RESEARCH ARTICLE

Psychostimulant Effect of Dopaminergic Treatment and Addictions in Parkinson's Disease

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ABSTRACT: Background: Dopamine replacement therapy in PD has been associated with both behavioral addictions and dopamine addiction.
Objectives: To investigate potential association between L-dopa induced neuropsychiatric fluctuations and addictions in PD.
Methods: A cohort of 102 patients with PD suffering from motor complications of L-dopa treatment was prospectively analyzed. We evaluated dopamine addiction, behavioral addictions, and neuropsychiatric fluctuations using the Ardouin scale of behavior in PD.
Results: Patients with (n = 51) or without (n = 51) neuropsychiatric fluctuations did not differ in age, disease duration, medication, or UPDRS III motor score during *on* and *off* drug condition. Patients with neuropsychiatric fluctuations had a higher H & Y stage in *off*-drug condition. A multivariate model showed that dopamine addiction (odds ratio: 8.9; $P = 0.02$) and behavioral addictions (odds ratio: 3.76; $P = 0.033$) were more frequent in the presence of neuropsychiatric fluctuations. Behavioral addictions and dopamine addiction were more frequent in the presence than in the absence of *on*-drug euphoria (46% vs. 13.9%; $P < 0.001$ and 27% vs 6.2 %; $P = 0.003$), while conversely, no association emerged between dopamine or behavioral addictions and presence of *off*-drug dysphoria. Patients with neuropsychiatric fluctuations had a poorer quality of life and a more frequent history of anxiety disorder.
Conclusions: The psychostimulant effects of dopamine treatment during *on*-drug euphoria, rather than avoidance of *off*-drug dysphoria, appear to drive both behavioral addictions and abuse of medication.

Key Words: Parkinson's disease; nonmotor fluctuations; addictions; dopamine dysregulation syndrome; impulsive control disorders

In the course of Parkinson's disease (PD), motor and nonmotor fluctuations occur, and severity of dopamine denervation and pulsatility of dopamine replacement treatment are the main risk factors.[1,2] Nonmotor fluctuations are classically categorized as autonomic, sensory, and/or neuropsychiatric.[3] In the present study, we focused on neuropsychiatric fluctuations characterized by variations of mood, motivation, and anxiety between *off*-drug and *on*-drug states.[4] In the *off*-state, patients typically experience a variable combination of apathy, anxiety, and depressed mood, known as hypodopaminergic behavior, a state we called *off*-drug dysphoria. In contrast, euphoria, hyperactivity and impulsivity characterize *on*-drug hyperdopaminergic behavior, which we baptized *on*-drug euphoria. Longer disease duration, presence of motor fluctuations, severity of PD, and younger age constitute a predisposition to the development of nonmotor fluctuations.[3,5]

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Addiction to dopamine replacement therapy or dopamine addiction is a relatively rare, but deleterious, condition, which occurs at an advanced stage of the disease, resulting in compulsive abuse of dopamine replacement therapy. The intake of dopaminergic drugs is superior to the dosage required to control motor symptoms, despite the possibility of severely destructive social behavior. Associated conditions are younger age, history of substance addiction, novelty-seeking personality traits, and occurrence is favored by short-acting drugs.[6] Hypersensitization of reward-related circuits particularly affecting the ventral striatum seems to be involved in the development of dopamine addiction,[7] as is the case for other substance addictions.[8,9] Dopamine addiction (compulsive use of levodopa and/or dopamine agonist drugs) can be part of the full-blown dopamine dysregulation syndrome when mood changes are observed and punctuated by the dopaminergic medication[10]; it can also is observed as an isolated feature and often is observed in combination with impulse control disorders (ICDs).[11-13]

ICDs are defined as failure to resist an impulse drive, or temptation to perform an action despite its negative consequences.[14] In addition to the four major ICDs described in PD (gambling disorder, hypersexuality, and compulsive shopping and eating), other addictive behaviors, including hobbyism, nocturnal hyperactivity, and risk-taking behaviors, are also observed. Given common behavioral and neurobiological aspects, ICDs and other repetitive impulsive behaviors have been categorized as behavioral addictions.[9,15-17]

