Outcomes of Patients with Parkinson Disease and Pathological Gambling

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ABSTRACT: Objective: To determine the outcomes of patients with Parkinson disease (PD) with pathological gambling (PG) from one Canadian Movement Disorders Clinic. Methods: Assessments were performed in-person during routine clinic visits of all patients currently followed by one neurologist (OS). Pathological gambling was defined according to DSM–IV-TR criteria. Chart review was performed to obtain details on medication use, dosages, and patient demographics. Follow-up of patients with PG collected information on gambling behavior, PG management interventions, medications, treatment, and psychosocial outcomes. Results: 146 patients were surveyed with an overall prevalence of PG of 4.1% (6/146). The rate of pathological gambling for those patients on dopamine agonist therapy (DA) was 8.1% (6/74). Only patients who were recreational gamblers prior to starting DA developed PG. All PG patients discontinued, decreased, or switched to another DA, and experienced a partial or full remission of PG. 3 (50%) patients described financial losses of $100,000 or more, and 75% (3/4) patients described significant marital stresses. At follow-up (August 2008), 4 of the 6 patients with PG continued to gamble in a controlled fashion despite medication changes. No significant difference in levodopa equivalent daily dose (LEDD) pre- and post-PG were observed; however, the relative amount of DA was decreased ($p = 0.0593$), while levodopa was relatively increased ($p = 0.5277$). Despite control of PG, patients still experience financial and marital strains. Conclusions: DA (in combination with levodopa) was associated with a significantly higher prevalence of PG in PD, particularly in patients who were recreational gamblers previously. Despite control of PG, patients continued to experience significant financial and marital stresses that should be regularly enquired upon in follow-up care and managed appropriately.

RÉSUMÉ: Prévalence et évolution du jeu pathologique chez des patients atteints de la maladie de Parkinson. Objectif : Le but de l'étude était d'étudier l'évolution de patients atteints de la maladie de Parkinson (MP) qui sont des joueurs pathologiques dans une clinique canadienne de désordres du mouvement. Méthodes : Nous avons réalisé des évaluations pendant des visites de routine à la clinique chez tous les patients suivis régulièrement par le même neurologue (OS). Le jeu pathologique (JP) était défini selon les critères du DSM-IV-TR. Nous avons effectué une revue de dossiers pour recueillir les données démographiques, la prise de médicaments et les doses des médicaments. Au cours du suivi des patients présentant du JP, nous avons colligé les données suivantes : les habitudes de jeux, les interventions pour la gestion du JP, la médication, le traitement et les conséquences psychosociales du JP. Résultats : Cent quarante-six patients ont participé à l'enquête et la prévalence du JP était de 4,1% (6/146). Le taux de jeux pathologique chez les patients qui prenaient un agoniste de la dopamine (AD) était de 8,1% (6/74). Seuls les patients qui étaient des joueurs récréatifs avant le début de l'AD ont présenté du JP. Tous les joueurs pathologiques ont cessé, diminué ou changé d'AD et ont eu une rémission partielle ou totale du JP. Trois (50%) des patients ont rapporté des pertes financières de $100 000 ou plus et 75% (3/4) ont décrit des tensions conjugales importantes. Au moment du suivi en août 2008, 4 des 6 patients qui présentaient du JP continuaient à jouer de façon contrôlée malgré un changement de médication. Nous n’avons pas observé de différence significative de la dose quotidienne équivalente de levodopa avant et après le JP. Cependant, la quantité relative d’AD était diminuée ($p = 0.0593$) et la levodopa relativement augmentée ($p = 0.5277$). Malgré le contrôle du JP, les patients éprouvaient toujours des tensions financières et conjugales. Conclusions : L’AD, en combinaison avec la levodopa, était associé à une prévalence significativement plus élevée de JP chez les patients atteints de la MP, surtout chez ceux qui étaient des joueurs récréatifs antérieurement. Malgré le contrôle du JP, les patients continuaient à éprouver des tensions financières et conjugales dont on devrait s’informer au cours du suivi et qu’on devrait traiter adéquatement.


Multiple reports have described the development of pathological gambling (PG) in patients treated for Parkinson Disease (PD) with dopamine replacement therapy, particularly dopamine agonists (DA).

The prevalence of PG in those treated with DA has been estimated to be between 2.6-6.1%.

The prevalence of PG in those treated with DA has been estimated between 8-12%.

In previous reports, only patients with a prior history of gambling have developed PG.

