Background: Pathological gambling is a rare potential complication related to treatment of Parkinson disease (PD). However, the etiology of this behavior is poorly understood.

Objective: To examine the relationship between medical therapy for PD and pathological gambling.

Methods: In our routine movement disorders practice (2002-2004), we encountered 11 patients with idiopathic PD who had recently developed pathological gambling. We assessed the relationship to their medical therapy and compared them with cases identified by systematic review of the existing literature on pathological gambling and PD.

Results: All 11 patients with PD and pathological gambling were taking therapeutic doses of a dopamine agonist; 3 of these patients were not treated with levodopa. In 7 patients, pathological gambling developed within 3 months of starting to take or escalating the dose of the agonist; in the other 4 with a longer latency, gambling resolved after the agonist use was discontinued. Pramipexole dihydrochloride was the agonist in 9 of 11 cases in our series and 10 of 17 in the literature (68% in total).

Conclusions: Dopamine agonist therapy was associated with potentially reversible pathological gambling, and pramipexole was the medication predominantly implicated. This may relate to disproportionate stimulation of dopamine D₃ receptors, which are primarily localized to the limbic system.

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GAMBLING IS COMMON IN our society, with multiple outlets, such as casinos, Internet Web sites, local sports betting, and so on. Gambling behavior, however, may become pathological, defined as failure to resist gambling impulses despite severe personal, family, or vocational consequences. Pathological gambling is classified as an impulse control disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria.¹

Parkinson disease (PD) is primarily treated by drugs that restore or improve brain dopaminergic neurotransmission. Brain dopamine also plays a central role in the behavioral reward system of both humans and animals, reinforcing a myriad of both productive and counterproductive behaviors.²⁻⁴ It has been implicated in mediating the reward of gambling behavior.⁵⁻⁷ Several recent reports have linked PD dopamine replacement therapy to pathological gambling.²⁻⁸⁻¹⁴ Within the last 3 years, 2 of us (J.H.B. and J.E.A.) encountered 11 patients with PD and pathological gambling in our routine neurology practice (movement disorders). The gambling addiction had recently developed and was temporarily related to use of dopamine agonist drugs.

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All patients were seen and prospectively tabulated in the routine practice of the Mayo movement disorders clinic (Rochester, Minn) between 2002 and 2004. All had idiopathic PD and were levodopa or dopamine agonist responsive. All met DSM-IV-TR criteria for pathological gambling. The gambling history was forthcoming during routine clinical interview of the patient (or family member). There was no a priori attempt to routinely screen for gambling behavior.
RESULTS

All patients had levodopa-responsive PD and were Hoehn-Yahr stage 2 to 3; the demographics at the time of their pathological gambling are presented in Table 1. None of the patients were thought to have dementia by the neurologist, although formal cognitive testing was not consistently performed. A Mayo Clinic staff psychiatrist evaluated 7 of the 11 patients. Gambling was often time-locked to initiation or discontinuation of dopamine agonist therapy, as summarized in Table 2, and as illustrated by the following representative patients.

REPORT OF PATIENTS WITH PD

Patient 1

This 53-year-old, married registered nurse had previously gambled once in 5 years. Pramipexole dihydrochloride was added to her therapy to control motor fluctuations, and within 3 months after reaching the maintenance dose of 4.5 mg/d, she experienced a strong compulsion to gamble at casinos. She started going about once a week (with moderate losses) and insisted this was an unusual behavior for her. Pramipexole therapy was tapered off, and she reported almost immediate cessation of her gambling compulsions.

Patient 2

This 54-year-old, married pastor previously gambled at a local casino about once every 4 or 5 years, spending about $20 a visit. Pramipexole therapy was subsequently initiated and escalated to 4.5 mg/d to control mild motor fluctuations. By the second year taking this dose, he began to gamble almost daily and over several months lost about $2500, which he kept secret from his wife. He reluctantly brought this up to his neurologist, who tapered off his pramipexole therapy. Within a month after stopping pramipexole therapy, he reported no interest in gambling.

