Markers of Impaired Motor and Cognitive Volition in Parkinson's Disease: Correlates of Dopamine Dysregulation Syndrome, Impulse Control Disorder, and Dyskinesias

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Abstract

Introduction—Dopaminergic therapy in Parkinson's disease (PD) can be associated with both motoric (e.g., dyskinesias) and neuropsychiatric adverse effects. Examples of the latter include Dopamine Dysregulation Syndrome (DDS) and impulse control disorder (ICD), which are separate but related behavioral/psychiatric complications of treatment in PD. Dysregulation of

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volition characterizes both dyskinesias and DDS/ICD; thus, we analyzed potential disease-related correlates in a large PD cohort.

Methods—We analyzed cross-sectional data from 654 participants collected through the NINDS Parkinson's Disease Biomarkers Program. DDS/ICD symptoms and dyskinesias were assessed using the Movement Disorders Society (revised) Unified Parkinson's Disease Rating Scale. Potential associated variables were selected from PD-validated or PD-specific scales of neuropsychiatric or motoric status. Multivariable models with DDS/ICD or dyskinesia presence outcomes were produced with backward stepwise regression to identify factors independently associated with DDS/ICD and/or dyskinesias.

Results—Fifty-three (8.1%) participants endorsed DDS and/or ICD symptoms and 150 (22.9%) were dyskinetic. In multivariable analysis, psychosis was independently associated with both dyskinesias (p=0.006) and DDS/ICD (p<0.001). Unpredictable motor fluctuations (p=0.026) and depression (p=0.023) were also associated with DDS/ICD; female sex (p=0.025), low tremor score (p=0.001) and high akinesia-rigidity score (p<0.001) were associated with dyskinesias.

Conclusions—Our findings suggest that psychosis may be an important marker of impaired volition across motor and cognitive domains. Unpredictable motor fluctuations, psychosis, and depression may together comprise a phenotypic profile of patients at increased risk for DDS/ICD. Similarly, dyskinetic PD patients should be closely monitored for psychotic symptoms and treated appropriately.

Introduction

Parkinson's disease (PD) is characterized by progressive deterioration of both motor and cognitive function. Dopamine (DA) replacement therapy can alleviate most motor symptoms, but tends to be complicated by a variety of unintended effects. Half of levodopa-treated PD patients develop dyskinesias within 6 years of initiation, although recent evidence demonstrates that duration of levodopa exposure is less relevant to dyskinesia onset than disease duration itself.[1] DA is a key modulator of motivation, impulsivity, and reward-oriented behavior;[2] thus, medications that facilitate DA neurotransmission can modify action selection in PD.

DA medications can engender a range of compulsive abnormalities related to negative reinforcement dysfunction, habit formation, incentive sensitization, and impulsivity, including multiple specific behaviors: (1) abuse of DA medications (DDS); (2) impulse control disorder (ICD) behaviors (excessive gambling or shopping, hypersexuality, hyperphagia, and kleptomania); and (3) punding.[2,3] The pathophysiology of DDS is unclear; potential positive reinforcement mechanisms include increased novelty-seeking and incentive sensitization.[3] Aversion to the "off" state may also predispose to excessive medication usage.[4] The relative preservation of DA neurons in the ventral tegmental area—compared to the substantia nigra—may facilitate DDS and ICD by enabling

hyperdopaminergic neurotransmission in the mesolimbic system.[5] Recent evidence has also highlighted the significance of impaired cognitive volition in PD patients with ICDs.[6] Due to commonalities between DDS and ICD more generally, the Movement Disorders Society's (revised) Unified Parkinson's Disease Rating Scale (MDS-UPDRS) assesses both using a single item (Part 1, question 6).

At a broader level, there is conceptual similarity between behavioral disorders marked by impaired cognitive volition (such as ICD and likely DDS) and involuntary bodily movements like dyskinesias. It has been proposed that these phenomena occupy a continuum of pathophysiologically similar mechanisms relating to topographically distinct basal ganglia circuits.[7] Hypersensitization of dorsal striatum neurons receiving coincident input from glutamatergic and nigrostriatal DA projections—in the context of pulsatile DA receptor stimulation—remains the current paradigm for dyskinesia etiology.[8] For DDS and ICD, the focus is shifted to mesocorticolimbic projections and the ventral striatum as the site of hyperdopaminergic dysregulation. Activity in signaling cascades that are implicated in substance use disorders—such as the ERK and DARPP-32/PPP1R1B pathways—are also altered in dyskinetic patients, suggesting molecular overlap between altered reward-processing and dyskinesias.[7] Similar considerations inspired a recent study demonstrating that PD patients with moderate to severe dyskinesias—assessed by the Unified Dyskinesia Rating Scale—more frequently had ICDs or related behaviors (such as DDS, hobbyism, and punding) than patients with only mild dyskinesias.[9]

