Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists

M. Tippmann-Peikert, MD; J.G. Park, MD; B.F. Boeve, MD; J.W. Shepard, MD; and M.H. Silber, MB, ChB

Abstract—Pathologic gambling is an impulse control disorder previously reported to complicate dopamine agonist therapy in patients with Parkinson disease. It has not been described in association with dopamine agonist therapy of other conditions. We report three patients treated in our sleep disorders center who developed pathologic gambling while receiving treatment with dopamine agonists for restless legs syndrome.

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Pathologic gambling is defined in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) as persistent and recurrent maladaptive gambling behavior that is characterized by at least five of the following actions: preoccupation with gambling; use of increasing amounts of money; inability to control, cut back, or stop gambling; irritability if not gambling; committing illegal acts to finance the behavior; lies to family or other persons to conceal the behavior; gambling to escape other problems; jeopardizing relationships (personal and professional); or relying on others to relieve desperate financial situations caused by the behavior. A recent meta-analysis evaluating the available literature reported a lifetime prevalence of pathologic gambling in the general US population of 1.93%.¹ A similar or even higher frequency has been suggested in patients with Parkinson disease (PD) treated with dopamine agonists.^{2–4} We report three patients who developed pathologic gambling while being treated with dopamine agonists for restless legs syndrome (RLS).

Methods. With approval of the institutional review board, we reviewed the charts and interviewed three patients treated at our sleep disorders center with dopamine agonists for RLS who developed pathologic gambling.

Case report: Index patient. A 56-year-old woman presented with a 5-year history of creepy–crawling leg sensations primarily occurring at night associated with an urge to move. Transient relief occurred with leg movement and ambulation. She was diagnosed with RLS and started on pramipexole treatment 2.5 years before presentation. Her RLS symptoms improved significantly on a dose of 0.25 mg pramipexole two to three times per day. As soon as she initiated the pramipexole regimen, she developed an uncontrollable compulsion to gamble at a nearby casino. The gambling behavior worsened as the pramipexole dose was increased. She did not have a prior history of gambling behavior before dopamine agonist treatment and, in fact, viewed gamblers as unfortunate individuals. There was no history of substance abuse or psychiatric disorders. Her comorbidities include hypertension, obstructive

sleep apnea, fibromyalgia, asthma, gastroesophageal reflux disease, and spinal stenosis. Neurologic examination and MRI scan of the brain were normal.

Pramipexole was tapered and discontinued, and ropinirole substituted at an initial dose of 0.25 mg daily. The dose was slowly increased to 1.5 mg twice daily. She felt the urge to gamble became even worse on that regimen. Overall she lost large amounts of money (exceeding \$140,000) and discontinued the agent owing to the considerable distress it caused her, despite the resultant emergence of severe RLS symptoms throughout the day. With discontinuation of ropinirole, the desire to gamble completely resolved. She has visited a casino rarely since and will play only a few games. She will not lose money and can easily decide to stop gambling. Treatment with gabapentin 600 mg twice a day led to resolution of restless leg symptoms without any side effects.

Results. The characteristics of the three patients are outlined in the table. The mean dose of pramipexole (three patients) at the time gambling commenced or worsened was 0.5 mg/day (range 0.125 to 0.75 mg). Gambling occurred at a daily dose of 0.25 mg of ropinirole in one patient. The average treatment duration with the dopamine agonist at the time of onset of gambling compulsions was 9.3 months. Minor pre-existing recreational gambling without associated financial losses worsened with agonist therapy in two patients, and gambling behavior occurred for the first time in the third patient. All patients described being preoccupied with gambling, using increasing amounts of money, irritability when unable to gamble, and being unable to control or stop the gambling behavior. One patient reported getting caught in lies and deceptions to conceal his gambling and the financial consequences. Patients lost large amounts of money. No other compulsive behaviors were reported by either patient. Pathologic gambling resolved in all three patients on discontinuation of dopamine agonist therapy; however, two patients continue to gamble infrequently and without considerable financial losses.

From the Mayo Clinic Sleep Disorders Center (M.T.-P., J.G.P., B.F.B., J.W.S., M.H.S.), Department of Neurology (M.T.-P., B.F.B., M.H.S.), and Division of Pulmonary and Critical Care Medicine (M.T.-P., J.G.P., J.W.S.), Mayo Clinic College of Medicine, Rochester, MN.

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Address correspondence and reprint requests to Dr. M. Tippmann-Peikert, Mayo Clinic Sleep Disorders Center, Eisenberg Bldg. 8 G, 200 First Street SW, Rochester, MN 55905; e-mail: tippmannpeikert.maja@mayo.edu

Table Characteristics of patients with compulsive gambling on dopaminergic therapy for restless legs syndrome

Characteristics	Patient 1	Patient 2	Patient 3
Age at onset of pathologic gambling, y/gender	53/F	64/M	54/F
Neurologic examination	Normal	Normal	Normal
Gambling experience before dopamine agonist therapy	Never	1–2×/y; no financial losses	Bingo 1×/m, lottery 2×/wk; \$200–300 loss/y
Gambling after commencing dopamine agonist therapy	4–5×/wk; casino, slot machines; \$140,000 loss	2–10×/mo; slot machines; “several hundred thousand dollars” loss	1–2×/wk casino, slot machines, bingo; daily lottery tickets; >\$750 loss in 1 y
Dose and duration of dopamine agonist when gambling started/worsened	Pramipexole 0.125 mg, ropinirole 0.25 mg; 1 mo	Pramipexole 0.5 mg; 8 mo	Pramipexole 0.75 mg; 17 mo
Gambling experience since discontinuation of dopamine agonist therapy	2×/mo	None	Return to baseline (as before dopamine agonist therapy)