Patient 4

This 63-year-old man previously gambled at casinos about once every 3 months with no overspending. Two months after reaching the target dose of 4.5 mg of pramipexole daily his gambling habits increased substantially. He gambled 2 to 3 times per week, with an “incredible compulsion” even when he “logically knew it was time to quit.” He described this as a “unique behavior” and stated that he “had never experienced anything like this before.” The patient recognized that pramipexole “may very well be the culprit,” so he discontinued taking it on his own. Within 1 month of not taking pramipexole, his gambling habits were “back to baseline” and were no longer problematic.

Patient 5

This 41-year-old, married computer programmer reported never gambling in his life. His parkinsonism was well controlled, but pramipexole therapy was added because of his young age. Within 1 month of reaching a dose of 4.5 mg/d, he described being “consumed” with the need to gamble on the Internet, losing $5000 within a few months. In addition to gambling, he compulsively purchased items that he did not need or want, plus he

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Table 1. Demographic Features of Consecutive Patients With Parkinson Disease (PD) and Pathological Gambling*

<table>
<thead>
<tr>
<th>Patient/ Age, y/Sex</th>
<th>Duration of PD, y</th>
<th>Medications for PD, Daily Dose</th>
<th>Other Psychoactive Medications, Daily Dose</th>
<th>Dyskinesias</th>
<th>Motor Fluctuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/53/F 5</td>
<td>Pramipexole, 4.5 mg; levodopa, 600 mg</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2/54/M 4</td>
<td>Pramipexole, 4.5 mg; levodopa, 1000 mg</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3/63/M 5</td>
<td>Pramipexole, 4.5 mg; amantadine, 200 mg</td>
<td>Amitriptyline, 30 mg; nortriptyline, 30 mg</td>
<td>No</td>
<td>No</td>
<td></td>
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<tr>
<td>4/63/M 17</td>
<td>Pramipexole, 4.5 mg; levodopa, 1000 mg</td>
<td>Trazodone</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5/41/M 2</td>
<td>Pramipexole, 4.5 mg; levodopa, 300 mg</td>
<td>Venlafaxine XR, 37.5 mg</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6/52/M 7</td>
<td>Pramipexole, 13.5 mg; levodopa, 600 mg</td>
<td>Venlafaxine, 75 mg</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>7/50/M 9</td>
<td>Ropinirole, 21 mg</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8/35/F 2</td>
<td>Pramipexole, 7.5 mg</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>9/56/M 5</td>
<td>Ropinirole, 15 mg; levodopa, 1500 mg</td>
<td>Quetiapine, 50 mg</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>10/68/M 3</td>
<td>Pramipexole, 4.5 mg; levodopa, 600 mg</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>11/53/M 10</td>
<td>Pramipexole, 8 mg; levodopa, 1000 mg; entacapone, 1000 mg; amantadine, 200 mg</td>
<td>Phenobarbital, 250 mg</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: XR, extended release.

*All patients received standard immediate-release carbidopa/levodopa in divided doses. All other PD medications were divided as per the daily dose. Pramipexole was given as pramipexole dihydrochloride; amantadine as amantadine hydrochloride; ropinirole as ropinirole hydrochloride; amitriptyline as amitriptyline hydrochloride; nortriptyline as nortriptyline hydrochloride; trazodone as trazodone hydrochloride; venlafaxine as venlafaxine hydrochloride; quetiapine as quetiapine fumarate; and phenobarbital as sodium phenobarbital.
was fixated on having sex with his wife several times daily. After seeing his neurologist for a routine visit, he was advised to taper his pramipexole use; instead, he discontinued it abruptly. Two days later, he recognized a rapid resolution of the desire to gamble, which he described “like a light switch being turned off.” There was no recurrence of gambling or any other of his compulsive behaviors over the next several months of follow-up.

### Patient 6

This 52-year-old, married man was initially treated with pramipexole monotherapy and later, carbidopa/levodopa was added. To improve motor function, his pramipexole dose was titrated to 2 mg 3 times per day. However, the patient on his own continued to titrate the medication up to 4.5 mg 3 times per day. Subsequently, his wife phoned his neurologist, reporting that her husband had begun to gamble “uncontrollably,” losing more than $100 000. Prior to this, he gambled only occasionally with losses less than $400 at a time. In addition, he developed compulsive eating (gaining 50 lb) and an obsession with sex, engaging in extramarital affairs and pornography. His pramipexole therapy was tapered off, and within 1 month after stopping, he reported that “all the problems are gone,” with a loss of interest in gambling and pornography. His wife reported that “I have my old husband back”; “he’s back to his old self.”

