Factors Associated With Dopaminergic Drug–Related Pathological Gambling in Parkinson Disease

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Objective: To evaluate factors associated with pathological gambling (PG) in Parkinson disease (PD).

Design: Case-control study.

Setting: Outpatient tertiary clinic.

Patients: Twenty-one patients with idiopathic PD with PG after the patients began receiving medications compared with a consecutive sample of 42 patients with idiopathic PD without compulsive behaviors.

Main Outcome Measures: Clinical features, comorbid psychiatric and substance use disorders, personality traits, and impulsivity scores.

Results: Patients with PG had a younger age at PD onset (P=.006), higher novelty seeking (P<.001), medication-induced hypomania or mania (P=.001), impaired planning (P=.002), or a personal or immediate family history of alcohol use disorders (P=.002). Novelty seeking, a personal or immediate family history of alcohol use disorders, and younger age at PD onset accurately predicted PG at 83.7% in a logistic regression model, with the model accounting for 62% of the variance.

Conclusions: Patients with PD having a younger age at PD onset, higher novelty seeking traits, and a personal or family history of alcohol use disorders may have a greater risk for PG with dopamine agonists.

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Patients and controls completed patient-rated scales and were assessed by a neuropsychologist (T.T. or J.M.M.) and a psychiatrist (V.V., M.D., or M.Z.) (duration, 3–4 hours). Age at PD onset, side of PD onset, Hoehn and Yahr scale score, medication type and dose in levodopa dose equivalents,10 Unified Parkinson Disease Rating Scale motor subscale III score while “on,” Mini-Mental State Examination score, Frontal Assessment Battery score, Beck Depression Inventory score, and Apathy Scale score were assessed. Pathological gambling (DSM-IV criteria), compulsive shopping (criteria by McElroy et al6), hypersexuality (our clinician-designed diagnostic criteria),2 and compulsive medication use (criteria by Giovannini et al6) were diagnosed. Past and present mood, anxiety, and substance use disorders (modified to include dopaminergic medications) were diagnosed using the Structured Clinical Interview for Axis I Disorders (psychiatric disorders). Immediate family history (in parents, siblings, or children) of alcohol use disorders (modified to include dopaminergic medications) at the time of assessment and dose in levodopa dose equivalents,7 Unified Parkinson Disease Rating Scale motor subscale III score while “on,” Mini-Mental State Examination score, Frontal Assessment Battery score, Beck Depression Inventory score, and Apathy Scale score were assessed. Smoking history was dichotomized into ±1 pack-year.

Impulsivity was measured with the Barratt Impulsivity Scale (BIS-11),8 which assesses planning (BIS planning subscale) (“I plan tasks carefully”; “I am more interested in the present than the future”), attention, and motor factors (“I do things without thinking”; “I buy things on impulse”). Novelty seeking and harm avoidance were assessed using the Temperament and Character Inventory.9

To compare PG and control groups, the Mann-Whitney U test was used for continuous variables and the Fisher exact test for categorical variables. Logistic regression analysis was used to determine a predictive model. Significance was assigned at P<.05. All of the statistics were calculated using SPSS version 12.0 statistical software (SPSS, Inc, Chicago, Ill).

The study was approved by the University Health Network Research Ethics Board. All of the subjects gave informed consent.

RESULTS

POPULATION

Twenty-one patients with PD and PG were identified. The analysis includes 1 patient with PG onset after subthalamic nucleus deep brain stimulation; a separate analysis excluding this patient did not alter the results.

Seventy-six potential controls were contacted; 9 could not participate owing to time constraints, 5 were unwilling to participate in studies, and 13 agreed to participate but were unable to do so owing to appointment time schedules. Seven controls with compulsive behaviors were excluded. Patients with PG were compared with 42 controls with PD without compulsive behaviors recruited specifically for this study (control A). Patients with PG were also compared with 286 patients with PD but without PG (control B) previously described during the prevalence study.1 Three control A patients overlapped with control B. Characteristics of patients with PG and controls are described in the Table.

CHARACTERISTICS

Compared with both control groups, patients with PG were younger and had a younger age at PD onset. Compared with control A, patients with PG had higher NS, medication-induced hypomania or mania (onset after PG onset), impaired BIS planning, and a personal or immediate family history of alcohol use disorders. The personal histories of alcohol use disorders had all started prior to PD onset. Patients with PG were more weakly associated with more frequent right-sided (ie, left-hemisphere) PD symptom onset, higher BIS motor subscale scores, a personal history of alcohol use disorders, and an immediate family history of alcohol use disorders. Sex, Hoehn and Yahr stage, and total levodopa dose equivalents were not different.

Age at PD onset remained associated with PG (logistic regression; P=.03) when adjusted for age, whereas the reverse relationship was not true (P=.26).

