J Gambl Stud (2009) 25:425–431
DOI 10.1007/s10899-009-9123-2

ORIGINAL PAPER

Impulse Control Disorder Behaviors Associated with Pramipexole Used to Treat Fibromyalgia

Andrew J. Holman

Published online: 25 February 2009

Abstract *Objective*: Compulsivity has been associated with use of dopamine agonists used to treat Parkinson's disease (PD). Increasing use of these agents to treat fibromyalgia (FM) raises concern for this unexpected toxicity in a new group of patients. This is the first report of compulsive gambling and shopping among patients taking dopamine agonists for treatment of FM. *Design*: A retrospective chart review of all patients in a large, active FM research practice was used to identify compulsivity associated with dopamine agonists and describe its remission following dug withdrawal. *Results*: Of 3006 patients with FM treated between 2002 and 2006, 1356 had taken $\geq$1 dose of a dopamine agonist (>95% pramipexole). Twenty-one (3 male, 18 female) were identified with compulsive gambling (33%), shopping (40%) or both (27%) after taking a 4.5 mg mean dose of pramipexole at bedtime for 14.4 $\pm$ 14.9 months. Compulsivity resolved in 3–10 days for 19 of 21 patients and by 3 months for all following a monitored, compulsory tapered discontinuation over 7 days. *Conclusions*: While biologic aspects of PD and FM differ considerably, compulsive gambling and shopping have become important, yet unexpected concerns related to use of dopamine agonists for patients with FM and their treating clinicians.

Keywords Pramipexole · Dopamine · Fibromyalgia · Compulsivity · Gambling · ICD

Impulse control disorder (ICD) behaviors, including hypersexuality, excessive gambling and shopping, have been recently reported among patients with Parkinson's disease (PD) treated with dopamine agonists, including pramipexole and ropinirole (Dodd et al. 2005). Although the mechanism of action leading to this toxicity remains unclear, the temporal association of compulsivity with induction of dopaminergic therapy and resolution of these behaviors upon withdrawal of therapy suggests a strong causal relationship. A similar association of ICD with use of pramipexole for treatment of fibromyalgia (FM) may also be present.

A. J. Holman (✉)
Pacific Rheumatology Research, 4300 Talbot Road South, Suite 101, Renton, WA 98055, USA
e-mail: AJHSeattle@aol.com

With the discovery of the role of deficient hippocampal dopaminergic neurotransmission (Wood 2004, 2006) in patients with FM by fDOPA PET scanning (Wood et al. 2007), and the validation of reduced pain, fatigue and improved function in patients with FM treated with dopamine agonists (Holman 2003a, b, 2004; Holman et al. 2004; Holman and Myers 2005), these medications, especially pramipexole, have become important treatment options for many patients with FM. Use of these agents has been endorsed by recent FM treatment guidelines published by the EUropean League Against Rheumatism (Carville et al. 2008). Unfortunately, six years after the first use of these agents in FM, similar behavioral concerns have been recently observed in some patients. ICD caused by dopamine agonist was initially reported by lay press articles, then in internet reports and finally, by solicitation for litigation. Unfortunately, current understanding of this problem remains limited and underreported.

While this important concern has been reviewed in the setting of PD treatment, this is the first report of ICD related to use of dopamine agonists in patients with FM. Because this behavioral concern is not easily detected, potentially leads to devastating social and financial loss for patients and their families, and is rarely spontaneously reported to monitoring clinicians, dissemination of this potential toxicity is important. And, given the remarkably different pathophysiology of FM compared to PD, and the ability to rapidly withdraw therapy in patients with FM, further insight into this unexpected adverse response may be possible.