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Though prevalence data is available, there is a paucity of literature on the treatment outcomes of PD patients with PG attributed to DA therapy. Once established, addictive behaviors like PG and their consequences often persist with ongoing vulnerability to relapse despite the underlying initiating factors being removed\textsuperscript{15-21}. Although previous reports have suggested that PG can be controlled through discontinuation of DA therapy, switching to another DA, or lowering the dose of a current DA\textsuperscript{6,22-24}, only one study\textsuperscript{24} has assessed the treatment outcomes of patients with PG. No information regarding the relative efficacy of various management strategies for PG in PD has been presented to date and the psychosocial sequelae of PG attributable to DA therapy in PD patients, particularly relating to marital and financial stresses, has been poorly described. The current study was initially undertaken to evaluate the prevalence of PG in patients treated for PD\textsuperscript{25}. Patients identified with PG were then followed prospectively to describe the outcome of their PD and PG when their DA treatment was altered. The sequelae of changes to DA treatment were also evaluated.

METHODS

Since 2005 all idiopathic PD patients with PG followed by one neurologist (OS) were identified as they came into clinic. Patients were diagnosed with PD according to the UK Brain Bank Criteria\textsuperscript{26}, and patients with dementia were excluded. Gambling behavior was identified and assessed through routine questioning on type and frequency of gambling and whether strains were experienced from gambling. ‘Recreational gamblers’ were defined as those patients who described their gambling as infrequent with no gambling-related financial or relational strains. All patients diagnosed with PG met DSM-IV-TR\textsuperscript{15} criteria. Results of this review were previously published\textsuperscript{25}.

Patients identified with PG were prospectively followed from July 2005 to June 2008 through clinical follow-up visits at the Movement Disorders Clinic and/or the Foothills Hospital Addiction Centre, where information on outcomes of PG was collected. Clinical follow-up of patients with PG assessed the efficacy of management strategies for PG, the outcomes of these treatment strategies, as well as the psychosocial sequelae of those patients with PG. Pathological gambling behavior, including the onset of PG, extent of losses, interventions for PG control and their effectiveness, as well as psychosocial sequelae, including relational and financial stresses, were queried.

Information regarding control of finances during PG was collected from family members/caregivers or patients directly during follow-up. Background information gathered via chart review included patient age, sex, disease duration, DA use history, and PD history.

ANALYSIS

Data processing and analysis was performed using STATA Version 9.0. A one-sample test of proportions was completed to compare the prevalence of PG among the study population with the general Alberta population\textsuperscript{14}, this observed increased prevalence was statistically significant (p= 0.0152). When compared to the 1.3% prevalence of PG in the general Alberta population\textsuperscript{14}, this observed increased prevalence was statistically significant (p< 0.001).

Demographics and disease-specific PG, history, and PD history.

Efficacy of medications in PG patients was determined through calculation of a levodopa-equivalent daily dose (LEDD) based on the following formula, which has been previously reported\textsuperscript{27}: 100 mg of levodopa = 130 mg of controlled-release levodopa = 70 mg of levodopa + catechol-O-methyl transferase inhibitor = 1 mg of pergolide = 1 mg of pramipexole = 5 mg of ropinirole = 10 mg of bromocriptine. Significance was set at p= 0.05.

RESULTS

We initially reported on 198 PD patients followed at the Movement Disorders Clinic\textsuperscript{25}. Thirty-nine patients were excluded as they had surgery for PD and will be reported on separately and 13 further patients were excluded due to dementia, recent death, or relocation to another city/town. Of the 146 remaining patients where long-term follow-up could be obtained, the overall prevalence of PG was 4.1% (6/146). When compared to the 1.3% prevalence of PG in the general Alberta population\textsuperscript{14}, this observed increased prevalence was statistically significant (p= 0.0152).

Demographics and disease-specific information are provided in Table 1. At the onset of PG, the mean age of the patients was 55 years (sd = 8.2) and the mean duration of PD from the time of diagnosis was 7.5 years (sd = 5.8). Of the six identified patients, two were female. The PG patient group was significantly younger than the PD population (58 ± 6.74 yrs vs. 68 ± 10.4 yrs, p= 0.0198). There was no significant difference in disease duration between the PG group and the general PD population (p= 0.0918).