We hypothesized that dyskinesias may share similar markers with DDS and ICD given the analogous impairment of volition and similarities in theoretical origins (hyperdopaminergic dysregulation). Shared clinical associations would strengthen the hypothesis of shared or parallel etiologies. To test this hypothesis, we performed a risk-factor analysis for potential neuropsychiatric and/or motoric markers of dyskinesias and DDS/ICD.

Methods

Database and Participants

Data were extracted from the NINDS Parkinson's Disease Biomarker Program (PDBP) dataset on December 28, 2016. Baseline data from participants enrolled in the PDBP study at seven academic centers in the United States were used in the present study. Each participating center's local IRB has approved the PDBP protocol and all participants provided informed consent.

Participant data were extracted for analysis only if a diagnosis of "probable or possible idiopathic Parkinson's disease" was made per UK Brain Bank criteria.[10] Other inclusion criteria were complete demographic and medication information and complete data for the following PD-validated or PD-specific scales: MDS-UPDRS; the 17 item Hamilton Depression Rating Scale (HAM-D); the 14 item Hamilton Anxiety Rating Scale (HAM-A); and the Montreal Cognitive Assessment (MoCA). Additionally, patients with a MoCA score 17 were excluded to remove participants with probable dementia.[11]

Measures

Supplementary table 1 provides an overview of components from the MDS-UPDRS utilized in the present study. The primary outcome variables of interest were MDS-UPDRS question 1.6—which assesses the impact of DDS and/or ICD symptoms on patient and caregiver/family life, scored using a Likert scale of 0–4—and the presence of dyskinesias, assessed using Part-IV (complications of therapy) of the MDS-UPDRS. Dyskinesias were deemed present if a patient reported a score of 1 on Q4.1, which assesses the daily duration of dyskinesias.

To determine the presence of clinically significant anxiety and depression, we used PD-validated cutoffs for the HAM-A (> 11) and HAM-D (> 9).[12,13] Medication data were used to calculate Levodopa Equivalent Daily Dosage (LEDD, mg/day) per convention.[14] LEDD from DA agonists was recorded separately ("DA-LEDD") and not included in the total LEDD; these were independent measures. Akinesia-rigidity (AR) and tremor motor impairment scores were calculated based on updated methodology for the MDS-UPDRS Motor Examination; however, rather than dividing mean AR score by mean tremor score to derive subtype classification, we utilized these mean scores separately for regression analysis to standardize and facilitate interpretation of odds ratios.[15]

Statistics

We used univariable methods to characterize differences among participants grouped by DDS/ICD and dyskinesia presence, including Kruskal-Wallis (nonparametric ANOVA) tests for continuous or ordinal data and Fisher's exact tests for nominal data (Table 2). For regression, the distributions of the primary outcome variables (MDS-UPDRS questions 1.6 for DDS/ICD, 4.1 for dyskinesias) were first evaluated. As they did not follow either a Poisson or a normal distribution, we dichotomized them as binary variables, such that any response 1 was scored as 1. LEDD values (mg/day) were divided by 100 in regression to improve interpretation of odds ratios. For all regression analyses, the MDS-UPDRS items assessing DDS/ICD and psychotic symptoms were treated as binary variables (1 scored as 1) due to the low prevalence of scores over 1.

We used backward stepwise logistic regression to identify independent variables for multivariable modeling. Sixteen of the variables in Table 2—all except age to avoid collinearity—were included for the DDS/ICD outcome model, plus a variable measuring the sum of the two dyskinesia items of the MDS-UPDRS IV (daily duration and functional impact of dyskinesias; q4.1 and 4.2 respectively). These seventeen variables were included in a logistic regression (with binary DDS/ICD scores as the outcome variable), which was then subjected to backward stepwise variable removal guided by corrected Akaike's information criterion (AICc). In parallel, a model for stepwise input with dyskinesia presence as the outcome variable was constructed, using the same variables, except with the DDS/ICD item substituting for the dyskinesia predictor. No measures of motor fluctuations were included, as fluctuations are intrinsic to certain classes of dyskinesias that are not differentiated by the MDS-UPDRS.[16] Each model also included an interaction term between AR motor score and disease duration to account for the observation that conversion to the AR phenotype over time is typical in PD.[17] An interaction term between LEDD and

disease duration was tested but did not reach significance. We report odds ratios with corresponding 95% confidence intervals and p-values for our multivariable logistic regression model. Odds ratios were calculated as the exponentiated regression coefficients and confidence interval endpoints. Statistical significance was set at $p < 0.05$.

