Impulse Control Disorders with the use of Dopaminergic Agents in Restless Legs Syndrome: a Case-Control Study

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Study Objectives: To determine the frequency of impulse control disorders (ICDs) with the use of dopaminergic agents in restless legs syndrome (RLS).

Design: Prospective case-control study using a screening questionnaire for ICDs, followed by phone interview to confirm diagnoses for those meeting preset scoring thresholds on the questionnaire.

Setting: Academic, comprehensive sleep medicine center.

Patients or Participants: (1) One hundred patients with RLS treated with dopaminergic agents, (2) 275 patients with obstructive sleep apnea (OSA) without RLS or exposure to dopaminergic agents; and (3) 52 patients with RLS who were never treated with dopaminergic agents. Subjects with parkinsonism were excluded.

Interventions: Not applicable.

Measurements and Results: Based on the questionnaire, frequencies of ICDs for the RLS treatment group were 10% compulsive shopping, 7% pathologic gambling, 23% compulsive eating, 8% hypersexuality, and 10% punding. These values were statistically significant when compared with control subjects with OSA for compulsive shopping and pathologic gambling. With additional information from the phone interview, adjusted frequencies for the RLS treatment group were 9% compulsive shopping, 5% pathologic gambling, 11% compulsive eating, 3% hypersexuality, 7% punding, and 17% any ICD. These values were statistically significant when compared with those of control subjects with OSA for compulsive shopping, pathologic gambling, punding, and any ICD, as well as for compulsive shopping when compared with control subjects with RLS who were not treated with dopaminergic agents. In the RLS treatment group, a statistically significant dose effect was found for pramipexole in those subjects confirmed to have ICDs by both the questionnaire and phone interview. Mean duration of treatment at ICD onset was 9.5 months.

Conclusions: ICDs are common with the use of dopaminergic agents for treatment of RLS. Given the potentially devastating psychosocial consequences of these behaviors, it is critical to actively screen for ICDs in this population.

Keywords: Restless legs syndrome, dopamine, impulse control

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AN INCREASED FREQUENCY OF IMPULSE CONTROL DISORDERS (ICDS) HAS BEEN RECOGNIZED WITH THE USE OF DOPAMINERGIC AGENTS IN A SUBSET OF patients with Parkinson disease (PD). The central dopaminergic reward system has been implicated, possibly due to overstimulation of mesolimbic dopamine receptors.[1] Recognized ICDs in this setting include pathologic gambling,[2-7] hypersexuality,[7-9] compulsive shopping,[7,9] compulsive eating,[10] punding,[11-14] and compulsive medication use.[15] Punding is characterized by complex, stereotyped, and often purposeless repetitive actions such as continued handling or sorting of common objects, manipulation of technical equipment, excessive grooming or cleaning, and hoarding.[13,14] Several of these entities are formally designated as "impulse control disorders" in the *Diagnostic and Statistical Manual of Mental Disorders (4th Edition),*[16] but this group of behaviors can be recognized as a whole by a common inability to resist impulses, drive, or temptation to engage in ultimately self-destructive acts. Controversy remains regarding their overall classification because of overlap with obsessive-compulsive and addiction processes.

In patients with PD, ICDs are relatively common, with estimated lifetime prevalence rates of 3% to 8% for pathologic gambling, 2.5% to 7.2% for hypersexuality, and 0.4% to 1.5% for compulsive shopping.[1,7] For comparison, the lifetime prevalence of pathologic gambling in the general population is between 0.3% and 2%.[1,3,17-19] Similar data for other ICDs are less well established. One questionnaire-based study demonstrated an overall lifetime prevalence of pathologic gambling, hypersexuality, or compulsive shopping in patients with PD of 6.1% but a statistically significant heightened rate of 13.7% with the use of dopaminergic agonists in this population.[9] The individual lifetime prevalence rates in the subset of patients using dopaminergic agonists in this study were 7.2% for pathologic gambling, 7.2% for hypersexuality, and 1.4% for compulsive shopping.[9] A recent retrospective analysis of 267 local patients with PD found new-onset compulsive gambling or hypersexuality in 18.4% of subjects taking therapeutic doses of dopamine agonists (defined as ≥ 2 mg of pramipexole or 6 mg of ropinirole daily).[20] Numerous reports in the literature confirm a similar striking relationship between ICDs and the use of dopaminergic agents in PD.[1-10,12,15] A consistent dose effect has not been demonstrated.[1]