PREDICTIVE MODEL

To increase statistical power for the purposes of logistic regression analysis, the data for the personal history of alcohol use disorders were combined with the immediate family history of alcohol use disorders given their known biological relationship. Age at PD onset (P values on entry into model; P=.02), personal or immediate family history of alcohol use disorders (P=.001), and NS (P<.001) accurately predicted PG at 83.7%, with the model accounting for 62% of the variance. The model sensitivity was 73.3% and the specificity was 89.3%. A 1-point increase in the NS score had a 38.4% (95% confidence interval, 9.0 to 74.8) increase in odds of PG. A patient with PG was 6.9 (95% confidence interval, 0.9 to 56.4) times more likely to have a personal or immediate family history of alcohol use disorders. The area under the receiver operating characteristic curve of the model was 0.92.

NS AND IMPULSIVITY

Compared with NS scores in the North American general population (mean NS score, 19.2),9 the control A group scored lower (1-sample t test; P<.001; mean difference, −8.3 [95% confidence interval, −9.9 to −6.9]) whereas the PG group scored the same as the general population (P=.73; mean difference, 0.7 [95% confidence interval, −3.0 to 4.3]).

Three patients with PG had NS scores below the median, 2 had symptoms remit without medication intervention, and 1 had PG onset after subthalamic nucleus deep brain stimulation without a new initiation of pramipexole monotherapy despite preoperative exposure to the same medication type and dose without behavioral complications.

To determine whether NS or BIS scores were related to underlying individual traits or were related to active PG or the presence of an agonist, patients with PG whose symptoms remitted (n=13; 11/13 patients had changes in dopaminergic medications) at the time of assessment were compared with patients whose symptoms did not remit (n=8). Compared with control A, the 3 groups differed on BIS planning (1-way analysis of variance; F = 10.3; P<.001), with post hoc Tukey comparisons demonstrating impaired planning in patients whose symptoms did not remit (BIS mean [SD] score, 31.4 [3.6]) vs controls (BIS mean [SD] score, 20.7 [4.3]) (P<.001); there were
no significant differences between patients whose symptoms remitted (24.3 [SD, 5.5]) and controls (P = .20). Patients whose symptoms did not remit were more impaired on BIS planning than those whose symptoms remitted (P = .03). The remitted and unremitted groups were not different in other variables. Age at PD onset was not correlated with NS (Pearson correlation, −0.2; P = .10) or BIS planning (Pearson correlation, −0.09; P = .62).

Novelty seeking remained associated with PG (logistic regression; P = .02) when adjusted for BIS planning, whereas the reverse relationship was not true (P = .51).

**MEDICATION TYPES**

To compare medication types, proportions of patients with PD receiving different dopamine agonists were presumed to be similar to screened patients with PD described previously (control B). Pathological gambling was associated with adjunctive dopamine agonist therapy (Fisher exact test; P < .001) but not with dopamine agonist monotherapy (P = .14). There was a trend toward higher dopamine agonist dose in the PG group when compared with the larger control group (control B) (P = .07) but not with the smaller control group (control A) (P = .69). There were no significant differences in total levodopa equivalence daily dose between PG and either control group.

In keeping with our hypotheses, patients with PD who developed PG when receiving dopamine agonists had a younger age at PD onset, higher NS scores, a personal or immediate family history of alcohol use disorders, and impaired planning on an impulsivity scale. A robust association was found with medication-induced mania. Left-hemisphere PD onset, younger age, and higher BIS motor subscale scores were weakly associated. Study strengths included rigorous diagnostic criteria in patient and control groups.

