)	1	1
	Moderate(1-11)	11 (28.2%)	38 (26.4%)	1.19 (0.54-2.62)	1.70 (0.73-3.97)
	High(>11)	14 (35.9%)	48 (33.3%)	1.18 (0.56-2.47)	1.70 (0.79-3.60)
Caffeine lifetime exposure, N (%)					
[weight (in mg) per day x years of exposure]	Never/Low(< 10,600)	17 (43.6%)	44 (30.6%)	1	1
	Moderate (10,600 - 16,400)	13 (33.3%)	48 (33.3%)	0.53 (0.26-1.10)	0.34 (0.15-0.76)
	High (>16,400)	9 (23.1%)	52 (36.1%)	0.50 (0.22-1.12)	0.57 (0.24-1.40)
Caffeine 3 years after diagnosis, N (%)					
	Never/Low (<513)	8 (20.5%)	53 (36.8%)	1	1
	Moderate(513-744)	18 (46.2%)	42 (29.2%)	1.59 (0.68-3.72)	1.58 (0.62-4.06)
	High(>744)	13 (33.3%)	49 (34.0%)	1.10 (0.46-2.67)	1.12 (0.44-2.89)

*Variables adjusted for the variables in the final multivariable model (age at diagnosis, sex, motor UPDRS at diagnosis, and cumulative levodopa dose 4). Abbreviation: PIGD= postural instability and gait disorder.

Table 2. Characteristics of patients who developed dyskinesias

Characteristics		Patients with dyskinesias N=52	Patients without dyskinesias N=131	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Age at diagnosis in years, median (IQR)		73 (70-78)	73 (65-80)	1.02 (0.99-1.05)	1.00 (0.97-1.03)
Sex: Female, N (%)		29 (55.8%)	49 (37.4%)	1.79 (1.03-3.10)	2.51 (1.40-4.51)
Weight at diagnosis in Kg, median (IQR)		67 (60-75)	75 (64-85)	0.97 (0.96-0.99)	0.99 (0.96-1.01)
Motor UPDRS at diagnosis, median (IQR)		29 (19-37)	23 (15-32)	1.03 (1.01-1.06)	1.01 (0.98-1.04)
MMSE at diagnosis, median (IQR) (N=14 missing)		29 (28-29)	29 (27-29)	1.07 (0.94-1.23)	1.17 (1.00-1.36)
Tremor at diagnosis, N (%)		49 (94.2%)	111 (84.7%)	2.82 (0.88-9.07)	3.68 (1.14-11.90)
Duration between symptom onset and diagnosis in years, median (IQR)		1.21 (0.71-2.15)	1.08 (0.75-2.00)	1.19 (1.05-1.35)	1.02 (1.01-1.03)
Started on Levodopa within 1 year from diagnosis, N (%)		41 (78.8%)	87 (66.4%)	2.20 (1.13-4.30)	1.55 (0.65-3.70)
Cumulative Levodopa dose 4 years from diagnosis, median (IQR)		4.48 (2.34-6.90)	2.37 (0.23-4.07)	1.19 (1.08-1.32)	1.23 (1.08-1.40)
Cumulative LED 4 years from diagnosis, median (IQR)		5.87 (3.06-7.10)	3.28 (1.73-4.99)	1.19 (1.06-1.35)	1.00 (0.75-1.30)
PD Subtype, N (%)					
	PIGD	26 (50.0%)	66 (50.4%)	1	1
	Intermediate	6 (11.5%)	20 (15.3%)	0.76 (0.31-1.85)	1.23 (0.50-3.10)
	Tremor dominant	20 (38.5%)	45 (34.3%)	0.96 (0.54-1.73)	1.64 (0.86-3.12)
Smoking lifetime exposure, N (%)					
Pack years [cigarettes per day / 20 x number of years of exposure]	Never	30 (57.7%)	75 (57.3%)	1	1
	Low (1-18)	10 19.2%)	33 (25.2%)	0.95 (0.46-1.95)	1.08 (0.52-2.23)
	High (>18)	12 (23.1%)	23 (17.6%)	1.40 (0.71-2.73)	1.21 (0.60-2.44)
Current smokers at diagnosis, N (%)		4 (8.0%)	8 (6.1%)	0.85 (0.30-2.37)	0.80 (0.30-2.30)
Alcohol lifetime exposure, N (%)					
[units of alcohol per week x years of exposure]	Never/Low(<40)	22 (42.3%)	39 (29.8%)	1	1
	Moderate(40-240)	14 (26.9%)	47 (35.9%)	0.53 (0.27-1.04)	0.63 (0.31-1.30)
	High(>240)	16 (30.8%)	45 (34.4%)	0.66 (0.35-1.30)	0.80 (0.38-1.68)
Alcohol 3 years after diagnosis, N (%)					
	Never/Low(<1)	21 (40.4%)	51 (38.9%)	1	1
	Moderate(1-11)	11 (21.2%)	38 (29.0%)	0.67 (0.32-1.39)	0.90 (0.42-1.92)
	High(>11)	20 (38.5%)	42 (32.1%)	1.09 (0.59-2.01)	1.63 (0.85-3.14)
Caffeine lifetime exposure, N (%)					
[weight (in mg) per day x years of exposure]	Never/Low(< 10,600)	16 (30.7%)	45 (34.4%)	1	1
	Moderate (10,600 - 16,400)	20 (38.5%)	41 (31.3%)	1.26 (0.65-2.43)	0.81 (0.40-1.64)
	High (>16,400)	16 (30.7%)	45 (34.4%)	1.13 (0.56-2.25)	0.80 (0.38-1.67)
Caffeine 3 years after diagnosis, N (%)					
	Never/Low (<513)	11 (21.2%)	50 (38.2%)	1	1
	Moderate(513-744)	20 (38.5%)	40 (30.5%)	1.56 (0.74-3.29)	1.40 (0.64-3.08)
	High(>744)	21 (40.4%)	41 (31.3%)	1.56 (0.75-3.24)	1.37 (0.65-2.87)

