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Motor phenotypes, medication and mood:

Further associations with impulsive behaviours in Parkinson's disease

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Abstract

Background: Dopaminergic drugs are the primary risk factor for Impulse Control

Behaviours (ICB) in Parkinson's disease (PD), others being early-onset disease and gender.

Objective: This report further explores ICB symptom relationships with motor and mood phenotypes, the complex relationship with dopaminergic medications, and hypothesizes a model with potential clinical implications.

Methods: Data from 500 PD patients were analyzed. Hypersexuality, gambling and shopping behaviour were assessed using selected questions from the Minnesota Impulsive Disorders Interview questionnaire. Local questions assessed hobbyism. Motor characteristics considered were akinetic-rigid/gait disturbance (PIGD) and 'non-PIGD' phenotypes, motor severity, motor progression, and presence/absence of motor fluctuations. Other variables included anxiety, depression, current levodopa and agonist use, age, gender and cognition.

Results: Overall, ICB symptom frequency was 17.8%. There was no relationship between PIGD/non-PIGD motor phenotypes and ICB symptoms. Those with ICB symptoms had higher total combined levodopa/agonist equivalent intake, but not current agonist-only equivalent intake. ICB symptoms were reported by 23.1% of those taking combined levodopa and agonist compared to 19.2% on agonist monotherapy and 11.6% levodopa monotherapy. Compared with non-ICB patients, patients with ICB symptoms were more likely to show an anxious mood phenotype, reported more motor fluctuations, and were younger.

Conclusions: Both PIGD and non-PIGD phenotypes are equally affected. Dose-related risk applies to total anti-parkinsonian medication and not just current agonist-only. Anxious mood phenotypes may carry increased risk. A role of anxiety, either as a marker of risk, indirect causal factor, or maintaining factor is incorporated into a preliminary model. We discuss implications for clinical management.

Introduction

Impulse Control Behaviours (ICB), including pathological gambling, compulsive shopping, eating, and sexual behaviour are more common in treated Parkinson's disease (PD) patients than in the general population, with prevalence rates of approximately 6-25% [1-3]. The association between PD and ICB may relate to the pathophysiology of PD, its treatment and their interactions, or other currently unidentified factors. Identifying ICB risk factors may enable better understanding of how ICB emerge and are maintained, and may provide new research avenues for management.

Converging evidence supports the existence of distinct motor phenotypes in PD, particularly a postural instability/gait difficulty (PIGD) and tremor-dominant subtypes[4-7]. One aim of the present study was to determine if motor phenotypes, have a relationship to ICB symptoms and thereby offer clues to pathophysiology. Other motor characteristics were also studied. Second, we assessed the complex relationship between antiparkinsonian medication (agonists and levodopa) and ICB symptoms, specifically current dopamine-agonist-only, levodopa-only, and total levodopa equivalent doses. Finally, we assessed whether specific mood phenotypes [8] had a relationship to ICB symptoms.

Methods

The PROMS-PD project is a prospective study of mood states in PD [8]. Briefly, participants were recruited consecutively from patients attending outpatient appointments at secondary neurology and care of the elderly clinics in 5 UK centres over a 12 month period. Diagnosis of idiopathic PD was based on the UK Brain Bank clinical diagnostic criteria [9]. Patients with other parkinsonian diagnoses, severe hearing or visual loss, severe communication difficulties or severe cognitive impairment and unable to give informed consent were

excluded. The study was approved by the South East NHS Research Ethics Committee, Ref:(07/MRE01/9). Information was collected from the patient and/or informant on clinical history, current treatment and socio-demographics. Motor symptoms were assessed at the time. Levodopa equivalent daily dose (LEDD) was calculated using conversion factors described previously [10].

