

Compulsive Eating and Weight Gain Related to Dopamine Agonist Use

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Abstract: Dopamine agonists have been implicated in causing compulsive behaviors in patients with Parkinson's disease (PD). These have included gambling, hypersexuality, hobbyism, and other repetitive, purposeless behaviors ("punding"). In this report, we describe 7 patients in whom compulsive eating developed in the context of pramipexole use. All of the affected patients had significant, undesired weight gain; 4 had other comorbid compulsive behaviors. In the 5 patients who lowered the dose of pramipexole or discontinued dopamine agonist

treatment, the behavior remitted and no further weight gain occurred. Physicians should be aware that compulsive eating resulting in significant weight gain may occur in PD as a side-effect of dopamine agonist medications such as pramipexole. Given the known risks of the associated weight gain and obesity, further investigation is warranted. © 2005 Movement Disorder Society

Key words: Parkinson's disease; dopamine agonist; compulsive eating; binge; weight gain

Recent reports have demonstrated that patients with Parkinson's disease (PD) who are treated with dopamine replacement therapy (DRT)—particularly dopamine agonists—are at risk for developing several different compulsive behaviors. These behaviors may include gambling, hypersexuality, hobbyism, and "punding" (repetitive, purposeless behaviors similar to those seen in the setting of amphetamine or cocaine abuse).^{1–13} The compulsive behaviors appear to be most common in men with young-onset PD.¹⁴ In some cases, they occur in the setting of the dopamine dysregulation syndrome, in which patients increase their DRT to higher than recommended (often toxic) levels.^{8,14}

PD itself has been strongly associated with weight loss, particularly in women; proposed mechanisms include increased energy expenditure, early satiety (due to decreased gastrointestinal motility), olfactory impairment, bulbar dysfunction, or decreased baseline dopami-

nergic stimulation of central reward systems.^{15–18} The weight loss can be dramatic, and often predates the diagnosis of PD. In contrast, the treatment of PD with pallidotomy, deep brain stimulation (DBS), or continuous subcutaneous apomorphine has been associated with rapid weight gain for unclear reasons.^{19–22}

Despite the general tendency for PD patients to lose weight, we have identified a subset of patients with new-onset food cravings, compulsive eating, and undesired weight gain in the setting of dopamine agonist use. In this report we present a series of 7 subjects in whom these symptoms were associated with the use of pramipexole (PPX), a non-ergot dopamine agonist. We postulate that compulsive eating is part of the spectrum of behavioral disturbances that may be precipitated by dopamine agonists.

SUBJECTS AND METHODS

We identified patients at our center with a clinical diagnosis of idiopathic PD who developed new-onset compulsive eating in the setting of dopamine agonist use. In this report, we present the findings from the first 7 patients who met those inclusion criteria. All of the study subjects were taking PPX, the dopamine agonist that is most frequently prescribed in our practice. We subsequently observed similar behavior in 2 patients who were taking ropinirole.

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TABLE 1. Pre- and post-treatment weights

Subject	Baseline weight (kg)	Baseline BMI (kg/m ²)	Baseline BMI category	Weight increase (kg)	BMI increase (kg/m ²)
A	57	22.2	Normal	13	5.0
B	114	35	Obese	18	5.5
C	125	22.9	Normal	16	6.4
D	73	25.1	Overweight	7	2.4
E	83	25.8	Overweight	7	2.2
F	78	26.8	Overweight	6	2.0
G	82	25.9	Overweight	24	7.5
Mean	87 ± 24	26 ± 4	–	13 ± 7	4 ± 2

BMI, body mass index; PPX, pramipexole.

After obtaining Columbia University Institutional Review Board approval and informed consent from each patient, we collected data from a combination of telephone interviews and retrospective chart reviews. For the purpose of this report we defined “compulsive eating” as uncontrollable consumption of a larger amount of food than normal, in excess of that necessary to alleviate hunger. We defined “binge eating” as compulsive eating that occurred over a short period of time. We present two representative cases in detail below.

Case 1

Subject A is a 54-year-old, left-handed woman with a family history of PD in her brother and a maternal uncle. She was diagnosed with PD after presenting with a 15-month history of left hand rest tremor. Her baseline weight was 57 kg, with a body mass index (BMI) of 22.2 kg/m².

