Prevalence and Pharmacological Factors Associated With Impulse-Control Disorder Symptoms in Patients With Parkinson Disease

Santiago Perez-Lloret, MD, PhD,† María Verónica Rey, PharmD,*† Nelly Fabre, MD,‡ Fabienne Ory, MD,‡ Umberto Spampinato, MD, PhD,§ Christine Brefel-Courbon, MD,‡ Jean-Louis Montastruc, MD, PhD,*|| and Olivier Rascol, MD, PhD*†*

Background: Impulse-control disorders (ICDs) occur in patients with Parkinson disease (PD), especially in younger patients on dopamine therapies.

Objective: To assess the prevalence of ICD symptoms and its pharmacological correlations in a sample of French patients with PD and without PD (poststroke).

Methods: Outpatients with PD and without PD (poststroke) were screened for compulsive behaviors related to hypersexuality, compulsive shopping, pathological gambling, or compulsive eating by means of the Questionnaire for Impulse-Control Disorders—short version. Full medical history and Unified Parkinson's Disease Rating Scale scores were also recorded. Dose of dopamine agonists were converted to defined daily doses (DDDs), according to the World Health Organization Anatomical Therapeutic Chemical classification system classification system.

Results: Two hundred three patients with PD and 52 patients without PD were recruited (mean ± SD age, 67 ± 1 vs 69 ± 2, $P = 0.4$; males: 62% vs 55% $P = 0.2$). Symptoms of ICDs were reported by 0% of poststroke patients and 25% of the patients with PD ($P < 0.001$). Hypersexuality was reported by 10% of the patients with PD, compulsive shopping by 6%, pathological gambling by 3%, and compulsive eating by 14%. A logistic regression analysis found that age younger than 68 years (odds ratio [OR], 3.3; 95% confidence interval, 1.6–6.6) and exposure to dopamine agonists (OR, 20.3; 95% confidence interval, 2.7–65.0) or monoaminooxidase-B inhibitor (OR, 3.7; 95% confidence interval, 1.1–12.6) were significant factors associated with increased ICD frequency. Patients with ICD symptoms were exposed to higher dopamine doses than those without them (1.6 ± 0.1 vs 1.0 ± 0.1 daily-defined doses; $P < 0.001$). A dose-response pharmacodynamic model disclosed a significant nonlinear dose-response relationship between dopamine agonists and frequency of ICD symptoms ($P < 0.01$).

Conclusions: Impulse-control disorder symptoms were more frequent in the patients with PD than in the poststroke patients with PD. Impulse-control disorder symptoms were related to younger age and exposure to monoaminooxidase-B inhibitors, and showed a nonlinear dose-response relationship with dopamine agonists.

Key Words: Parkinson disease, impulse-control disorders, dopamine agonists, monoaminooxidase-B inhibitors, amantadine

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Impulse-control disorders (ICDs) are characterized by a failure to resist an impulse, drive, or temptation to perform a typically pleasurable activity that is ultimately harmful to the person or to others owing to its excessive nature.[1] Hypersexuality, compulsive shopping, pathological gambling, and compulsive eating are considered the most frequent ICDs in PD, globally affecting 8% to 15% of patients.[1–4] Treatment with a dopamine agonist has been consistently correlated with ICD, although levodopa therapy, younger age, personal traits, treatment with drugs such as amantadine or disturbed decision-making abilities, and psychiatric and cognitive impairments are also considered as risk factors.[3–7] Impulse-control disorders can be psychosocially devastating (with one study reporting losses of $100,000 because of pathological gambling[8]) and frequently generate important legal problems for the patients and their families, treating physicians, as well as for drug manufacturers.

We have recently conducted an exploratory survey aimed at comparing the rate of any adverse event to antiparkinsonian medications reported spontaneously by patients with PD or collected in the same patients by a physician using a systematic questionnaire.[9] As a part of this study, we had the opportunity to assess ICD symptoms. Therefore, we report herein the prevalence and pharmacological factors related to ICD symptoms in this sample of patients.

MATERIALS AND METHODS

Study Population

Consecutive patients with PD fulfilling United Kingdom PD Society Brain Bank criteria[10] for idiopathic PD were recruited. Patients with a Mini Mental State Examination score of less than 24 or with surgical intervention for PD treatment were excluded. Age- and sex-matched ambulatory cognitively intact nonaphasic patients without PD who had recovered from a stroke were also recruited from the outpatient clinic of the same neurological departments.

