
Dopamine agonist
2mg TID

Pathological Gambling and Other Impulse Control Disorders in Parkinson's

What is the nature of the relationship between dopamine replacement therapy and impulse control disorders in Parkinson's disease? Two experts review the latest literature and offer clinical guidance on detection and management.

By Daniel Weintraub, MD and Marc N. Potenza, MD, PhD

Impulse control disorders (ICDs), including pathological gambling (PG), constitute a group of psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).[1] Other ICDs without formal DSM-IV-TR diagnostic criteria include compulsive sexual behavior and compulsive buying.[2,3] Past-year prevalence estimates in the United States general population have been reported as approximately one percent for PG,[4] five percent for compulsive sexual behavior,[5] and two to eight percent for compulsive buying.[6]

Recent observational studies suggest that ICDs, particularly PG[7-11] and compulsive sexual behavior,[12] can co-occur with Parkinson's disease (PD) and may be associated with the use of dopamine agonists (DAs). Other terms used to describe ICDs in PD include "dopamine dysregulation syndrome,"[13] "hedonistic homeostatic dysregulation,"[14,15] "dopamimetic drug addiction,"[16] "compulsive behaviors,"[17] "compulsive dopaminergic drug use"[18] and "repetitive behaviors,"[19] but for the purposes of this discussion, "impulse control disorder" or "ICD" will be used from this point forward.

There exist few systematic investigations of the frequencies of ICDs in Parkinson's disease or their clinical correlates. This paper provides an overview of the phenomenology, frequency, correlates and management of ICDs in PD.

Neural Substrate of ICDs

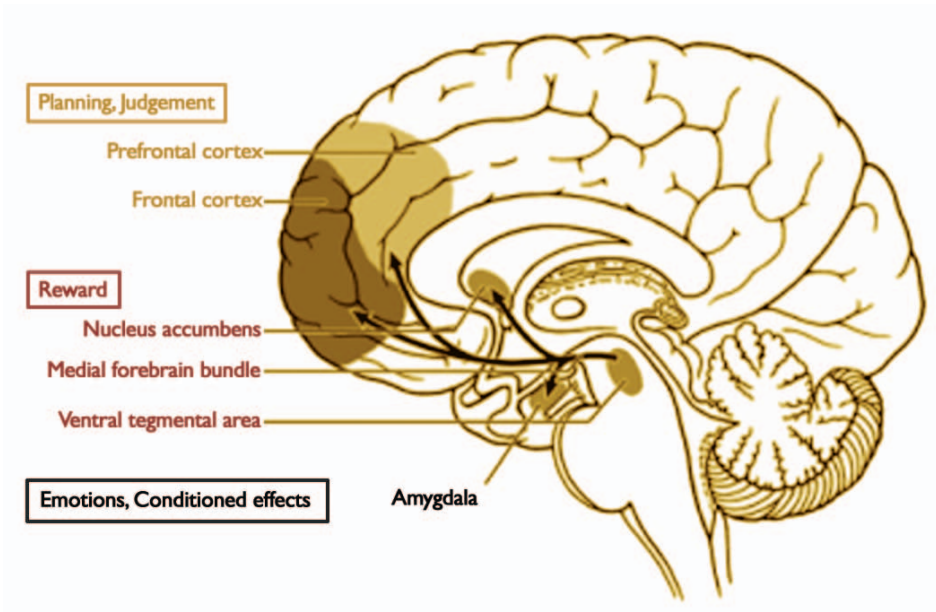
The pathophysiology of ICDs has been reported to involve alterations in specific neurotransmitter systems, brain regions and neural circuits (see Figures 1 and 2). Dopamine function, particularly within the mesocorticolimbic pathways, is critical in the mediation of reward and reinforcement behaviors.[20] The prefrontal cortex,[21,22] ventral striatum (particularly nucleus accumbens),[20,23] and amygdala[24,25] mediate aspects of motivated behaviors underlying engagement in risky or addictive behaviors. Data support a role for cortico-striato-thalamo-cortical circuits in determining engagement in risky or addictive behaviors, with projections coursing through the more ventral component of the striatum (including the nucleus accumbens) more implicated in urges and impulsive aspects, and those involving the dorsal striatum more implicated in motoric habits and compulsive aspects.[26,27] This neurocircuitry involves additional brain regions (*e.g.*, the amygdala imparting affective information and the hippocampus contextual memory information) that function in concert, with perturbations in one area having the potential to influence structure/function in a broader array of brain regions.