Materials and Methods

A comprehensive chart review of all patients treated at a suburban rheumatology practice between 2002 and 2006 was conducted to identify patients with FM. Although an exemption for consent was authorized by Western Institutional Review Board (Olympia, WA, USA) for a chart review, consent was requested from each subject who had developed ICD by the investigator. From patient telephone contact, monitoring visits and occasionally lost patients contacting this office after reading lay press reports, patients were identified as having ICD leading to excessive shopping and gambling with serious social or financial consequences consistent with ICD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria. Hypersexuality and other compulsive behaviors associated with ICD were not assessed.

All patients were evaluated in the clinic within one week of identifying compulsivity and tapered off the dopamine agonist over 7 days in the course of routine clinical care. No clinical decisions were made for research purposes. Patients, and often their accompanying families, were counseled and asked to fill out questionnaires related to their potential risk of ICD, demographics, FM treatment response and to provide comments. Patients were asked to return for reevaluation within 10–14 days to monitor their response to medication withdrawal and their FM status. No patients were advised to continue pramipexole, even at a lower dosage, following the 7-day withdrawal schedule.

Statistical analysis of data was completed using SPSS 14.0 (SPSS, Chicago, IL.) to describe patient characteristics, including use of Pearson correlation to screen this exploratory data for potential risk factors.

Results

Initial chart screening identified 3006 patients with fibromyalgia, of which, 1356 had taken at least one dose of a dopamine agonist (>95% pramipexole). Of 21 subjects identified

with compulsive gambling or shopping, all had been treated with pramipexole at a mean dose of 4.5 mg po qhs for 40.0 ± 21.4 (range 8–96) months consistent with the most efficacious dose of pramipexole use to treat FM in a randomized, controlled trial (Holman and Myers 2005). All had been advised to taper pramipexole by 0.75 mg qhs until discontinued without authorization to reinitiate this therapy. All 21 patients were monitored by telephone follow-up and 19 patients agreed to further evaluation consisting of interview and examination. Fifteen provided completed detailed questionnaires and provided permission to publish their comments.

Demographics are described in Table 1. Most patients were women of middle-age, well educated, married, employed and described a positive clinical response to treatment of FM with pramipexole. Over 73% of patients described their clinical response to this treatment option as 'good' or better, including 40% who designated 'excellent'. Most patients did not smoke cigarettes or consume alcohol. Compulsive behaviors were split between gambling (33%), shopping (40%) or both (27%). Some patients also noted compulsive eating (13%), cleaning (7%) and crafting (13%). Mean onset of compulsive behavior was 14.4 ± 14.9

Table 1 Characteristics of patients with compulsive behavior

	*N**	Range	
Gender (%female)	21		86%
Age(yrs ± SD)	21	34–63	50.8 ± 8.3
Duration of FM(yrs ± SD)	21	3–25	13.5 ± 6.2
Employed	15		67%
Marital status	15		
Single			7%
Married			60%
Divorced			27%
Widowed			6%
Cigarette use	15		13%
Alcohol (drinks per week)	15		
None			74%
1–2			13%
6–8		13%	
Education	15		
High School			20%
Some college			40%
College degree			27%
Post Graduate			13%
Treatment outcome	15		
Poor			13.3%
Fair			13.3%
Good			20.0%
Very good			13.3%
Excellent			40.0%

* *N* reflects available data from questionnaires received and/or, since not all patients agreed to provide this information charts reviewed

Table 2 Demographic features of patients with impulse control disorder (ICD) behavior and fibromyalgia treated with dopamine agonists