Table 1: Demographic and Parkinson Disease specific information of patients

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Mean Age (y ± SD)</th>
<th>Mean Duration of PD (y ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Males</td>
<td>99</td>
<td>67 ± 10.2\textsuperscript{a}</td>
<td>9 ± 6.8</td>
</tr>
<tr>
<td>Total Females</td>
<td>47</td>
<td>71 ± 10.3\textsuperscript{a}</td>
<td>10 ± 5.3</td>
</tr>
<tr>
<td>PG Males</td>
<td>4</td>
<td>57 ± 7.7\textsuperscript{b}</td>
<td>11 ± 7.4</td>
</tr>
<tr>
<td>PG Females</td>
<td>2</td>
<td>62 ± 4.2\textsuperscript{b}</td>
<td>12 ± 0.7</td>
</tr>
</tbody>
</table>

PG - Parkinson Disease, PG - pathological gambling, y - years, SD - standard deviation. Mean age of total PD group\textsuperscript{p} significantly greater (p < 0.001) than PG group\textsuperscript{b}. 

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Table 2: Prevalence rates of pathological gambling in PD patients on dopamine replacement therapy

<table>
<thead>
<tr>
<th>Medication/Treatment</th>
<th>Number of Patients</th>
<th>Number of Recreational Gamblers (Prevalence %)</th>
<th>Number of Pathological Gamblers (Prevalence %)</th>
<th>Mean Medication Dose (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa alone</td>
<td>80</td>
<td>10 (13)</td>
<td>0 (0)</td>
<td>665</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>41</td>
<td>14 (34)</td>
<td>5 (12.2)*</td>
<td>3.3</td>
</tr>
<tr>
<td>Pergolide</td>
<td>11</td>
<td>1 (9)</td>
<td>1 (9.1)*</td>
<td>5.1</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>9</td>
<td>3 (33)</td>
<td>0 (0)*</td>
<td>14</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)*</td>
<td>22.7</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>28</td>
<td>6 (4)*</td>
<td></td>
</tr>
</tbody>
</table>

* Non-significant difference in PG risk among DA; Only patients who were recreational gamblers prior to starting dopamine replacement therapy developed PG.

Twenty eight of 146 (19.1%) patients were infrequent or “recreational” gamers before starting treatment. Patients who did not gamble prior to treatment did not develop PG with medication (Table 2). None of the patients on levodopa monotherapy developed PG. There was a statistically significant difference in prevalence of PG between patients on levodopa monotherapy versus patients on DA (p < 0.01). Of the PD patients on levodopa and DA combination therapy, the prevalence of PG was 8% (6/74).

All three commonly used DA appeared to be associated with PG. No patients on bromocriptine developed PG. No patients with PG on DA monotherapy were identified. Pathological gambling onset did not start upon initiation of DA treatment, but tended to begin once the drug was titrated to a clinically effective dose.

Treatment of PG varied among the patients and included changing from one DA to another, lowering the DA dose, discontinuation of the DA, counseling, and/or participation in support groups. One of the six patients (Patient 6) exhibited PG on more than one agonist (pergolide and ropinirole) (Table 3). The other five patients developed PG from only one agonist with resolution once they switched to another DA or the DA was discontinued.

Table 3 describes gambling behavior following changes to DA therapy. Despite control of PG following a switch from pramipexole to ropinirole, one patient (Patient 3) opted to continue on pramipexole as ropinirole provided little motor benefit, and she did not feel ‘as good’ on it. She remains on a lower dose of pramipexole, and continues to experience gambling urges, but has transferred control of finances to her husband. Another patient (Patient 6) showed PG behavior even after being switched from pergolide to ropinirole. He remains on ropinirole, and controls his gambling through self-control, and by abstaining from visiting casinos. Two patients (Patients 1 and 5) discontinued DA altogether as they could not tolerate/received little motor benefit from other DA. Tapering of DA was only performed in one patient (Patient 2), and was found to be ineffective in controlling PG. Once this patient’s DA was switched from pramipexole to ropinirole, gambling behavior came under control.

Gambling behavior improved or disappeared in all six patients. Two patients (33%) (Patients 3 and 6) described a continued, but controllable, urge to gamble following treatment. At follow-up, four of the six patients (67%) continued to gamble, but in a subjectively occasional or controlled fashion. To thwart PG behavior, family members and caregivers limited access to money in most cases.

The mean DA doses at the time when PG was initially identified and at the end of the follow-up period (June 2008) are reported in Table 3. Patients received relatively lower DA and higher levodopa dosages at follow-up, but neither of these differences were statistically significant (p=0.0593 and 0.5277, respectively). The LDD of patients when PG was first identified clinically and at follow-up, an average of 33 months (sd=13.5), was also not found to be significantly different (p=0.9084).