She was started on PPX, which was gradually increased to a target dose of 1.5 mg/day. During that time she developed new-onset cravings for cookies, crackers, and pasta. She began to eat compulsively, with binging in the middle of the night. Over a period of 7 months she gained 13 kg; her BMI increased to 27.2 kg/m² (overweight).

Because of compulsive eating and excessive daytime sleepiness, PPX was discontinued and no other dopaminergic medications were started. Since that time she has had no further cravings, compulsive eating, or weight gain.

Case 2

Subject B is a 64-year-old, right-handed man with a family history of PD in his maternal grandmother and a maternal aunt. He developed left-hand dystonia at the age of 50, followed by left hand rest tremor at the age of 60; he was diagnosed with PD at that time. His baseline weight was 114 kg, with a BMI of 35 kg/m² (obese).

At the age of 61, he began treatment with PPX. His dose was gradually increased to 4.5 mg/day, at which time toxic side effects began to occur including compulsive gambling, hypersexuality, visual hallucinations, and excessive daytime sleepiness. When driving, he often had to pull over to the side of the road to avoid falling asleep at the wheel. Despite these toxic side-effects and repeated warnings from his treating physician, he continued to self-adjust his medications, increasing the dose of PPX to as high as 9 mg/day.

While taking high-dose PPX, he developed new-onset cravings for chocolate and other sweets, with compulsive eating and uncontrollable nocturnal binging. His weight increased to 132 kg, with a BMI of 40.5 kg/m² (obese). He was fitted with a mouth plate in an attempt to decrease his caloric intake (by slowing down his eating), without apparent benefit.

Because of ongoing weight gain and other toxic side-effects he was eventually convinced to lower his dose of PPX to 3 mg/day, supplemented with levodopa (300–400 mg/day) to control his motor symptoms; he subsequently discontinued PPX and remained on L-dopa monotherapy (600 mg/day). After lowering his PPX dose his food cravings and compulsive eating improved, as did his hypersexuality, hallucinations, and excessive daytime sleepiness. When he discontinued PPX these symptoms resolved completely, although he continued to self-adjust his medications (increasing his L-dopa to 1,000–1,200 mg/day). Three months later his weight had decreased to 126 kg (BMI = 39 kg/m²).

RESULTS

All of the patients in this case series experienced unintentional and undesired increases in their weight and BMI (Table 1). The mean weight gain in these patients was 13 kg ± 7 kg, or approximately 15% of their initial

TABLE 2. Patient characteristics

Subject	Gender	Age at onset (yr)	Family history of PD	Other PD medications	Other compulsions
A	F	53	Brother, maternal uncle	None	None
B	M	50	Maternal grandmother and aunt	None	Gambling, hypersexuality, self-adjusted meds
C	F	58	None	None	None
D	F	60	Paternal grandmother, aunt, and cousin	None	None
E	M	61	Father (rest tremor)	L-dopa	Hypersexuality
F	F	47	None	None	Punding
G	M	45	None	L-dopa	Gambling, self-adjusted meds

PD, Parkinson's disease; F, female; M, male; meds, medications.

body weight; this is comparable to the 13% increase in body weight reported after continuous subcutaneous apomorphine treatment²² and the 12.8 to 14.8% increase in body weight observed after DBS.¹⁹ The mean increase in BMI was 4 ± 2 kg/m². Of the 7 identified subjects, 5 were overweight (BMI ≥ 25) or obese (BMI ≥ 30) at baseline (Table 1); the other 2 became overweight during PPX treatment.

In some patients, the weight gain was clearly early and rapid (e.g., subject A, who gained 13 kg during the first 7 months of treatment). However, in most subjects the time course of the weight gain and cumulative exposure to PPX could not be determined from the available records. The maximum dose of PPX taken by the affected patients before the onset of weight gain was highly variable (1 to 9 mg), with no obvious relationship between the highest dose taken and the amount of weight gained.

