

Gambling disorder in the context of parkinson's disease

Abstract

This paper briefly reviews Gambling Disorder in the context of Parkinson's disease. This disorder, as other impulsivity disorders, is seen in a significant number of Parkinson's disease patients, especially those treated with dopamine agonists. There is continued controversy about the role of different elements (genetic factors, early disadvantage, substance abuse, personality factors, age, gender, early onset or long duration of Parkinson's disease, cognitive problems, neurotransmitter dysfunction, specific dopamine agonists, their dose or their delivery) in the emergence of Gambling Disorder. There is also controversy about how best to treat Gambling Disorder in Parkinson's disease patients. Nevertheless, the controversies shed light on the nature of both Parkinson's disease and impulse control disorders such as pathological gambling.

Keywords: parkinson's disease, dopamine agonists, gambling disorder, impulse control disorder

Volume 5 Issue 1 - 2018

Mary V Seeman

Department of Psychiatry, University of Toronto, Canada

Correspondence: Mary V Seeman, Professor Emerita, Department of Psychiatry, University of Toronto, 260 Heath St. West, Suite 605, Toronto, Ontario, Canada M5P 3L6, Canada, Tel | 416 486 3456, Email mary.seeman@utoronto.ca

Received: December 30, 2017 | **Published:** January 09, 2018

Abbreviations: PET, positron emission tomography; COMT, catechol-o-methyl transferase; MAO, monoamine oxidase; CBT, cognitive behaviour therapy; PD, parkinson's disease; GD, gambling disorder

Introduction

Impulse control disorders such as compulsive gambling or compulsive shopping or uncontrollable sexual and eating behaviour, are well-recognized complications of Parkinson's disease (PD). They occur in up to 20% of PD patients.¹ These disorders impair quality of life and function, place incalculable burdens on interpersonal relationships and on caregivers, and are associated with significant psychiatric co-morbidity.² The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V)³ has classified Gambling Disorder (GD), previously viewed as an impulse control disorder, as a behavioural addiction. To qualify for this diagnosis, patients must meet at least four of the following nine criteria in the course of one year:

- Gambling increasing amounts of money in order to keep obtaining the same level of excitement.
- Experiencing restlessness or irritability when trying to stop gambling.
- Trying repeatedly and unsuccessfully to stop.
- Being constantly preoccupied with gambling.
- Gambling when distressed.
- Continually returning to gambling in order to make up for monetary losses.
- Covering up the extent of one's involvement in gambling.
- Jeopardizing relationships and careers because of gambling.
- Borrowing money from others to cover gambling debts.

Gambling can be viewed as an impulse disorder or as an addiction. There are many forms of gambling, including card games, electronic

games, betting on results of athletic or political contests. The most frequent forms of gambling in North America are reportedly playing the slot machines, buying lottery scratch cards and playing bingo.⁴

Having a gambling addiction means preferentially selecting immediate, albeit risky, opportunities to make money instead of relying on a longer-range strategy that is both safer and more lucrative. A small amount of immediate gain takes precedence for the pathological gambler over a larger gain that requires a period of waiting. Decisions made by pathological gamblers appear to be rash, with little thought of probable consequences such as financial burden, interference with career, or dissolution of family bonds. Immediate satisfaction is valued over potential risks. Even repeated negative consequences do not seem to act as deterrents. Individuals with PD who suffer from GD exhibit uncontrollable cravings, develop tolerance, and experience withdrawal symptoms in the same way as those who suffer from drug or alcohol addiction, and there is a high degree of co-morbidity between these conditions.^{5,6}

Aim

The aim of this brief overview is to determine whether GD can help to shed light on the etiology of Parkinson's disease, and whether aspects of Parkinson's disease, including its treatment, can help to clarify the basis of GD.

Method

There is a substantial literature on GD in Parkinson's. Via the PubMed database, articles from the most recent few years were selected preferentially for this overview.

