Dopamine Agonist Use is Associated with Impulse Control Disorders in Parkinson's Disease

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Abstract

Objective—To determine the frequency and correlates of impulse control disorders (ICDs) in Parkinson's disease (PD).

Design—An unstructured screening interview for ICDs (compulsive gambling, buying, and sexual behavior) followed by a telephone-administered structured interview for screen-positive patients.

Setting—Two university-affiliated movement disorders centers.

Participants—A convenience sample of 272 patients with idiopathic PD who were screened for psychiatric complications.

Main Outcome Measures—Presence of compulsive gambling, buying, or sexual behavior as assessed by the Minnesota Impulsive Disorders Interview.

Results—Eighteen (6.6%) PD patients met criteria for an ICD at some point during the course of PD, including 11 (4.0%) with an active ICD. Compulsive gambling and compulsive sexual behavior were equally common. In a multivariate model, treatment with a dopamine agonist ($P = .01$) and a history of ICD symptomatology prior to PD onset ($P = .02$) predicted current ICD. There were no differences between the dopamine agonists in their association with ICDs ($P = .21$), and daily doses of dopamine agonists were higher in patients with an ICD than in dopamine agonist-treated patients without an ICD ($P < .001$).

Conclusions—PD patients treated with a dopamine agonist should be made aware of the risk of developing an ICD and monitored clinically. As dopamine agonists are increasing being used for other indications, future research should assess the dopamine agonist-associated risk for ICDs in other populations.

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INTRODUCTION

Recent observational studies suggest that impulse control disorders (ICDs), particularly pathological gambling, may have increased frequency in Parkinson's disease (PD) (1–3). ICDs constitute a group of psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)(4), their essential feature being a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. Other ICDs without formal diagnostic criteria in DSM-IV-TR include compulsive sexual behavior and compulsive buying(5).

Although there are case reports of levodopa-induced ICDs in PD(6), recent case series have implicated treatment with dopamine agonists as a more frequent cause of pathological gambling. Driver-Dunckley et al.(2) identified 9 patients (0.5% of clinic sample) with a documentation of pathological gambling, 8 of whom were treated with pramipexole and 1 with pergolide. In another case series, all 11 PD patients identified as meeting DSM-IV criteria for pathological gambling were taking a dopamine agonist, 9 of whom were on pramipexole and 2 on ropinirole(3).

Regarding other ICDs in PD, in a series of 15 patients with either PD or multiple system atrophy and compulsive hypersexuality, dopamine agonist treatment was implicated as the cause of the behavior in 14 cases(7). There have also been anecdotal reports of compulsive buying in association with dopamine replacement therapies(8).

We report the results of a screening and assessment study of ICDs in PD investigating the: (1) the frequencies of compulsive buying, gambling, and sexual behaviors; (2) demographic and clinical correlates of aforementioned ICDs; and (3) association between ICDs and dopamine agonist use. We hypothesized that ICDs in PD are associated with dopamine agonist treatment, and that this association is dose-dependent and similar across the entire class of dopamine agonists.

METHODS

Participants

The study population was outpatients diagnosed with idiopathic PD, predominantly of mild to moderate severity, confirmed by a movement disorders specialist. Subjects were established patients at one of two movement disorders centers (either the University of Pennsylvania or the Philadelphia Veterans Affairs Medical Center [VAMC]) and were thought to represent a cross-section of the clinics' populations, save the exclusion of patients unable to provide informed consent due to cognitive impairment. Participants completed a psychiatric screening interview as part of a study of the frequency and correlates of depression in PD. The Institutional Review Boards at the two institutions approved the study, and written informed consent was obtained from all subjects.

Data Collection and Measures

Patients were screened between July 2004 and June 2005. Movement disorders clinicians were instructed to refer any willing PD patient, without regard for their psychiatric status (e.g., no patient was referred for having an ICD), for the screening interview at the conclusion of his or her clinic appointment.

Two trained research assistants administered the screening battery, which included open-ended questions about the existence (lifetime, anytime during PD, and currently) of recurrent compulsive buying, gambling, or sexual behaviors. Subjects were also administered the 15-

item Geriatric Depression Scale (GDS-15)(9) and the Mini-Mental State Examination (MMSE)
(10) as part of the screening process.

