Dopamine Agonists, Pathologic Gambling, and Parkinson Disease: A Connection?

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Parkinson disease (PD) patients treated with dopamine receptor agonists are prey to a number of symptoms over and above classic motor disturbances. Some of the common symptoms—dyskinesia, nausea, and hallucinations—are more or less foreseeable consequences of excessive dopamine stimulation and are justifiably perceived as adverse effects of therapy. Other symptoms—confusion, depression, and punding—are more difficult to account for. They may be a result of the disease, its treatment, or both. Over the past 5 years, case reports and series have noted the onset of pathologic gambling in PD patients treated with levodopa and dopamine agonists.1-4

The case reports have named dopamine receptor agonists as the likely culprits, but the role of levodopa has been unclear and the possibility that the symptom is a manifestation of PD itself has been posited.5 In the September 2005 issue of Archives of Neurology, a team headed by Maryellen Dodd, MD, a psychiatrist at the Mayo Clinic, wrote about 11 patients with PD in whom pathologic gambling developed.4 In all cases, the gambling behavior arose after the beginning of treatment with dopamine agonists. In the 8 patients for whom follow-up information was available, the gambling abruptly stopped when the dopamine agonist was tapered or discontinued. Pathologic gambling did not develop in any of the patients who were receiving levodopa alone, and 3 of the pathologic gamblers had not received levodopa. Pramipexole (Mirapex, Boehringer Ingelheim) was the agonist taken by 9 of the 11 patients studied.

The findings presented by Dodd and colleagues provide persuasive evidence that treatment with dopamine agonists, particularly pramipexole, can precipitate pathologic gambling. Dodd noted that this effect might not be limited to Parkinson patients. Since publication of the article in Archives of Neurology, she has learned of people who became pathologic gamblers after being treated with ropinirole (Requip, GlaxoSmithKline) for restless legs syndrome. The idea that pathologic gambling—i.e., uncontrollable gambling that typically results in personal, legal, and financial trouble—can be precipitated by drug therapy challenges conventional views about complex behaviors and the effects that drugs can have.

The novice pathologic gambler (many of the PD patients given to pathologic gambling had never gambled before) suddenly acquires the desire to gamble, locates a casino, gets hold of some money, chooses a game, plays the game, and deceives others about what he or she is up to. It's hard to imagine how behavior this specific and complex can be caused by a dopamine agonist. "I don't understand it," said Joseph Friedman, MD, a neurologist in Warwick, RI, "but it's real; it's really real." Friedman has seen about 10 PD patients who began gambling excessively while receiving dopamine agonists.

One of the features of this behavior that intrigues Friedman is that unlike other behavioral effects of Parkinson treatment such as punding, patients who are pathologic gamblers don't find their behavior strange. Even if they've never gambled before, they suddenly have an urge to gamble. They don't link the compulsion with drug therapy, they don't view it as a problem, and they don't discuss it, according to Friedman. "You have to ask about it," he said.

MANIA OR COMPULSIVITY?

Excessive gambling is a well-known feature of mania. Drugs that enhance dopamine stimulation—levodopa in particular—are known to bring on manic episodes in vulnerable patients. So one plausible explanation for pathologic gambling in PD patients is that the gambling is a symptom of mania. Six of Dodd's 11 patients experienced additional behavioral symptoms along with the pathologic gambling, some of which are symptoms of mania (e.g., increased spending, hypersexuality, increased alcohol consumption). For 5 of the patients, though, pathologic gambling occurred in isolation.
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Published on Psychiatric Times
(http://www.psychiatrictimes.com)

Dodd pointed out that the study patients underwent thorough psychiatric evaluation and none met the criteria for a manic syndrome. She doesn't believe that mania or hypomania explains the pathologic gambling seen in PD patients. Friedman agreed. The pathologic gamblers he has come across have not had concurrent hypersexuality or other manic symptoms. In his experience, pathologic gambling turns up on its own. Parkinson patients treated with dopamine agonists occasionally handle, sort, and arrange objects incessantly. This behavioral pattern, known as punding, is attributed to dopamine stimulation.