Motor characteristics

The Unified Parkinson's Disease Rating Scale III (UPDRS) [11] and Hoehn and Yahr scale [4] were used to assess motor symptoms. Patients were examined in the on-state for practical reasons. Further, patients were classified as akinetic-rigid with gait disturbance (PIGD), tremor-dominant (TD), or no clear subtype as described previously [13] based on the classification proposed by Jankovic and colleagues [5]. We hypothesised that the PIGD phenotype, typically being more severe, requiring more aggressive medical therapy, [7,9,12] would have a higher prevalence of ICB symptoms. It was also hypothesised that patients with faster progression rates could potentially have greater and more frequent escalation in dopaminergic medication and therefore be at greater risk of ICB symptoms. An index of progression was obtained from the summed scores of UPDRS parts I-III divided by disease duration (years) as described previously [6, 13]. Participants were classified as 'fast' or 'slow' progressers depending on whether their index was higher (fast) or lower (slow) than the group median (Table 3). An index of motor variability was assessed as those reporting unpredictable or sudden off (UPDRS IV)[13].

Affective and cognitive assessments

Based on previously described psychiatric symptoms [8], participants' mood was classed as depressed, anxious, anxious and depressed or 'healthy'. The Hospital Anxiety and Depression

Scale (HADS), validated for use in PD[14], was also used to assess severity of depression and anxiety. A subscale score >10 indicates clinically significant depressive or anxiety symptoms. The Addenbrooke's Cognitive Exam-Revised (ACE-R), validated for use in PD[15], was used to assess cognition, with a score of < 84 indicating cognitive impairment.

ICB symptoms

As part of a larger semi-structured psychiatric interview, ICB symptoms were assessed using questions from the Minnesota Impulsive Disorders Interview (MIDI) [16]. They were considered to have an ICB if they responded positively to one or more questions relating to sexual behaviour, gambling and shopping respectively. In addition, local screening questions were included concerning the presence of hobbies and other repetitive activities that took up large amounts of time and interfered with other activities including sleep (see appendix). The term Impulse Control Behaviour (ICB) symptoms will be used in this manuscript to describe symptoms of only sexual behaviour, gambling, shopping and hobbyism collectively, as a subset of known impulsive / compulsive states in PD. Other ICBs and related problems (including excessive eating, walkabout, punding, creativity, risk-taking behaviour or Dopamine Dysregulation Syndrome (DDS)) were not assessed as part of the PROMS-PD project and cannot be included in this manuscript.

Statistical Analysis

Descriptive statistics were used to explore the prevalence and type of ICB symptoms. Univariate tests (independent samples t-tests (normally distributed data) and Mann-Whitney U tests (non-normally distributed data)) were performed to explore relationships between ICB symptoms and the clinical and demographic variables. Chi-squared analysis was used to explore the relationships between gender, motor phenotype, motor symptoms, mood

phenotype and ICB symptoms. Mann-Whitney U tests were used to compare medication levels between ICB and non-ICB participants. Finally, a binary logistic regression analysis was performed to explore statistical predictors of ICB symptoms. Only variables showing significant relationships in the univariate analyses were entered into the model.

Results

Demographics

In this study, 525 patients participated but 25 were excluded as they were not taking dopaminergic medication and did not demonstrate ICBs. Males numbered 326, females 174. The sample was 96.2% white British. Mean age was 67.9 years (SD 10.4), median disease duration was 7.1 years (Interquartile range 6.0) and mean “on” UPDRS III score was 26.8 (SD12.0). At least one ICB symptom was identified in 17.8% of participants. Five percent reported two or more ICBs (Table 1).

Men were statistically more likely than women to report compulsive gambling (Table 1), but no relationship was found between gender and presence of ICB symptoms overall (Table 1). Participants with ICB symptoms were younger by a mean of 5.7 years and had marginally better cognitive function (Table 2).

Motor phenotypes

Most patients were classified as PIGD (78.8%), 13.4% as TD, and 7.8% had no clear subtype. With the exception of slightly lower UPDRS-III scores in the TD participants, the two non-PIGD subtypes did not differ in age, gender, anxiety, depression, cognition, disease duration, progression or motor fluctuations, suggesting similar clinical and demographic profiles. For this reason, they were combined into a ‘Non-PIGD’ group (21.2%).