The relationship between ICDs and the use of dopaminergic medications in disease processes other than PD has not been as well studied. Several case reports suggest that pathologic

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gambling may have an increased frequency with the use of dopaminergic agonists in restless legs syndrome (RLS).[19,21,22] A recent retrospective survey of 77 patients with idiopathic RLS actively taking dopaminergic medication found increased gambling in 6% and excessive sexual behaviors in 4% of the subjects.[23]

RLS is a common and important neurologic disorder. Epidemiologic studies suggest that 10% to 15% of adults in European and North American countries meet criteria for diagnosis, including 2.5% in which the condition seriously affects quality of life.[24-27] Although the precise pathophysiology remains unknown, dysfunction of central dopaminergic systems has been implicated, and dopaminergic agents are widely used for treatment of symptoms.[28] Given the potentially devastating psychosocial consequences of ICDs, a better understanding of the frequency of these behaviors is essential to improve medical management of RLS. We performed a prospective, case-control study to determine the frequency of ICDs in patients with RLS using dopaminergic agents. Our primary hypothesis was that the frequency would be higher than in a comparative group of patients with obstructive sleep apnea (OSA).

METHODS

The study was approved by the Mayo Clinic Institutional Review Board. One hundred patients with RLS seen at the Mayo Clinic Center for Sleep Medicine in Rochester, Minnesota, were recruited between February and July 2008 (RLS treatment group). In an effort to maintain consecutive enrollment, study materials were mailed to those unable to complete the questionnaire at the time of their recruitment. Inclusion criteria were patient consent, a diagnosis of RLS by a board-certified sleep specialist using standard clinical criteria,[29] and treatment with dopaminergic agents either at the time of recruitment or previously during the course of their illness. Dopaminergic agents were defined as levodopa, pramipexole, ropinirole, bromocriptine, pergolide, cabergoline, rotigotine patch, or apomorphine injection. Two comparative groups presenting to the Center for Sleep Medicine between February and November 2008 were also recruited following patient consent: (1) 275 patients with a polysomnogram-confirmed diagnosis of OSA[29] but no exposure to dopaminergic agents and a definitive statement in the sleep-center clinical documentation that the patient did not have RLS (OSA control group) and (2) 52 patients with RLS who were never treated with dopaminergic agents (RLS control group). Subjects were excluded from any study group on the basis of prior diagnoses of parkinsonism, including PD and related disorders, and inability to complete the questionnaire.

The subjects were asked to complete a questionnaire consisting of a modified compulsive shopping survey,[30] a modified version of the South Oaks Gambling Screen,[31] a clinician investigator-designed compulsive-eating questionnaire, a modified hypersexuality questionnaire,[9] and a modified punding questionnaire (Appendix—available online only at www.journalsleep.org).[12] Based on available diagnostic criteria and the use of similar surveys in the PD literature,[1,9,12,16,30,31] a threshold score was established for each section of the questionnaire: a total score of at least 9 for compulsive shopping, *yes* to question #1 and a total score of at least 5 for pathologic gambling, *yes* to question #1 and a total score of at least 5 for compulsive eating, *yes* to question #1 and a total score of at least 2 for hypersexuality, and a total score of at least 4 for punding. Age, sex, and body mass index (BMI) were obtained by chart review for study participants. In addition, the past medical and social history sections of the medical record were searched for current or previous psychiatric diagnoses (depressive disorders, including any form of major depression, dysthymia, and symptoms of depression; anxiety disorders, including symptoms of anxiety, obsessive-compulsive disorder, generalized anxiety disorder, social phobia, and panic disorder; or other psychiatric diagnoses), as well as current or previous substance abuse (alcohol or illicit drugs).