Patient/ Age, y/sex	Duration of FM (yr)	Onset on DAs (mo)	Pramipexole dosage (qhs)	Prior ICD	BPD*	Depression	GAD**	FH# ICD	FH BPD
1/52/F	25	52	4.5	No	No	No	No	No	No
2/53/F	8	4	4.5	Yes	No	Yes	Yes	No	No
3/63/F	3	5	4.5	Yes	No	Yes	No	Yes	No
4/43/F	8	12	4.5	No	No	Yes	Yes	No	No
5/52/F	15	13	4.5	No	No	Yes	No	No	No
6/52/F	18	6	4.5	Yes	No	No	No	Yes	No
7/61/F	16	6	4.5	No	No	Yes	No	No	No
8/40/F	20	13	4.5	Yes	Yes	Yes	No	Yes	Yes
9/42/F	20	12	4.5	No	Yes	No	No	Yes	No
10/48/M	16	12	4.5	Yes	Yes	Yes	No	No	No
11/49/F	7	1	4.5	No	No	Yes	No	Yes	No
12/61/F	15	48	4.5	No	No	No	No	Yes	No
13/59/F	6	12	4.5	No	No	No	No	Yes	Yes
14/34/F	10	8	4.5	No	No	No	No	Yes	No
15/53/F	15	12	4.5	No	No	No	No	Yes	No

* Bipolar disorder; ** Generalized anxiety disorder; # family history

(range 1–52) months after initiating pramipexole. Resolution of these behaviors occurred within 3–10 days after discontinuation for 19 of 21 patients and for all within 3 months.

Potential risk factors and similar compulsive behavior prior to initiation of pramipexole were noted by some patients. Prior psychiatric care and a family history (FH) of similar compulsive behaviors were common (Table 2). Statistically significant correlations were unavailable due to lack of a control cohort.

Case Examples

Given the unique and unexpected variety of clinical vignettes and the difficulty of identifying compulsivity among patients with FM, case descriptions are provided to assist clinicians.

Patient 6

This 52 year-old, divorced woman noted an 'excellent' response to pramipexole, but noted compulsive gambling within 6 months of treatment and loss of >$ 60,000. She had forgotten to renew her prescription and within 3 days of sudden discontinuation, "my compulsion stopped. It was like a light switch that had gone off in my head. While gambling (and working at a casino), I was so incredibly focused on the games that no one and nothing mattered. I was evading questions and even lied about how much money I was spending and where I was getting it. I never lie—totally out of character." A few years prior, she had moved to a rural area to avoid department stores due to compulsive shopping not attributed to medication. Compulsivity and FM symptoms have not returned.

Patient 13

This 59 year-old woman described a history of compulsive shopping and a FH of compulsivity and bipolar disorder. "About 20 years ago, I used to have all my cupboards full of food and I always (bought) more groceries. I spend my husband's check before he got it." She had noted a 'good' response to pramipexole, but noted compulsive gambling, without compulsive shopping, after treatment for 12 months. While lost to follow-up, pramipexole was discontinued and restarted three times by a different physician. Compulsive behavior resolved and returned with each discontinuation and reinitiation of pramipexole. However, she concluded "I just think I was always compulsive and it wasn't the medicine."

Patient 15

This 53 year-old employed, divorced woman with post-graduate education and an 'excellent' response to pramipexole noted a FH of compulsivity (parents and 2 siblings), but not prior excessive gambling or shopping. After one year of treatment with pramipexole, compulsive gambling and shopping began and ultimately involved $150,000. "I just couldn't stop. It was a very, very unusual feeling. I bought a new house and just kept buying things without any feeling of monetary consequences. Some people close to me laughed it off—others (my children) became very concerned I would gamble away everything I had." After 18 months, the association of pramipexole and compulsivity was noted, and behavior resolved within one week of discontinuation.

Discussion

ICD behaviors, including excessive gambling, shopping, hypersexuality and binge eating, have been observed in patients with PD treated with dopamine agonists. Initial reports were sporadic after FDA approval of these agents in 1997, but recently, controlled assessment of pathological gambling has been reported in 8% of Scottish PD patients receiving pramipexole (Grosset et al. 2006). Similar, but unquantified reports have described pathological gambling in patients using lower doses these agents for restless legs syndrome (Quickfall and Suchowersky 2007; Evans and Butzkueven 2007). As patients with FM also begin treatment with dopamine agonists, development of ICD may be an important new concern for them as well.

