Implications of impulse control disorder in Parkinson disease

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The challenges of recognizing behaviors such as hypersexuality, gambling, and excessive buying in Parkinson disease are discussed, as are ways to address them while still managing the underlying condition.

Parkinson disease (PD) is a progressive neurodegenerative illness that is recognized clinically by its cardinal motor features: tremor, rigidity, and bradykinesia. However, it is increasingly clear that much of the suffering and disability associated with PD is caused by psychiatric disorders. Some of these seem to be intrinsic to PD and likely emerge from the same pathogenic process that gives rise to the motor symptoms. For example, depression, anxiety disorders, and dementia are all common in PD and likely occur because the same process that damages motor circuits can also affect brain regions that subserve mood and cognition. Other psychiatric problems are associated with PD because they are caused—at least in part—by the dopaminergic medications prescribed for motor symptoms. These include delirium, psychosis, and impulse control disorders.

Impulse control disorders, also described as “behavioral addictions,” include phenomena such as pathological gambling, compulsive shopping, hypersexuality (including paraphilic behavior), and binge eating. The failure to resist engaging in these behaviors rises to the level of a disorder when it causes distress or impaired occupational or social functioning. Such disorders often go unrecognized, only becoming obvious once they have wreaked havoc on the lives of patients and their families.

There may be a “Parkinson personality” characterized by cautious temperament and a decreased tendency to indulge in hedonic pleasures.1 Yet when treated with dopaminergic medication, a substantial portion of such patients have problems with an overzealous pursuit of pleasurable experiences. A better understanding of how this happens and why it happens in some but not others, might shed light on the underlying mechanisms of impulsivity and related behavioral disturbances in both persons with PD and the general population.

Epidemiology
The association between impulse control disorders and PD seems to be driven by the dopamine replacement medications used to treat the motor symptoms of PD. A recent case-control study that compared 168 patients with newly diagnosed PD who had never received treatment with 143 healthy controls found no evidence for an increased prevalence of impulse control disorders.2 However, most studies that compare PD patients who are receiving treatment for their motor symptoms with healthy controls do find an increased prevalence of impulse control disorders in the PD patients. One cross-sectional study by Weintraub and colleagues3 of more than 3000 patients being treated for PD found a point prevalence of at least one impulse control disorder of 13.6%. The study looked specifically for pathological gambling (5.0%), sexual impulsivity (3.5%), impulse buying (5.7%), and binge eating disorder (4.3%) and found that 3.9% of patients engaged in more than one of these behaviors.

Impulse control disorders are much more common in patients who are receiving treatment with a dopamine agonist (such as pramipexole or ropinirole) than in patients treated only with the
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dopamine precursor levodopa. In the study by Weintraub and colleagues,\textsuperscript{3} 17.1% of patients who were taking a dopamine agonist had an impulse control disorder compared with 6.9% of patients who were treated with levodopa. The increased risk of an impulse control disorder developing during treatment with a dopamine agonist does not seem to be dose-dependent. Indeed, there have been reports of impulse control disorders in patients treated with dopamine agonists for conditions such as restless legs syndrome, for which these drugs are prescribed in substantially lower doses than in PD. By contrast, treatment with very high doses of levodopa seems to confer higher risk than treatment with low or moderate doses. Patients receiving treatment with both dopamine agonists and levodopa seem to be at the highest risk.\textsuperscript{3}

Other risk factors for impulse control disorders in patients being treated for PD include having a personal or family history of impulse control disorders or addictions and having premorbid novelty-seeking or impulsive traits.\textsuperscript{4} There are sex differences in risk for particular impulse control disorders, with men more likely to engage in hypersexual behavior and women more likely to engage in impulse buying or binge eating.\textsuperscript{3} Other clinical factors that appear to be associated with impulse control disorders include depressive symptoms, irritability, and appetite changes.\textsuperscript{5}

Possible mechanism
The motor symptoms in PD are caused by the destruction of dopaminergic neurons in the ventral portion of the substantia nigra pars compacta within the midbrain. These neurons project to the caudate and putamen and are involved in regulating motor function. This is the same system implicated in the extrapyramidal adverse effects of neuroleptics that block dopamine receptors. Medications for the motor symptoms of PD work by increasing dopaminergic neurotransmission within this circuit. Levodopa is a precursor to dopamine, while dopamine agonists act directly on dopamine receptors.

While dopaminergic neurons in the ventral part of the substantia nigra modulate motor circuits, other dopamine-producing neurons located in the dorsal part of the substantia nigra project to forebrain and limbic regions. These mesocortical and mesolimbic circuits are involved in voluntary driven behaviors through the assessment of and response to rewards and risks. While the ventral neurons are primarily destroyed in PD, the treatments for PD increase dopaminergic transmission in both sets of circuits. It is likely that excessive stimulation of dopamine receptors in limbic and forebrain regions contributes to the pathophysiology of impulse control disorders.\textsuperscript{6}

How does this explanation account for the fact that dopamine agonists seem to pose a higher risk than levodopa for the development of impulse control disorders? This is likely due to the localization of different receptor subtypes within these circuits. While D1 and D2 receptors are primarily located within motor circuits, D3 receptors are distributed within both motor and limbic circuits. In some individuals, increased agonism of D3 receptors seems to weaken mechanisms that would normally keep risky, pleasure-seeking behaviors in check.\textsuperscript{7}

Compared with the dopamine that is synthesized from levodopa, dopamine receptor agonists in use today have increased affinity for D3 receptors relative to D1 and D2 receptors. Higher affinity for D3 receptors might explain not only the elevated risk for impulse control disorders with dopamine agonists, but also their increased association with hallucinations and delusions. Similarly, dopamine metabolized from levodopa has relatively greater affinity for D1 and D2 receptors, which may be why levodopa is more effective than dopamine agonists as a first-line treatment for motor symptoms.