Those who screened positive for an ICD during the course of PD were contacted by phone in
August or September 2005 by one of the study authors (DW or JG) and administered a modified
Minnesota Impulsive Disorders Interview (MIDI)(11), which includes queries for the presence
of clinically-significant compulsive gambling, sexual, and buying behaviors. Patients were
instructed to answer the questions based on their state at the time they were symptomatic. ICDs
were defined as answering in the affirmative to 1 (compulsive sexual behavior and compulsive
shopping) or 2 (compulsive gambling) gateway questions plus an affirmative answer to ≥1 of
the remaining questions of the relevant ICD module of the MIDI. The same threshold has been
used to define problem gambling in other studies(12). The MIDI was administered to confirm
the presence of ICDs during the course of PD only (i.e., not applied to pre-PD onset ICD
symptomatology).

To verify data accuracy, the study PI (DW) reviewed the charts of all patients identified as
having an ICD sometime during the course of PD. For patients with an ICD sometime during
the course of PD but no longer symptomatic, their charts were reviewed and their medications
recorded for the time period when they were most symptomatic.

For analytic purposes, a levodopa equivalent daily dose (LEDD) was calculated on the basis
of the following formula, similar to that previously reported(13;14): 100 mg levodopa = 130
mg controlled-release levodopa = 70 mg levodopa + COMT inhibitor = 1 mg pergolide = 1
mg pramipexole = 5 mg ropinirole. Other PD medications (e.g., anticholinergics and
monoamine oxidase inhibitors), which have not been associated with ICDs, were not included
in the analyses. LEDDs were calculated both for dopamine agonists only (dopamine agonist
LEDD) and for dopamine agonists + levodopa (total LEDD).

To probe for possible risk factors for the development of ICDs in PD, data was obtained for
factors that have been reported to be associated with ICDs in PD (type and dose of dopamine
replacement therapy, disease duration, age, and sex)(1–3) or were factors of interest (history
of ICD behavior, global cognition, educational level, and marital status). For the purposes of
this study, dopamine agonists were considered to be pramipexole, ropinirole, and pergolide.
Amantadine, which has an unclear mechanism of action but has some dopamine agonist
properties(15), was considered separately, and no patient was prescribed bromocriptine or
apomorphine. Reliable data was not available for the duration of treatment with dopamine
replacement therapies. All clinical and demographic data was obtained directly from the patient
during the screening interview, and when possible verified by chart review.

Analysis

Demographic and clinical characteristics of ICD and non-ICD subjects were compared using
Fisher's exact test for categorical variables and the Wilcoxon two-sample test for continuous
variables. A comparison of the frequency of ICDs on different dopamine agonists was made
using Fisher's exact test. The association between dopamine agonist dosage and ICDs was
determined using the Wilcoxon two-sample test. Variables significant at the 0.1 significance
level (uncorrected for multiple comparisons) in the univariate analysis were entered as
independent variables in an exact logistic regression model, with presence of an active ICD as
the dependent variable. For the logistic regression model, all continuous measures were
dichotomized at the median. Results of the exact logistic regression model are presented in
terms of odds ratios, 95% confidence intervals, and P values. Analyses were performed with
SPSS version 13.0 (SPSS Inc., Chicago, IL) and SAS version 9.1 (SAS Institute, Inc., Cary,
NC).

RESULTS

Patient Characteristics

Two hundred seventy-two patients, ranging in age from 35 to 91 years, completed the screening process. The use of the Philadelphia VAMC as a site led to a preponderance of men in the study population. One-half of subjects (137/272 [50.4%]) were taking a dopamine agonist at screening. For patients taking a dopamine agonist, there were no between-group differences in mean dopamine agonist LEDD ($F_{[2,134]} = 2.6$, $P = .08$), but pergolide-treated patients were more likely to be on a dopamine agonist LEDD ≥500 mg/day (Fisher's exact test $P = .002$).

Frequency of ICDs

Twenty-one patients screened positive for an ICD during PD, but two patients did not meet MIDI criteria for an ICD and one other could not be reached for follow-up. The frequencies of one or more ICDs were 4.0% (N=11) for an active ICD and 6.6% (N=18) for anytime during PD. Of patients with an active ICD, the problem was documented in their clinical record in 3 (27.3%) cases.

Compulsive sexual behavior was as common as compulsive gambling among both active cases (2.6% [N=7] vs 2.2% [N=6], respectively) and those with an ICD anytime during PD (2.6% [N=7] vs 2.6% [N=7], respectively). The frequency of compulsive buying was 0.4% (N=1) for active cases and 1.5% (N=4) for anytime during PD.