In this retrospective chart review, an accurate prevalence of compulsivity has not been determined. As a likely underestimate, 15 cases in 1358 patients (1.1%) were identified with serious compulsive gambling and shopping. Other ICD behaviors noted in patients taking dopamine agonists for PD, such as binge eating and hypersexuality, were not assessed. A direct link to use of pramipexole was supported by resolution of these behaviors within 1–2 weeks following a mandatory, monitored and gradual discontinuation of pramipexole over one week. This causal relationship has also been reported in patients with PD treated with DAs, although their rate of dose reduction and discontinuation has generally required many months (Mamikonyan et al. 2008).

Understanding of the pathogenesis of compulsive gambling is developing slowly. Dopamine genes, specifically the DRD1-800 T/C allele, may be associated with pathological gambling (da Silva Lobo et al. 2007) Manipulation of dopamine is thought to play an important role in risk/reward behaviors (Ondo and Lai 2008) as well as some psychiatric disorders already associated with excessive compulsivity and pathological gambling:

notably bipolar disorder (McIntyre et al. 2007). Ironically, pramipexole has also been reported as an effective treatment for both bipolar and unipolar depression (Aiken 2007). As a risk factor for patients taking dopamine agonists for PD, bipolar disorder has not been reported. But, a FH of both bipolar disorder and compulsivity were common among our patients with FM who excessively gambled or shopped. Controlled study of pathological gambling in PD has identified risk factors, including younger age and larger doses of dopamine agonists in PD, but not in RLS (Gallagher et al. 2007; Singh et al. 2007). Males with PD were over-represented, but are underrepresented in FM cohorts that usually include a female to male ratio of 4:1.

As our understanding of a dopaminergic pathogenesis of FM emerges and clinical trials demonstrate the benefits of treating FM with dopamine agonists, monitoring and preventing unexpected adverse events becomes increasingly important. Patients must be counseled about a broader risk profile for these agents. It is also incumbent upon patients to collaborate and provide their prescribing clinician with feedback about these behaviors.

Monitoring the onset of compulsivity is fraught with logistical hurdles, and most clinicians do not routinely monitor for ICD. Fortunately, at least for a majority of patients with FM, these behaviors appear rapidly reversible and timely appraisal for ICD is possible with tools, such as the Minnesota Impulse Disorder Interview (Grant 2008). These preliminary findings suggest a need for more formal, controlled studies as well as validation of tools used to assess ICD among patients with FM.

References

Aiken, C. B. (2007). Pramipexole in psychiatry: A systemic review of the literature. *The Journal of Clinical Psychiatry, 68*(8), 1230–1236.

Carville, S. F., Arendt-Nielsen, S., Bliddal, H., Blotman, F., Branco, J. C., Buskila, D., et al. (2008). EULAR evidenced based recommendations for the management of fibromyalgia syndrome. *Annals of the Rheumatic Diseases, 67*(4), 536–541. doi:10.1136/ard.2007.071522.

da Silva Lobo, D. S., Vallada, H. P., Knight, J., et al. (2007). Dopamine genes and pathological gambling in discordant sib-pairs. *Journal of Gambling Studies, 23*(4), 421–433. doi:10.1007/s10899-007-9060-x.

Dodd, M. L., Klos, K. J., Bower, J. H., Geda, Y. E., Josephs, K. A., & Ahlskog, J. E. (2005). Pathological gambling caused by drugs used to treat Parkinson's disease. *Archives of Neurology, 62*, 1–5. doi:10.1001/archneur.62.9.noc50009.

Evans, A. H., & Butzkueven, H. (2007). Dopamine agonist-induced pathological gambling in restless legs syndrome due to multiple sclerosis. *Movement Disorders, 22*(4), 590–591. doi:10.1002/mds.21303.