Prevalence

The estimated prevalence of GD in the general adult population ranges between 0.2% and 5.3%.⁷ It is more common in men than in women. A U.S. survey found the lifetime prevalence in men to be 0.64% versus 0.23% in women.⁸ Along with other similar conditions such as compulsive shopping, binge eating and hypersexuality, gambling addiction is much more common in patients with PD than in the general population, ranging from 6% in PD patients not receiving

dopamine agonists to 17% among those on dopamine agonists.⁹ While most PD patients do receive treatment with some form of dopamine agonist, GD is induced in only a subset of PD patients, suggesting—in those who do develop GD—an underlying genetic susceptibility that is enhanced by brain impairments intrinsic to PD, impairments that serve to dysregulate dopamine transmission.

Risk factors

Risk factors for GD, other than PD, are male sex, young age at PD onset, a history of an impulse disorder and a personal or family history of substance abuse or of bipolar disorder, a disadvantaged background, a low socioeconomic neighborhood, prior gambling problems, and impulsive personality traits.^{10,11} Impulsive personality traits include novelty and sensation seeking, delay discounting (the preference for small immediate rewards over delayed rewards even when those are larger),¹² reflection impulsivity (short response time and a high number of errors when faced with a decision).^{13,14}

Etiology

Since not all PD patients, whether treated or not treated, develop impulse control disorders, protective or predisposing genetic factors must exist. The current estimate is that genes account for 33–57% of the overall variance in the risk of developing pathological gambling behaviour in the context of PD.⁶ Dysregulation of the mesocorticolimbic dopamine system is thought to be the major route by which the relevant genes lead to impulse disorders in PD, but there is also evidence for alterations in other neurotransmitter systems.¹ Candidate genes encode receptors or metabolic enzymes of neurotransmitter pathways, particularly monoamine pathways. Dopamine, serotonin, and norepinephrine genes have been shown to contribute approximately equally to the risk of pathological gambling, but together explaining only 15–21% of the variance.^{6,15,16} Dopamine is thought to affect decision-making by specifically modulating the perceived attractiveness of potential choices.¹⁷ In animal experiments, impulsivity has been shown to result from amphetamine-induced release of dopamine in the striatum of the brain.

Imaging evidence

Imaging studies have been used to identify the neural networks and receptor abnormalities that underlie the impulse control disorders in PD. Following the presentation of a reward, positron emission tomography (PET) studies show an increase of dopamine release and a reduction of dopamine transporter in the ventral striatum of PD patients who have been diagnosed with pathological gambling. Radiotracers with high-affinity for extrastriatal D2/D3 receptors have implicated extrastriatal regions in the pathogenesis of impulse control disorders in PD patients. This does not, however, necessarily implicate exogenous dopamine in pathological gambling. PET studies suggest PD itself may predispose patients to impulsivity because of disease-induced impairments in the ventral striatum, orbitofrontal cortex, anterior insula, and dorsal cingulate cortex.^{6,18}

Role of psychiatric co-morbidities

Problem gambling is very frequently comorbid with mental health disorders, often compromising treatment engagement and effectiveness for both conditions.²

Management

A degree of prevention of GD can be instituted by a comprehensive

assessment of all PD patients that identifies risk factors and avoids medication that is selective for D3 receptors in those most likely to be at risk (young males with a mental illness and substance abuse history, an early onset of PD). An important next step in the management of GD and related disorders is educating and counselling patients and family members, acquainting them with the potential adverse effects of drugs, and monitoring patients carefully and frequently to facilitate early diagnosis and treatment. There is limited evidence for cognitive behaviour therapies and psychoactive drug administration. The usual strategy for impulse control disorders, including GD, is the modification of dopamine replacement therapy.⁹ The approaches most commonly used are to reduce the dose of the dopamine agonist needed to control motor symptoms, or to discontinue the dopamine agonist altogether, or to switch to a different dopamine replacement protocol. These strategies can worsen the motor effects of PD and can also induce dopamine withdrawal syndrome, characterized by anxiety, panic attacks, dysphoria, depression, agitation, irritability, suicidal ideation, fatigue, orthostatic hypotension, nausea, vomiting, diaphoresis, generalized pain, and drug cravings. About one-third of patients with impulse control disorders who attempt to taper dopamine agonists develop a dopamine withdrawal syndrome. There is no known effective treatment for this syndrome; it may abate with time, but often the original dopamine agonist has to be reinstated.^{19,20}