No significant relationships were found between motor phenotypes, or rate of progression (as assessed by our index), and ICB symptoms (Table 3). ICB symptoms were however more common in patients with motor fluctuations. No significant associations were found between individual ICBs and motor phenotype (hobbyism = $\chi^2=0.256$, $df=1$, $p=0.613$, compulsive gambling = Fisher's Exact Test $p=0.546$, compulsive shopping= $\chi^2=0.399$, $df=1$, $p=0.527$, hypersexuality = Fisher's Exact Test $p=0.331$). Hobbyism ($\chi^2=7.837$, $df=1$, $p=0.005$) and compulsive shopping ($\chi^2=7.112$, $df=1$, $p=0.008$) were more common in patients with motor fluctuations.

Medication

The median current total LEDD in the ICB group was significantly higher than the non-ICB group. A significant difference was found for current agonists use, in that by 74.2% of participants with ICB symptoms used current agonists, compared with 56.7% without ICBs ($\chi^2=9.284$, $df=1$, $p=0.002$). However, the median current agonist-only and levodopa-only LEDD did not differ significantly between groups (Table 3). Rates of ICB symptoms were higher in participants on combined levodopa/agonist therapy (23.1%) than those on monotherapy (agonist only 19.2%, levodopa only 11.6%) ($\chi^2=9.915$, $df=3$, $p=0.019$).

Mood

Patients with ICB symptoms had significantly higher HADS anxiety scores than those without ICB (Table 2) but not depression scores. Chi-squared tests (Table 3) identified a clear relationship between the presence of ICB symptoms and both anxiety-related phenotypes (anxious alone phenotype, and anxious/depressed phenotypes) relative to the 'Healthy' group, but no association with the phenotype characterised by depression without anxiety. This

pattern was also seen in the relationships between individual ICBs and mood phenotypes. Hobbyism was more common in the anxious/depressed (34%) and anxious (22%) groups than the depressed (10%) and healthy groups (8%) ($\chi^2=16.914$, $df=3$, $p=0.001$). Gambling was more common in the anxious/depressed group (13%) than the depressed (2%), anxious (4%) and healthy (2%) groups ($\chi^2=9.765$, $df=3$, $p=0.021$). Shopping was more common in the anxious/depressed (13%) and anxious groups (13%) than the depressed (2%) and healthy (4%) groups ($\chi^2=12.470$, $df=3$, $p=0.006$).

Predictors of ICB

Variables significantly associated with ICB symptoms were entered into a binary logistic regression model (Table 4), initially individually (unadjusted odds ratio) and then combined (adjusted odds ratio). All variables, with the exception of depressed mood phenotype, significantly predicted ICB in the unadjusted models. In the combined adjusted model, only two significant predictors were identified: mood phenotype and age. Medication related variables did not contribute significantly to the adjusted model. The model suggests that younger participants and those with an anxious or anxious/depressed mood phenotype were more likely to experience ICB. The final model correctly classified 82.5% of cases as ICB symptoms or non-ICB although this is biased by the high prevalence of non-ICB cases.

Discussion and hypothesis

This large cohort study investigated relationships of ICB symptoms with clinical characteristics. Although smaller than the study of Weintraub [1] and assessing a narrower set of ICB and related problems, we explored a broad range of features, including motor, medication and affective phenotypes. The demographics, prevalence data and ICB characteristics were comparable with previous studies, e.g.[1], suggesting that our cohort was

similar to previously published cohorts, and is a clinically representative sample. Our data are largely confirmatory and we use them to develop a hypothesis with potential clinical and research implications.

Motor phenotypes

Data on the relationships between motor phenotypes and impulsivity to date are conflicting. Two recent studies suggest that akinetic-rigid patients may have more susceptibility to ICB [17, 18]. In contrast, our data, and those of Voon et al [19], suggest a similar prevalence of ICB symptoms among different PD motor subtypes. These variations are potentially explained by differences in impulsivity measures (reaction time studies vs. ICB screening tools). We suggest that both PIDG and non-PIDG motor phenotypes require similar surveillance for development of these behaviours.