All subjects reported that they had increased their food intake dramatically in the setting of new-onset food cravings for carbohydrates, sweets, and/or salty foods. Four (Subjects A, B, C, and D) reported new-onset binge eating; the others (Subjects E, F, and G) reported compulsively eating both larger portions of food at mealtimes and more frequent snacks throughout the day. Of the 7 subjects, 6 reported a tendency to compulsively snack or binge in the middle of the night (Subjects A, B, C, D, F,

G). Subject F reported the subjective feeling that she had lost her "inner sense of control."

Men ($n = 3$) and women ($n = 4$) were similarly represented among the study subjects (Table 2). The average age of onset of PD was 53, which is slightly lower than that of an unselected population of PD patients (Table 3). Of the 7 patients, 2 (Subjects F and G) had young-onset PD (age of onset < 50). Four had a family history of PD or undiagnosed rest tremor, either in a first-degree relative (Subjects A and E) or in two or more second-degree relatives (Subjects B and D).

Several of the study subjects reported the concurrent development of other compulsive behaviors (Table 2), including hypersexuality (Subjects B and E), purposeless rearrangement of items (subject F), compulsive gambling (Subjects B and G), or self-adjustment of the dose of PPX to higher than recommended levels (Subjects B and G). Subject F, who had a remote history of tobacco use, also reported the reemergence of cigarette cravings.

Pertinent medical comorbidities included severe depression in 1 patient (Subject D) and anxiety in 2 patients (Subjects C and G). The other subjects had no known history of psychiatric disease, although none had undergone a formal evaluation to exclude this possibility. Subject G had a remote history of a left pallidotomy. Subjects E and G were concomitantly treated with car-

TABLE 3. Response to changes in dopaminergic therapy

Subject	Treatment	Behavioral response to treatment	Change in weight after treatment
A	Discontinued PPX	Improved	Decreased
B	Discontinued PPX	Improved	Decreased
C	Lowered PPX dose	Improved	Decreased
D	Discontinued PPX	Improved	No change
E	Discontinued PPX	Improved	Decreased
F	Switched to pergolide	Improved	Increased
G	No change	No change	No change

PPX, pramipexole.

bidopa-L-dopa (Table 2); the remainder were on no other dopaminergic treatment. None of the patients were taking amphetamines, amphetamine-precursors such as selegiline, or other PD medications.

Of the 7 patients, 6 (subjects A, B, C, D, E, F) were concerned enough about their compulsive eating and weight gain that they chose to discontinue or reduce the dose of PPX (Table 3). All 5 patients who discontinued dopamine agonist treatment (subjects A, B, D, and E) or lowered the dose of PPX (subject C) reported decreased food cravings and associated weight loss (subjects A, B, C, and E) or the absence of further weight gain (subject D). One patient (subject F) switched from PPX to pergolide, after which she had ongoing compulsive eating and weight gain but reduced food cravings. Another patient (subject G) continued PPX at the same dose (against the advice of his physician) and reported ongoing food cravings and compulsive eating.

DISCUSSION

We report on 7 cases of PD patients who developed food cravings, compulsive eating, and undesired weight gain in the context of PPX use. The symptoms remitted in all 5 subjects who discontinued dopamine agonist treatment or lowered the dose of PPX, improved in the patient who switched to pergolide, and persisted in the patient who continued with the same dose of PPX.

The PPX-related food cravings and compulsive eating that we observed share many similarities with other known DRT-related behavioral disturbances. These findings have been attributed to excessive activation (and perhaps sensitization) of the mesocorticolimbic dopaminergic pathway, which under physiological conditions mediates the response to natural rewards.^{8,23} In this report, compulsive eating was associated with the tonic administration of PPX, a low-potency, long-acting dopamine agonist. Compulsive DRT use, in contrast, has been more closely associated with the pulsatile delivery of high potency, short-acting medications such as L-dopa, and subcutaneous apomorphine.^{8,23} There is considerable overlap, however, in the types of cravings and compulsive behaviors that may occur with each of the dopaminergic medications. Subject G in this report, for example, developed symptoms of the dopamine dysregulation syndrome while on PPX monotherapy. Moreover, the affected subjects—in this and prior studies—frequently developed more than one DRT-related behavioral disturbance. This finding may reflect what has been termed a “global sensitization” of appetitive behaviors in susceptible patients.^{8,9,23}