Results

Demographic and clinical characteristics data for the 654 participants in our study are presented in Table 1. The age of participants ranged from 35 to 87, with an average of 65.0 ± 9.0 years (±, standard deviation) and an average age of disease onset of 58.5 ± 10.0 years. Half of the participants (50.6%) were using DA agonist medications at the time of their assessment and two-thirds (61.6%) of the participants were male. Fifty-three participants had clinically significant anxiety (8.1%) and 66 (10.1%) had clinically significant depression. Responses to select items from parts I (Non-motor Aspects of Experiences of Daily Living) and IV (Motor Complications) of the MDS-UPDRS scale were also characterized for our sample. Fifty-three participants (8.1%) scored 1 on q1.6, which assesses DDS/ICD symptom impact on daily functioning, while 150 participants (22.9%) scored 1 on question q4.1, which measures the daily duration of dyskinesia presence on average over the past week. For all remaining analyses, these participants were considered to have DDS/ICD and/or dyskinesias, respectively.

We next performed univariable comparisons of patients grouped by the presence of DDS/ICD symptoms and/or dyskinesias (Table 2). Participants with both dyskinesias and DDS/ICD had the earliest disease onset age of any group (p=0.002), whereas dyskinesias were specifically associated with longer disease duration (p<0.001). All groups with DDS/ICD and/or dyskinesias were taking higher total non-DA agonist LEDD (p<0.001), but dopamine agonist use frequency and DA-LEDD were not significantly different among groups. Depression was most common in participants with both DDS/ICD and dyskinesias (38.9%), but also more frequent in the presence of either alone compared to participants with neither DDS/ICD nor dyskinesias (p<0.001). Participants with dyskinesias alone had the lowest tremor scores (p=0.016), whereas AR scores were lowest in participants with neither dyskinesias nor DDS/ICD (p<0.001) Participants with both dyskinesias and DDS/ICD had the highest frequency of psychotic symptoms, wearing-off, and motor fluctuations measures (p<0.001 for all).

Backward stepwise regression—conducted separately for the outcomes of dyskinesia presence and DDS/ICD presence—identified an optimal multivariable model for either outcome (Table 3). Collinearity among independent variables was assessed using correlation estimates for each unique independent variable pair; no pairwise correlation coefficient (Kendall's tau) was greater than 0.30 in magnitude. However, we included an interaction term for AR motor impairment and disease duration, motivated by prior reports showing conversion to the AR disease phenotype over time.[17]

For DDS/ICD, the final model included five covariates. Of these, three were significantly associated with DDS/ICD in multivariable regression: psychosis (OR: 4.30; 95% CI: 2.07–8.62; p<0.001), clinically significant depression (OR: 2.37; 95% CI: 1.09–4.86; p=0.023),

and unpredictability of motor fluctuations score (MDS-UPDRS q4.4; OR: 1.36; 95% CI: 1.02–1.79; p = 0.0326). Younger age at diagnosis was only significantly associated in univariable. The final model using dyskinesias as the outcome of interest included nine covariates. Corroborating previous reports,[1] we found that disease duration was the strongest marker of dyskinesias in multivariable analysis (OR: 1.25; 95% CI: 1.17–1.33; p<0.001). Like DDS/ICD, dyskinesias were positively associated with psychosis (OR: 2.43; 95% CI: 1.27–4.57; p=0.006), but depression was not. Lower mean tremor motor impairment scores were associated with dyskinesia presence (OR: 0.49; 95% CI: 0.28–0.83; p=0.0096). Conversely, higher mean AR score was significantly associated with dyskinesias (OR: 2.43; 95% CI: 1.42–4.17; p=0.002). Additionally, there was a significant negative interaction between mean AR score and disease duration (OR: 0.92; 95% CI: 0.87–0.96; p<0.001). Finally, increased LEDD was associated with dyskinesias (OR: 1.05; 1.01–1.09; p=0.013), but not DA-LEDD. Male sex was associated with a lower likelihood of dyskinesias (OR: 0.62; 95% CI: 0.40–0.94; p=0.025). In summary, the main overlapping factor associated with both DDS/ICD and dyskinesias was the presence of psychotic symptoms.