### Table. Characteristics of Patients With Parkinson Disease With and Without Pathological Gambling

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With PD and PG Value†</th>
<th>PD Control A Group* Value Value§</th>
<th>P Value</th>
<th>PD Control B Group‡ Value</th>
<th>P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No. (%)</td>
<td>15 (71)</td>
<td>21 (50)</td>
<td>.16</td>
<td>172 (60)</td>
<td>.36</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60.2 (8.9)</td>
<td>65.7 (9.9)</td>
<td>.03</td>
<td>65.8 (11.2)</td>
<td>.007</td>
</tr>
<tr>
<td>Age at PD onset, mean (SD), y</td>
<td>50.9 (8.8)</td>
<td>58.4 (10.1)</td>
<td>.006</td>
<td>57.8 (8.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PD duration, mean (SD), y</td>
<td>9.2 (5.2)</td>
<td>6.9 (4.2)</td>
<td>.07</td>
<td>8.0 (9.6)</td>
<td>.57</td>
</tr>
<tr>
<td>Patients receiving levodopa alone, No. (%)</td>
<td>0</td>
<td>11 (26.1)</td>
<td>NA</td>
<td>150 (52.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Patients receiving dopamine agonist monotherapy, No. (%)</td>
<td>1 (4.8)</td>
<td>1 (2.4)</td>
<td>.38</td>
<td>24 (8.6)</td>
<td>.14</td>
</tr>
<tr>
<td>Patients receiving dopamine agonist adjunctive therapy, No. (%)</td>
<td>20 (95.2)</td>
<td>30 (71.4)</td>
<td>.01</td>
<td>105 (37.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pergolide, No. (%)</td>
<td>7 (33.3)</td>
<td>10 (23.8)</td>
<td>.70</td>
<td>21 (7.5)</td>
<td>.17</td>
</tr>
<tr>
<td>Pramipexole, No. (%)</td>
<td>5 (23.8)</td>
<td>12 (28.6)</td>
<td>.70</td>
<td>48 (17.2)</td>
<td>.17</td>
</tr>
<tr>
<td>Ropinirole, No. (%)</td>
<td>8 (38.1)</td>
<td>15 (35.7)</td>
<td>.70</td>
<td>36 (12.9)</td>
<td>.17</td>
</tr>
<tr>
<td>LEDD, mean (SD), mg/d</td>
<td>874.2 (495.6)</td>
<td>746.9 (322.5)</td>
<td>.20</td>
<td>746.7 (442.3)</td>
<td>.21</td>
</tr>
<tr>
<td>Dopamine agonist LEDD, mean (SD), mg/d</td>
<td>268.3 (194.3)</td>
<td>192.1 (105.3)</td>
<td>.69</td>
<td>209.0 (123.1)</td>
<td>.07</td>
</tr>
<tr>
<td>Hoehn and Yahr score, mean (SD)</td>
<td>2.0 (0.5)</td>
<td>2.2 (0.8)</td>
<td>.29</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>UPDRS-III score while “on,” mean (SD)</td>
<td>15.2 (6.9)</td>
<td>22.1 (13.9)</td>
<td>.42</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with left-hemisphere PD onset, No. (%)</td>
<td>16 (76.2)</td>
<td>15 (44.1)</td>
<td>.03</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>27.4 (3.2)</td>
<td>28.6 (1.5)</td>
<td>.51</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Frontal Assessment Battery score, mean (SD)</td>
<td>15.4 (2.2)</td>
<td>15.5 (1.5)</td>
<td>.65</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Apathy scale score, mean (SD)</td>
<td>5.6 (2.6)</td>
<td>8.0 (0.9)</td>
<td>.39</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with current or past depression, No. (%)</td>
<td>6 (28.6)</td>
<td>11 (26.8)</td>
<td>.80</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Beck Depression Inventory score, mean (SD)</td>
<td>12.4 (6.0)</td>
<td>10.3 (7.9)</td>
<td>.30</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with medication-induced hypomania or mania, No. (%)</td>
<td>6 (30.0)</td>
<td>0</td>
<td>.001</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with any anxiety disorder, No. (%)</td>
<td>6 (30.0)</td>
<td>21 (50.0)</td>
<td>.25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients smoking &gt;1 pack-year, No. (%)</td>
<td>10 (47.6)</td>
<td>11 (26.1)</td>
<td>.13</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Patients with personal or immediate family history of alcohol use disorder, No. (%)</td>
<td>12 (60.0)</td>
<td>8 (19.0)</td>
<td>.002</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Barratt Impulsivity Scale 11 score, mean (SD)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Attention subscale</td>
<td>16.9 (3.8)</td>
<td>15.6 (4.1)</td>
<td>.36</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Motor subscale</td>
<td>20.9 (5.6)</td>
<td>17.3 (4.4)</td>
<td>.02</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Planning subscale</td>
<td>27.0 (6.0)</td>
<td>21.1 (4.6)</td>
<td>.002</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>65.2 (12.2)</td>
<td>54.1 (10.1)</td>
<td>.006</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Novelty seeking score, mean (SD)</td>
<td>20.3 (6.6)</td>
<td>19.9 (4.2)</td>
<td>&lt;.001</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Harm avoidance score, mean (SD)</td>
<td>12.8 (5.3)</td>
<td>16.5 (8.9)</td>
<td>.17</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: LEDD, levodopa equivalence daily dose; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson disease; PG, pathological gambling; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Control A indicates controls assessed for current study.
†P value for patients with PD and PG vs PD control A group.
‡Control B indicates control data from prevalence study.
§P value for patients with PD and PG vs PD control B group.
¶Compared with levodopa monotherapy.
‖Compared with other dopamine agonist.
trol groups. Study statistical power was limited by sample size. The scales we used do not assess for cognitive processes that may underlie facets of NS or impulsivity such as reward or aversive learning, risk taking, cognitive flexibility, or response inhibition. As the levodopa cycle time during which patients completed scales was not known, changes in affect may have influenced scores.