Subjects meeting preset scoring thresholds for ICDs on the questionnaire were contacted by phone and informed that their scores suggested behavior symptoms that might require medical attention. The investigator offered to arrange for consultation at the Mayo Clinic or notify a local care provider when appropriate. With verbal consent, a standardized structured interview took place to confirm suspected diagnoses of ICDs using available diagnostic criteria.[1,9,12,14,16,32,33] An attempt was made to identify aspects of obsessive-compulsive spectrum disorder or mania or hypomania present at the time of ICDs. For the group of patients with RLS who were treated with dopaminergic agents, the phone interview also sought to define the temporal association between medication use and the onset of ICDs, the dose of medication at onset of ICD symptoms, perceived negative consequences of the condition, and whether the presumed offending medication had been discontinued or adjusted.

Using an estimated ICD prevalence of 7% in the RLS treatment group and 1% in the OSA control group, the study was designed to achieve 81% power in detecting statistically significant differences between the groups with respective sample sizes of 100 and 275 subjects. The study was not designed to be powered to evaluate the anticipated limited number of RLS control subjects. The Fisher exact test with a 2-sided significance level set at a P value of less than 0.05 was used to compare the questionnaire and phone interview results of the RLS treatment group with the OSA and RLS control groups. The Kruskal-Wallis test evaluated total scores on each section of the questionnaire between study groups. The Fisher exact test and a 2-sample *t* test with significance level set at a P value of less than 0.05 were used to compare demographics in the study populations. Wilcoxon (rank-sum) 2-sample test was used for analysis of dose effect in the RLS treatment group. Linear and multivariable logistic analyses were performed to adjust for covariables.

RESULTS

Four patients were excluded from the study because of prior diagnoses of parkinsonism. Eight patients (7 from the OSA control group and 1 from the RLS control group) were ineligible to participate due to incomplete questionnaires. One hundred subjects in the RLS treatment group, 275 OSA control subjects, and 52 RLS control subjects were enrolled in the study. Demographics for each study group are shown in Table 1. When compared with the RLS treatment group, mean age was higher in the OSA control group, which also contained a greater proportion of men. Mean BMI was increased in both control groups

Table 1—Demographics of the study population

	Men	Age, y	BMI, kg/m^2	History of any psychiatric diagnosis	Depressive disorders	Anxiety disorders	History of substance abuse
RLS treatment group (n = 100)	52 (52)	59.0 ± 14.6	29.8 ± 5.2	62 (62)[a]	54 (54)	16 (16)	3 (3)
OSA control group (n = 275)	176 (64)[b]	62.9 ± 12.1[c]	35.0 ± 7.1[c]	128 (47)[c,d]	74 (27)[c]	39 (14)	8 (3)
RLS control group (n = 52)	25 (48)	60.8 ± 14.9	34.0 ± 8.6[c]	19 (37)[c,e]	17 (33)[b]	4 (8)	1 (2)

Data are presented as number (%) except age and body mass index (BMI), which are shown as mean ± SD. The control groups comprised patients who had been diagnosed with their respective disorders (obstructive sleep apnea [OSA] or restless legs syndrome [RLS]) but who had never received treatment with dopaminergic agents.

[a]Psychiatric diagnoses other than depressive and anxiety disorders included single cases of obsessive compulsive tendencies, schizophrenia, somatoform disorder, post-traumatic stress disorder, adjustment disorder not otherwise specified, and borderline personality disorder.

[b]Statistically significant at the $P \leq 0.05$ level compared to RLS treatment group

[c]Statistically significant at the $P \leq 0.01$ level compared with the patients with RLS who received treatment with dopaminergic agents (RLS treatment group).

[d]Psychiatric diagnoses other than depressive and anxiety disorders included 5 cases of eating disorders, 2 cases of personality disorder not otherwise specified, and 2 cases of adjustment disorder not otherwise specified, as well as single cases of bipolar disorder, obsessive compulsive disorder, and schizoaffective disorder.