Further exploration showed no clear relationships between rate of progression (as assessed by the methods in this study) and ICB symptoms. It has been reported previously that young-onset PD patients typically develop motor fluctuations and dyskinesias earlier [20]. Our data showed that younger patients and those with motor variability reported more ICB symptoms. These findings could be explained if young-onset disease and fluctuating (motor or non-motor) disease share a distinct pathological mechanism, but pathological evidence is currently lacking. Alternatively these associations may simply reflect that younger patients with fluctuations are more likely to take more medication to combat this, and consequently develop more drug-induced ICB. One important aim of future research will be the examination of associations of ICB and/or motor and non-motor fluctuations and the bearing that is imposed on these by pulsatile versus continuous delivery of treatment (whether by subcutaneous or intrajejunal dopaminergic therapy or by continuous high frequency deep

brain stimulation). Evidence of these effects is currently lacking but recent publications are beginning to explore this concept [21]. If such associations are confirmed, then these could lead to better identification of susceptible patients and to potential choice of therapy.

Medication

The relationship of medication with ICB is complex because of the large number of medications available to treat motor symptoms in PD over time. The discussion and hypotheses in this manuscript are confined to agonists and levodopa, as these have been the focus of the majority of previously published reports. Our results add to this field by supporting the positive association between ICB symptoms and treatment with agonists (proposed as a class effect) and levodopa [1]. More patients with ICBs were taking agonists and although the current median dose of agonist-only LEDD was higher in the ICB group, this difference did not reach statistical significance even in this large sample, suggesting the absence of a substantial dose-dependent effect, similar to previous conclusions [1,19]. However, from the general clinical experience, some ICBs can sometimes improve by dose reduction and evidence of a dose-related agonist association has been described in two recent ICD studies [22,23]. One explanation for these differences could be considerable individual differences in dose thresholds for the appearance of ICB. The identification of which PD patients would be susceptible to the development of ICBs, and, if possible the identification of a threshold dose, could have clinical implications in directing treatment. For example, for an analogous clinical scenario, one can consider the management of patients who have suffered transient ischaemic attacks (identified as susceptible individuals) being offered stroke prophylaxis (an appropriate dose of drug depending on the risk factor for the transient ischaemic attack).

The relationship of ICB symptoms with levodopa is also complex, and therefore in this manuscript, we additionally explore the role that levodopa may have in ICB symptoms because Levodopa's role has received less recent attention than agonists. The recent study [23] did not report a relationship with levodopa use and a recent review reported that levodopa monotherapy is not associated with pathological gambling [24]. In contrast, and in line with the largest study [1], we found that a higher total LEDD was related to ICB symptoms. Further, and perhaps related to this, ICB symptoms were present in more patients taking combined levodopa and agonist than agonist alone. Almost 12% of patients in the non-agonist group developed ICB symptoms, similar to previous reports [1] and confirming the need to raise awareness of the role of levodopa in ICB. Voon et al.[19] extend this concept further by showing differential levodopa doses with ICB subtypes. In that study patients with ICBs (single or multiple) were receiving more levodopa when compared with those without ICBs, but the highest levodopa doses were seen in patients with compulsive shopping and sexual behaviour, in contrast to those with problem / pathological gambling and binge eating. From these large studies, three considerations can be contemplated for risk management and communication: (i) patients on levodopa monotherapy can develop ICB symptoms and therefore also require counseling, (ii) some patients on agonists may be at risk even at low dose of the agonist, (iii) patients on combined levodopa and agonist seem to have the highest frequency of ICB symptoms, particularly as total LEDD increases. Patients with early PD often are managed on a single drug (whether agonist or levodopa alone) early in the disease. These results suggest that the risks of development of ICB symptoms might increase further at the time of increasing overall medication intake by the addition of the second agent. We do not know if this finding is dependent on which class of drug is offered first, or is uniform across all ICB, but it suggests that additional counseling should be offered to patients at the time of starting combined pre-synaptic and postsynaptic dopaminergic medications. Other

medication factors require future detailed exploration, including assessing the combined use of agonist and levodopa in different proportions but with constant total LEDD, the nature of delivery (pulsatile or continuous), or introduction of a third or fourth class of antiparkinsonian medication eg COMT inhibitors or MAO inhibitors and the controversy over the use of amantadine [25].