The risk factors for behavioral addictions and dopamine addiction are similar,[6,18] and in both conditions, reduction in dopamine replacement therapies may induce dopamine withdrawal syndrome.[19-21] In the same way, dopamine and behavioral addictions in PD share enhanced ventral striatal release of dopamine attributed to dopamine mesolimbic sensitization substance addictions.[9,16,22,23] Neuropsychiatric fluctuations, which depend, at least in part, on diffuse mesocorticolimbic dopaminergic denervation[21] also depend on mesolimbic sensitization as shown by the increase in ventral striatal dopamine concentrations after L-dopa intake, explaining the stimulant psychotropic effects of L-dopa.[3,24,25] Moreover, associated conditions between neuropsychiatric fluctuations and addictions are similar.[6,26,27] Altogether, a series of observations point to a potential association between neuropsychiatric fluctuations on the one hand and behavioral and dopamine addictions on the other. We investigated this further, using systematic behavioral assessment in a large, prospective sample of surgical candidates.

Materials and Methods

We performed a prospective analysis in a cohort of consecutive PD patients hospitalized for STN-DBS that has already been previously reported on.[15,21] Inclusion criteria were: clinically diagnosed PD, disabling L-dopa-related motor complications, age under 70 years, and the absence of surgical contraindications, dementia, or major ongoing psychiatric illness other than behavioral disorder induced by antiparkinsonian medications. Demographic parameters, disease duration, fluctuations, and dyskinesia onset are shown in Table 1. Individual daily medication dose was calculated as the sum of the L-dopa and dopamine agonists converted into L-dopa equivalent daily dose (LEDD). All patients had an L-dopa challenge for assessment of their motor symptoms using the UPDRS motor score *off* and *on* medication. Improvement in motor scores were calculated. Neuropsychological assessment was performed in chronic *on* drug state by trained psychologists, including evaluation of global cognitive efficiency using the Mattis Dementia Rating Scale (MDRS), neuropsychiatric fluctuations, addiction to dopamine, and behavioral addictions (including ICDs), using the Ardouin Scale of Behavior in PD.[12] This scale encompasses behavioral changes encountered in PD, whether directly related to the disease or induced by dopaminergic treatment. By means of a semistructured clinical interview and specific guidelines, the psychologist estimates the severity of each item on an ordinal scale from 0 (no change) to 4 (severe/frequent symptomatology). *On*-drug euphoria and *off*-drug dysphoria are two items of this scale. For the purpose of this study, clinically relevant neuropsychiatric fluctuations were defined by a score $\geq$3/8 based as used before[15,21] and based on clinician and neuropsychologists experience, who considered this cutoff as clinically relevant. Clinically relevant fluctuations, present either in the *on* and/or the *off* state, were defined with the specific nonmotor *on* and *off* items of the Ardouin scale scoring $\geq$2/4 based on clinician and neuropsychologists experience, who considered this cutoff as clinically relevant.[15] Behavioral addictions were considered when at least one of the following hyperdopaminergic items of the Ardouin scale scored marked to severe (score $\geq$ 3/4): nocturnal hyperactivity, diurnal somnolence, eating behavior, creativity, hobbyism, punding, risk-taking behavior, compulsive shopping, gambling disorder, hypersexuality, and overall excessive motivated behaviors.[12,15] Dopamine addiction was defined by the presence of a score $\geq$2 in the specific item, to be in accord with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV) definition of substance dependence. This lower cutoff for dopamine addiction compared to behavioral addiction was chosen because of the specificity of the drug addiction in PD, where the physician is the drug provider, the patient does not have to spend excessive time to obtain the substance he or she is addicted to, and where the physical dependence is explained by the

TABLE 1. Clinical features of PD patients with presence or absence of neuropsychiatric fluctuations