To better characterize the temporal relationship between DDS/ICD and associated markers, we graphed the frequencies of unpredictable fluctuations, DA agonist usage, and psychotic symptoms among the 53 DDS/ICD cases as a function of disease duration (Figure 1). Unpredictable fluctuations were more common in participants with a five-year or greater PD history, whereas there was no clear temporal grouping of psychotic symptoms among DDS/ICD cases. Of 35 DDS/ICD cases with a PD duration over 5 years, 25 (71.4%) reported unpredictable fluctuations.

Discussion

With respect to our stated hypothesis of shared clinical correlates between DDS/ICD and dyskinesias in PD, we observed that psychotic symptoms were strongly and independently associated with both disorders in a cross-sectional analysis of a large PD cohort. Clinically significant depression and motor fluctuations characterized as irregular or unpredictable were associated specifically with DDS/ICD. DDS is not a highly prevalent complication of PD,[18] making it difficult to investigate risk factors, although previous smaller studies have suggested mood and perceptual alterations to be implicated in both DDS and ICD.[18,19] Our observed prevalence for DDS and ICD (8.1%) is difficult to compare to prior reports of DDS, as no study has utilized the MDS-UPDRS scale for this purpose. Existing studies have estimated prevalence at 3–4% for DDS[18] and 14% for ICD.[20] Importantly, PD patients are often more reticent than their caregivers to discuss DDS and ICD symptoms, which constitutes a substantial barrier to disclosure in a patient-reported context and may lower sensitivity.[21]

Our findings suggest that psychosis may be an important marker for disruption of motor and cognitive volition. The intrinsic disease processes of PD predisposing patients to psychotic symptoms may affect dopaminergic neurotransmission in a manner that also increases vulnerability to DDS and/or ICD. Indeed, a recent study linked low dopamine transporter (DAT) availability in the ventral striatum of PD patients to the later development of visual

hallucinations, [22] an association previously observed for ICDs.[23] Similarly, disease duration has emerged as the principal risk factor for dyskinesias in PD,[1] but an association with psychosis has not been previously observed. Dyskinesias and psychosis are often considered a complication of DA therapy, even though the relative contributions of PD treatment and the disease process itself to the onset of psychotic symptoms in individual patients remain unclear.[7] Serotonergic dysfunction in PD has been linked to both dyskinesias and psychosis, suggesting serotonin networks modulate dopaminergic circuits related to these disorders.[24] A prior investigation[25] found no association between psychotic symptoms and compulsive behaviors, including hypersexuality, gambling, and shopping. However, the most frequent psychotic symptom reported in that study was altered dream phenomena, which are not included in the recent NINDS/NIMH criteria for PD psychosis.[26] The MDS-UPDRS emphasizes the presence of illusions, hallucinations, and delusions, which are key components of the NINDS/NIMH criteria.

Previous evidence of an association between motor fluctuations and compulsive disorders has been indirect. A case-control study[4] showed that DDS participants had more severe motor impairment and decreased positive affect than non-DDS participants when both were rated during the "off" state. Patient aversion to debilitating "off" state symptoms may be important for DDS etiology and trigger compulsive dopaminergic medication overuse. Although other factors, such as pulsatile DA levodopa therapy, genetic vulnerability, and personality[2] are likely more relevant causes of DDS in early PD before fluctuation onset, we show that motor fluctuations perceived as being unpredictable or complex are themselves associated with altered reward-oriented behavior. Generally, motor fluctuations signal declining satisfaction with dopamine replacement efficacy, which may induce patients to use higher doses of medications than previously required, initiating an addictive response to increasing dosages of reinforcing dopaminergic medications.[27]

The MDS-UPDRS assesses ICD and DDS behaviors together based on the theory that although these are discrete clinical entities, they share some etiological elements of reward system dysfunction and compulsivity, including altered positive reinforcement.[27] For example, DDS is linked to potentiated levodopa-induced DA release in the ventral striatum of PD patients[3] and a prospective study showed that PD patients who go on to develop ICDs have lower baseline DAT availability in the ventral striatum,[23] either of which would bias striatal reinforcement pathways toward positive outcome-coding. Notably, we did not identify DA-LEDD as a significant marker of DDS/ICD. The association between ICDs and DA agonists is well-recognized,[2,20] whereas DDS is most frequently seen with pulsatile levodopa exposure.[2] Because of this distinction, our approach may not capture the differential associations of DDS and ICD with different types of DA medication. Our analysis is mainly relevant for identifying general markers shared by these conditions of impaired cognitive volition and compulsion and is likely not sensitive enough to capture all factors associated with ICD or DDS specifically. Additionally, our data only records prescribed dosages and thus would not accurately model abnormal medication use related to DDS.