Mood phenotype

Patients with anxiety were more likely to experience an ICB symptom than psychologically healthy or depressed patients, consistent with previous findings of increased state and trait anxiety in ICD [19]. We have previously reported that anxiety-related phenotypes are associated with younger onset-disease [8], potentially suggesting that they share common risk factors. Furthermore, the anxious phenotypes were associated with motor fluctuations [13] possibly describing a broad clinical phenotype of motor and neuropsychiatric features associated with young-onset disease. In PD, anxiety influences quality of life [26] but the mechanism by which anxiety may influence expression of other parkinsonian symptoms, including ICB, requires exploration. Appreciation of these mechanisms is important to aid understanding of the evolution and maintenance of the problem behaviours. For hypothesis generation and future research, we suggest a preliminary model that draws together the main factors considered in this study. The model (Figure 1) does not seek to be comprehensive and the directions of causality are speculative, but should be testable with new research.

PD pathophysiology and dopaminergic stimulation remain central in the proposed model. ICB symptoms may arise from, or could be maintained by, a combination of direct and indirect factors related to the individual, the disease or treatment. Young-onset disease, perhaps because of distinctive pathophysiology or the nature and duration of treatment, may

contribute to higher medication levels. Higher medication levels are associated clinically with motor fluctuations. Other trait factors, such as harm avoidance (high in PD)[27] predating the onset of PD may prompt patients to seek more medication due to perceived under-treatment, while those patients (particularly younger) high in reward dependence trait[28] may be seeking a stimulant-like response. In anxiety-prone patients, unpredictable non-motor fluctuation may increase anticipatory anxiety, exacerbate anxiety or dysphoria during off-periods [29]. A recent qualitative study suggested that for some patients ICB is used as a strategy helping them cope with a chronic uncontrollable condition [30]. While ICB symptoms may offer a short-term coping response (e.g. distraction), the longer-term negative consequence may feed the mood problem in a vicious cycle, maintaining the behaviour. Where this anxiety or the ICB drives a request for escalation of medication, the problems are exacerbated further. The model of anxiety as a direct or indirect influence on ICB symptoms suggests new avenues for research and treatment for ICB. Indeed, a recent randomized trial of Cognitive Behaviour Therapy for the management of ICB symptoms showed a positive outcome [31] and included targeted treatment of anxiety as part of the treatment protocol.

Limitations of our results and hypotheses require mention. The logistic regression model identified only two significant predictors of ICB symptoms: mood phenotype and age. Interestingly the effect of mood was much stronger than that of medication, suggesting that in this cohort, ICB are not simply a consequence of dopaminergic medication. However, only 82.5% of the cases were correctly classified as ICB/Non-ICB and this figure will be inflated by the high proportion of non-ICB patients, suggesting that other factors not assessed in this study play a role in determining whether patients develop ICB. Additionally, patients were recruited through hospital clinics. Consequently the prevalence rates may not fully translate to patients managed in the community, who may have fewer motor or non-motor

