# Dopamine Agonists and Impulse Control Disorders in Parkinson's Disease

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## Abstract

The emergence of the behavioral syndrome known as impulse control disorder (ICD) in Parkinson's disease (PD) has increasingly been associated with dopamine agonist (DAA) use. Clinical reports emphasize the presence of excessive, disruptive, and 'atypical' behaviors in PD patients that resolve after discontinuation or reductions of DAA therapy. The severity of these behaviors has resulted in a heightened clinical vigilance, especially in patients prescribed DAA. This review will discuss the historical rationale for the clinical use of DAA in PD, highlighting the increased association of ICD in patients prescribed DAA therapy. The association between DAA and the emergence of ICD supports the hypothesis that altered mesocorticolimbic function, further emphasized in behavioral and imaging studies, may account for the distinct compulsive hedonic behaviors that characterize the clinical features of this disorder. While the first-line treatment option is reduction and discontinuation of DAA therapy, other therapeutic options are discussed.

## Keywords

Impulse control disorders, dopamine agonist, Parkinson's disease

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## Dopamine Agonists for the Treatment of Parkinson's Disease

The widespread clinical use of dopamine agonists (DAAs) was influenced largely by clinical trials comparing levodopa to DAAs (Ropinirole and Pramipexole) for the treatment of early Parkinson's disease (PD).[1–4] These trials were completed by 2000, and sought to determine if early DAA use could reduce the burden of levodopa-induced side effects, such as dyskinesia, motor fluctuations, and wearing-off phenomenon. Of course, the role of agonists in the treatment of PD was not 'new' *per se*. Already, the ergoline agonists, such as Pergolide, Lisuride, and Bromocriptine were a part of clinical practice by the 1990s.[5] These medications were shown to be effective in the treatment of PD,[6] but they went out of favor largely in part due to concerns of cardiac fibrosis.[7] The role of 'nonergot' agonists as a treatment option for patients was therefore pushed to the forefront of clinical care, especially as the well-advertised 'neuroprotective potential' offered an opportunity to slow the progression of PD. Their use was appealing in early-onset PD patients who appear more prone to develop motor complications from levodopa therapy. Several trials showed the presence of DAA specific side effects, such as sleep attacks,[8] peripheral extremity edema, and hallucinations[1,9] but, as a whole, DAA were associated with fewer motor side effects than levodopa therapy, even though the motor benefit (as evaluated by the Unified Parkinson's Disease Rating Scale [UPDRS]) was not as significant.[1,9]

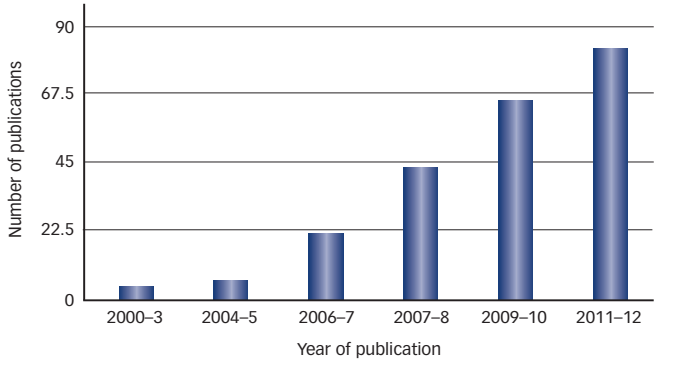
## Parkinson's Disease Impulse Control Disorders

The earliest reports of DAA-induced behavioral changes were about the same time as the completion of the DAA versus levodopa trials. Early reports cited pathologic gambling,[10,11] hypersexuality, and, later, compulsive eating and shopping were recognized.[12] The term impulse control disorder (ICD) was borrowed from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to describe behaviors that appeared 'impulsive' in that patients appeared to act without foresight, and 'uncontrolled' as evidenced by excessive participation in certain activities. ICDs are distinguished from other behavioral side effects seen in patients on dopamine therapy: dopamine dysregulation syndrome and punding (nonpurposeful repetitive movements).[13,14] The latter are seen typically with levodopa therapy, although punding has been reported with DAA use.[15]