We found a novel inverse association between current dyskinesias and tremor in PD after adjusting for disease duration and LEDD, among other factors; a previous study[28] in a

smaller cohort identified resting tremor at the time of diagnosis to be a negative predictor of eventual dyskinesia onset, but no association between current dyskinesia and tremor was noted. Additionally, we identified AR as a positive marker of dyskinesias and observed a significant negative interaction between AR motor impairment and disease duration. This suggests that marked AR impairment, especially in early PD, may portend a high likelihood of dyskinesias. Bradykinesia and rigidity—but not resting tremor—are correlated with nigrostriatal dopamine depletion and are more responsive to levodopa therapy than tremor. [29] Our findings are consistent with the increasingly compelling evidence that while dyskinesias are a dopaminergic phenomenon, tremor has extranigral origins.

There are several limitations to our analysis. The MDS-UPDRS item (1.6) used in our analysis does not differentiate ICD and DDS, which may not share an identical pathophysiology. However, because ICDs and medication abuse may share similar dopaminergic pathology as discussed above, grouping these behaviors together seems appropriate and facilitated our objective of identifying characteristics of patients with impaired cognitive volition. The developers of the MDS-UPDRS scale released a statement in 2012 acknowledging that the original item loading value of the DDS/ICD question did not replicate during a re-analysis. However, this appears to be more relevant to the MDS-UPDRS scale itself than to the validity of the DDS/ICD question specifically. Interestingly, the DDS/ICD question is one of the few non-motor questions that independently correlates with a validated quality of life measurement, the PDQ-39, validating the clinical relevance of this question alone in PD cohorts.[30] Finally, only single MDS-UPDRS items were used to measure psychosis and DDS/ICD. However, a validation study[31] demonstrated high correlation (0.86) of the MDS-UPDRS psychosis item with the Parkinson's Psychosis Rating Scale.

Overlapping mechanisms of DDS and ICD in general remain an area for further investigation. The fact that psychosis was a strong marker of both DDS/ICD and dyskinesias may speak to disease-specific commonalities between DDS/ICD and dyskinesias, although the pathological basis of this nexus is unclear. Additionally, our findings and other emerging evidence linking ICDs and psychosis[22] prompt re-evaluation of potential pathophysiological connections. Fluctuations are already recognized as being intrinsic to the experience of dyskinesias for many PD patients. However, our findings may speak to a common pathophysiology in patients who are experiencing disabling fluctuations, DDS/ICD, and psychosis. PD patients with this phenotype may be at risk when using DA agonists (for ICD) or pulsatile levodopa therapy (for DDS). We suggest that clinicians ensure that patients who have begun to experience motor fluctuations are counseled on the addictive properties of dopaminergic medications and their potential for adverse behavioral effects. Similarly, dyskinesias should indicate evaluation for changes in neuropsychiatric status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Author Roles

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2) Statistical analysis: A. Design, B. Execution, C. Review and Critique

