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Treatment of Parkinson's disease—where do we go from here?

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The introduction of levodopa for the treatment of Parkinson's disease (PD) in the 1960s was hailed as a major breakthrough. Unfortunately, however, it was soon followed by the realization that the benefits gradually lessened with time, accompanied by development of significant adverse effects such as dyskinesias.

The 1980s saw the introduction of the dopamine agonists. Several studies, in which patients were randomly assigned to levodopa or dopamine agonists and followed for 3–5 years, showed that the rate of development of dyskinesia was significantly less in the group using dopamine agonists than in the group using levodopa (Parkinson Study Group [2000] *JAMA* 284: 1931–1938). Associated neuroimaging studies showed reduced neuronal loss in the dopamine agonist group (Whone *et al.* [2003] *Ann Neurol* 54: 93–101). Use of dopamine agonists became widespread, and these drugs were recommended by some as first-line treatment both for symptomatic benefit and possible neuroprotection. Over the past 7 years, however, a new set of side effects has begun to emerge.

In 1999, reports of drowsiness and sudden-onset sleep attacks in patients on dopamine agonists resulted in driving restrictions. In 2002, several cases of cardiac valvular fibrosis in patients on the dopamine agonist pergolide were documented. Now, reports of pathological gambling are coming to light.

Although pathological gambling is generally classified as an impulse control disorder, it has much more in common with addictions, such as alcoholism and drug abuse, than with other impulse control disorders, such as kleptomania. It is defined as a failure to resist the impulse to gamble in spite of severe personal or financial consequences. Although little is known about the pathophysiology of pathological gambling, it might be related to the dopaminergic projections in the limbic system that are involved in emotions and the internal reward system. Several studies have shown an association between certain dopamine receptor alleles and abnormal dopamine turnover in individuals with pathological gambling behavior. Recently, functional MRI scanning identified differential brain activity between pathological gamblers and healthy controls when exposed to gambling tasks.

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Since 2000, a number of case reports and chart reviews have indicated an association between pathological gambling and PD or its medications, particularly the dopamine agonists. A recent systematic assessment has shown that the risk of pathological gambling is at least twice that of the general population in PD patients using agonists either as monotherapy or adjunctive therapy (Voon V *et al.* [2006] *Neurology* 66: 1750–1752). All agonists appear to be equally implicated. The risk of other compulsive behaviors, such as shopping, hypersexuality and overeating, might also be increased.

Why would our PD patients—typically rigid, obsessive–compulsive, low risk-takers—start to gamble? This is unknown, but it could be related to flooding of the limbic dopaminergic system by dopaminergic agonists in genetically predisposed individuals.

Should we start avoiding the use of dopamine agonists? Of course not. Most patients do well and have good motor benefit. However, just as we use the Epworth sleepiness scale to look for drowsiness, and perform echocardiograms on patients who are taking pergolide, we now need to start monitoring PD patients for gambling and other addictive and compulsive behaviors.

Further research is needed to document the full spectrum of this problem, identify which patients are most at risk, and determine appropriate treatment, not only to tackle the gambling behaviors, but also to devise the optimal PD management strategy for these individuals.

Finally, we should remember that levodopa remains the most effective medication for the duration of the PD patient's illness, improving quality of life, and increasing life expectancy.

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Competing interests
The author has declared associations with the following companies: Allergan, Boehringer Ingelheim, GlaxoSmithKline, Kyowa, Elan, Merck, Novartis and Teva. See the article online for full details of the relationship.

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