[e]Psychiatric diagnoses other than depressive and anxiety disorders included 1 case of post-traumatic stress disorder.

compared with the RLS treatment group. Patients with RLS who were treated with dopaminergic agents were more likely to have a history of psychiatric diagnoses, specifically depression, than either of the control groups. No significant difference in substance abuse history or anxiety disorders was found between the groups.

Based on the questionnaire alone, frequencies of ICDs for the RLS treatment group were 10% compulsive shopping, 7% pathologic gambling, 23% compulsive eating, 8% hypersexuality, and 10% punding (Table 2). The frequency of any ICD for the RLS treatment group was 32%. Excluding the large number of compulsive-eating cases, this value was 20% (13% OSA controls; 12% RLS controls). Frequencies were significant when compared with the OSA control group for compulsive shopping ($P = 0.004$) and pathologic gambling ($P = 0.005$).

Mean total scores for each questionnaire section were evaluated between study groups (Table 3). There were no statistically significant differences between the RLS treatment group and the 2 control groups. A linear regression analysis compensating for the variations in sex, age and BMI in the different groups confirmed no significant differences. To further assess the possible effect of these demographic differences, a posthoc multivariable logistic regression analysis was conducted on the questionnaire results, based on those subjects above and below the threshold scores for each ICD. When the model was adjusted for age and sex, statistically significant increased rates were found for the RLS treatment group compared with the OSA control group with respect to pathologic gambling ($P < 0.006$) and compulsive shopping ($P < 0.025$). When adjustments were also made for BMI, rates remained significantly different for pathologic gambling ($P < 0.01$) and approached significance for compulsive shopping ($P < 0.08$), even though the low number of subjects with ICDs resulted in the logistic regression models being underpowered. Because the adjusted frequencies of ICDs following the interviews were still lower, a logistic regression analysis could not be accurately performed using this data. Similarly, the frequency of ICDs in the RLS control group was too low to perform statistical subanalyses, but the only demographic difference between this control group and the RLS treatment group was in BMI.

To increase the specificity of the findings, the data were reanalyzed based on additional information obtained from phone interviews. Of the 32 subjects in the RLS treatment group who scored above threshold on the questionnaire, phone-contact information was available for all but 1 subject. All 13 of such patients from the RLS control group completed the interview, and 73 of 77 OSA controls who scored above threshold could be reached by phone. All interviews were conducted within 4 months of the time the questionnaires were completed. When considering additional information obtained from the phone interview, adjusted frequencies of ICDs for the RLS group treated with dopaminergic agents were 9% compulsive shopping, 5% pathologic gambling, 11% compulsive eating, 3% hypersexuality, and 7% punding (Table 2). These values were significant when compared with the OSA control group for compulsive shopping ($P = 0.0002$), pathologic gambling ($P = 0.006$), and punding ($P = 0.005$), as well as for compulsive shopping ($P = 0.03$) when compared with the RLS control group. The frequency of any ICD based on the phone interview was 17%, a statistically significant finding when compared with the OSA control group (6%; $P = 0.004$).

In the group of patients with RLS who were treated with dopaminergic agents, 1 patient with an ICD confirmed by phone interview reported a diagnosis of obsessive-compulsive tendencies. In the OSA control group, 1 subject with a confirmed ICD was working with a therapist for obsessive-compulsive disorder, and another was diagnosed with bipolar disorder, including episodes of mania during the time of impulse control behaviors. No patients from the RLS control group had recognized obsessive-compulsive spectrum disorder or mania or hypomania.

Further analysis was completed for the 17 subjects from the RLS treatment group confirmed during the phone interview to have experienced ICDs. There were no significant differences in age, sex, BMI, frequency of psychiatric diagnoses, or frequency of substance abuse in this subgroup when compared with the rest of the RLS treatment group. Fifteen of these 17