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

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L.T.: 1C

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M.G.: 1C

N.Y.: 1C

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C.B.: 3B

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E.M.: 3B

T.M.D.: 1A, B; 3B

G.P.: 1A, B; 2C; 3B

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Highlights

1. In PD, dyskinesias and DDS or ICD may have analogous pathophysiologies.

2. Shared correlates of dyskinesias, DDS, and ICD were investigated.

3. Psychosis was a prominent marker of both dyskinesias and DDS/ICD.

4. Depression and complex motor fluctuations were associated with DDS/ICD.

5. High akinesia-rigidity—but low tremor—impairment was associated with dyskinesias.
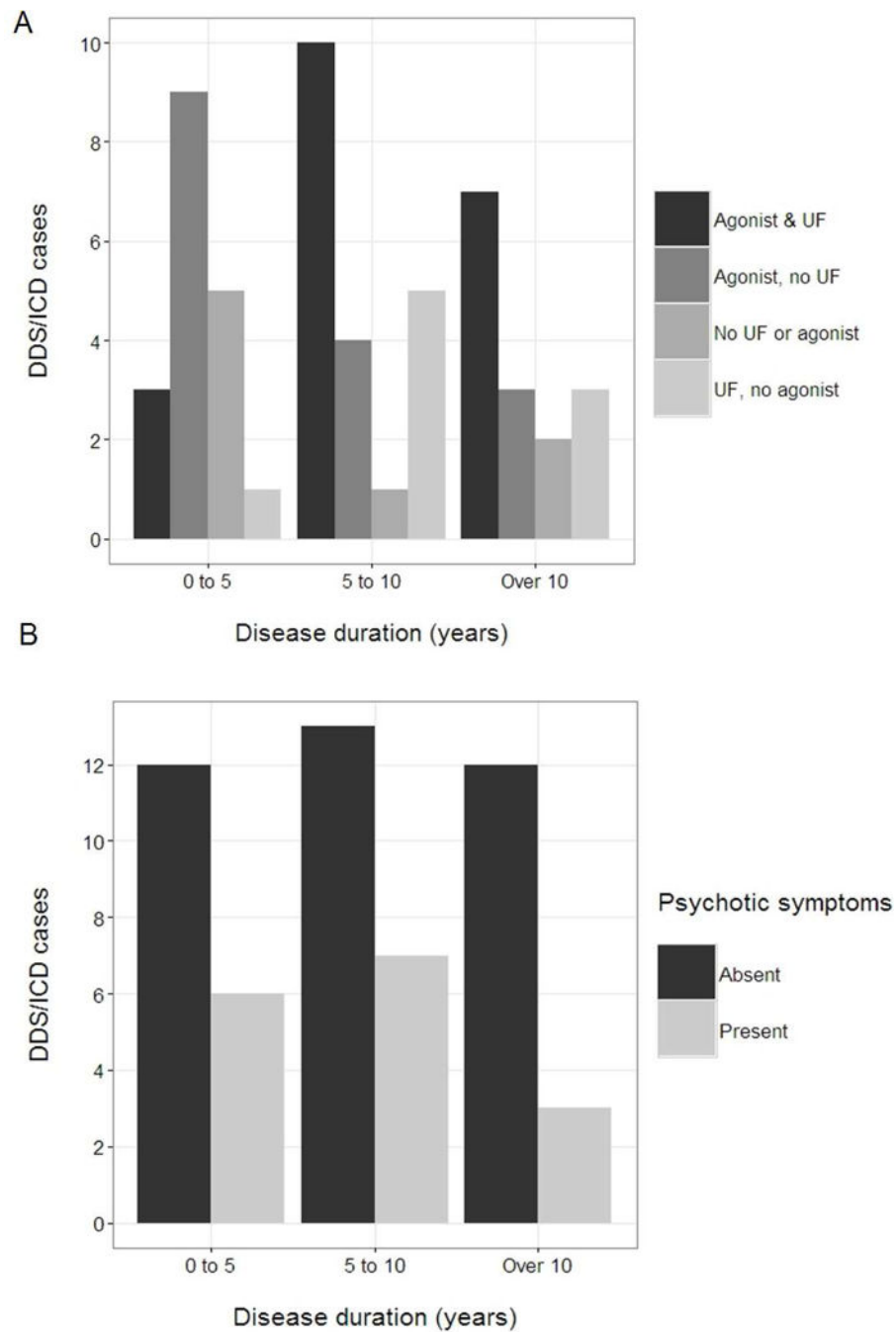
Figure 1. Unpredictable fluctuations accompany DDS/ICD later in PD than hallucinations or clinically significant anxiety

We compared the relative frequencies of (A) unpredictable fluctuations and dopamine agonist use and (B) hallucinations in participants reporting DDS/ICD symptoms (n=53). Scores 1 on q1.2 and q4.5 of the MDS-UPDRS were considered indicative of the presence of hallucinations and unpredictable fluctuations, respectively. The number of DDS/ICD cases in the "0–5", "5–10", and "over 10" disease duration groups were 18, 20, and 15, respectively.