This study was approved by the local ethical committee. Informed consent was obtained from all patients before inclusion in the study.

Procedures

Screening for current ICD symptoms was conducted by means of the short version of the Questionnaire for Impulsive-Compulsive

*Laboratoire de Pharmacologie Médicale et Clinique, Faculté de Médecine, Toulouse, France; †INSERM Centre d'Investigation Clinique CIC 9203, Toulouse, France; ‡Services de Neurologie, CHU Toulouse, France; §Department of Neurology, CHU Bordeaux, France; and ||INSERM U 1027 Equipe de PharmacoEpidémiologie, Toulouse, France.

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Address correspondence and reprint requests to Santiago Perez-Lloret, MD, PhD, Department of Clinical Pharmacology, Faculty of Medicine, 37 Allées Jules Guesde, 31000, Toulouse, France; E-mail: splloret@fleni.org.ar

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Disorders in Parkinson's disease (QUIP-s).[11] Self-report questionnaires were administered to patients by one of the investigators, and they were asked to answer all questions by themselves, with the help of caregivers when possible.

All medications taken by the patients were recorded and codified according to the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system.[12] Levodopa equivalent daily dose (LDED) was calculated by the usual formula.[9] Doses of dopamine agonists were further converted to defined daily dose (DDD) according to the WHO-ATC classification system[12] to allow for comparisons. Defined daily doses were obtained by dividing the real agonist dose for each patient by a predefined dose, considered as the standard daily dose for each agonist.

In the group of patients with PD, parkinsonian symptoms were evaluated by means of the Unified Parkinson's Disease Rating Scale (UPDRS) parts I to IV.[9] All patients with PD were assessed in the *on* condition.

Statistical Analysis

A power analysis made with G*Power 3.1.3 software[13] found that 200 patients would allow prevalence estimations of ICD symptoms with a 3% precision, assuming prevalence estimates of up to 25%. It was calculated that 50 controls would be needed to detect up to 10% differences in prevalence of symptoms. Finally, 200 patients with PD would be enough for the detection of odds ratio of 2.5 or more when analyzing factors related to ICD symptoms.

Unpaired *t* test or the χ^2 test was used for comparing numerical or categorical variables between the patients with PD with or without ICDs. Forward logistic regression was used to identify independent factors related to ICDs. The independent variables tested were age; sex; UPDRS I, II, or III scores; PD duration, or exposure to antiparkinsonian or concomitant drugs. The model's goodness of fit was explored by using the Hosmer and Lemeshow test. Potential interactions and multicolinearity were found to be absent. Numerical independent variables were dichotomized to their median values to facilitate results interpretation. Only variables attaining significance level in the bivariate comparisons were included in the multivariate models.

Agonist doses expressed in DDDs were compared between subjects with or without ICD symptoms by a *t* test. Afterward, a logistic pharmacodynamic model for binary responses[14] was used to quantify the relationship between agonist doses and probability of ICD symptoms. According to this model, the probability of response $p(R)$ can be obtained by solving the following equation,

$$\mathrm{p(R)} = \frac{1}{1 + \mathrm{e}^{-(\beta_0 + \beta_1 * x + \beta_2 * \mathrm{c} + \ldots)}},$$

where x = drug dose and c = covariates.

In this case, p(R) represents the probability of manifesting at least 1 ICD symptom. Four models were considered. In the first one, exposure to dopamine agonists was considered, irrespective of dose. In the second and third models, agonist dose was considered in DDD tertiles, which were compared to the reference category (ie, no dopamine agonist exposure). No assumptions were made regarding the nature of the dose-response relationship in the second model, whereas such relationship was assumed to be linear in the third one. These are hierarchical models, and thus they were compared by a likelihood ratio test.

The concordance statistic (*c* statistic), which is equivalent to the area under the receiver operating characteristic curve,[15] was used to assess the discriminative accuracy of the finally retained model.[16] The *c* statistic ranges from 0 to 1, with 1 indicating a perfect prediction and 0.5 indicating a chance prediction. It has been suggested that *c* statistics of 0.7 to 0.8 could be considered acceptable and those of 0.8 to 0.9 could be considered excellent.