Table 2—Frequencies of impulse control disorders

	Compulsive shopping	Pathologic gambling	Compulsive eating	Hypersexuality	Punding	Any ICD
2A—Raw frequencies based on questionnaire results						
RLS treatment group (n = 100)	10 (10%)	7 (7%)	23 (23%)	8 (8%)	10 (10%)	32 (32%)
OSA control group (275)	7 (3%)[a]	3 (1%)[a]	54 (20%)	15 (5%)	17 (6%)	77 (28%)
RLS control group (n = 52)	1 (2%)	1 (2%)	9 (18%)	1 (2%)	4 (8%)	13 (25%)
2B—Adjusted frequencies based on phone interview results						
RLS treatment group (n = 100)	9 (9%)	5 (5%)	11 (11%)	3 (3%)	7 (7%)	17 (17%)
OSA control group (n = 275)	2 (0.7%)[a]	1 (0.4%)[a]	14 (5%)	1 (0.4%)	3 (1%)[a]	17 (6%)[a]
RLS control group (n = 52)	0 (0%)[b]	1 (2%)	3 (6%)	0 (0%)	0 (0%)	4 (8%)

Data are presented as number (%). ICD refers to impulse control disorder. The control groups comprised patients who had been diagnosed with their respective disorders (obstructive sleep apnea [OSA] or restless legs syndrome [RLS]) but who had never received treatment with dopaminergic agents.
[a]Statistically significant at the P ≤ 0.01 level compared with the patients with RLS who had received treatment with dopaminergic agents (RLS treatment group).
[b]Statistically significant at the P ≤ 0.05 level compared with the RLS treatment group.

Table 3—Mean total scores for each questionnaire section

	Compulsive shopping	Pathologic gambling	Compulsive eating	Hypersexuality	Punding
RLS treatment group (n = 100)	3.2	1.4	2.0	0.4	1.6
OSA control group (n = 275)	2.4	1.0	2.0	0.2	1.4
RLS control group (n = 52)	3.0	0.9	1.9	0.2	1.5

subjects (71%) had been treated with pramipexole at some point during their disease course, with a mean dose of 1.35 ± 0.62 mg of pramipexole daily. A statistically significant dose effect (P = 0.0001) was found in comparison with the other 66 participants from the RLS treatment group without phone interview-confirmed ICDs (mean dose 0.67 ± 0.48 mg daily). Similar analyses for ropinirole and levodopa did not demonstrate dose effect.

Twelve of the 17 subjects from this subgroup were taking pramipexole at the time of ICD onset, and the other 5 were using ropinirole. The average daily dose of medication at compulsive-behavior onset was 1.25 mg (range 0.5-2.0 mg) for pramipexole and 3.6 mg (range 0.5-6.0 mg) for ropinirole. The mean duration from initiation of medication to onset of ICD or ICDs was 9.5 months (range 2 weeks-3 years). Dopaminergic medications were discontinued due to ICDs in 8 of 17 patients. Symptoms resolved completely within several weeks in 7 of these cases, and the 1 remaining case noted substantial improvement. The association between dopaminergic agents and ICDs had not been recognized in 3 cases despite documentation of physician inquiry regarding these behaviors in the medical record—these patients were referred for expedited appointments to consider medication adjustment. Six patients had taken levodopa at doses ranging from 100 to 200 mg daily for 4 months up to more than 10 years without experiencing any behavior changes but later developed ICDs after being switched to pramipexole. Four patients had no impulse-control problems on pramipexole at doses ranging from 0.50 to 2.25 mg daily for 1 week up to 6 years but experienced behavior changes after changing to ropinirole.

Case Reports

1. A 60-year-old woman with no previous gambling history was on pramipexole for several months at a daily dose of 0.50 mg before she developed an "uncontrollable urge" to play slot machines. She visited casinos at least twice per week, with approximately $6000 in losses per month because "it was impossible to stop until all of my resources were exhausted." Gambling behaviors improved when the patient was switched to gabapentin, but the patient later resumed pramipexole on her own.

2. After approximately 3 months on ropinirole at 4.0 mg per day, a wealthy 79-year-old man started to entertain "multiple girlfriends at a time that were half my age." He spent more than $50,000 on cars for 2 of these girlfriends and had purchased a $1.25 million penthouse for another. In addition, he reported an intense urge to eat "something crunchy" for several hours after taking ropinirole. These behaviors were not previously recognized as problematic by the patient.