Table 1

Sample Characteristics (N=654)

Demographic and Medication Information	Mean	SD	Range
Age, years	65.0	9.0	35.8–87.5
Age at diagnosis, years	58.5	10.0	31–82
Disease duration, years	6.5	5.1	0.1–38.3
Levodopa equivalent daily dosage (LEDD), mg/day	673	549	0–3396
Dopamine agonist LEDD (mg/day)	116	151	0–900
Dopamine agonist usage	331 (50.6%)		
Clinically significant anxiety (HAM-A 12)	53 (8.1%)		
Clinically significant depression (HAM-D-17 10)	66 (10.1%)		
Hoehn & Yahr stage			
(1)	99 (15.4%)		
(2)	461 (68.2%)		
(3)	82 (13.0%)		
(4)	11 (2.2%)		
(5)	1 (1.2%)		
Sex, male	403 (61.6%)		
PD-Validated Scales	**Mean**	**SD**	**Range**
Montreal Cognitive Assessment (MoCA)	25.3	3.0	18–30
MDS-UPDRS Part III (Motor Examination)	24.8	13.2	2–81
MDS-UPDRS	**Patient Scores (0/1/2/3/4)**	**Scores > 0, n (%)**	
Q1.2 Hallucinations and Psychosis	90.7 / 8.0 / 1.4 / 0 / 0	61 (9.3%)	
Q1.6 DDS/ICD	91.9 / 4.9 / 2.8 / 0.3 / 0.2	53 (8.1%)	
Q4.1 Time spent with Dyskinesias	77.1 / 16.5 / 4.1 / 1.7 / 0.6	150 (22.9%)	
Q4.2 Functional Impact of Dyskinesias	88.5 / 7.5 / 2.6 / 1.2 / 0.2	75 (11.5%)	
Q4.3 Time spent in the off state	65.9 / 27.7 / 5.8 / 0.5 / 0.2	223 (34.1%)	
Q4.4 Functional Impact of Fluctuations	72.6 / 15.3 / 6.6 / 4.7 / 0.8	179 (27.4%)	
Q4.5 Unpredictability of Motor Fluctuations	67.4 / 24.5 / 3.5 / 2.6 / 2.0	213 (32.6%)	

SD, Standard deviation. Patient scores on MDS-UPDRS items in parts I & IV are presented as proportions of total responses. Question 1.6 ("Dopamine Dysregulation Syndrome") assesses the interference of either DDS or ICD behaviors with patient functionality and quality of life. Clinically significant depression and anxiety were considered present for participants with HAM-A > 12 and HAM-D > 10, respectively.

Table 2

Patient Characteristics by DDS/ICD and Dyskinesia presence (n=654)

Variable	No DDS/ICD or dyskinesia (n=469)	Dyskinesias only (n=132)	DDS/ICD only (n=35)	DDS/ICD and dyskinesia (n=18)	p
Demographic and Medication Information Variables					
Age, years	64.8 (64.0–65.6)	66.2 (64.6–67.8)	63.3 (60.4–66.3)	64.0 (60.4–67.5)	0.219
Age at diagnosis, years	59.4 (58.5–60.2)	56.5 (54.5–58.5)	56.9 (53.6–60.1)	52.8 (48.8–56.9)	0.002 [**]
Disease duration, years	5.4 (5.0–5.8)	9.7 (8.8–10.6)	6.5 (4.8–8.1)	11.2 (8.6–13.7)	<0.001 [***]
Total levodopa equivalent daily dosage (LEDD) mg/day	599 (551–647)	889 (800–978)	687 (487–887)	994 (734–1254)	<0.001 [***]
Dopamine agonist usage	228 (48.6%)	67 (50.8%)	23 (65.7%)	13 (72.2%)	0.063
Dopamine agonist LEDD (mg/day)	112 (98–125)	123 (96–150)	130 (87–173)	149 (82–216)	0.214
Hoehn & Yahr stage					
&smap:(1)	81 (17.3%)	13 (9.8%)	5 (14.3%)	0	
&smap:(2)	334 (71.2%)	88 (66.7%)	25 (71.4%)	14 (77.8%)	
&smap:(3)	48 (10.2%)	27 (20.5%)	4 (11.4%)	3 (16.7%)	<0.001 [***]
&smap:(4)	5 (1.1%)	4 (3.0%)	1 (2.9%)	1 (5.6%)	
&smap: (5)	1 (0.2%)	0	0	0	
Mean Hoehn & Yahr stage	2.0 (1.9–2.0)	2.2 (2.1–2.3)	2.0 (1.8–2.2)	2.3 (2.0–2.5)	
Sex, male	296 (63.1%)	75 (56.8%)	23 (65.7%)	9 (50%)	0.380
PD-Validated Scales					
Montreal Cognitive Assessment (MoCA)	25.4 (25.2–25.7)	25.1 (24.6–25.6)	25.3 (24.3–26.3)	24.8 (23.1–26.5)	0.594
Clinically significant anxiety (HAM-A > 12)	29 (6.2%)	15 (11.4%)	6 (17.1%)	3 (16.7%)	0.013 [*]
Clinically significant depression (HAM-D-17 > 10)	32 (6.8%)	21 (15.9%)	6 (17.1%)	7 (38.9%)	<0.001 [***]
MDS-UPDRS					