Discussion. Pathologic gambling is thought to be caused by an altered function of the dopaminergic reward system, and changes in the CSF concentration of monoamines and their metabolites have been shown in patients compared with normal controls.⁵ Dopamine is decreased and the metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) increased, resulting in an increased DOPAC/dopamine and HVA/dopamine ratio. Those increased ratios are thought to correlate with an increased dopamine turnover, suggesting an increased dopamine release in the brain of pathologic gamblers.^{5,6} It has been speculated that stimulation of mesolimbic dopamine receptors may result in the gambling behavior in patients with PD who receive dopaminergic treatment.⁷

A recent report describes development of pathologic gambling in 11 patients with PD who were treated with pramipexole, ropinirole, pergolide, and bromocriptine.² Others have reported pathologic gambling developing in patients with PD who were receiving levodopa monotherapy, although development of the condition appears to be much less frequent in that situation.⁴ A possible explanation for that finding may be that the newer nonergot dopamine agonists, especially pramipexole and ropinirole, are relatively selective for and have a much higher affinity to dopamine D3 receptors rather than other dopamine receptor subtypes. This disproportional stimulation of D3 receptors, the highest concentration of which is found in the mesolimbic pathways implicated in motivation, emotion, and reward behaviors, could lead to the development of pathologic gambling.^{2,8,9}

The gambling behavior was seen in patients with and without a prior history of gambling, but if it predated dopamine agonist therapy, it markedly worsened after commencement of treatment. The gambling behaviors appeared to be dose dependent, with daily doses used ranging from 2 to 13.5 mg for

pramipexole and 15 to 21 mg for ropinirole in different reports.^{2,3,7,10} Improvement or resolution was seen with dose reduction or discontinuation of the dopaminergic agent.^{2,3,7,10}

We report three patients who received dopaminergic treatment for RLS and did not have signs of parkinsonism on neurologic examination. To our knowledge, none of the patients was aware of the reported association of dopamine agonists and pathologic gambling in patients with PD prior to initiation of their treatment trial. In contrast to the higher doses associated with pathologic gambling behavior in patients with PD, our patients reported commencement of gambling compulsions at a mean pramipexole dose of 0.46 mg and ropinirole at 0.25 mg/day. The behavior further worsened with dose increments. Gambling behaviors rapidly resolved or markedly decreased to nonconcerning levels once dopamine agonist therapy was discontinued. The duration of dopamine agonist therapy prior to development of pathologic gambling in our RLS patients was similar to that previously reported in patients with PD (mean 9.3 vs 8.1 months) in one report, although the majority of the PD patients developed the problem within 1 to 3 months after dopamine agonist initiation.² However, others have reported a much more protracted onset of pathologic gambling in PD patients after treatment with dopamine agonists for as long as 5 or 9 years.¹⁰

We cannot comment on the prevalence of pathologic gambling in patients treated with dopamine agonists for RLS as we did not perform systematic screening of our entire patient population. Future studies are needed to establish if the prevalence of this condition in this population is different from that in the general population. However, the close time relationship of development or significant worsening of gambling behaviors in our patients as well as the resolution upon discontinuation of the dopaminergic agents suggest a causative association.

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Figure 1. High resolution coronal CT sections through the jugular bulb on the right (A) and left (B) sides shows high riding jugular bulb on the right side with a medial diverticulum. (1) Mastoid air cells, (2) posterior semicircular canal, (3) jugular diverticulum, (4) high riding right jugular bulb, (5) atlas vertebra, (6) dens process of axis vertebra, (7) hypoplastic left jugular bulb.

An unusual case of pulsatile tinnitus and deafness

Bejoy Thomas, MD, DNB, PDCC;
and Chandrasekharan Kesavadas, MD, DMRD,
Trivandrum, India

A 49-year-old man presented with pulsatile tinnitus and deafness on the right side of 6 years duration associated with occasional positional vertigo. Examination revealed sensory neural deafness on the right side. Otoscopy was unremarkable. On compression of right side neck vessels, the tinnitus was noted to be

Figure 2. (A, B, C) High resolution serial axial CT sections through the skull base from inferior to superior. (D) Sagittal source images of MR venogram. (1) High riding right jugular bulb, (2) hypoplastic left jugular foramen, (3) mastoid air cells, (4) external auditory canal. (5) right sigmoid sinus, (6) left carotid canal, (7) head of malleus, (8) right internal auditory meatus, (9) jugular diverticulum, (10) transverse sinus.

decreasing. A cerebral MR venogram and HRCT of skull base revealed high riding right jugular bulb with a medial jugular diverticulum, which was just adjacent to the posterior semicircular canal with no bony dehiscence (figures 1 and 2). The right transverse sinus was dominant.

Jugular bulb diverticula may extend either laterally in the tympanic cavity or medially to the petrous bone close to the inner ear.¹ Both can be symptomatic and the medial one can present with vertigo, pulsatile tinnitus, and sensorineural hearing loss.^{1,2}

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Address correspondence and reprint requests to Dr. Bejoy Thomas, Associate Professor, Department of Imaging Sciences and Interventional Radiology, SCTIMST, Trivandrum, India-695011; e-mail: drbejoy2002@yahoo.com

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Bejoy Thomas and Chandrasekharan Kesavadas

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