3. A 47-year-old woman reported concerning behaviors after she had been taking pramipexole at 0.50 mg daily for 6 months. She lost an estimated $5000 on purchases from the shopping channel ("ugly clothes and jewelry that I didn't even need") and set her alarm clock for early morning hours "because I just couldn't miss a sale." She had food binges, eating an entire pizza or a dozen donuts at one sitting "even though I wasn't hungry." Sometimes she would stay up "all hours of the night" cross-stitching. Finally, she reported "being more risky" by performing sexual acts in public. Although present for almost 2 years, these behaviors resolved completely in 1 to 2 months after pramipexole was discontinued.

4. A 59-year-old man is dealing with ongoing litigation related to inappropriate sexual behaviors involving the Internet that prompted police to raid his home, much to the shock of his wife and grandchildren. He gained more than 200 pounds with food binges, his wife constantly returned unneeded purchases to the store, and he spent 10 to 12 hours per day on the computer in chat rooms, playing games, and viewing pornography. All of the behaviors started within a year of his taking ropinirole 4.0 mg daily and resolved quickly when he was taken off the medication.

DISCUSSION

This study demonstrates that ICDs are common with the use of dopaminergic agents for the treatment of RLS. Statistically significant increased rates were found for compulsive shopping and pathologic gambling, in comparison with the large group of OSA controls, based on questionnaire results alone, and, for compulsive shopping, pathologic gambling, and punding, when additional information from follow-up phone interviews was considered.

Using the phone interview to confirm diagnoses of ICDs for those subjects that scored above preset thresholds on the questionnaire, we found that the frequencies in RLS patients treated with dopaminergic agents were 9% for compulsive shopping, 5% for pathologic gambling, 11% for compulsive eating, 3% for hypersexuality, 7% for punding, and 17% for any ICD. These findings are similar to those for compulsive shopping, pathologic gambling, and hypersexuality described with the use of dopaminergic agents in PD; limited data are available for interpreting the rates of compulsive eating and punding.[1-10,12,13,15] Although the increased frequency of ICDs in PD has garnered much attention, limited information is available regarding these behaviors with the widespread use of dopaminergic medications in RLS. Perhaps this is due to both patient underreporting and clinician assumption that the lower medication doses used to treat RLS would not predispose patients to developing the same compulsions. However, our results further confirm that this same association exists in RLS, as previously suggested by several case reports and a recent retrospective survey.[19,21-23]

For those subjects from the RLS treatment group confirmed to have experienced ICDs by phone interview, we found mean daily doses of 1.25 mg for pramipexole and 3.6 mg for ropinirole at behavior onset. These represent common maintenance levels for treatment of RLS in clinical practice and are considerably lower than doses conventionally used to treat PD. A statistically significant dose effect was found in this subgroup for pramipexole, but not for ropinirole or levodopa, when compared with the rest of the RLS treatment group. As in a prior case series, a mean treatment duration of 9.5 months at the time of compulsive-behavior onset was demonstrated.[19] This suggests that physicians need to continue to monitor for ICDs after initial titration of the medication.

Numerous individual factors have been associated with vulnerability to ICDs in patients with PD, including high novelty-seeking personality traits, depression, male sex, substance abuse, and younger age of PD onset.[1,17] Age, sex, BMI, psychiatric history, and history of substance abuse were evaluated in our study. Subjects from the RLS treatment group were more likely to have depression than were subjects in either of the control groups. However, no statistically significant demographic differences were noted when comparing the subgroup of patients from the RLS treatment group confirmed to have ICDs by phone interview with other subjects from the RLS treatment group. Additional research is needed to identify risk factors that predispose patients to developing these behaviors.

Many of our patients with RLS who were treated with dopaminergic medications suffered devastating consequences from ICDs, as highlighted by the included case reports. It is extremely important to actively screen for ICDs in this population by discussing the risks of, benefits of, and alternatives to the use of these medications. Discontinuation of the dopaminergic agent and/or switching to another medication in this class of medications can be effective management strategies.[1,17,18] We found that symptoms resolved completely within several weeks in 7 out of 8 patients with ICDs when the offending medication was discontinued; the other patient had substantial improvement in prior compulsions.