Nevertheless, most patients who are able to discontinue or significantly decrease their dopamine agonist or be successfully switched to a different one, do experience a remission of GD, sometimes a partial remission and sometimes a permanent one.¹ If the usual strategies do not work, there have been reports of good results with deep brain stimulation bilaterally of the subthalamic nucleus,²¹ although this is still controversial. When pathological gambling resolves after deep brain stimulation, it is sometimes attributable to the concomitant discontinuation or decrease of dopamine agonist medication. In some patients after deep brain stimulation, the GD paradoxically increases. This may depend on the localization of the stimulus, whether in the limbic or the motor part of the subthalamic nucleus.²²

Controversies

There are several ongoing controversies in this field:²³

Cognition

PD patients who develop gambling disorders may be more cognitively impaired than other patients with PD.²⁴ In a meta-analysis of 34 studies exploring this question Santangelo et al.²⁵ found no association between impulse control disorders in PD and global cognitive ability, but a significant relationship between these disorders and frontal cortex dysfunctions i.e. abstraction ability/concept formation, set-shifting, visuospatial/constructional abilities and decision making. These findings suggest that PD-induced frontal cortex dysfunctions contribute to the development of impulse control disorder, especially upon addition of a dopamine agonist. These results are compatible with the idea that DA treatment can trigger GD in susceptible people with PD who have a pre-existing defect in set-switching, concept formation, and decision making, functions dependent on intact dopamine circuitry.⁶

Pharmacology

The role of PD therapeutic agents in GD is not altogether clear. Dopamine agonists are used in conditions other than PD, in Restless

Leg Syndrome for instance, or prolactinoma. Patients with these conditions also develop impulse control disorders, more often than the general population but far less often than patients with PD.²⁵ Another question is whether levodopa treatment without added dopamine agonists can induce pathological gambling.²⁶ Some argue that cases where L-Dopa has seemed to induce impulsive acting out have been due to artefacts of sampling²⁷ and that the only true culprits are dopamine agonist drugs. Dopamine agonists are commonly divided into two groups: ergoline- and non-ergoline-derived agonists. The common drugs in the ergoline class are bromocriptine, cabergoline, pergolide, and lisuride. These drugs are currently rarely used.²⁸ Newer agents, the non-ergoline agonists, bind mainly to D2 and D3 receptors. The most common drugs in this group are pramipexole and ropinirole²⁹ and they do provoke impulsivity, but they may not be the only drugs that do. Drugs such as monoaminoxidase-B inhibitors and amantadine, may also be responsible.³⁰ There is an especially close association between impulsivity and pramipexole, a recent study showing that 32 percent of PD patients treated with pramipexole as an add-on agonist exhibited impulse control disorder. This has been attributed to selective D3 receptor stimulation.^{31–33} Pramipexole and ropinirole, as well as the rotigotine transdermal patch have a high affinity for dopamine D3 receptors, an affinity that has been closely associated - although this remains disputed - with the emergence of impulse control disorders.²⁸

Some experts are of the opinion that continuous, rather than pulsatile, drug delivery might result in superior impulse control. To this end, the effects of rotigotine transdermal patch and continuous subcutaneous apomorphine infusion are being studied. No studies have compared extended release agonists against three daily doses, but impulse control disorder seems to occur just as often with longer-acting dopamine agonists, meaning that this issue is imperfectly understood.²⁴ It is still not clear whether impulsivity is dose-related. Some patients improve when the dose of their dopamine agonist is reduced, but, for a minority, it seems to be an all or none phenomenon.²⁴ Whether duration of treatment with dopamine agonists is a factor is also disputed.²⁸ The usual management, dopamine agonist dose reduction or complete withdrawal, is complicated by two potential clinical consequences:

- a. Worsening of motor function.
- b. The development of dopamine withdrawal syndrome in one third of cases.²⁴