complications. We assessed only a limited subset of ICB symptoms, determined through the use of the MIDI questionnaire rather than through a structured clinical interview or formal diagnostic criteria, while hobbyism was assessed using local questions which captured the presence of ICB, but not the severity. However the aim was to detect symptoms and formulate hypotheses, rather than diagnose ICB. Threshold symptoms suggest increased risk of more serious ICB in the future[29], consequently the inclusion of these symptoms may provide important risk factor information. Other problems associated with ICB, such as DDS, and punding, were not assessed. A recent conceptual paper [29] proposed that ICB such as gambling, hypersexuality, eating and shopping are best classified as ‘behavioural addictions’ whilst other ICBs including punding, hoarding, walkabout and DDS represent qualitatively different behaviours with potentially different causal mechanisms. Further, for the present manuscript, we have combined the different behaviours under one umbrella term (ICBs) for hypothesis testing, and the present manuscript has not separated the different types of ICBs into classes. Different ICBs seem to have different associations with medications (eg gambling, sexuality, eating and shopping more with agonists, while punding / hobbyism more with levodopa), although overlap is not excluded. The subclassification of ICBs into groups is not without difficulty in interpretation as even within the same subtype of ICBs, some may have differing associations with medications [19] as shown previously. Currently, the best level of subclassification remains to be agreed uniformly. We did not address comprehensively previous (or peak) doses of medications which may have been reduced at the time of this study, thus reducing the reliability of our prevalence rates and associations with medications. Previous drug reduction themselves may have contributed to anxiety symptoms. Previous history of ICBs and family history of ICB, or substance abuse, psychiatric disturbances were not included. Lastly, at present there is no gold-standard definition of progression in PD and the index used provides only an estimate. Despite these

limitations, the present manuscript has generated hypotheses for future potential clinical testing.

In conclusion, motor phenotype was not associated with ICB symptoms. Motor fluctuations when analyzed independently were significant associations. Dopamine agonist use was associated with higher ICB risk, but as previously suggested this relationship did not appear to be dose-dependent. More complex medication effects, including total dose and interactions with levodopa, may further enhance ICB manifestation. A role of anxiety, either as a marker of risk, indirect causal factor or maintaining factor is suggested, and may be a modifiable factor, and therefore a target for therapy. Identification of those at greater risk, however, does not imply no risk to those in low risk groups. Pre-treatment counseling and post-treatment surveillance should be available to all patients. The identification of clearer risk factors would, however, allow enhanced pre-treatment counseling for some. This could include the advantages/disadvantages of other forms of therapy, which have either more long-term motor side-effects (e.g. levodopa), or the acceptance by the patient to maintain less anti-parkinsonian medication in general. Secondly, it would encourage both physicians and patients to accept frequent post-treatment surveillance.

Table 1. ICB symptom prevalence and association with gender

	Point prevalence N, (%)	Gender – % male	p value
No ICB	411 (82.2)	63.7	-
Any ICB	89 (17.8)	71.9	(p = 0.143)
Gambling	17(3.4)	88.2	(p = 0.042)
Shopping	30 (6.0)	66.7	(p = 0.855)
Hypersexuality	15 (3.0)	86.7	(p = 0.076)
Hobbyism	59 (11.8)	67.8	(p = 0.656)

ICB = impulse control behaviour

Table 2. Clinical and demographic features of patients with and without ICB symptoms.

	No ICB		ICB		p value
	Range	Mean (SD)	Range	Mean (SD)	
Age	39-94	68.9 (9.9)	32-85	63.2 (11.2)	p < 0.001
PD duration (years)	0-39	5.0 (8) †	0-25	6.0 (8)†	p = 0.464
Hoehn & Yahr	0-5	2.4 (0.9)	1-5	2.4 (0.8)	p = 0.952
UPDRS III	4-78	27.1 (12)	5-53	25.0 (11.9)	p = 0.130
HADS Anxiety Score	0-20	6.9 (4.4)	0-17	8.5 (4.3)	p = 0.004
HADS Depression Score	0-17	6.2 (3.6)	1-17	6.7 (3.9)	p = 0.315
ACE-R score	46-100	89.0 (14) †	53-100	91.0 (9.75)†	p = 0.003

†Median and interquartile range

Table 3. Motor, medication and mood characteristics of patients with and without ICB symptoms