Pathological gambling patients experienced substantial financial and marital stress, even after control of PG. Five (83%) patients described financial losses that they felt had caused them significant distress; three (50%) patients experienced losses of over $100,000. One patient was forced to re-mortgage his house and needed to borrow money from family members. Of the four (67%) patients who were married, all remained married, but three described marked marital stress related to their PG even following changes in DA treatment. Over the course of their PG and even after reduction or cessation of their gambling, spouses were less trusting of the patients’ behavior, and blamed them for the financial stresses they experienced. One patient attended regular marriage counseling sessions with her husband following group cognitive behavioral therapy for PG.

**Discussion**

Dopamine agonists therapy (in combination with levodopa) has been found to be associated with an increased prevalence of PG in PD1-10,24, particularly in younger patients6,8,10,24. Of the current study’s sample of 146 treated PD patients, a PG prevalence of 4.1% was found. This finding is consistent with previous reports6-8,10,11 and statistically significantly greater (p= 0.0152) than the rate of PG in the general population12-14. An overall PG prevalence of 8.1% (6/74) for all patients treated with medication (Table 2). None of the patients on levodopa medication (Table 2). None of the patients on levodopa alone 80 10 (13) 0 665 did not gamble prior to treatment did not develop PG with PG. No patients on bromocriptine developed PG. No patients did not develop PG with medication (Table 2). None of the patients on levodopa alone 80 10 (13) 0 665 did not gamble prior to treatment did not develop PG with medication (Table 2). None of the patients on levodopa monotherapy developed PG. There was a statistically significant difference in prevalence of PG between patients on levodopa monotherapy versus patients on DA (p < 0.01). Of the PD patients on levodopa and DA combination therapy, the prevalence of PG was 8% (6/74).

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Similar to results of Mamikonyan and colleagues24, all patients who had their DA discontinued or changed upon identification of their PG had a partial or full-remission of PG at follow-up, despite LEDD remaining not statistically different. These observations may be interpreted to suggest that DA exposure contributes to the development and persistence of PG, but it is recognized that changes in gambling behavior are inherently less predictable than other addictive behaviors. Changes in gambling behavior may be related to the problems caused by the gambling itself or natural remission rather than alterations in the medication regimen28-29.

Some patients with PG were reluctant to discontinue DA because of the perceived benefits of therapy. Patients’ subjectively assessed their motor performance as poorer when switched to another, when they discontinued DA, or lowered the dose of DA. As no PG was observed on levodopa alone in our sample, discontinuation of DA while increasing levodopa was helpful in several of the patients. In others, due to poor control of
Table 3: Long-term outcomes and psychosocial sequelae of patients with PG

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of PD (years)</th>
<th>Time of gambling</th>
<th>LEDD</th>
<th>Intervention(s) (DA mg/day)</th>
<th>Outcome (patient reported)</th>
<th>Evidence of gambling?</th>
<th>Dopamine agonist used and dose (mg/day)</th>
<th>LEDD</th>
<th>Psychosocial sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>Pramipexole (4.5)</td>
<td>911.53</td>
<td>1. Switched to ropinirole (15) – no gambling but little motor benefit 2. DA stopped altogether 3. Psychiatrist consult 4. Re-started SSRI</td>
<td>Full remission</td>
<td>No</td>
<td>None</td>
<td>879.12</td>
<td>Financial losses of approximately $100,000; Significant marital strain</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>Pramipexole (5)</td>
<td>2105.49</td>
<td>1. Pramipexole tapered (7.5) – continued PG 2. Switched to pergolide (2) – controlled gambling but little motor benefit 3. Switched to ropinirole (10) – controlled gambling with better motor control 4. Attended gamblers anonymous 5. Psychiatrist consult</td>
<td>Not gambling excessively</td>
<td>Occasional controlled gambling</td>
<td>Ropinirole (10)</td>
<td>1603.85</td>
<td>Financial losses of $3000; Strain on marriage</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>Pramipexole (4.5)</td>
<td>1103.85</td>
<td>1. Switched to ropinirole (20) – controlled gambling but little motor benefit 2. Pramipexole re-started (4.5) despite increased risk of gambling 3. Spouse took control of finances</td>
<td>Gambling urge present</td>
<td>Yes, but finances controlled</td>
<td>Pramipexole (1.5 mg)</td>
<td>1103.85</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>Pramipexole (1.5)</td>
<td>457.69</td>
<td>1. Switched to ropinirole (15) – no gambling with good motor benefit</td>
<td>Full remission</td>
<td>No</td>
<td>Ropinirole (15mg)</td>
<td>607.69</td>
<td>Financial losses of $20,000</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>Pramipexole (7.5)</td>
<td>2178.57</td>
<td>1. Pramipexole discontinued 2. Psychiatrist consult</td>
<td>Full remission</td>
<td>Occasional controlled gambling</td>
<td>None</td>
<td>1714.29</td>
<td>Strain on marriage, six-figure financial losses</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>pergolide (3)</td>
<td>600</td>
<td>1. Abstained from visiting casinos 2. Psychiatrist consult</td>
<td>Partial remission (through abstinence) but still an urge to gamble</td>
<td>Occasional controlled gambling</td>
<td>Ropinirole* (15)</td>
<td>1200</td>
<td>Financial losses of over $100,000; borrowed money from family members; re-mortgaged house</td>
</tr>
</tbody>
</table>