Thirteen subjects reported a history of ICD symptomatology prior to PD onset, including 5 of the 18 subjects with an ICD sometime during the course of PD. For these 5 subjects, their ICD behavior during the course of PD was the same as the behavior exhibited prior to PD onset (3 cases of compulsive sexual behavior and 1 each of compulsive gambling and buying).

Demographic and Clinical Correlates

On univariate analysis, younger age, longer PD duration, history of ICD symptomatology prior to PD, and use of a dopamine agonist or amantadine were associated with the presence of an active ICD, with a suggestion for higher total LEDD (Table 1). All 11 active ICD cases were currently taking a dopamine agonist.

Examining the larger group of 18 patients who had experienced an ICD sometime during the course of PD, all were taking a dopamine agonist while symptomatic. Based on the follow-up interview and review of medical records, 7 of them became asymptomatic either with discontinuation of dopamine agonist treatment (N=4), a reduction in the dopamine agonist dosage (N=2), or counseling (N=1).

Exact Logistic Regression Model

Based on the univariate results, age, PD duration, history of ICD symptomatology prior to development of PD, dopamine agonist or amantadine use, and total LEDD met criteria to enter the multivariate model. In this model, dopamine agonist use and history of ICD symptomatology prior to PD were the only significant predictors of an active ICD (Table 2).

Specific Dopamine Agonists

At screening, approximately half of PD patients were taking a dopamine agonist (Table 3). Pramipexole was most frequently prescribed (53.3% of dopamine agonist use), followed by ropinirole (35.8%) and pergolide (10.9%). There were no differences between the three dopamine agonists in their association with ICDs ($P = .21$, Fisher's exact test). Examining the

larger group of patients who had experienced an ICD sometime during the course of PD, 8 were taking ropinirole, 7 pramipexole, and 3 pergolide while symptomatic.

Dopamine Agonist Dose

Examining only patients currently on a dopamine agonist, ICDs were associated with exposure to higher daily doses of pergolide ($t_{[13]} = -3.38$, $P = .05$), but not pramipexole ($t_{[71]} = -2.14$, $P = .06$) or ropinirole ($t_{[47]} = -0.81$, $P = .40$). Using LEDDs and examining the three dopamine agonists as a class, treatment with higher doses was associated with the presence of an ICD ($t_{[135]} = -4.06$, $P = .001$).

COMMENT

Estimated frequencies of compulsive gambling in PD range from 0.5%(1) to 4.9%(2). Our frequency estimate for compulsive gambling (2.2% for active cases and 2.6% for anytime during PD) fell in the intermediate range of those previously reported. We may have underestimated the frequency of ICDs in our population, as patients may have been either hesitant to acknowledge symptoms or less likely to be present in the clinic and therefore unavailable for screening.

There is no published literature on the estimated prevalence of other ICDs in PD. We found that compulsive sexual behavior was as common as compulsive gambling, though may have been due to the predominance of males in our sample. Regardless, our findings are consistent with recent reports(7) suggesting an association between dopamine agonist treatment and compulsive sexual behavior in PD.

Of the six potential risk factors for ICDs identified in preliminary analyses, only dopamine agonist treatment and a history of ICD symptomatology prior to PD predicted presence of an active ICD in the multivariate model. Previous reporting of younger PD patients being disproportionately affected with ICDs may reflect prescribing patterns (e.g., older patients are less likely to be treated with a dopamine agonist). Our data suggest that a history of ICD symptomatology prior to PD is the main demographic or clinical variable that predicts an increased risk for the development of an ICD in the setting of dopamine agonist treatment.

The risk associated with ICDs was specific to the dopamine agonist medication class. Although there was a suggestion on univariate analysis of an association between the total LEDD and ICDs, this relationship was no longer observed after controlling for dopamine agonist use. These results suggest a distinct mechanism of action, as opposed to an additive effect, for dopamine agonists in the development of ICDs.

Our findings did not support a differential association between specific dopamine agonists and ICDs, suggesting a class effect. Two case series(2;3) implicated pramipexole as the agent most likely to cause an ICD, but neither accounted for the relative frequency of pramipexole use in comparison with other dopamine agonists.

There is great variability in the dosing of dopamine agonists in PD. Using LEDDs to examine the three dopamine agonists as a class, ICD cases were treated with higher dopamine agonist doses. These findings are consistent with two case series(2;3) suggesting that the greatest risk for ICDs may involve dopamine agonist doses at the high end of the therapeutic range. If true, that may help explain why the highest frequency of ICD cases, even though not statistically significant, was in pergolide-treated patients, as this group was more likely to receive doses at the upper end of the therapeutic range.