*Variables are adjusted for the variables in the final multivariable model (age at diagnosis, sex, motor UPDRS at diagnosis, and cumulative levodopa dose). Abbreviation: PIGD= postural instability and gait disorder.

Table 3: Kaplan-Meier probabilities of developing motor fluctuations and dyskinesias after five years from dopaminergic treatment initiation, from levodopa initiation, and from diagnosis.

Baseline for time measurement	Motor fluctuations	Dyskinesias
Any complication		
Starting dopaminergic treatment (N=183)	29.2% (21.5–38.8)	37.0% (28.5–47.1)
Starting levodopa treatment (N=160)	30.6% (22.6–40.7)	43.6% (33.7–54.9)
Diagnosis (N=189)	22.8% (16.7–30.7)	29.6% (22.7–37.8)
Severe complications		
Starting dopaminergic treatment (N=183)	19.8% (13.4–28.8)	4.0% (1.5–10.4)

95% confidence intervals are in parentheses.

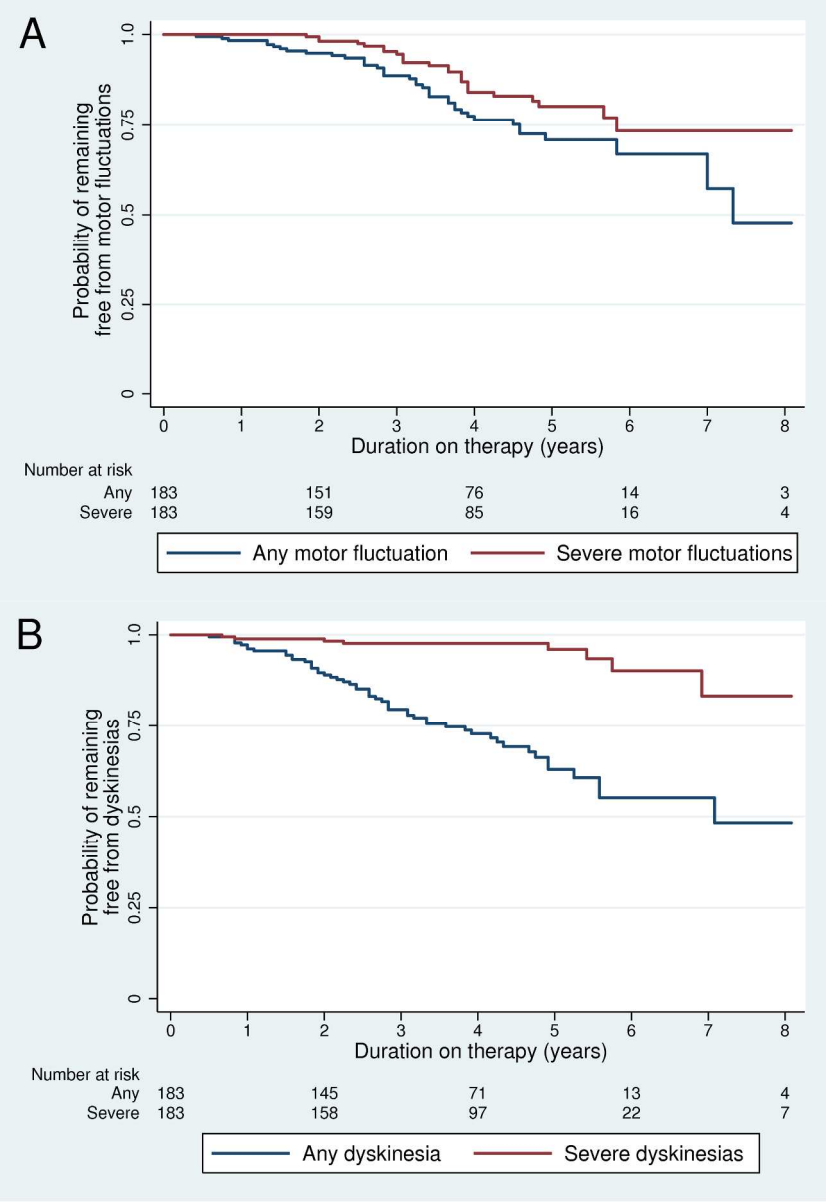

Figure 2
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