	Presence of Neuropsychiatric Fluctuations (n = 51)	Absence of Neuropsychiatric Fluctuations (n = 51)	*P* Value
Demographics			
Age (y)	58.1 ± 7.5	58.1 ± 6.4	0.838
Men	43.1%	78.4%	≤0.001
Disease characteristics			
Disease duration (y)	10.8 ± 3.0	10.0 ± 3.1	0.227
Duration of motor fluctuation (y)	5 [4; 7]	4 [3; 6]	0.024
Duration of dyskinesia (y)	4 [3; 5]	3 [2; 5]	0.011
Treatment			
L-dopa therapy duration (y)	9.0 ± 3.8	9.9 ± 3.3	0.217
L-dopa daily doses (mg/d)	947 ± 431	964 ± 407	0.842
Dopamine agonist LEDD (mg/d)	334 ± 376	310 ± 142	0.174
Cumulated LEDD doses (mg/d)	1,282 ± 513	1,274 ± 417	0.932
Dopamine agonist (presence)	94.1% (48)	94.1% (48)	1.000
UPDRS			
UPDRS III *on*	10 [6; 15]	9 [6; 12]	0.369
UPDRS III *off*	36 [32; 49]	35 [29; 40]	0.070
UPDRS III *on-off*	−28.2 ± 9.8	−24.8 ± 8.6	0.072
Dyskinesia duration (per day)	1.73 ± 1.06	1.46 ± 0.86	0.171
Dyskinesia disability	1.22 ± 1.14	1.14 ± 0.88	0.890
Pain related to dyskinesia	1.67 ± 0.77	1.60 ± 0.70	0.835
H & Y *on*	1.93 ± 0.63	1.69 ± 0.67	0.031
H & Y *off*	3.21 ± 0.86	2.50 ± 0.64	≤0.001
MDRS	140 [138; 142]	140 [137; 142]	0.586

Quantitative values are reported as mean ± SD or median [25th; 75th percentile] and qualitative values as frequency in percentage.

biology of the disease and thus cannot be an objective criterion to address addiction. We differentiated isolated dopamine addiction from the full-blown dopamine dysregulation syndrome as initially described by Giovannoni and colleagues, who described the frequent association of behavioral addictions with dopamine dysregulation.[10] A full-blown diagnosis of dopamine dysregulation syndrome was made in the presence of the combination of dopamine addiction with at least one severe behavioral addiction as previously described.[15]

Psychiatric history and any current psychiatric comorbidities were assessed according to DSM-IV criteria using the Mini International Neuropsychiatric Interview (MINI). Past or present anxiety disorder was defined by the presence of at least one of the following diagnoses: panic disorder, agoraphobia, social phobia, post-traumatic stress disorder, or generalized anxiety disorder as defined by the MINI.

Quality of life was evaluated using the 39 items of the disease-specific Parkinson's Disease Questionnaire (PDQ-39), which has eight dimensions with subscores ranging from 0 to 100. Higher scores reflect poorer quality of life. The summary index was also calculated.

The primary objective of our analysis was a comparison of the occurrence of dopamine addiction and behavioral addictions in patients with and without neuropsychiatric fluctuations. We then separately studied the relationship of dopamine and behavioral addictions with the presence of *on*-drug euphoria and *off*-drug dysphoria. Finally, we analyzed quality of life and psychiatric comorbidity in the groups with and without neuropsychiatric fluctuations.

Qualitative parameters were expressed as effectives and percentages, and quantitative parameters as mean ± standard deviation (SD) or median [25th; 75th percentile]. We used parametric methods for variables after testing for normal distribution (Shapiro-Wilk W statistic) to compare the two groups. Comparisons between continuous variables were performed using the Mann-Whitney U test or the Student *t* test, when appropriate, according to normal distribution of data. Differences in categorical variables were assessed using the χ^2 test or Fisher's exact test, when appropriate. Relationships between both addictions and neuropsychiatric fluctuations were analyzed in two multivariate models using a logistic regression including significant variables found in the univariate analysis. *On* and *off* neuropsychiatric fluctuations relationships with addictions were post-hoc analyses. Statistical analyses were performed with STATA software (release 13; StataCorp LP, College Station, TX).

This study was approved by the ethics committee of Grenoble University and all patients gave informed, written consent.