Could pathologic gambling be a variant of this repetitive, driven behavior? Probably not. Unlike pathologic gamblers, who typically see nothing amiss, patients with punding usually recognize the behavior as odd. Whereas pathologic gambling involves the orchestration of thinking, desire, and behavior, punding is primarily repetitive motor activity. What's most intriguing about the pathologic gambling seen in PD patients is not that these patients suddenly take on a new activity, but the activity itself. The patients aren't beset with a desire to smoke cigars, drink tequila, or play the piano. They want to gamble.

To be sure, the occasional PD patient who receives dopamine agonists begins to engage in other activities-often familiar ones-with increased intensity. Dodd recalled a patient who began fishing more often than usual. Friedman spoke of a patient who began nonstop comparison-shopping. The patient didn't buy anything; she just went about comparing prices. But pathologic gambling, rare as it is, does stand out as the complex behavior most likely to be precipitated by dopamine agonists.

TRIGGERING D3 RECEPTORS

Dodd speculated that stimulation of D3 receptors in the nucleus accumbens plays a role in pathologic gambling. She pointed out that the nucleus accumbens, an integral part of the pleasure/reward circuit, is rich in D3 receptors and that pramipexole both is highly selective for the D3 receptor and has a greater affinity than other dopamine agonists for that receptor. In her case series, most patients (82%) were receiving pramipexole, as were the majority of patients (59%) in previously published reports.

Along the same lines, a retrospective study of 1884 PD patients found that 8 (1.5%) of 529 who took pramipexole but only 1 (0.3%) of 331 who took pergolide (Permax, Eli Lilly) engaged in pathologic gambling.3 No patients receiving levodopa alone or ropinirole engaged in excessive gambling. Seven patients started gambling within 1 month of having their dopamine agonist dose increased; 6 stopped after therapy was switched to ropinirole.

Jon Grant, MD, JD, an expert on so-called impulse-control disorders, including pathologic gambling, has found the relationship between dopamine agonist treatment and pathologic gambling "truly bewildering." Going along with the D3 receptor-nucleus accumbens theory, he suggested that a dopamine agonist might well cause a problem with any type of rewarding behavior. But why pathologic gambling? To Grant, associate professor of psychiatry at the University of Minnesota, it would make more sense for a dopamine agonist to trigger compulsive shopping or hypersexuality. He wondered whether the Parkinson patients who become pathologic gamblers are prone to addictive behaviors. Are they genetically vulnerable to addiction? he asked. Have they "minimized previous addiction"?

Pathologic gambling appears to occur rarely in patients with PD. In fact, the prevalence of such behavior may be no greater in PD patients than in the general population. The prevalence of pathologic gambling in the retrospective study was 0.05%,3 whereas in the general population, it averages 1.6%.6 Rare as it is, pathologic gambling may occur more frequently in PD patients than clinical impression and the existing data suggest; patients seldom report this behavior-the majority of published cases came to light because concerned relatives spoke out about the patient's behavior. A proper prevalence study remains to be done.

The prevalence of pathologic gambling in PD patients may not be greater, but the condition in these patients differs substantially from that in the general population. The link to dopamine agonist treatment seems clear, and the abrupt onset and resolution with cessation of the offending agonist are unique features. Although pathologic gambling seems to be the complex behavior most likely to be triggered by dopamine agonists, the possibility remains that other driven, complex behaviors-less troublesome and less likely to be complained about by patients or their family members-may arise with dopamine agonist treatment.

Do some of the patients treated with these agents start browsing the Internet, shopping, or playing golf all day long? Friedman now routinely asks his Parkinson patients whether they have noticed any changes in their behavior or activities. And given its potential for dire consequences, he specifically asks about gambling. My patients "never bring it up," he said, "but now I always ask." For references, please go to www.appneurology.com.
Disclosures:
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