Challenges in diagnoses
Unlike other, more conspicuous psychiatric adverse effects, such as hallucinations and delusions, impulsivity is often missed. Patients often lack insight that the impulse control disorder represents a problem because the impulsivity may be within the normal range of human behaviors except for the unusual extent or frequency. One of our patients, a married man in his 60s, took a several hundred–mile road trip during which he visited strip clubs and erotic massage parlors, shortly after he had started taking the dopamine agonist pramipexole. However, it was not until much later, after experiencing negative consequences from this behavior, that he recognized that he had a problem. Another reason why impulse control disorders can be difficult to identify is that patients may not be forthcoming because they are ashamed or embarrassed. Thus, many patients are reluctant to discuss impulse control disorders with their clinicians unless asked directly. Even then, patients may minimize the extent of these behaviors. Thus, when performing psychiatric evaluations, especially in patients being treated with dopamine agonists, it is important to ask directly about gambling and other financial indiscretions as well as about changes in sexual and eating behaviors. It is also important, when possible, to ask collateral informants about such behavior. A final challenge in
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Diagnosing dopamine agonist–induced impulse control disorders is that they often emerge insidiously, sometimes years after the offending medication is first prescribed. Thus, patients and their clinicians must remain vigilant.

Impulse control disorders in patients with PD should be distinguished from other pathological behavioral phenomena that arise from treatment with dopaminergic medications. Impulsive behaviors are distinct from compulsive behaviors in that the former are motivated by a potential hedonic reward with inadequate consideration of risk, whereas the latter are attempts to relieve anxiety or avoid harm. Compulsive behaviors seen in PD include punding (repetitive, purposeless behaviors, such as arranging or taking apart objects), hobbyism (eg, compulsive exercise, Internet use, work on projects), walkabouts (aimless wandering), and hoarding.

Another important phenomenon seen in patients treated for PD is the dopamine dysregulation syndrome. This describes the pathological overuse of dopaminergic medications. Like other chemical addictions, this behavior can be motivated by both a desire for an intrinsic reward associated with these drugs and a desire to avoid anxiety and other dysphoric emotions associated with withdrawal. Unsurprisingly, the overuse of dopaminergic medications commonly co-occurs with, and likely worsens, other impulsive behaviors as well as other psychiatric syndromes, including mania and psychosis.

**Clinical management**

The key to managing impulse control disorders in patients with PD is close coordination between the patient’s psychiatrist and neurologist. If a dopamine agonist has been prescribed, the first step is usually to discontinue this medication. However, abrupt discontinuation can theoretically precipitate a neuroleptic malignant-like syndrome. Therefore, it must be tapered carefully. Even when a patient requires higher doses of levodopa to control his or her motor symptoms, impulsive behavior may improve once the dopamine agonist is stopped.

Although case studies describe the use of neuroleptics and other psychotropic medications in the management of impulse control disorders in PD, benefits have generally been seen while concomitantly reducing dopamine agonist medications. There has been some excitement around using naltrexone. However, a 2014 randomized control trial that included 50 patients with PD and various impulse control disorders, including gambling, impulse buying, sexual impulsivity, and binge eating disorder, did not show any benefit. In our experience, there is no clear role for psychotropic medications in isolated impulse control disorders attributable to dopamine agonist therapy. That said, impulse control disorders are often comorbid with other psychiatric syndromes, such as mood and anxiety disorders. It is important that any comorbid disorders be identified and managed appropriately.

Of course, some patients do not tolerate completely eliminating dopamine agonist therapy and others have residual impulse control disorder symptoms even when treated with levodopa monotherapy. In many cases, the management of impulse control disorders in patients with PD represents a balancing act. We work closely with our patients, their families, and our neurology colleagues to find the lowest amount of dopaminergic medication necessary and to manage impulsivity through behavioral interventions. In fact, for many patients, once a dysfunctional pattern of behavior has been established, it takes more than pharmacological optimization to break this pattern. Thus, it is common for us to refer patients for behavioral therapy and 12-step groups aimed at interrupting these behaviors once their dopaminergic medications have been reduced as much as possible.

**Conclusions**

Impulse control disorders are common in patients with PD. They result from treatment with dopaminergic medications targeting parkinsonian motor symptoms. Their pathophysiology is likely related to increased dopaminergic transmission in mesolimbic and mesocortical circuits that play a role in assessing and acting upon information about potential rewards and risks of volitional behaviors. These disorders can have devastating effects on the lives of patients and their families. Yet they are often insidious and difficult to recognize clinically, only coming to attention as the result of major consequences.

More judicious prescribing of dopamine agonists for PD and greater efforts to educate patients and their families about the risks of impulse control disorders would likely reduce the frequency of these disorders. When these disorders are discovered, their management requires close coordination between psychiatry and neurology. Reducing offending medications as much as possible, treating comorbid psychiatric illness, and using interventions aimed at interrupting dysfunctional reward-seeking behavior are keys to optimal management.
Disclosures:
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