### Patient 7

This 50-year-old, married man had no history of gambling before taking ropinirole hydrochloride. He had initially been treated with pramipexole but was then treated with ropinirole, which was titrated up to 7 mg 3 times per day. One month after reaching this dose, he began to gamble compulsively, staying at casinos for days at a time, feeling “unable to pull myself away from the tables” and ultimately joining and attending Gamblers Anonymous for a brief time. In addition, his wife noted that for that same period he had increased sex drive, was drinking alcohol more frequently, and was eating excessively. After describing these behaviors to his neurologist, the ropinirole dose was reduced, with dramatic improvement; he stopped gambling and reverted to having sex once weekly instead of 4 times daily.
Table 3. Published Studies—Gambling and Parkinson Disease (PD) Drugs*

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Age, y</th>
<th>Levodopa</th>
<th>Dopamine Agonist</th>
<th>Selegiline</th>
<th>COMT Inhibitor</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seedat et al.16 2000</td>
<td>1</td>
<td>59</td>
<td>Yes</td>
<td>Pergolide</td>
<td>Yes</td>
<td>Tolcapone when began therapy, then entacapone</td>
<td></td>
</tr>
<tr>
<td>Gschwandtner et al.2 2001</td>
<td>2</td>
<td>50</td>
<td>Yes</td>
<td>Pergolide</td>
<td>Yes</td>
<td>Amantadine</td>
<td></td>
</tr>
<tr>
<td>Driver-Dunckley et al.11 2003</td>
<td>9</td>
<td>30</td>
<td>Yes</td>
<td>Pramipexole</td>
<td>Yes</td>
<td>Amantadine</td>
<td></td>
</tr>
<tr>
<td>Montastruc et al.12 2003</td>
<td>1</td>
<td>61</td>
<td>Yes</td>
<td>Pramipexole</td>
<td>Yes</td>
<td>Entacapone</td>
<td></td>
</tr>
<tr>
<td>Kurlan,14 2004</td>
<td>2</td>
<td>48</td>
<td>Yes</td>
<td>Pramipexole</td>
<td>Yes</td>
<td>Tolcapone</td>
<td></td>
</tr>
<tr>
<td>Avanzi et al.13 2004</td>
<td>2</td>
<td>64</td>
<td>Yes</td>
<td>Ropinirole</td>
<td>Yes</td>
<td>Cabergoline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>Yes</td>
<td>Cabergoline</td>
<td></td>
<td>Fluoxetine</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: COMT, catechol O-methyltransferase.

*Meditation doses are not shown because they were inconsistently provided. Pergolide was given as pergolide mesylate; ropinirole as ropinirole hydrochloride; pramipexole as pramipexole dithydrochloride; amantadine as amantadine hydrochloride; trihexyphenidyl as trihexyphenidyl hydrochloride; amitriptyline as amitriptyline hydrochloride; citalopram as citalopram hydrobromide; bromocriptine as bromocriptine mesylate; and fluoxetine as fluoxetine hydrochloride.

**Comment**

This 68-year-old man reported no history of gambling. About 30 months after initiating pramipexole monotherapy, he developed a new and escalating interest in gambling, losing more than $200,000 at casinos over 6 months. In addition, he had delusional thoughts about his wife’s fidelity, became hypersexual, and had episodes of leaving town for days without anyone knowing his whereabouts. Within 2 months of reducing his pramipexole therapy by 50%, his compulsion for gambling was substantially attenuated; after 6 months, he denied feeling any need to gamble or engage in other compulsions.

**SUMMARY**

Pathological gambling developed in 7 of these 11 patients within 1 to 3 months of achieving the maintenance dose or with dose escalation of dopamine agonist therapy. None developed new gambling or an increase in gambling while receiving levodopa monotherapy. The other 4 patients did not report compulsive gambling until 12 to 30 months after initiating dopamine agonist therapy; however, in those cases, gambling resolved within months after discontinuing agonist treatment with stable doses of levodopa. Three patients were treated with a dopamine agonist without levodopa. Of these 11 patients, 4 had never gambled before beginning dopamine agonist treatment.