Results

A total of 102 patients met the inclusion criteria (mean age: 58.1 ± 7.0 years; men, 60.8%) including

TABLE 2. Occurrence of dopamine addiction, behavioral addictions, or both depending on presence or absence of neuropsychiatric fluctuations

	Univariate Analysis			Multivariate Analysis	
	Presence of Neuropsychiatric Fluctuations (n = 51)	Absence of Neuropsychiatric Fluctuations (n = 51)	*P* Value[a]	OR [95% CI]	*P* Value[b]
Dopamine treatment addiction	21.6% (11)	5.9% (3)	0.021	8.9 [1.4; 56.2]	0.020
Behavioral addictions	31.4% (16)	19.6% (10)	0.173	3.76 [1.11; 12.75]	0.033
Dopamine dysregulation syndrome	9.8% (5)	0.0% (0)	0.056		

Values in percentage and effectives (n).
[a]Chi^2 or Fisher's test.
[b]Multivariate analysis after logistic regression including the following variables: sex, H & Y *on* and *off* stage, dyskinesia and fluctuation duration, and neuropsychiatric fluctuations. CI, confidence interval.

51 patients with and 51 without neuropsychiatric fluctuations. General characteristics are shown in Table 1.

The proportion of female patients, years of presence of motor complications (both motor fluctuations and dyskinesia), and H & Y stage (both in *off* and *on* drug conditions) were significantly higher in the neuropsychiatric fluctuation group and were subsequently included as controlled variables in a multivariate model. Disease duration, UPDRS III *on* and *off* scores did not differ significantly between groups. There was a trend to more severe motor *off* states according to UPDRS ($P = 0.07$) and for the amplitude of the L-dopa response (UPDRS *on-off*; $P = 0.072$). LEDDs and duration of treatment were the same in both groups.

Dopamine addiction was more frequent in the neuropsychiatric fluctuation group than in the group without neuropsychiatric fluctuations (21.6% vs. 5.9%; $P = 0.02$). This association persisted in the multivariate model, which included the following variables: sex, H & Y *on* and *off* stage, dyskinesia, and fluctuation duration (odds ratio [OR]: 8.9 [1.4; 56.2]; $P = 0.02$).

Behavioral addictions were more frequent in the neuropsychiatric fluctuation group (31.4% vs. 19.6%), and this difference was significant in the multivariate analysis (OR, 3.76 [1.11; 12.75]; $P = 0.033$).

A full-blown dopamine dysregulation syndrome was observed only in patients with neuropsychiatric fluctuations, with merely a trend for significance given the small number of patients involved (5 vs. 0; $P = 0.056$; Table 2). Potential confounding variables included in multivariate analyses are shown in Table 3.

Of the 37 patients who presented *on*-drug euphoria, 17 (46%) presented with at least one behavioral addiction, compared to 9 of 65 (13.9%) in the group without *on*-drug euphoria ($P < 0.001$). Dopamine addictions were also more frequent in the *on*-drug euphoria group (27% vs. 6.2%; $P = 0.003$). Nine of the 46 patients with *off*-drug dysphoria had a dopamine addiction (19.6%), compared to 5 of 56 (8.9%) patients in the group without *off*-drug dysphoria ($P = 0.12$) and 12 of 46 (26.1%) with versus 14 of 56 (25%) without *off*-drug dysphoria had behavioral addictions respectively ($P = 0.9$; Fig. 1A,B).

Past occurrence of anxiety disorder was more frequent in the neuropsychiatric fluctuation group (37.3% vs. 15.7%; $P = 0.014$), whereas occurrence of previous depressive disorder did not differ between groups (21.6% vs. 23.5%; $P = 0.813$), nor was there any difference regarding other psychiatric comorbidities. Current anxiety did not differ significantly between the two groups (17.7 % vs. 5.9%; $P = 0.065$).

The PDQ-39 summary index score was higher in the neuropsychiatric fluctuation group (7 [6;9] vs. 6 [4;8]; $P = 0.005$), with significantly higher subscores (reflecting poorer quality), for mobility, emotional well-being, and stigma (Fig. 2).

TABLE 3. Multivariate analyses including significant variables associated with dopamine treatment and behavioral addictions

	Dopamine Addiction		Behavioral Addictions	
	OR [95% CI]	*P* Value[a]	OR [95% CI]	*P* Value[a]
Male sex	0.39 [0.14; 1.08]	0.069	0.33 [0.12; 0.91]	0.033
Motor fluctuation duration	0.96 [0.75; 1.23]	0.725	0.94 [0.75; 1.18]	0.586
Dyskinesia duration	1.28 [0.93; 1.75]	0.127	1.30 [0.95; 1.77]	0.101
H & Y *on*	1.55 [0.68; 3.51]	0.293	1.26 [0.59; 2.73]	0.551
H & Y *off*	2.59 [1.13; 5.97]	0.025	2.78 [1.25; 6.18]	0.012

OR [95% CI], odds ratio with 95% confidence interval.
[a]*P* value after logistic regression for potential confounding variables.