All statistical tests were performed with SPSS version 18 (IBM, Chicago, Ill).

RESULTS

A total of 203 outpatients with PD and 52 poststroke outpatients were included in the study. The patients with PD and the poststroke patients had similar age (67 ± 1 vs 69 ± 2, $P = 0.4$) and sex (males: 62% vs 54%, $P = 0.2$). The patients with PD had a mean ± SEM duration of 9 ± 1 years, mean±SEM UPDRS II+ III ON score of 37.2 ± 1.4, mean ± SEM LDED of 1188 ± 88 mg/d, and 41% had dyskinesias. Sixty-nine percent of the patients with PD received levodopa in combination with a dopamine agonist, whereas 11% received a dopamine agonist without levodopa and 18% levodopa without an agonist. Eight percent of the patients with PD were on monoaminooxidase-B (MAO-B) inhibitors (selegiline, 13 patients; rasagiline, 4 patients), 23% on entacapone and 15% on amantadine. None of the patients was on monotherapy with MAO-B or amantadine. Mean SEM daily dose of dopamine agonists were as follows: bromocriptine, 50 ± 7 mg (n = 13); ropinirole, 13 ± 1 mg (n = 68); pramipexole, 2.2 ± 0.2 mg (n = 40); apomorphine, 60 ± 1 mg (n = 22); and piribedil, 152 ± 11 mg (n = 29). Only one patient was on pergolide at a dose of 9 mg. Mean SEM LDED was 1188 ± 88 mg/d. No poststroke patient received any antiparkinsonian dopaminergic medications.

Whereas none of the poststroke patients disclosed any ICD symptom, 52 patients (25%) with PD disclosed at least one such symptom, of whom 5% disclosed more than one ICD (Table 1). As shown in Table 2, independent factors associated with the presence of ICD symptoms as assessed by multivariate logistic regression were younger age or exposure to dopamine agonists or MAO-B inhibitors. The frequency of patients with at least 1 ICD among those exposed to levodopa alone (n = 37), dopamine agonists alone (n = 22) or levodopa+agonist (n = 129) or levodopa + agonist + MAO-B inhibitors (n = 12) was 0%, 23%, or 32% or 50%, respectively ($P < 0.001$). None of the patients with PD were on monotherapy with MAO-B inhibitors.

The relationship of individual dopamine agonists and ICD frequency was explored by logistic regression. Odds ratios (95% confidence intervals) for each agonist, adjusting for

TABLE 1. Prevalence of ICDs in PD Patients (n = 203) and Poststroke Patients (n = 52)

	n (%)	95% CI (%)
At least 1 ICD in poststroke patients	0 (0)	—
At least 1 ICD in patients with PD	52 (25)	19.5–31.7
Hypersexuality	20 (10)	5.7–13.9
Compulsive shopping	13 (6)	3.0–9.8
Pathological gambling	5 (3)	0.3–4.6
Compulsive eating	28 (14)	9.0–18.6
Number of ICDs per patients with PD		
1	41 (20)	14.6–25.8
2	8 (4)	1.2–6.7
3	3 (1)	0.0–3.2

95% CI, 95% confidence intervals.

TABLE 2. Factors Related to ICDs in PD Patients

	No ICDs (n = 151)	At Least 1 ICD (n = 52)	Adjusted OR (95% CI)
Age <68 yrs	83 (56%)	14 (26%)†	3.31 (1.65–6.61)
Males	86 (59%)	38 (70%)	
PD duration	8.8±0.5	9.4±0.7	
UPDRS I >3	51 (34%)	17 (32%)	
UPDRS II >12	77 (52%)	23 (44%)	
UPDRS III >23	78 (52%)	18 (36%)*	—
Dyskinesias	59 (40%)	24 (44%)	
Wearing-off	53 (36%)	27 (50%)*	—
Antimuscarinics	10 (7%)	2 (4%)	
Levodopa	130 (87%)	48 (89%)	
Agonists	109 (73%)	52 (100%)†	20.3 (2.70–65.01)
MAO-B inhibitors	9 (6%)	8 (15%)*	3.74 (1.11–12.64)
Entacapone	33 (22%)	14 (26%)	
LDED ≥1050 mg/d	63 (42%)	34 (63%)†	—
Amantadine	7 (5%)	2 (4%)	
Benzodiazepines	19 (13%)	9 (17%)	
Hypnotics	37 (25%)	13 (24%)	
Antidepressants	7 (5%)	2 (4%)	
Opioids	4 (3%)	2 (4%)	

The following variables were entered in the multivariate logistic regression in a stepwise fashion according to their level of significance: age, presence of wearing-off, exposure to dopamine agonists or MAO-B inhibitors and LDED. Odds ratios are shown for those retained in the final model. Entering LDED as a continuous variable did not change the results.