The broad categories of hypersexuality, eating, shopping, and gambling, are still seen as the major clinical problems faced by patients, but additional compulsive activities, such as compulsive hobby participation extend the observation in certain patients, participation in rewarding activities can become excessive.[16]

In order to emphasize the growing clinical and scientific interest in these behaviors, we performed an Ovid MEDLINE search with terms 'Parkinson's Disease, Compulsive Behavior, Addictive Behavior, Impulse Control Disorder,' yielding 228 publications. The publication year was plotted, per publication result, showing a growing trend for increasing interest in this topic, beginning in the year 2000 (see *Figure 1*). The association of DAA use and ICD was convincingly made in the DOMINION study, which showed that roughly 14 % of patients taking DAA had the presence of behaviors consistent with the *a priori* definition of ICD.[17]

## Figure 1: Pubished Studies on Behavioral Changes in Parkinson's Disease




*Increase in reporting of impulse control disorder in the last decade.*

## D2-like Receptors and Dopamine Agonist Effects

Since these clinical reports emphasized the unique role of DAA in the emergence of atypical behaviors, hypotheses regarding the reason for DAA-induced effects have focused on the unique DAA mechanism of action. Distinctions between the ergot and nonergoline dopamine receptor predilection suggest that D2-like receptors (D2 and D3 receptors) were likely responsible for the association with DAA use.[18] While nonergoline agonists such as Ropinirole and Pramipexole target the G-protein coupled D2 and D3 receptors, ergot-agonists had an additional D1 receptor activity, which may account for the increased recognition of ICD subsequent to the adoption of nonergoline agonists in routine clinical care.[19] Notwithstanding, there are scattered reports of ICD-type behaviors in patients taking ergoline agonists.[20,21] Furthermore, the observation that DAA induced atypical behaviors can occur in patients without PD, such as restless leg syndrome (RLS), points to a 'class-specific' side effect. Interestingly the prevalence of ICD in RLS closely mirrors that seen in PD, with roughly 17 % of RLS patients susceptible to DAA-induced alterations in behavior.[22]

D2-like receptors are located in greater density along the mesocorticolimbic pathway, thus they influence important mesolimbic and mesocortical cognitive processes, such as reward-based decision-making, craving, and appetitive behaviors.[23–26] D2 receptors function largely as autoreceptors, and exist in the soma, dendrites, and nerve terminals of dopamine neurons, where somatodendritic autoreceptors slow the rate of DA firing, and receptors on the nerve terminal inhibit synthesis and release of DA.[27–29] D2 receptors in the nucleus accumbens and other striatal regions are located both presynaptically, where they mediate the inhibition of DA and acetylcholine release, and postsynaptically, where they mediate the ability of DA to influence striatal function.[29] Thus, the receptor-specific actions of DAA are thought to confer an increased risk for atypical behaviors due to mesolimbic and mesocortical action.[30,31]

## Mesocorticolimbic Function in Patients with Impulse Control Disorders

Behavioral and imaging studies also point to differential DAA-associated mesocorticolimbic function in patients susceptible to ICD. For instance, several studies associate a premorbid propensity for risky behavior, including a history of gambling, substance use or abuse, and novelty-seeking behavior, with a predisposition to the development of a behavioral change.[13,32,33] This suggests that DAAs heighten a premorbid trait by targeting mesocorticolimbic regions. However, studies looking at premorbid personalities are challenging to interpret due to the difficulties with retrospective personality inventories.