1 Patient resumed pathologically gambling on higher dose, and was subsequently kept on a very low dose of pramipexole (1.5 mg/day).
* Patient switched from pergolide to ropinirole due to pergolide’s risk of causing valvular damage, rather than as a gambling intervention.

motor symptoms with discontinuation of the DA, substitution of another DA resulted in improved motor control without recurrence of gambling behavior. In a minority of patients, the same DA needs to be restarted but kept at a lower dose. Thus, treatment needs to be individualized for each patient. In contrast to previous reports suggesting motor control is relatively unchanged following DA switching, lowering, or discontinuation, our data suggests that motor performance can be affected adversely despite LEDD maintenance in a minority of patients.

As previously reported, we also found that only those patients who were recreational gamblers prior to initiating DA developed PG. This suggests that pre-morbid non-pathological gambling behavior may confer a potential risk for developing PG upon initiation of a DA and should be screened for early in PD treatment. As such, non-pathological and ‘recreational’ gamblers should be closely monitored clinically to assess for any change in their gambling behavior as DA may be a contributor.

To our knowledge this is the first study to look at the psychosocial sequelae of PG developing during PD treatment with dopamine replacement therapy. In the patients where PG was identified, substantial marital and financial stress was described even after PG abated. Three (50%) of the patients described losses of over $100,000, and three out of four (75%) of the married patients with PG described their relationship with their spouse was negatively affected in an ongoing fashion by their prior PG. It is well recognized that PG impacts on the family and financial, personal, and vocational endeavors adversely and that the sequelae often have lasting effects even when gambling behavior is addressed. PD patients with PG face similar psychosocial sequelae that need to be addressed in concert with reviewing their dopamine replacement therapy regimen. The psychosocial consequences related to PG should be sought involving family members or caregivers. Based on the reports of the ongoing loss of trust in their relationships, particularly considering that many of the identified patients continued to gamble (albeit less frequently), abstinence from gambling should be emphasized with specific plans put in place as to how to limit access to funds by patients and engage them in known effective treatments for PG.

There are a number of limitations in our study. No validated screening tools were used to systematically assess patients for PG. Other investigators have used tools such as the South Oaks Gambling Screen or Minnesota Impulsive Disorders Inventory. However, as all patients met DSM-IV-TR criteria for PG it is likely that this represents an underestimation of prevalence rather than an overestimation. This is not surprising, as one year prevalence rates in other studies have generally been higher than what is presented here, including recent data from our own clinic. In assessing the gambling outcomes of patients in follow-up, we relied on patient and family member assessments of gambling behavior; we did not use similar instruments to assess whether the patient was in full remission from PG.

It is important to note that we did not systematically check for other potentially associated behavioral disturbances but...
discovered these upon patient assessments. These included hypersexuality and other apparent compulsive activities such as shopping, eating, and video game playing. These behaviors and other impulse control disorders (ICD) have been reported to be caused by DA use in PD^{1,8,22-24}. Future work and follow-up should not only assess the treatment outcomes of patients with ICD, but assess the psychosocial sequelae of patients during and after the ICD has purportedly been treated.

CONCLUSION

Our study identified an increased overall prevalence of PG in the PD population consistent with that previously reported, particularly in PD patients treated with DA. Parkinson disease patients who developed PG all previously reported prior non-pathological gambling involvement. Discontinuation or changing DA was associated with the cessation or reduction of gambling, but patients reported ongoing psychosocial sequelae from their prior PG with regards to their finances and relationships. The findings suggest that gambling behavior should be inquired of before initiating dopamine replacement therapy in order to identify those who may be at higher risk of developing PG and as part of the routine follow-up to determine if problematic gambling is developing. Altering DA therapy if PG develops appears to be helpful, but control of movement disorder symptoms may be reduced, emphasizing that rather than limiting the use of these effective therapies, physicians should inform all patients of the potential risk for developing PG with DA therapy for PD. For those patients who develop PG, management should go beyond altering dopamine replacement therapy, including family or caregivers in treatment plans, and utilizing known effective treatments for PG.

REFERENCES