Variable	No DDS/ICD or dyskinesia (n=469)	Dyskinesias only (n=132)	DDS/ICD only (n=35)	DDS/ICD and dyskinesia (n=18)	p
Tremor items total score (Part III)	5.0 (4.7–5.4)	4.1 (3.5–4.8)	6.2 (4.8–7.7)	5.2 (2.4–7.9)	0.016 [*]
Akinesia-rigidity items total score (Part III)	2.8 (2.5–3.1)	4.5 (3.8–5.1)	4.2 (3.1–5.3)	4.4 (3.1–5.8)	<0.001 [***]
Psychotic symptoms present (Q1.2)	28 (6.0%)	17 (12.9%)	7 (20%)	9 (50%)	<0.001 [***]
Wearing-off present (Q4.3)	108 (23.0%)	85 (64.4%)	13 (37.1%)	17 (94.4%)	<0.001 [***]
Functional impact of motor fluctuations (Q4.4)	83 (17.7%)	71 (53.8%)	9 (25.7%)	16 (88.9%)	<0.001 [***]
Unpredictable motor fluctuations (Q4.5)	102 (21.7%)	82 (62.1%)	12 (34.3%)	17 (94.4%)	<0.001 [***]

Means and 95% confidence intervals are presented for demographic and medication information variables and PD-validated scale variables. Patient scores on MDS-UPDRS items in parts I & IV are presented as proportions of total responses. P-values were produced using Kruskal-Wallis (nonparametric ANOVA) tests for continuous or ordinal data and Fisher's exact test for nominal data (sex, dopamine agonist usage, and primary source of MDS-UPDRS information) across all groups. LEDD from DA agonists is not included in total LEDD.

[*]
p<0.05;

[**]
p<0.01;

[***]
p<0.001

Table 3

Markers of DDS/ICD symptoms or dyskinesias in logistic regression (n=654)

Outcome	Independent Variable	Univariable		Multivariable	
		Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
DDS/ICD symptom presence	Psychotic symptom presence	5.34 (2.71–10.22)	<0.001 ***	4.30 (2.07–8.62)	<0.001 ***
	Depression (clinically significant)	3.36 (1.64–6.54)	<0.001 ***	2.37 (1.09–4.86)	0.023 *
	Complexity of fluctuations score	1.55 (1.19–1.97)	<0.001 ***	1.36 (1.02–1.79)	0.026 *
	DA-LEDD (mg/day)/100	1.10 (1.01–1.28)	0.067	1.07 (0.98–1.22)	0.180
	Age at diagnosis	0.97 (0.94–0.996)	0.024 *	0.97 (0.94–1.00)	0.0504
Dyskinesia presence	Disease duration (years)	1.18 (1.13–1.22)	<0.001 ***	1.25 (1.17–1.33)	<0.001 ***
	Mean akinesia-rigidity score	1.22 (0.88–1.67)	0.222	2.43 (1.42–4.17)	0.002 **
	Interaction: Disease duration and mean akinesia-rigidity score	—		0.92 (0.87–0.96)	<0.001 ***
	Psychotic symptom presence	2.81 (1.62–4.83)	<0.001 ***	2.43 (1.27–4.57)	0.006 **
	Mean tremor items score	0.47 (0.27–0.80)	0.007 **	0.49 (0.28–0.83)	0.0096 **
	LEDD (mg/day)/100	1.10 (1.06–1.14)	<0.001 ***	1.05 (1.01–1.09)	0.013 *
	Male sex	0.74 (0.51–1.07)	0.107	0.62 (0.40–0.94)	0.025 *
	Depression (clinically significant)	2.81 (1.65–4.76)	<0.001 ***	1.75 (0.94–3.20)	0.074
	DA-LEDD (mg/day)/100	1.01 (0.92–1.09)	0.816	0.91 (0.80–1.01)	0.166

Independent variables for regression were identified through backward stepwise regression. Two separate models were produced, one with DDS/ICD symptom presence as the outcome, the other with dyskinesia presence as the outcome. Clinically significant depression was considered present if a score of 10 was reached on the HAM-D-17.

*
p<0.05;

**
p<0.01;

***
p<0.001