Neuropsychologic behavioral studies in ICB have assessed patients with a history of ICD symptoms rather than exclusively assessing individuals with active ICD symptoms. These studies are useful in that patients susceptible to ICD show alterations in reward-related decision-making: preferring smaller immediate rewards to larger delayed rewards, tolerating greater risk for the opportunity of a reward in spite of the potential of a negative consequence, and responding 'more impulsively' to rewarding choices.[34–37] Recently, our group looked at DAA-induced alterations to reward and risk processing in patients with active ICD symptoms.[38] We used a version of the Balloon Analogue Risk task in patients both Off (24-hour withdrawal) and On DAA. The task pairs the potential for reward (allowing the balloon to inflate and earn money) to the risk for a negative consequence (the balloon popping). The main result was that ICD patients tolerated more risk when taking DAA. That is, they allowed for an increased number of balloon inflations, but only when taking DAA. Behavior was equivalent to non-ICD patients when abstaining from DAA. This finding emphasizes that DAA use seems to alter reward-based decision-making in certain patients susceptible to developing ICD behaviors.

Further support to altered mesocorticolimbic function comes from brain-imaging studies. Reported studies were performed in small samples of patients with and without ICD, but also point to differential mesocorticolimbic biology in patients with ICD. For instance, at baseline, ICD patients have reduced D2 nondisplaceable binding potential (BPND) in the ventral striatum, and this region shows a differential response to rewarding stimuli.[39–41] In seven patients with pathologic gambling as a consequence of DAA use, reduced D2 levels at baseline were noted in the ventral striatal areas, and more so during a gambling task.[39] This was replicated in 11 patients with a visually rewarding stimuli.[42] Thus, it appears ICD is associated with excess mesolimbic DA release in response to rewarding stimuli. The presence of DAA then may cause a nonphysiologic enhanced mesocorticolimbic stimulation, which functionally results in an individual uniquely susceptible to behavioral changes in response to rewarding stimuli.

Recent evidence supporting this hypothesis was presented in a study comparing 12 patients with hypersexuality to 12 without, addressing differences in neural activation in response to visual cues of a sexually charged nature. In patients with ICD, the mesocortical and mesolimbic networks showed a greater blood-oxygen-level-dependent contrast (BOLD) signal, when patients were on dopamine therapy. While this study did not specifically address DAA therapy, it does support the hypothesis that mesocorticolimbic activation is particularly enhanced in PD patients susceptible to developing ICD.[43]

## Clinical Recognition and Treatment Options

While the recognition of ICD behaviors has improved, clinical diagnosis remains difficult particularly if patients are unaware or unwilling to describe behavioral changes. To this extent, the Questionnaire for Impulse Control Disorders (QUIP) was developed as a screening tool.[44] This tool can potentially alert the clinician to the presence of atypical behaviors, but

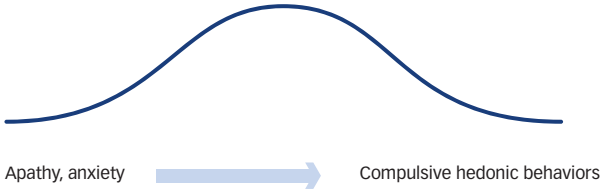
does not replace the need of a formal interview or even neuropsychologic evaluation. It is our practice to also interview the significant other or spouse of the patient, as this can often prove more useful in determining the presence and onset of atypical behaviors. If behaviors are suspected, it is our practice to first document and describe the areas of concern, then to reduce (by at least 50 %) the dose of DAA. In some cases, this must also be accompanied by a slight increase in levodopa. Then, re-interview should occur soon afterwards, and the decision to stay at the current dose, or discontinue altogether can be made.

Patient anecdotes describing behavioral improvements after reductions in DAA are compelling. For instance, one patient with compulsive eating noted less than a week after stopping DAA therapy: "I no longer feel compelled to snack every free moment of the day, nor do I think constantly about food, when I can get some, and whether my refrigerator is full enough … and when I do eat, the amount that appeals to me is much less, and therefore it has been much easier to control the size of the portions I choose." When describing compulsive computer use: "I have felt less compelled to spend so much time on the computer and have been able to stop more easily at the deadline I usually set for myself." Thus recognizing ICD and reducing DAA can be the sole treatment for patients.