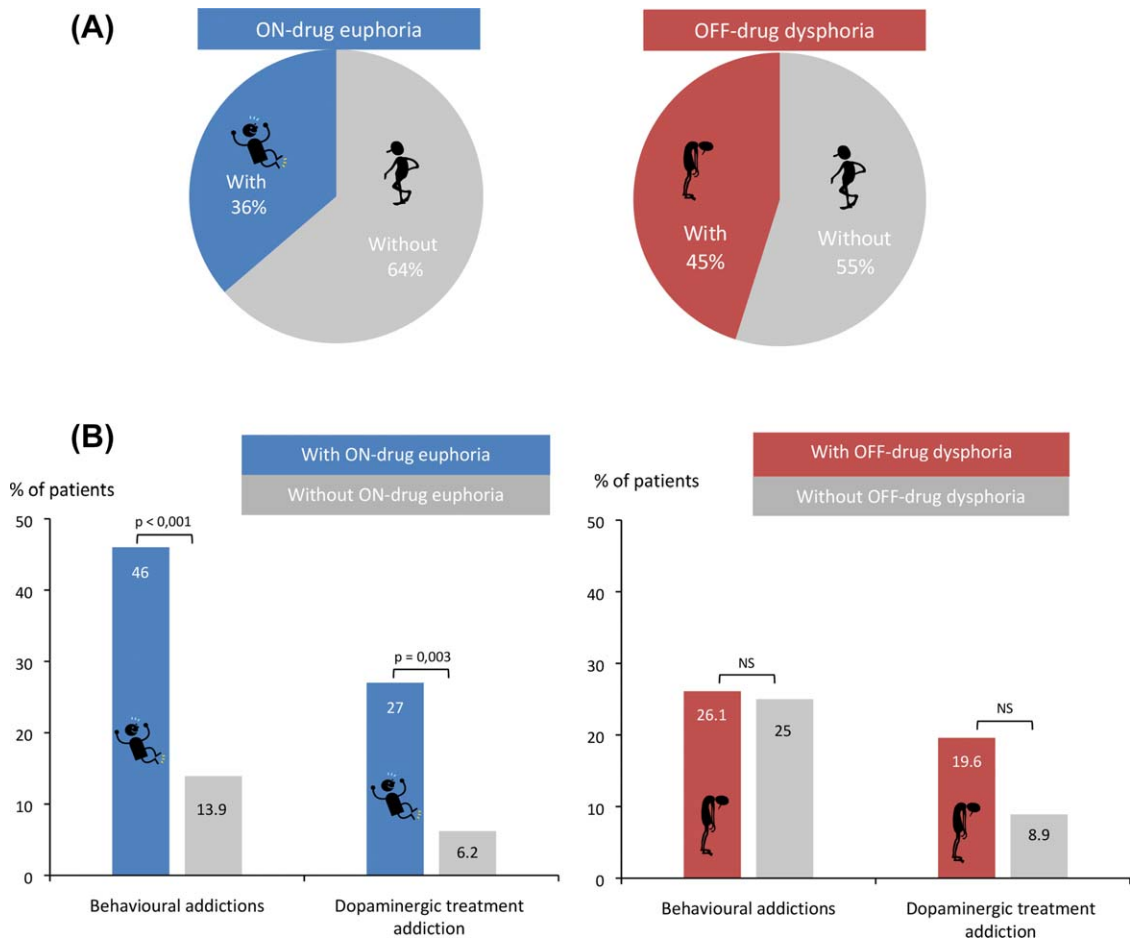

FIG. 1. (A) Frequency of *on*- and *off*-drug neuropsychiatric fluctuations. (B) Relationship between *on*-drug euphoria/*off*-drug dysphoria and addictions. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