There are plausible explanations for a possible association between ICDs in PD and treatment with DAs. First, PD causes a loss of dopaminergic neurons in the substantia nigra, resulting in a pronounced depletion of dopamine in the nigrostriatal pathway.[28] This depletion influences dopaminergic cortical-subcortical circuits, leading to cognitive and emotional impairment that may predispose to the development of psychiatric disorders, including ICDs.

Second, PD patients commonly display impairment in executive function,[29,30] which has been linked to degeneration in the frontal-striatal tracts secondary to cell loss within the substantia nigra.[31,32] In a non-imaging study of PD patients and non-PD control subjects, PD patients were significantly more impaired in performance on a gambling task (both number of disadvantageous choices and ability to use negative feedback for a decision-shift to an advantageous alternative), and the frequency of disadvantageous choices correlated with greater severity of impairment on other measures of executive abilities.[32]

Finally, DAs, in addition to activating D_1 and D_2 receptors

Figure 1. Main brain areas and neurotransmitter pathways implicated in reward processes



Source: Tomkins DM and Sellers EM. Canadian Medical Association Journal 2001;164:817-821.

in the dorsal striatum that are associated primarily with their motor effects, also bind to the D_3 receptor.[33] The D_3 receptor is localized to limbic areas of the brain, including the ventral striatum, and may mediate psychiatric manifestations of dopamine receptor stimulation.[34] Thus, excessive dopamine stimulation of an inherently vulnerable brain may contribute to the development of ICDs in Parkinson's patients.

Epidemiology of ICDs in Parkinson's Disease

Case reports have implicated DAs (*e.g.*, pramipexole, ropinirole and pergolide), and less commonly levodopa,[35] as precipitating pathological gambling in PD. Driver-Dunckley et al.[10] reviewed 1,884 charts at a PD research center and identified nine patients (0.5 percent of the sample) with documentation of PG, eight of whom were treated with pramipexole and one with pergolide. In a recent case series, all 11 PD patients identified as meeting DSM-IV criteria for PG were taking a DA, nine of whom were on pramipexole and two on ropinirole.[11] Finally, in a very recent retrospective study,[36] the cumulative incidence of PG in PD was reported to be 6.4 percent (12/188), and all affected patients developed PG in the context of dopamine agonist treatment. In addition, all patients who developed PG had gambled recreationally prior to initiating DA treatment.

Regarding other ICDs in PD, in a series of 15 patients with compulsive sexual behavior and either PD or multiple system atrophy, DA treatment was implicated in the emergence of the sexual behavior in 14 cases.[12] More recently,[37] a cumulative incidence rate (after starting dopamine replacement therapy) of 2.4 percent was reported for compulsive sexual behavior in PD. Compulsive buying and compulsive eating (*e.g.*, cravings for sweet-tasting foods) in association with a variety of PD medications have also been reported.[14,37]

Among the published case reports, PD patients with ICDs have disproportionately been younger males,[11,12] suggesting age and sex as potential risk factors for the development of impulse control disorders in PD. These findings are consistent with those from epidemiological and clinical studies that observe high rates of PG and compulsive sexual behaviors in young males in the general population and treatment settings.[3] In some instances,[10-12] substantial time elapsed between initiation of DA treatment and the onset of ICD behavior in PD patients. This delay could reflect either a priming effect, a threshold in the neurodegenerative process that must be crossed before ICD behavior manifests itself, or the importance of patients having been on a DA for an extended period of time before crossing a necessary dosage threshold prior to demonstrating symptoms of an ICD.