Limitations of our study include the following: (1) Our study population was not randomly chosen; (2) Subjects came from two centers (including one veterans' hospital) in one region of the country, limiting the generalizability of our findings; (3) The follow-up phone interview to verify the history of ICD behaviors was conducted up to 15 months after the screening process, which may have affected the validity of the data; (4) No measures of PD severity, other than duration of illness, were available for analysis; (5) ICD status was determined through the use of the MIDI rather than formal diagnostic interviews, and determination of ICD symptomatology prior to PD onset was based on the unstructured screening interview only; and (6) Only 11 ICD cases were identified, limiting the conclusions that can be reached about the nature of the associations between dopamine agonist treatment and ICDs in PD. Multi-site studies involving larger, random samples of patients are needed to definitively determine the prevalence and clinical correlates of ICDs in PD.

Our findings highlight the importance of screening for a variety of ICDs in PD patients treated with a dopamine agonist, particularly since only one-quarter of active ICD cases in this study had been identified clinically. It is not known whether the risk for ICDs with exposure to this medication class is specific to PD patients. As dopamine agonists are increasingly prescribed for other indications (e.g., recent FDA approval of ropinirole for the treatment of restless legs syndrome), it will be important to assess the prevalence and risk for ICDs in other dopamine agonist-treated populations.

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Table 1

Demographic and Clinical Correlates of ICDs

Variable	No Active ICD[a] (N=261)	Active ICD (N=11)	P value
Age, years	68.6 (10.2)	59.5 (9.4)	.006[b*]
Male, N (%)	182 (69.7)	10 (90.9)	.184[c]
Married, N (%)	206 (79.2)	9 (81.8)	>.999[c]
Education, years	14.7 (3.0)	14.7 (3.1)	.981[b]
PD duration, years	6.9 (5.8)	11.2 (7.5)	.039[b*]
Levodopa dosage, mg/day	448.1 (335.2)	543.6 (453.5)	.493[b]
Total LEDD, mg/day[d]	569.3 (369.1)	925.5 (534.9)	.037[b*]
Dopamine agonist use, N (%)	126 (48.3)	11 (100.0)	<.001[c*]
Amantadine use, N (%)	49 (18.8)	6 (54.5)	.011[c*]
MMSE score	28.3 (2.0)	28.6 (1.4)	.964[b]
GDS score	4.0 (3.8)	6.0 (5.5)	.262[b]
ICD behavior prior to PD, N (%)	9 (3.5)	4 (36.4)	<.001[c*]

Note: Values are mean (±standard deviation) unless otherwise indicated.

[a] Includes patients who once had an ICD, either prior to onset of or sometime during the course of PD

[b] Wilcoxon two-sample test

[c] Fisher's exact test

[d] Levodopa equivalent daily dose for dopamine agonists + levodopa from other medications

[*] P value ≤.05

Table 2

Exact Logistic Regression Model (Adjusted Values are Adjusted for Other Five Variables)

Variable	Crude		Adjusted	
	Exact Odds Ratio	95% Confidence Limit	Exact Odds Ratio	95% Confidence Limit
Age	0.21	(0.02, 1.04)	0.44	(0.04, 2.87)
PD duration	3.03	(0.71, 18.10)	2.10	(0.27, 20.79)
Total LEDD[a]	1.84	(0.46, 8.79)	0.55	(0.08, 4.12)
Dopamine agonist use	16.27	(2.61, -[c*])	10.47[b]	(1.54, -[c#])
Amantadine use	5.15	(1.25, 22.26)[#]	3.16	(0.55, 20.52)
ICD behavior prior to PD	15.54	(2.83, 76.16)[*]	10.73	(1.48, 83.78)[#]

[a] Levodopa equivalent daily dosage for dopamine agonists + levodopa from other medications

[b] Median unbiased estimate due to boundary

[c] Upper bound approaches infinity

[*] $P < .01$

[#] $P < .03$

Table 3

Association Between Specific Dopamine Agonists and Active ICDs

	No Dopamine Agonist Use[a]	Pramipexole	Dopamine Agonist Ropinirole	Pergolide
# Treated	135	73	49	15
# ICD Cases	0	5	3	3
ICD frequency	0%	6.8%	5.8%	20.0%

[a]114/135 (84.4%) of patients not on a dopamine agonist were taking levodopa. The rest were on other non-dopamine agonist medications or no PD medications at all.