In a population of surgical candidates, half of the patients had neuropsychiatric fluctuations. There was no difference between the groups with and without neuropsychiatric fluctuations in terms of motor sign severity in *on*- and *off*-drug conditions as measured by the UPDRS, duration of dopaminergic treatment, or of L-dopa or dopamine agonist daily dosage. In the univariate analysis, patients with neuropsychiatric fluctuations were more frequently female, had a longer presence in years of motor complications (both fluctuations and dyskinesia), and were at higher H & Y stages in both *on*- and *off*-drug conditions. Only the H & Y stage in the *off* condition was higher in the group with neuropsychiatric fluctuations after controlling for multiple comparisons. We show a strong association between neuropsychiatric fluctuations on the one hand and behavioral addictions and dopamine addiction on the other. Importantly, behavioral and

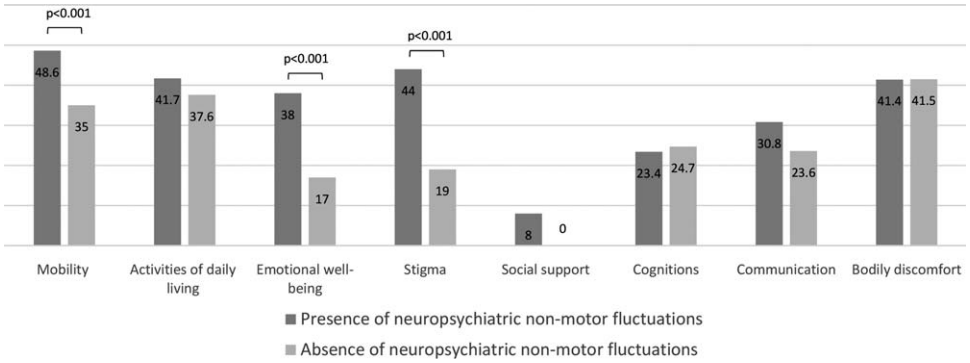

FIG. 2. Impact of neuropsychiatric fluctuations on subscores of quality of life as assessed by the PDQ-39.

dopamine addictions were more frequent in the presence of *on*-drug euphoria, but not *off*-drug dysphoria.

Several pathophysiological mechanisms, which are not mutually exclusive but rather interact, have been found to explain behavioral and/or substance addictions in PD. They include, among others: (1) a selective mesolimbic D3 receptor stimulation[28]; (2) the pulsatile administration of dopamine replacement treatments, resulting in rapid increase in synaptic dopamine concentrations in the mesolimbic dopamine synapse in the nucleus accumbens[29]; and (3) the presence of diffuse midbrain dopamine neurodegeneration of the SNpc and the ventral tegmental area.[30-32] This last point means that with progression of the disease, the same dose of L-dopa would induce increasing psychostimulant effects. Imaging studies have shown that the brain structures involved in substance addiction are also involved in behavioral addictions, with increased activation of bottom-up appetitive drive areas and inhibition of prefrontal cortical areas involved in top-down behavioral control.[33] Similarly, neuroimaging studies of PD patients with ICDs showed lower level of dopamine transporters in the ventral striatum,[34] suggesting a mesocorticolimbic dopamine loss on top of the nigrostriatal degeneration.

The presence of *on*-drug euphoria was specifically associated with both dopamine and behavioral addictions. The compulsive-addictive behavior of ICDs thus seems to be initially driven by pleasure seeking (or positive reinforcement) and not by harm avoidance, as is the case also for substance addiction in nonparkinsonian patients.[35]

Mesocorticolimbic sensitization could be seen as the common link between addictions and *on*-drug euphoria. In PD, imaging studies found a greater release of dopamine in the ventral striatum in PD patients suffering from dopamine dysregulation syndrome after L-dopa intake, arguing for a specifically enhanced activation of the reward circuitry in drug addictions.[7] A selective increase of ventral striatal dopamine release in PD patients with ICDs was found in an imaging study.[36] This sensitization, also demonstrated in other substance addictions,[8,23] leads to phasic firing of mesolimbic dopamine neurons in response to salient stimuli.[37] It has been proposed that compulsive misuse of dopaminergic drugs may be driven by a desire to avoid the unpleasant *off*-drug dysphoria expressed as a withdrawal state.[20] Our findings suggest, on the contrary, a link with the pleasurable psychotropic effects of dopaminergic treatment experienced in the *on*-drug state.[4,25]