If compulsive hedonic activities describe the behaviors that dominate so-called ICD in PD, the other end of the behavioral spectrum could be termed 'apathetic anxiousness with inactivity.' Several reports of an entity termed dopamine agonist withdrawal syndrome have emerged in patients who have reductions or discontinuation of DAA after ICD is recognized clinically. In these cases, patients develop additional symptoms ranging from anxiety, to insomnia, dizziness, and nausea that start after the discontinuation of DAA therapy.[45] Typically, these cases are notable for mild motor symptoms, but a dramatic improvement to low dosing of DAA. Often, additional medications such as serotonin reuptake inhibitors can prove beneficial. These reports illustrate a potential spectrum of mesocorticolimbic activation by DAA, where overstimulation results in compulsive hedonic behavior and 'withdrawal' is characterized by apathy and anxiety (see *Figure 2*). Thus, the role of DAA in patients with apathy and anxiety is a potential avenue for study.

Other treatment options for DAA-induced ICD have focused on medications as add-on options. These reports have not been performed in a systematic manner, but are adjunct therapies in patients with ICD. The use of the N-methyl-D-aspartate (NMDA) receptor antagonist amantadine has had mixed results. Some case reports indicate that amantadine may reduce punding, and a small sample crossover study of gambling in patients with ICD found that the behavior was reduced or completely resolved in the majority of patients (12/17).[14,46,47] However, Weintraub et al. found that amantadine use was associated with a higher rate of ICD.[48] The adverse side effects sometimes associated with amantadine (i.e., confusion, insomnia, visual hallucinations) may reduce the efficacy of the drug as a treatment for ICD. Other medications include selective serotonin reuptake inhibitors, atypical antipsychotic agents (e.g., clozapine), and mood stabilizers (e.g., lithium).[31,49,50] In the absence of controlled clinical trials, it remains unclear how these medications affect ICD behaviors; however, the treatment of comorbid depression may provide additional benefits to patients with ICD.[31] Finasteride, a 5-alpha reductase inhibitor

## Figure 2: Proposed Spectrum of Mesocorticolimbic Function




*Range of hypothesized mesocorticolimbic clinical symptoms, from dopamine agonist withdrawal state to compulsive reward-driven behavior.*

traditionally used to treat benign prostatic hyperplasia, has been reported to reduce pathologic gambling; the noted reduction is most likely a result of the drug's antidopaminergic properties.[51] Another report indicated that the opioid antagonist naltrexone had successfully eliminated pathologic gambling symptoms in three patients.[52]

Controlled clinic trials are needed to further evaluate the use of pharmacologic treatments in reducing or eliminating behaviors associated with ICD.

The results of cognitive behavioral therapy (CBT) and other nonpharmacologic methods as treatment for ICD have been disappointing.[11,31] In a 2012 study by Jimenez-Murcia et al. on CBT, 54 % of PD patients struggling with pathologic gambling had either dropped out or relapsed by the end of the first month.[53] A more recent study by Okai et al. found that Parkinson's patients with impulse control behaviors demonstrated improved symptomology after receiving cognitive behavioral therapy. However, it is unclear whether the demonstrated benefit was a result of the CBT or a combination of CBT and the practical approaches that the study utilized to reduce impulse control behaviors, such as credit card handling by spouses or voluntary banishment from gambling establishments.[54] Further investigation is required to determine the effectiveness of nonpharmacologic methods in treating ICD.

## Future Directions

The well described and sometimes astonishing accounts of ICD have made neurologists aware of the importance of recognizing atypical behaviors in PD patients. Certainly, the internet has provided an unmatched ease of access to gambling, shopping, and pornography for patients. Thus, increased reward-based activities are easily accessible to the vast majority of PD patients, where dopamine therapy initiation can cause, and discontinuation abruptly ameliorates, compulsive behaviors. When one contemplates the compulsive participation in reward-based activities and role of DAA on dopamine receptors localized to the mesocorticolimbic region, it reasons that future studies must answer: why do certain patients appear uniquely vulnerable to this side effect, and what differences in mesocorticolimbic function confer susceptibility to developing ICD?

Progress toward answering these questions will provide important understandings as to the heterogeneous nature of PD, and potentially inform and direct novel medication trials for PD and affective disorders. ■

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