If motor symptoms increase, there is a choice of adding or increasing levodopa, catechol O methyl transferase (COMT) inhibitors, or monoamine oxidase (MAO) inhibitors. Impulse control disorders do not result from the use of anti-cholinergic drugs or COMT inhibitors, but MAO inhibitors have been known to result in impulsive behaviour. Another potential dopamine agonist, amantadine, remains controversial. Some studies indicate that it can alleviate impulse control disorders whereas others conclude that it can induce them.^{34,35}

Some experts advocate the use of antipsychotics (dopamine blockers) for impulse control disorders, since they are dopamine antagonists. There is no clear evidence, however, that their addition helps. Anti-depressants, anxiolytics, and anticonvulsants have also been used but without clear effect. The older antipsychotics and some of the newer ones worsen the motor disability of PD. Quetiapine and clozapine do this less, but evidence for their efficacy against impulse control disorders remains limited²⁴

Cognitive therapy

There is also controversy about the usefulness of cognitive behaviour therapy (CBT). While there is no evidence that it helps with GD in PD, CBT has worked for Gambling Disorder in the general population, when used along with medications.³⁶

Conclusion

What has this brief review taught with respect to Gambling Disorder and Parkinson's Disease? The take away lesson is that impulse control disorder in PD is not wholly iatrogenic -i.e. it is not caused solely by the medications used to treat the motor symptoms. The bulk of the evidence indicates that a neurotransmitter impairment intrinsic to PD, especially prominent in early onset PD, interacts with dopamine agonists to result in impulsivity problems. In other words, Parkinson's Disease is not only a disease of motor function; many areas of the brain are affected and they sensitize the brain to treatment with dopamine agonists. PD also sheds light on the nature of gambling addiction. While many of the determinants of GD have to do with environmental exposure and learning, the vulnerability to GD and to other impulse control disorders depends on genetic factors, developmental factors, and some degree of brain compromise. Future studies are needed to resolve controversies and identify novel and improved therapeutic targets.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

References

- Weintraub D, Claassen DO. Impulse control and related disorders in Parkinson's Disease. *Int Rev Neurobiol*. 2017;133:679–717.
- Chaudhuri R, Titova N. Nonmotor Parkinson's: The Hidden Face. 1st ed. Elsevier, Amsterdam, Netherlands; 2017. 794 p.
- Manning V, Dowling NA, Lee S, et al. Problem gambling and substance use in patients attending community mental health services. *J Behav Addict*. 2017;6(4):678–688.
- Diagnostic and Statistical Manual of Mental Disorders DSM–5*. 5th ed. USA: American Psychiatric Association; 2013. 991 p.
- Odlaug L, Marsh PJ, Kim SW, et al. Strategic vs nonstrategic gambling: characteristics of pathological gamblers based on gambling preference. *Ann Clin Psychiatry*. 2011;23(2):105–112.
- Clark CA, Dagher A. The role of dopamine in risk taking: a specific look at Parkinson's disease and gambling. *Front Behav Neurosci*. 2014;8:196 p.
- Napier TC, Corvol JC, Grace AA, et al. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. *Mov Disord*. 2015;30(2):141–149.
- Hodgins D, Stea JN, Grant JE. Gambling disorders. *Lancet*. 2011;378(9806):1874–1884.
- Petry NM, Tinson FS, Grant BF (2005) Comorbidity of DSM–IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2005;66(5):564–574.