One patient had PG onset after subthalamic nucleus deep brain stimulation linked to agonist monotherapy despite similar preoperative exposure without behavioral complications. The implications of subthalamic nucleus deep brain stimulation on these behaviors are discussed elsewhere.10

Susceptibility to PG can be mediated by PD-specific factors such as the neurobiology of PD (which may also modulate underlying temperamental traits or cognitive processes), PD-specific medication practices, or individual factors underlying the vulnerability to PG, addiction, or impulse control disorders. Pathological gambling in the general population has been most consistently associated with being male, having comorbid mood and substance use disorders11,12 and having higher NS13 or impulsivity traits.13

In this study, higher NS, a personal or immediate family history of alcohol use disorders, and younger age at PD onset were predictive factors for the development of PG with dopamine agonists.

Novelty seeking was robustly associated with PG following logistic regression analysis. High NS, characterized by exploratory approach behaviors, excitement with novel situations, impulsivity, and rapid decision making,9 is associated with PG.13 Low NS, characterized by reflectiveness, rigidity, and slow temper,9 has been variably but not consistently13 associated with PD. The NS differences in this study were due to lower control scores in the patients with PD without compulsive behaviors compared with patients with PG who scored similarly to the general population. The neuropathological process of PD may result in a relative decrease in NS. However, individuals with premorbid high NS temperament may have scores similar to the general population in the context of PD.

Novelty seeking appears to be trait specific, predictive, and not modified by agonists. High NS is a heritable temperamental trait that may underlie the observed associations with alcohol use disorders, impulsivity, medication-induced hypomania, and medication-induced PG that may be variably expressed depending on the age at disease onset, exposure to medications, and environment. However, conclusions are limited because although agonists may increase NS in those receiving agonists compared with those not receiving agonists, this may not be detectable owing to insufficient sample size.

Younger age at PD onset rather than younger age was associated with PG. This may be mediated in subgroups such as genetic variants of PD or early-onset PD, which have been associated with greater risk for behavioral disorders.10,12 However, preferential use of dopamine agonists in younger patients with PD may be a confounder.

The implication of the left-hemisphere PD onset association, albeit weaker, is not clear. In the clinical PD literature, left-hemisphere PD onset has been associated with lower NS,13 and the availability of right insular D2 receptors is negatively associated with NS.18

Parkinson disease–specific medication practices (higher doses, longer exposure to dopamine agonists, or levodopa use) may play a role.1 Similar to our previous results, PG was associated with dopamine agonist adjunctive therapy but not agonist monotherapy. However, there were no statistical differences in patients with PG receiving agonist adjunctive therapy vs monotherapy, although this may be a statistical power issue. Patients with PG had a trend toward higher dopamine agonist dose, suggesting a potential role for higher dopamine agonist dose that may be limited by statistical power. However, total levodopa equivalence daily dose was not associated with PG.

Similar to our previous findings, there were slightly but not significantly more male patients with PG, although this may be a statistical power issue.

Pathological gambling was also associated with medication-induced hypomania or mania. These mood symptoms occurred temporally after PG onset in contrast to the known early age at bipolar onset in the general population. Rather than bipolar disorder as a risk factor, dopaminergic medication–induced mania may be part of the spectrum of dopamine dysregulation.9 Although depression is associated with PG in the general population16 and with compulsive medication use in PD,5 we were unable to identify any association.

Alcohol use disorders are associated with PG in the general population.11 Between 12% and 20% of genetic risk for PG may be accounted for by the risk for alcohol dependence.14 This supports our findings of an association with alcohol use disorders and suggests similar underlying genetic vulnerabilities.

In keeping with the literature,5 our results suggest that BIS planning (characterized by forethought for future consequences) was impaired in PG. However, BIS planning impairment appears to be related to the state of dopamine agonist use or active PG and possibly mediated by NS.

Patients with PD and higher NS, a personal or immediate family history of alcohol use disorders, or younger age at PD onset may be at greater risk for developing PG with dopamine agonists, although further confirmatory studies are required. Screening for such features and advising those at higher risk may be warranted.

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Author Contributions: Dr Voon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Voon, Miyasaki, Duff-Canning, and Zuroski. Acquisition of data: Voon, Thomsen, Miyasaki, de Souza, Shafro, and Zuroski. Analysis and interpretation of data: Voon, Shafro, Fox, and Lang. Drafting of the manuscript: Voon and Shafro. Critical revision of the manuscript for important intellectual con-
tent: Voon, Thomsen, Miyasaki, de Souza, Fox, Duff-Canning, Lang, and Zurowski. Statistical analysis: Shafro and Fox. Administrative, technical, and material support: Thomsen, Miyasaki, de Souza, Shafro, Duff-Canning, and Zurowski. Study supervision: Voon and Miyasaki.

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REFERENCES