*$P<0.05$.

†$P<0.01$ versus patients without any ICD (t test or χ^2 test).

age and exposure to MAO-B inhibitors, were as follows: bromocriptine, 6.05 (1.34–27.30); ropinirole, 6.02 (2.04–17.75); pramipexole, 5.82 (1.81–18.73); apomorphine, 1.87 (0.64–5.50); and piribedil, 2.18 (0.56–8.53).

Mean SEM dopamine agonist was 1.17 ± 0.08 DDD (range, 0–4.5). Such dose was significantly higher in patients manifesting ICD symptoms compared to those not manifesting them (1.61 ± 0.14 vs 1.02 ± 0.09, $P < 0.001$). In Figure 1, the frequency of ICD symptoms in subjects exposed to increasing dopamine agonists doses are shown. The model, which considered exposure to agonists in a dose-response fashion, offered a better fit compared to the one considering raw exposure not taking the dose in consideration (log-likelihood = −184.4 vs −203.17, respectively; $\chi^2 = 37.4$, $P < 0.001$). In turn, the model making no assumptions regarding the nature of dose-response relationship offered a better fit compared to the one assuming a linear relationship (log-likelihood = −184.4 vs −192.04, respectively; $\chi^2 = 15.2$, $P<0.001$).

DISCUSSION

This is one of the first times that the prevalence of ICD symptoms was estimated in a population of French patients with PD attending an outpatient movement disorders clinic. The present survey had the advantage of including a control group to rule out the influence of confounding factors unrelated to PD, such as cultural or environmental ones. Poststroke patients were selected as controls because they were similar in age and were treated in the same neurology departments as the patients with PD, thus minimizing potential selection bias.

The sample size was calculated to detect factors strongly related to ICDs (ie, odds ratios >2.5), but the power of the study was insufficient to detect milder correlations. Additionally, this survey was centered on pharmacological factors potentially related to ICDs, whereas others, such as psychiatric and cognitive impairments, substances abuse, or familial ICD history, have not been explored. Finally, we only screened for ICD symptoms by using QUIP-s questionnaire, but it should be noted that this questionnaire proved to have good clinimetric properties, with sensitivity and specificity values between 85% and 100% for all explored ICDs.[11]

We observed that 25% of the French patients with PD reported at least one symptom of ICD versus none of the poststroke patients. Global prevalence of ICDs observed in our PD sample was unexpectedly high compared to previous studies. For example, Weintraub et al[3] found a prevalence of approximately 14% in a survey conducted in North America. In France,

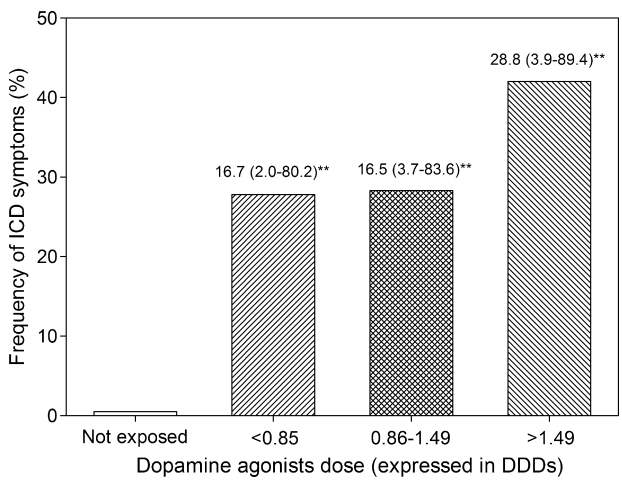

FIGURE 1. Frequency of ICD symptoms in subjects exposed to increasing dopamine agonists dose compared to subjects not exposed to them. Defined daily doses of dopamine agonists were categorized according to tertiles. A logistic regression pharmacodynamic model disclosed a significant nonlinear dose-response relationship. Odds ratio (95% confidence interval) for each dose tertile are shown.