The results of two studies that systematically screened for ICDs in PD were recently published. In the first study,[38] 297 patients with idiopathic PD at a tertiary clinic were screened for PG with a modified version of the South Oaks Gambling Scale (SOGS).[39] Lifetime and current (past-three-month) frequencies of pathological gambling were 3.4 percent and 1.7 percent, respectively, and lifetime prevalence of pathological gambling within patients on any DA was 7.2 percent. Pathological gambling was significantly more common in DA-treated patients than in those on levodopa monotherapy. On univariate analysis, PG was associated with earlier PD onset and DA treatment, but not with DA subtype or dosage. In addition, the majority (60 percent) of patients with a history of PG had either a premorbid personal or family history of alcohol use disorder or a family history of bipolar disorder.

In the second study,[40] 272 patients with idiopathic PD at two movement disorders centers were screened for the presence of several ICDs (compulsive gambling, sexual behavior and

buying). Those who screened positive for one or more ICDs during the course of PD were contacted by phone for follow-up and administered a modified Minnesota Impulsive Disorders Interview (MIDI),[41] which includes queries for the presence of clinically-significant compulsive gambling, sexual, and buying behaviors.

The frequency of one or more active ICDs was 4.0 percent, and the frequency of one or more ICDs sometime during the course of PD was 6.6 percent. Among active cases (*i.e.*, those with an ICD at the time of interview), compulsive sexual behavior was as common as problem gambling (2.6 percent vs. 2.2 percent, respectively), and the frequency of compulsive buying was 0.4 percent.

On univariate analysis, younger age, longer duration of PD, history of ICD symptomatology prior to PD, and use of a DA or amantadine each were associated with the presence of an active ICD, and a trend for higher total levodopa equivalent daily dose (LEDD) was observed. All active ICD cases were currently taking a DA. Entering the aforementioned variables into a multivariate model, only current DA use and history of ICD symptomatology prior to PD were significant predictors of an active ICD.

No differences were observed between the three DAs examined (pramipexole, ropinirole, and pergolide) in their association with ICDs. Examining only patients who were on a DA at the time of screening and converting the daily dose of each DA to a LEDD and examining the three agonists as a class, treatment with higher DA doses was associated with the presence of an impulse control disorder.

The results of these two studies suggest that pathological gambling, compulsive sexual behavior or compulsive buying occurs in up to five percent of PD patients at any given time, including up to eight percent of patients on a DA. The occurrence of these ICDs is associated with exposure to the class of DAs, perhaps particularly when prescribed at higher dosages and to patients with a history of ICD or related behavior prior to PD. This latter finding highlights the importance of careful clinical assessment for a broad range of ICDs prior to initiating DA treatment in patients with PD.

Clinical Perspectives

The prevalence of ICDs in Parkinson's disease is not precisely known. Most studies have focused on problem or pathological gambling, and estimated point or cumulative frequencies in PD from published case series range from 0.57 to 6.4 percent.[36] These values may underestimate the true frequencies, particularly as some studies relied on information documented in charts during routine clinical care, and in one of the aforementioned screening studies[40] only 27 percent of active ICD cases had their ICD documented in their clinical record. Patients may be reluctant to acknowledge ICD behaviors to a physician or unaware of a possible connection between ICD behaviors and their PD medications.