Characteristic	No ICB	ICB	Chi-squared statistic/ Mann-Whitney U statistic (p value)
Motor phenotypes	N (%) [†]	N (%) ^{††}	
PIGD	323 (78.6)	71 (79.8)	
Non-PIGD	88 (21.4)	18 (20.2)	$\chi^2=0.06$, df=1 (p=0.804)
Total	411	89	
Rate of progression	N (%) [†]	N (%) ^{††}	
Slow	203 (49.4)	51(57.3)	
Fast	206 (50.1)	38 (42.3)	$\chi^2=1.72$, df=1 (p=0.190)
Total	409	89	
Missing ^{****}	2 (0.5)	0 (0)	
Fluctuations	N (%) [†]	N (%) ^{††}	
No	303 (73.7)	54 (60.7)	
Yes	108 (26.3)	35 (39.3)	$\chi^2=6.10$, df=1 (p=0.014)
Total	411	89	
Medication	Median (IR) (Range)	Median (IR) (Range)	
Total current LEDD (N=500)	730.0 (695) (37.5-3641.0)	880.0 (795) (100.0-7565.0)	U=21267.50 (p = 0.016)

Agonist-only current LEDD (N=299)	300.0 (240) (25.0-2500.0)	330.0 (285) (60.0-6340.0)	U=8681.50 (p = 0.108)
Levodopa-only current LEDD (N=410)	510.0 (480) (50.0-2340.0)	520.0 (415) (70.0-2660.0)	U=13225.00 (p=0.313)
Mood phenotypes	N (%) [†]	N (%) ^{††}	
Healthy [*]	259 (63.0)	35 (39.3)	-
Anxious	77 (18.7)	33 (37.1)	$\chi^2=18.72$, df=1 (p≤0.001)
Anxious/depressed	29 (7.1)	14 (15.7)	$\chi^2=12.88$, df=1 (p≤0.001)
Depressed	38 (9.2)	6 (6.7)	$\chi^2=0.11$, df=1 (p=0.743)
Total ^{**}	403	88	
Missing ^{***}	8 (1.9)	1 (1.1)	

^{*}Healthy group: patients with no affective symptoms. ^{**}Total number of patients who have full data. ^{***}Missing participants who did not have full data=9 patients, therefore could not be classified by mood phenotype. ^{****}Missing participants who did not have full data=2 patients, therefore could not be classified by progression.

[†] % refers to the percentage of patients in each group as a proportion of the total sample without ICB symptoms (N=411)

^{††} % refers to the percentage of patients in each group as a proportion of the total sample with ICB symptoms (N=89). IR Interquartile Range