“Self-medication” for depression is another potential explanation for the carbohydrate cravings and compulsive eating that were observed. Carbohydrates increase serum tryptophan levels and, thus, may ameliorate the symptoms of depression by facilitating the synthesis of serotonin in the central nervous system.²⁴ In this study, however, both food cravings and abnormal eating patterns occurred only during treatment with PPX. Thus, if depression were to account for these symptoms, then PPX itself would have had to be the cause. None of the study subjects, however, reported the development or exacerbation of depression during PPX treatment. Moreover, PPX has been shown to have antidepressant properties in PD and other neuropsychiatric disorders^{25–28} and, therefore, would be expected to alleviate rather than precipitate depressive symptoms. For these reasons, it is unlikely that the observed PPX-related cravings and compulsive eating are attributable to depression.

In prior reports, the compulsions related to dopaminergic medications have occurred more frequently in male than female PD patients.⁹ In our case series, both genders were represented equally; moreover, in subsequent patients identified at our center, PPX-related compulsive eating was considerably more common in women than men (unpublished observations). Because compulsive behaviors in PD are usually related to (or exaggerations of) the patient’s baseline tendencies,^{8,9,11} this gender disparity may reflect the fact that food cravings and eating disorders are generally more common in women.^{29,30} Of the 7 subjects in this report, 5 were also overweight or obese at baseline, whereas most PD patients are normal or underweight. Thus, PPX may have unmasked an “overeating diathesis” by simultaneously increasing food cravings and decreasing the ability to control the response to these cravings.

More than half of the patients in this report had a family history of PD. In fact, 6 of the 7 patients in this series had either young-onset PD (Subjects F and G) or a family history of PD/rest tremor (Subjects A, B, D, E). These findings presumably reflect that younger patients are more commonly treated with dopamine agonists, particularly at high doses. Nonetheless, they raise the question of whether some patients may have a genetic predisposition to develop PPX-related compulsions.

To date, the most effective treatment for PPX-related compulsions has been to lower the dose of PPX and/or substitute other dopaminergic medications. L-Dopa, for example, appears to be less likely to elicit certain types of compulsive behaviors—including compulsive eating—than dopamine agonists such as PPX. PPX may also have a greater propensity to produce compulsions than other dopamine agonists; in one case series, for example, there was a sustained resolution of compulsive

behaviors in all 6 patients who were switched from PPX to ropinirole.²

Aside from changing the regimen of dopaminergic medications, the compulsive behaviors related to dopaminergic therapy have been refractory to medical treatment. Selective serotonin reuptake inhibitors (SSRIs), which are highly effective for treating both depression and compulsions due to obsessive-compulsive disorder (OCD), have proven to be ineffective in the small number of patients in whom they have been tested.^{9,31} To our knowledge, clomipramine—which is also effective in treating OCD—has not yet been tested for compulsions in the setting of PD; the anticholinergic properties (and other side effects) of this medication, however, are often poorly tolerated in PD patients. Atypical neuroleptics such as clozapine³² and quetiapine might potentially be helpful, although there was one report of 2 patients in whom punding behaviors actually emerged after quetiapine treatment was initiated.³¹ Unfortunately, all of these potential pharmacological treatments—SSRIs, clomipramine, and atypical neuroleptics—can themselves cause weight gain.

Nonpharmacological interventions should also be considered. DBS, for example, might potentially improve symptoms by allowing for reduction of the doses of dopaminergic medications. Unfortunately, DBS has itself been associated with both rapid weight gain and uncontrolled appetitive behaviors,^{19,20,33} and is, therefore, contraindicated in this setting. Cognitive-behavioral therapy could be considered, particularly in the presence of comorbid depression or anxiety; it is unlikely to be successful, however, in the absence of concomitant medication changes.¹

Given the serious medical consequences that have been associated with overweight and obesity, we recommend that physicians inquire about possible compulsive eating behavior and closely monitor patients' weights before and throughout dopamine agonist therapy. Further investigation is warranted to identify safe and effective treatments for dopamine agonist-induced compulsive eating and to determine whether specific dopaminergic medications are less likely to induce this behavior.