Additional behavioral problems simultaneously developed in 6 patients and resolved as the pathological gambling subsided. These included compulsive eating with weight gain, increased alcohol consumption, increased spending, and hypersexuality (manifest as increased interest in pornography, extramarital affairs, or increased libido bothersome to the spouse).

These 11 patients developed pathological gambling only after starting therapy with a dopamine agonist, either pramipexole (9 of 11 cases) or ropinirole (2 of 11 cases). The gambling resolved when the dopamine agonist was tapered or discontinued in 8 of the 11 cases; follow-up was not available in the other 3 cases. Although levodopa therapy might have been a contributory factor, none developed these problems when receiving levodopa monotherapy, and 3 patients had not been treated with levodopa. The relationship of pathological gambling to dopamine agonist therapy in these cases is striking.

The association of dopamine agonist treatment with pathological gambling does not reflect disproportionate use of agonists in our practice. In our movement disorders clinic, many patients aged 50 years, and nearly all older than 60 years, initially start with carbidopa/levodopa therapy rather than a dopamine agonist; dopamine agonists are typically added later to treat levodopa complications.

In view of the striking association with dopamine agonist therapy, we elected to compare our experience with that in the medical literature. We performed a MEDLINE search with the general term gambling or the text word gamble and cross-referenced that with the general term Parkinson disease as well as the text word parkinson. This produced 9 references, of which 6 contained descriptions of pathological gambling in PD, plus a listing of medications; these are presented in chronological order in Table 3. The largest series (N = 12) is not shown in the table since medications were not specified, other than to indicate that all were receiving levodopa therapy.9

What is apparent from Table 3 is that all patients with...
PD and pathological gambling were taking a dopamine agonist and all but 1 was receiving levodopa therapy. Included in Table 3 is a retrospective report of all PD cases from 1 clinic during the prior year; pathological gambling was documented in 1.5% of 529 patients treated with pramipexole and 0.3% of pergolide mesylate–treated patients but none receiving levodopa monotherapy.11 This article, as well as others from this systematic review, revealed that all patients were taking a dopamine agonist but none were receiving levodopa monotherapy.

All of the commonly prescribed dopamine agonists have been associated with pathological gambling, as presented in Table 3. Pramipexole, however, is disproportionately represented in both our series (82% of our patients) and in prior reports (59% of patients in Table 3). Pramipexole is a unique drug that is highly selective for the dopamine D3 receptor, with an affinity at least 2 orders of magnitude greater than for other receptors.15-18 The other 2 drugs most commonly implicated in this and prior series are pergolide and ropinirole; these account for 25% of all 28 cases from our series plus the literature (Table 3). These 2 drugs are also relatively selective for the D3 receptor, although their specific affinity for the D3 receptor is less than pramipexole.16,18 Thus, 93% of the agonists implicated in this and the prior series (Table 3) were relatively selective for the D3 receptor. This suggests a pharmacologic substrate for this gambling behavior, which makes intuitive sense in view of the localization of D3 receptors to limbic areas of the brain.19

Giovannoni and colleagues8 described a pervasive behavioral syndrome associated with inappropriate self-administration of ever-increasing amounts of dopaminergic drugs, which they termed hedonistic homeostatic dysregulation. The excesses of dopaminergic treatment resulted in severe dyskinesias and often hypomania or manic psychosis; 2 of their cases developed pathological gambling. One of our patients displayed clinical features similar to these patients, with self-escalation of pramipexole use to the extremely high dose of 13.5 mg/d, associated with a variety of addictive behaviors (patient 6). None of our other patients, however, fit criteria for this syndrome and were unlike their description. Rather, in our patients, the gambling behavior was more circumscribed, although 6 patients simultaneously developed other inappropriate behaviors, which included hypersexuality in 4 patients.

In summary, dopamine agonist drugs appear to be uniquely implicated as a cause of pathological gambling. Both our series and prior reports have especially linked this to administration of the selective dopamine D3 agonist pramipexole. Disproportionate stimulation of dopamine D3 receptors might be responsible for pathological gambling in these PD cases.

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