Regarding potential risk factors for the development of ICDs in PD, the strongest association appears to be with DA use,[38,40] with additional possible risk factors being male sex, a previous history of ICD behavior[36,40] or substance use disorder,[38] and earlier PD onset.[38] Although case reports have suggested that younger patients are disproportionately affected, older patients are less likely to be treated with DAs due to concerns about adverse events.[40] Considering only patients on a dopamine agonist, younger patients in one study[40] were found to have been treated with higher dosages. Thus, the previous reporting of younger PD patients being disproportionately affected with ICDs may in part reflect prescribing patterns. Regarding the prior history of ICD behavior or substance use disorder, differences in the neural substrate that predisposed to the development of ICDs prior to PD onset could make the same patients vulnerable to manifest similar behaviors during the course of PD in the context of DA treatment.

The risk associated with ICDs appears specific to the DA medication class, as no association was found between daily levodopa dosage and the presence of an ICD.[38,40] These results suggest a distinct mechanism of action, as opposed to an additive effect, for DAs in the development of ICDs.

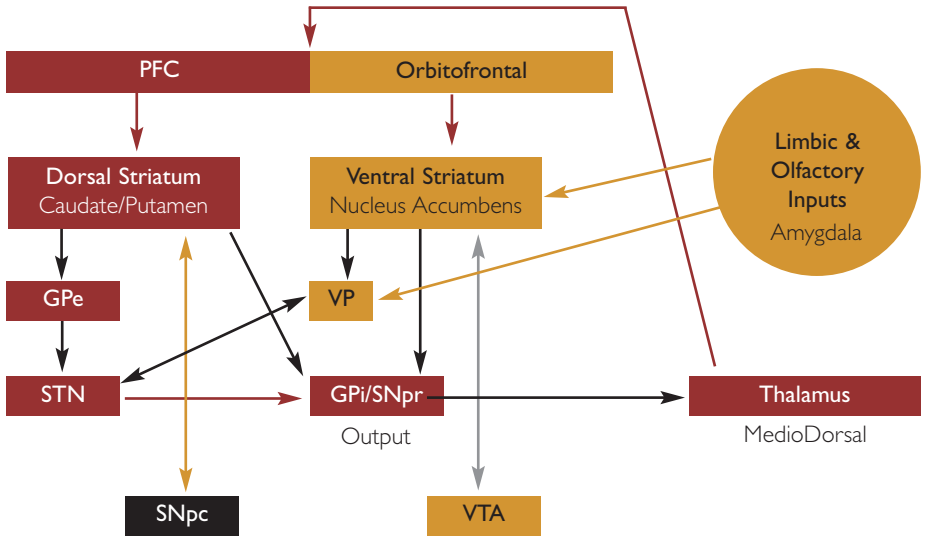
A differential association between specific DAs and ICDs was not supported in two larger studies,[38,40] suggesting a class, as opposed to specific medication, effect. Two case series[10,11] implicated pramipexole as the agent most likely to cause an ICD, but neither accounted for the relative frequency of pramipexole use or dosage employed in comparison with other DAs. In one of the studies utilizing systematic screening,[40] 53 percent of patients taking a DA were on pramipexole, with 36 percent on ropinirole and 11 percent on pergolide. Thus, increased exposure alone would raise the number of ICD cases treated with pramipexole compared with other DAs.

Substantial variability exists in the dosing of DAs in Parkinson's patients. For instance, pramipexole is commonly used in doses ranging from 0.75mg/day to 6.0mg/day, an eight fold difference. Using LEDDs to examine the three dopamine agonists as a class, ICD cases were treated with higher DA doses,[40] a finding consistent with those from two case series that reported ICD in association with pramipexole dosed at the high end of the therapeutic range.[10,11] Thus, the greatest risk for development of an ICD with DA treatment may involve doses at the high end of the therapeutic range.

Screening and Assessment

The apparent under-recognition of ICDs in Parkinson's disease should be addressed through a careful history and patient edu-

Figure 2. Areas implicated in reward processing



cation prior to initiating DA treatment, and by regular monitoring or screening for ICDs throughout the course of treatment. Once a clinician has introduced the topic of a possible association between dopamine replacement therapy (particularly DA treatment), and ICDs in PD, it is appropriate and important to inquire about impulse control behaviors in the context of routine clinical care.