a survey using the South Oaks Gambling Screen and the Hypersexuality questionnaire showed a prevalence of pathological gambling or hypersexuality of 12% and 3%, respectively.[17] It is possible that the use of more stringent criteria than the QUIP-s questionnaire would have resulted in lower number or that patients attending specialized movement disorders clinic might be at greater risk than the general population of patients with PD. It is, however, interesting to note that the prevalence estimates of hypersexuality, compulsive shopping, or pathological gambling observed in our population fell within the range of what has been previously reported in other studies (ie, 2%–10%, 1%–6%, or 2%–6%, respectively).[1,3] Conversely, compulsive eating turned out to be much more frequently reported than in other surveys (14% vs 4%).[1,3] This might be related to cultural differences, with patients and investigators paying more interest toward food in France than in other countries. The influence of cultural differences in expressing and reporting ICD might deserve further investigations.

As expected and previously reported, ICD symptoms were more frequent in patients with PD receiving a dopamine agonist.[1,3] In our study, all the dopamine agonists were related to an increased frequency of ICDs, thus further supporting a class effect.[3,4] In an attempt to explore a potential dose-response relationship between dopamine agonists and ICD, we expressed the daily doses of the different agonists in equivalent terms, using the DDDs as defined by WHO-ATC.[12] This approach may be a good candidate to allow for dopamine agonist dose comparison, as DDDs represent recommended doses. We observed that subjects manifesting ICD symptoms were exposed to significantly higher doses of dopamine agonists. Furthermore, a significant nonlinear dose-response relationship was revealed by a logistic pharmacodynamic model, which is in line with empirical experience, indicating that dose reductions may help manage ICDs.[18] When considered superficially, our results seem at odds with those of the DOMINION study, which did not show a dose-response relationship between ICDs and dopamine agonists.[3] Nonetheless, a closer look reveals that authors based their analysis only on the subgroup of patients exposed to agonists and did not use the same pharmacodynamic model as ours, which may explain why they were not able to observe such a relationship. Our findings can only be considered as exploratory owing to the limited numbers. Nevertheless, they support further exploring the role of dopamine agonist dose in relationship with the risk of ICD, a question of practical importance for the management of the patients.

Interestingly, we also found that exposure to MAO-B inhibitors was correlated with an increased frequency of ICDs in patients with PD. Monoaminooxidase-B inhibitors have been seldom connected to ICDs in the past, mainly as isolated case reports.[4] Nonetheless, such a correlation is not entirely unexpected because MAO-B inhibitors are known to increase central dopaminergic tone.[19] Additionally, selegiline has a methamphetaminic metabolite that could also contribute to the development of addictive behaviors.[19] The use of levodopa has been previously connected with ICDs.[3] In our study, the frequency of ICDs in subjects exposed only to levodopa was lower than in those on dopamine agonists monotherapy, which in turn was lower than in those exposed to levodopa+agonists. This finding is in line with previous findings[3] and further suggests that proper attention should be paid to the contribution of drug-drug interactions between dopaminergic agents in the genesis of ICDs and not only to dopamine agonist exposure.

In our study, we did not detect a greater risk of ICD in patients on amantadine. This is in contrast with a previous survey[6] and a recent case report[20] and could be due to a lack of power of our survey. However, amantadine has also been recently reported to improve pathological gambling in a double-blind placebo-controlled crossover study conducted in patients with PD.[21] Patients with PD are frequently treated with amantadine to improve dyskinesias because this is the only symptomatic antidyskinetic medication currently available for PD.[22] Younger age and dopaminergic medications are known to increase the risk of dyskinesias,[23] and common mechanisms have been speculated between dyskinesias and ICDs.[24] However, we did not find any correlation between the presence of dyskinesia and ICD in our survey. Further studies are then needed to better understand the putative relationships between the use of amantadine and the risk of ICD.

In summary, this French survey confirms that symptoms of ICDs were significantly more frequently disclosed by patients with PD than those without PD (poststroke). Compulsive eating was the single ICD most frequently reported in this series and with a greater rate than in previous surveys conducted in different countries. The present results confirm younger age and exposure to dopamine agonists in a nonlinear dose-response fashion as important factors related to occurrence of ICD symptoms and suggest a role for MAO-B inhibitors.

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