Findings from this study may also be helpful to our understanding of how ICDs develop in the context of PD. Although most clinical reports suggest at least some contributing role of dopaminergic agents, unanswered questions remain as to whether ICDs are related primarily to pathologic features of the disease itself.[13] Since our study demonstrates that dopaminergic medications used in a non-PD population trigger the same behaviors, it further supports the concept that the medications, rather than the underlying disease process, are predominantly to blame. Alternatively, it is possible that RLS and PD share a common underlying pathophysiology because some studies suggest that RLS is more common in patients with PD than in control subjects.[1,24-26] However, although the precise pathophysiology of RLS is unknown, there are a number of arguments for a different underlying process, including the lack of Lewy body pathology or neuronal degeneration in RLS, the occurrence of dopaminergic medication augmentation in RLS but not PD despite treatment with the same medications at higher doses, and the common occurrence of dyskinesias and motor fluctuations with long-term dopaminergic therapy in PD but not generally in RLS.[28,34]

It is thought that aberrancy of the central dopaminergic reward system leads to development of ICDs in the setting of exposure to dopaminergic medications. Dopaminergic mesolimbic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, as well as associated frontostriatal circuitry, play a major role in the mechanisms of reward and reinforcement.[35] Of note, pramipexole and ropinirole have relative selectivity and higher affinity for dopamine D_3 receptors, which are concentrated in mesolimbic pathways.[36,37] Dopaminergic agents may act on these pathways through a number of mechanisms: altering the physiologic role of dopamine as an error-prediction and teaching signal, stimulation of a particular region of dopamine receptors causing a shift from goal-directed behaviors to habit formation, or chronic neuronal stimulation leading to behavior sensitization.[1] Using brain perfusion single-photon emission computed tomographic imaging, 1 study confirmed that PD patients on dopaminergic therapy who had pathologic gambling had significant resting-state overactivity in brain areas involved in reward-based learning, motivation, and impulse control.[38]

Strengths of this study include the systematic prospective screening process for 5 separate ICDs with case-control comparisons. The follow-up clinician-directed telephone interview provided an additional structured assessment to improve diagnostic accuracy. However, there are several limitations. ICDs often occur without subjective distress and are frequently hidden or unnoticed by patients,[1] so self-reporting of these socially unacceptable behaviors may actually lead to an underestimation. Strict consecutive enrollment was hindered by time constraints for filling out the lengthy questionnaire during an office visit. Patients with obsessive-compulsive disorder were not excluded from participation in the study, but only 2 patients reported symptoms or a diagnosis of this condition—1 from the RLS treatment group and 1 from the OSA control group. Although questionnaire design and scoring were based on available diagnostic criteria for ICDs and the use of similar surveys in the PD literature, they were not independently validated. The study population was representative of a large academic sleep medicine practice, but the results cannot be extrapolated to a community-based population. This study was not powered for analysis of the comparative group of patients with RLS who had never been treated with dopaminergic agents. We anticipated limited enrollment in this study group, given that the majority of patients with RLS evaluated at our tertiary referral center have been tried on a least 1 dopaminergic agent in the past. Several demographic differences were noted between the RLS treatment group and the OSA control group. To adjust for these differences, multivariable logistic regression analyses were performed that supported statistically significant differences between the RLS treatment group and the OSA control group with respect to pathologic gambling and compulsive shopping. The investigator performing the phone interviews (JRC) was not blinded to study group, as the protocol required questions regarding the time and dose relationships between the use of the drug and the onset of symptoms, as well as whether the drug had been discontinued. Although this may have introduced some bias into the interpretation of the answers, the presence or absence of ICDs was usually very clear without ambiguity.

In summary, our case-control study demonstrates that 17% of patients treated with modest doses of dopaminergic agents for RLS will develop ICDs. Physicians treating RLS should be familiar with this potentially serious side effect and counsel patients prior to initiation of therapy.

DISCLOSURE STATEMENT

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