10. Pirritano D, Plastino M, Bosco D, et al. Gambling disorder during dopamine replacement treatment in Parkinson's disease: A comprehensive review. *BioMed Res Int.* 2014;2014(2014):1–9.
11. Martins SS, Storr CL, Lee GP, et al. Environmental influences associated with gambling in young adulthood. *J Urban Health.* 2013;90(1):130–140.
12. Welte JW, Barnes GM, Tidwell MO, et al. Predictors of problem gambling in the U.S. *J Gambl Stud.* 2017;33(2):321–342.
13. da Matta A, Gonçalves FL, Bizarro L. Delay discounting: Concepts and measures. *Psychol Neurosci.* 2012;5(2):135–146.
14. Banca P, Lange I, Worbe Y, et al. Reflection impulsivity in binge drinking: behavioural and volumetric correlates. *Addict Biol.* 2016;21(2):504–515.
15. Nombela C, Rittman T, Robbins TW, et al. Multiple modes of impulsivity in Parkinson's Disease. *PLoS One.* 2014;9(1):e85747.
16. Erg AH, Alves G, Larsen J, et al. Impulsive and compulsive behaviours in Parkinson's Disease: the Norwegian ParkWest study. *J Parkinson's Dis.* 2017;7(1):183–191.
17. Kraemmer J, Smith K, Weintraub D, et al. Clinical–genetic model predicts incident impulse control disorders in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2016;87(10):1106–1111.
18. Rigoli F, Rutledge RB, Chew B, et al. Dopamine Increases a value-independent gambling propensity. *Neuropsychopharmacol.* 2016;41(11):2658–2667.
19. Voon V. Decision-making and Impulse Control Disorders in Parkinson's Disease. *Decision Neurosci.* London: Academic Press; 2017. p. 305–314.
20. Nirenberg MJ. Dopamine agonist withdrawal syndrome: implications for patient care. *Drugs Aging.* 2013;30(8):587–592.
21. Yu XX, Fernandez HH. Dopamine agonist withdrawal syndrome: A comprehensive review. *J Neurol Sci.* 2017;374:53–55.
22. Merola A, Romagnolo A, Rizzi L, et al. Impulse control behaviours and subthalamic deep brain stimulation in Parkinson disease. *J Neurol.* 2017;264(1):40–48.
23. Heiden P, Heinz A, Romanczuk-Seiferth N. Pathological gambling in Parkinson's disease: what are the risk factors and what is the role of impulsivity? *Eur J Neurosci.* 2017;45(1):67–72.
24. Samuel M, Rodriguez-Oroz M, Antonini A, et al. Impulse Control Disorders in Parkinson's Disease: Management, controversies, and potential approaches. *Mov Disord.* 2015;30(2):150–159.
25. Santangelo G, Raimo S, Barone P. The relationship between Impulse Control Disorders and cognitive dysfunctions in Parkinson's Disease: A meta-analysis. *Neurosci Biobehav Rev.* 2017;77:129–147.
26. Grall-Bronnec M, Victorri-Vigneau C, Donnio Y, et al. Dopamine agonists and Impulse Control Disorders: a complex association. *Drug Saf.* 2018;41(1):19–75.
27. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients. *Arch Neurol.* 2010;67(5):589–595.
28. Grosset DG, Cardoso F, Lees A. Dopamine agonists vs levodopa in impulse control disorders. *Arch Neurol.* 2011;68(4):544–546.
29. Borovac JA. Side effects of a dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology. *Yale J Biol Med.* 2016;89(1):37–47.
30. Sáez-Francás N, Martí Andrés G, Ramírez N, et al. Clinical and psychopathological factors associated with impulse control disorders in Parkinson's disease. *Neurologia.* 2016;31(4):231–238.
31. García-Ruiz PJ, Martínez Castrillo JC, Alonso-Canovas A, et al. Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. *J Neurol Neurosurg Psychiatry.* 2014;85(8):840–844.
32. Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Intern Med.* 2014;174(12):1930–1933.
33. Seeman P. Parkinson's disease treatment may cause impulse-control disorder via dopamine D3 receptors. *Synapse.* 2015;69(4):183–189.
34. Thomas A, Bonanni L, Gambi F, et al. Pathological gambling in Parkinson disease is reduced by amantadine. *Ann Neurol.* 2010;68(3):400–404.
35. Weintraub D, Sohr M, Potenza MN, et al. Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. *Ann Neurol.* 2010;68(6):963–968.
36. de Brito AM, de Almeida Pinto MG, Bronstein G, et al. Topiramate combined with cognitive restructuring for the treatment of Gambling Disorder: A two-center, randomized, double-blind, clinical trial. *J Gambl Stud.* 2017;33(1):249–263.