Full-blown dopamine dysregulation syndrome was encountered in 5 cases, all within the neuropsychiatric fluctuation group. All patients had both *on*-drug euphoria and *off*-drug dysphoria. This point suggests that these patients could have a lower hedonic baseline threshold, represented by their *off*-drug neuropsychiatric state. This reinforces the concept of a hedonic homeostatic dysregulation occurring in an advanced stage of drug addictions, which led to the denomination of dopamine dysregulation syndrome in PD.[10,20,35] The sensitization of the more severely affected mesocorticolimbic pathway could be the key driving force underlying both dopamine and behavioral addictions.[8,9,38]

The presence of neuropsychiatric fluctuations, and particularly *on*-euphoria, should raise vigilance of the neurologist and call for active screening of behavioral and dopamine addictions. *On*-euphoria is not a complaint of the patient. However, if we conceptualize *on*-euphoria as an early clinical expression of ongoing behavioral sensitization, early detection and integration into therapeutic decisions might be useful in the prevention of addictive behaviors in PD.

Anxious and depressive symptoms, which are the most common mood fluctuation symptoms, characterize *off*-drug neuropsychiatric states. A previous study showed that depressive patients were more at risk of developing neuropsychiatric fluctuations.[27] A past history of depression is, moreover, encountered more frequently in dopamine addicts[39] and ICD patients.[26] We observed an association between a past history of anxiety and neuropsychiatric fluctuations. Anxiety can be an early sign of PD, predisposing to rapid development of more severe fluctuations with the introduction of dopaminergic treatment.[40]

Neuropsychiatric fluctuations had a significant negative impact on quality of life as evaluated by the PDQ-39 summary index. Nonmotor symptoms are known to worsen quality of life more than motor symptoms.[41] We have shown here that fluctuations in neuropsychiatric nonmotor symptoms can also specifically alter quality of life. The domains of well-being, stigma, and, more surprisingly, of mobility (but not objective evaluation of parkinsonism using UPDRS III) were significantly altered by the presence of neuropsychiatric fluctuations. Different thresholds for objective motor and subjective nonmotor *off*-period symptoms could explain this apparent paradox, which might be related to the cognitive apathy frequently associated with *off*-drug dysphoria. This hypothesis is corroborated by the recent finding of subjective worsening in mobility in a patient group with apathy who actually had an objective improvement in UPDRS motor scores.[42]

Although dealing with comprehensive assessment in a large, prospective sample, the number of addictions per group was relatively limited. In order to reach enough statistical power, all behavioral addictions were grouped, even if they do not necessarily all share exactly the same underlying mechanisms. Indeed, punding seems triggered more by D1/D2 receptor stimulation and is more often encountered in dementia.[28] However, it clearly shares common clinical aspects with hyperdopaminergic behaviors and, as other impulse control

disorders (ICDs), can be reversible reducing dopaminergic medication.[43] This is also the case of diurnal somnolence, which does not correspond to a behavioral addiction, but very frequently indirectly reflects excessive nocturnal activities leading to chronic lack of sleep explaining a narcolepsy-like clinical picture. These two behavioral changes loaded with ICDs in an Ardouin scale validation study.[12] Even if validated in PD, the choice of Ardouin scale, that "simply" opposes hypo- and hyperdopaminergic behaviors, can be discussed. The more recently constructed tools, that is, the Questionnaire of Impulsive Control Disorders in PD Rating Scale[44] and the Parkinson's Impulse-Control Scale,[45] however, do not assess the whole array of behavioral modifications in PD, as is the case with the Ardouin scale. The study population was restricted to surgical candidates. It has indeed been shown that behavioral complications of dopaminergic treatment are more frequent in this surgical candidates as compared to the general PD population.[46] Nevertheless, the surgical candidates with a relatively pure idiopathic PD and absence of dementia can be considered a good model to study pathophysiological mechanisms.

Our study aimed to provide evidence of the complex interactions between neuropsychiatric fluctuations induced by dopaminergic treatments and behavioral modifications in advanced PD. We found that both dopamine and behavioral addictions were associated with neuropsychiatric fluctuations, and particularly with the presence of *on*-drug euphoria, which is related to the well-known psychostimulant effects of dopaminergic treatments. The sensitization of the mesolimbic dopaminergic pathways as their common underlying mechanism needs to be confirmed by further studies. ■

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