Gallagher, D. A., O'Sullivan, S. S., Evans, A. H., Lees, A. J., & Schrag, A. (2007). Pathological gambling in Parkinson's disease: Risk factors and differences from dopamine dysregulation. An analysis of published case series. *Movement Disorders, 22*(12), 1757–1763. doi:10.1002/mds.21611.

Grant, J. E. (2008). *Impulse control disorders: A clinician's guide to understanding and treating behavioral addictions*. New York: WW Norton.

Grosset, K. A., Macphee, G., Pal, G., et al. (2006). Problematic gambling on dopamine agonists: Not such a rarity. *Movement Disorders, 21*(12), 2206–2208. doi:10.1002/mds.21110.

Holman, A. J. (2003a). Ropinirole, a dopamine agonist, for refractory fibromyalgia: Preliminary observations. *Journal of Clinical Rheumatology; Practical Reports on Rheumatic & Musculoskeletal Diseases, 9*(4), 277–279. doi:10.1097/01.rhu.0000081264.26484.e5.

Holman, A. J. (2003b). Pramipexole and fibromyalgia: Promise and precaution. *Journal of Rheumatology, 30*(12), 2733. letter.

Holman, A. J. (2004). Treatment of fibromyalgia with the dopamine agonist ropinirole a 14-week double-blind, pilot, randomized controlled trial with 14-week blinded extension. *Arthritis and Rheumatism, 50*(9), S698. abstract.

Holman, A. J., & Myers, R. R. (2005). A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis and Rheumatism, 52*(8), 2495–2505. doi:10.1002/art.21191.

Holman, A. J., Neiman, R. A., & Ettlinger, R. E. (2004). Preliminary efficacy of the dopamine against, pramipexole for fibromyalgia: The first, open label, multicenter experience. *Journal of Musculoskeletal Pain, 12*(1), 69–74. doi:10.1300/J094v12n01_10.

Mamikonyan, E., Siderowf, A. D., Duda, J. E., Potenza, M. N., Horn, S., Stern, M. B., et al. (2008). Long-term follow-up of impulse control disorders in Parkinson's disease. *Movement Disorders, 23*(1), 75–80. doi:10.1002/mds.21770.

McIntyre, R. S., McElroy, S. L., Konarski, J. Z., Soczynska, J. K., Wilkins, K., & Kennedy, S. H. (2007). Problem gambling in bipolar disorder: Results of the Canadian Community Health Survey. *Journal of Affective Disorders, 102*(1–3), 27–34. doi:10.1016/j.jad.2006.12.005.

Ondo, W. G., & Lai, D. (2008). Predictors of impulsivity and reward seeking behavior with dopamine agonists. *Parkinsonism & Related Disorders, 14*(1), 28–32. doi:10.1016/j.parkreldis.2007.05.006.

Quickfall, J., & Suchowersky, O. (2007). Pathological gambling associated with dopamine agonist use in restless legs syndrome. *Parkinsonism & Related Disorders, 13*(8), 535–536. doi:10.1016/j.parkreldis.2006.10.001.

Singh, A., Kandimala, G., Dewey, R. B., Jr, & O'Suilleabhain, P. (2007). Risk factors for pathological gambling and other compulsions among Parkinson's disease patients taking dopamine agonists. *Journal of Clinical Neuroscience, 14*(12), 1178–1181. doi:10.1016/j.jocn.2007.01.009.

Wood, P. B. (2004). Stress and dopamine: Implications for the pathophysiology of chronic widespread pain. *Medical Hypotheses, 62*, 420–424. doi:10.1016/j.mehy.2003.10.013.

Wood, P. B. (2006). Mesolimbic dopaminergic mechanisms and pain control. *Pain, 120*, 230–234. doi:10.1016/j.pain.2005.12.014.

Wood, P. B., Patterson, J. C., Sunderland, J. J., Tainter, J. H., Glabus, M. F., & Lilien, D. L. (2007). Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: A pilot study. *Pain, 8*(1), 51–58. doi:10.1016/j.jpain.2006.05.014.