Screening instruments that lend structure to the questioning can assist in making a determination if a clinically significant problem exists. One such instrument is the MIDI, which queries for the presence of numerous ICDs.[2] The SOGS is widely used to screen for PG.[42] The Early Intervention Gambling Health Test (EIGHT) is a brief screen that has been validated in primary care settings.[43] If a clinician suspects the presence of an ICD and needs assistance in the assessment and management process, then the patient should be promptly referred to a psychiatrist for a comprehensive evaluation and ongoing care.

Treatment of ICDs

Regarding the clinical management of ICDs in Parkinson's patients, case reporting and anecdotal experience suggest that ICD behaviors often resolve after reducing the dose of the existing DA, switching to a different agonist, discontinuing DA treatment entirely, or perhaps receiving counseling.[10,11] Anecdotally, psychiatric medications, usually selective serotonin reuptake inhibitors, have been used in the treatment of ICDs in PD, but there is only mixed empirical evidence to support their use for this indication in non-PD subjects,[44] and no empirical evidence in PD patients. There is a single case report of successful treatment of pathological gambling in PD with low-dose risperidone,[11] although the only controlled study of an atypical antipsychotic drug (olanzapine) for PG in non-PD subjects was negative.[44] In non-PD patients, recent research suggests that nalmefene, an opioid antagonist, is efficacious in the treatment of PG.[45]

Pharmacotherapy selection for treating ICDs such as pathological gambling are currently guided in part by co-occurring psychiatric disorders.[42,46] The extent to which the treatment of co-occurring psychiatric disorders (*e.g.*, depression or anxiety) in individuals with PD and ICDs influences ICD symptom severity warrants investigation. Behavioral treatments (*e.g.*, cognitive behavioral therapy and motivational interviewing) appear effective in specific groups of patients with PG,[47] but their efficacy has not been examined in individuals with PD, and one might predict that certain Parkinson's patients (*e.g.*, those with cognitive impairment) might not respond as well to structured behavioral treatments. Similarly, although attendance at Gamblers Anonymous meetings has been associated with better treatment outcome in non-PD samples,[47] no studies have examined its effectiveness in individuals with PD and PG.

Conclusions

Mounting data suggest that dopamine agonist treatment is associated with the development of ICDs in a subset of PD patients. Given the often substantial impact of ICDs on personal, familial, social and financial well-being, these disorders warrant close clinical consideration (active inquiry and assessment) in patients with PD. The risk for an ICD may be heightened at higher DA dosages and in patients with a pre-PD history of similar or related behaviors (*e.g.*, ICD or substance use disorder). These findings highlight the importance of screening for impulse control disorders, and not just PG, in PD patients treated with a DA.

Existing data suggest that clinical management of ICDs in PD should involve serious consideration of promptly decreasing or discontinuing DA treatment. The risk:benefit ratio of

continuing with DA therapy should be evaluated with regard to PD status, ICD behaviors and alternative treatments for the PD and ICDs. In addition, empirically-validated treatments are emerging for ICDs and should be considered for patients with co-occurring PD and ICDs.

As DAs are increasingly prescribed for other indications (*e.g.*, restless legs syndrome), it will be important to assess the prevalence and risk factors for ICDs in non-PD patient populations treated with DAs. Prevention and treatment strategies involving appropriate patient education, clinical assessment (including questioning regarding prior history of ICD or related behaviors), careful DA dosing (using lowest effective dosages), and ICD symptom monitoring throughout treatment should be performed in order to minimize the risk for emergent ICD behaviors and facilitate early interventions. **PN**

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Acknowledgements

Supported by grants from the NIMH (#K23MH067894 – Weintraub, PI), NIDA, and Mental Illness Research, Education and Clinical Centers (MIRECC) at the Philadelphia and West Haven Veterans Affairs Medical Centers.

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