REFERENCES

1. Avanzi M, Uber E, Bonfa F. Pathological gambling in two patients on dopamine replacement therapy for Parkinson's disease. *Neurol Sci* 2004;25:98–101.
2. Driver-Dunckley E, Samanta J, Stacy M. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003;61:422–423.
3. Montastruc JL, Schmitt L, Bagheri H. [Pathological gambling behavior in a patient with Parkinson's disease treated with levodopa and bromocriptine]. *Rev Neurol (Paris)* 2003;159:441–443.
4. Drugs can trigger pathological gambling. *Prescrire Int* 2002;11:16.
5. Gschwandtner U, Aston J, Renaud S, Fuhr P. Pathologic gambling in patients with Parkinson's disease. *Clin Neuropharmacol* 2001;24:170–172.
6. Molina JA, Sainz-Artiga MJ, Fraile A, et al. Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov Disord* 2000;15:869–872.
7. Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005;62:1377–1381.
8. Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? *Lancet Neurol* 2003;2:595–604.
9. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. *Mov Disord* 2004;19:397–405.
10. Voon V. Repetition, repetition, and repetition: compulsive and punding behaviors in Parkinson's disease. *Mov Disord* 2004;19:367–370.
11. Fernandez HH, Friedman JH. Punding on L-dopa. *Mov Disord* 1999;14:836–838.
12. Friedman JH. Punding on levodopa. *Biol Psychiatry* 1994;36:350–351.
13. Romana Pezzella F, Colosimo C, Vanacore N, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. *Mov Disord* 2005;20:77–81.
14. Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry* 2000;68:423–428.
15. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2003;2:107–116.
16. Durrieu G, Llau ME, Rascol O, Senard JM, Rascol A, Montastruc JL. Parkinson's disease and weight loss: a study with anthropometric and nutritional assessment. *Clin Auton Res* 1992;2:153–157.
17. Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Weight loss in Parkinson's disease. *Ann Neurol* 2003;53:676–679.
18. Beyer PL, Palarino MY, Michalek D, Busenbark K, Koller WC. Weight change and body composition in patients with Parkinson's disease. *J Am Diet Assoc* 1995;95:979–983.
19. Barichella M, Marczevska AM, Mariani C, Landi A, Vairo A, Pezzoli G. Body weight gain rate in patients with Parkinson's disease and deep brain stimulation. *Mov Disord* 2003;18:1337–1340.
20. Macia F, Perlemoine C, Coman I, et al. Parkinson's disease patients with bilateral subthalamic deep brain stimulation gain weight. *Mov Disord* 2004;19:206–212.
21. Ford B, Winfield L, Pullman SL, et al. Subthalamic nucleus stimulation in advanced Parkinson's disease: blinded assessments at one year follow up. *J Neurol Neurosurg Psychiatry* 2004;75:1255–1259.
22. Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. *Mov Disord* 2002;17:1235–1241.
23. Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. *Curr Opin Neurol* 2004;17:393–398.
24. Wurtman RJ, Wurtman JJ. Brain serotonin, carbohydrate-craving, obesity and depression. *Obes Res* 1995;(Suppl. 4):477S–480S.
25. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur J Neurol* 2003;10:399–406.

26. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry* 2004;161:564–566.
27. Lattanzi L, Dell’Osso L, Cassano P, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord* 2002;4:307–314.
28. Ostow M. Pramipexole for depression. *Am J Psychiatry* 2002;159:320–321.
29. Lewinsohn PM, Seeley JR, Moerk KC, Striegel-Moore RH. Gender differences in eating disorder symptoms in young adults. *Int J Eat Disord* 2002;32:426–440.
30. Carter JD, Joyce PR, Mulder RT, Luty SE, McKenzie J. Gender differences in the presentation of depressed outpatients: a comparison of descriptive variables. *J Affect Disord* 2000;61:59–67.
31. Miwa H, Morita S, Nakanishi I, Kondo T. Stereotyped behaviors or punding after quetiapine administration in Parkinson’s disease. *Parkinsonism Relat Disord* 2004;10:177–180.
32. Kurlan R. Disabling repetitive behaviors in Parkinson’s disease. *Mov Disord* 2004;19:433–437.
33. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson’s disease and subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2002;72:701–707.