Table 4: Logistic Regression Model of Predictors of ICB symptoms

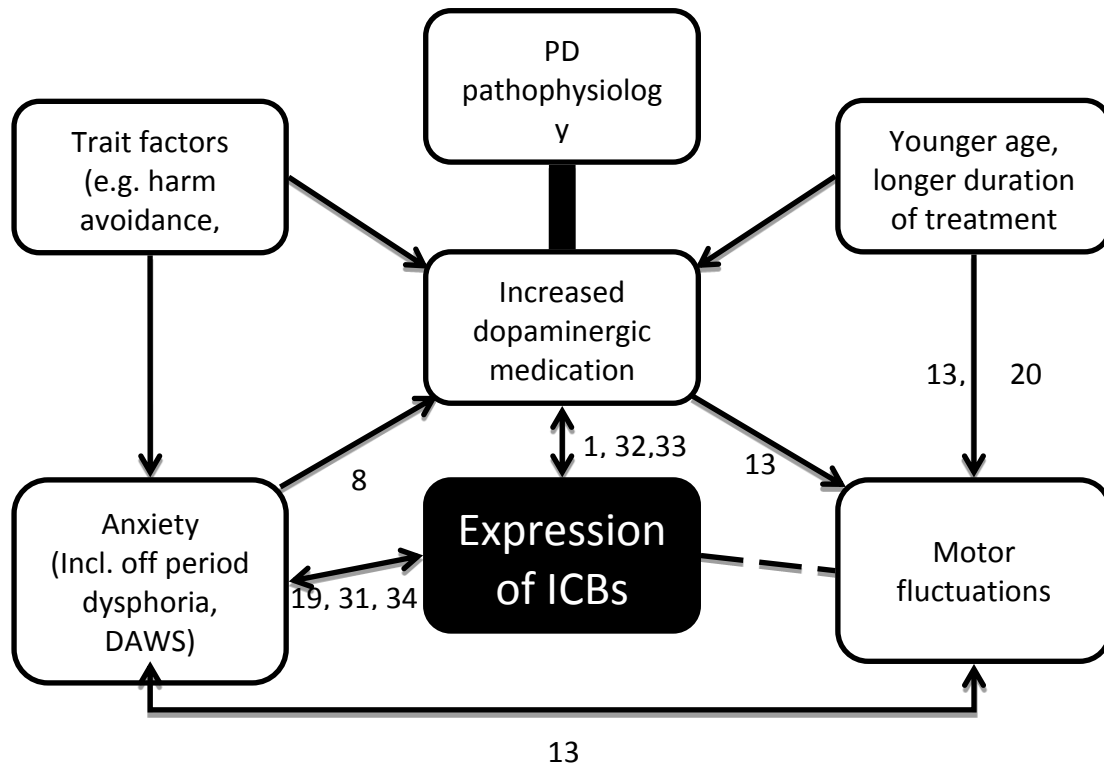
	Unadjusted Odds Ratio (p)	CI	Adjusted Odds Ratio (p)	CI
Age (years)	0.95 (<0.001)**	0.93-0.97	0.97 (0.022)*	0.94-1.00
ACE-R	1.04 (0.005)**	1.01-1.07	1.02 (0.136)	0.99-1.05
Fluctuations	1.82 (0.014)*	1.13-2.94	1.00 (0.995)	0.57-1.74
Total LEDD (mg)	1.06 (0.004)**	1.02-1.10	1.03 (0.234)	0.98-1.07
Taking an agonist	2.19 (0.003)**	1.31-3.66	1.28 (0.549)	0.57-2.85
Taking an agonist and levodopa	1.90 (0.007)**	1.20-3.03	1.14 (0.745)	0.52-2.50
Anxious vs healthy	3.17 (0.001)**	1.85-5.44	2.41 (0.003)**	1.36-4.26
Anxious/depressed vs healthy	3.57 (0.001)**	1.72-7.41	2.70 (0.017)*	1.20-6.08
Depressed vs healthy	1.17 (0.743)	0.46-2.96	1.38 (0.516)	0.52-3.65

*Significant at P<0.05

**Significant at P<0.01

Figure 1

Hypothetical model of compound factors contributing to the onset and/or maintenance of ICBs in PD



Arrows indicate suggested unidirectional or bi-directional causality, dashed line indicate association without clear causation. Numbers refer to references supporting associations.

DAWS = Dopamine Agonist Withdrawal Syndrome.

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Appendix

Hobbyism Questions

1. Do you have any hobbies or pastimes? What sort of interests do you have?
2. How often do you spend time on (hobby)? : Daily (7 days per week)/4-6 days per week/2-3 days per week/1 day per week or less frequent
3. On these days how many hours would you spend doing the hobby? : < 1 hour, 1-3 hours, 4-6 hours, ≥ 7 hours
4. Do you sometimes spend excessive amounts of time doing (hobby)? : No/Yes
5. Do you find (hobby) calming, or brings you relief from feeling of tension? : No/Yes
6. Has doing (hobby) interfered with your sleep at all in the past month – for example you have gone to bed later than usual because of it? No/Yes
7. In the past month have you missed a whole night's sleep doing (Hobby)? : No/Yes
8. Do you feel that (hobby) sometimes interferes with other aspects of your life or daily routine? Does it stop you doing other things that you want to do? : No/Yes

Patients responding positively to questions 6, 7 or 8 were classified as reporting excessive hobbyism.

MIDI Questions

1. Do you, or others that you know, think that you have a problem with being overly preoccupied with sex? (if 'yes', ask -) for how long?: No/yes/ns
2. Do you or others think that you have ever had a problem with gambling?: No/yes/ns
3. Do you or others think that you have a problem with buying things too often or with spending too much money?: No/yes/ns

Patient classified as having an ICB symptom if answering 'yes' to any question

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