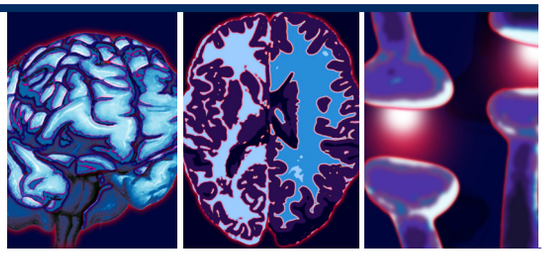
REVIEW



Impulse control disorders in Parkinson's disease: clinical characteristics and implications

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Practice points

- Dopamine replacement therapies (DRTs), including levodopa (LD) and, particularly, dopamine agonists (DAs), have demonstrated efficacy in reducing motor and cognitive dysfunction in patients with Parkinson's disease (PD).
- There is also evidence from small case–control studies to support the effects of deep-brain stimulation in ameliorating symptoms of PD.
- Impulse control disorders (ICDs), related to excessive gambling, sex, shopping and eating, have been observed in PD patients.
- ICDs in PD have been associated with factors related to PD (e.g., age at PD onset) and its treatment (e.g., DAs and perhaps to a lesser extent LD), as well as factors seemingly unrelated to PD (e.g., impulsivity, ICDs prior to PD onset, familial or personal history of alcoholism, family history of a gambling problem, marital status and geographic location).
- Given the associations between DRTs and ICDs in PD, ICDs should be considered when discussing the potential risks, benefits and alternatives to DRTs in the treatment of PD.
- Given associations between ICDs and LD equivalent daily dose measures, DRT dosing magnitude should also be considered and discussed with patients.
- PD patients should be evaluated for possible ICDs. Brief self-report screening instruments (e.g., the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease) are available to aid in identifying PD patients with ICDs and other possibly related disorders or behaviors. Patients responding in a manner suggestive of possible ICDs can then be further evaluated and treated.
- For PD patients exhibiting features of an ICD, reductions in DA dose, potentially accompanied by an increase in LD, may help to reduce impulse control behaviors, although controlled trials are currently lacking.
- Given neurobiological similarities between ICDs with and without PD, treatments found to be efficacious in ICD patients in the general population (e.g., opiate antagonists and cognitive behavioral therapy) may help PD patients with ICDs. However, the potential impact of PD on treatment outcome for these approaches has not yet been tested.

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SUMMARY Impulse control disorders (ICDs), specifically those related to excessive gambling, eating, sex and shopping, have been observed in a subset of people with Parkinson's disease (PD). Although some initial case reports claimed that dopamine replacement therapies, particularly dopamine agonists, cause ICDs, more recent, larger and better controlled studies indicate a more complicated picture. While dopamine replacement therapy use is related to ICDs, other vulnerabilities, some related to PD and/or its treatment directly and others seemingly unrelated to PD, have also been associated with ICDs in PD. This suggests a complex etiology with multiple contributing factors. As ICDs occur in a sizable minority of PD patients and can be associated with significant distress and impairment, further investigation is needed to identify factors that can predict who may be more likely to develop ICDs. Clinical implications are discussed and topics for future research are offered.

The relatively high rate of impulse control disorders (ICDs) among Parkinson's disease (PD) patients is an issue that has gained considerable clinical and research attention in the past decade. While ICDs are observed in a minority of PD patients, a considerable number of patients are affected and the disorders can have a profound impact [1,2]. Furthermore, many patients may not reveal the existence of an ICD to care providers for reasons of shame, denial, motivations to continue the behavior or other reasons. As such, the true prevalence might be higher than existing estimates. Over the past decade, progress has been made in understanding the clinical, cognitive and neurobiological correlates of ICDs in PD. The primary focus of this article is to review recent findings (from 2006 to 2010) in the literature. While we will touch upon earlier research, prior review articles have addressed findings published prior to 2006 [3,4].

Overview of PD & ICDs

Parkinson's disease is a condition characterized by progressive degeneration of dopamine production in the substantia nigra, particularly in the ventrolateral and caudal areas of the substantia nigra pars compacta, adversely affecting dopaminergic projections from these areas to the dorsal striatum [5–7]. Dopaminergic pathways that project to the striatum not only are involved in motoric behaviors, but have also been implicated in the prediction of rewarding situations and outcomes [8]. PD is characterized by various neuropsychiatric, cognitive, motor and autonomic impairments, and these may result from depleted dopaminergic activity [4,9].

Impulse control disorders are a heterogeneous class of disorders that are characterized by repeated and excessive performance of typically or initially hedonic behaviors [10]. ICD behaviors may begin as more hedonically motivated actions during initial engagement and become less driven by pleasurable motivations over time. ICDs are grouped in a category called 'ICDs not elsewhere classified' in the *Diagnostic and Statistical Manual, 4th Edition* (DSM-IV) [11]. Specific ICDs described in the DSM-IV include intermittent explosive disorder and pathological gambling (PG), arguably the most well-studied ICD both in the general population and among PD patients [10]. The category of ICDs in the DSM-IV also includes a 'not otherwise specified' subcategory. The ICD not otherwise specified subcategory can be used to diagnose several conditions that have been noted in PD, including hypersexuality (possibly the earliest identified ICD in PD patients) and compulsive shopping [10]. Research in PD has investigated other conditions and patterns of behavior [12] that, like ICDs, involve repeated excessive activities, may share common neurobiologies and may result from similar underlying vulnerabilities as ICDs [13]. One such condition is dopamine dysregulation syndrome (DDS), which is defined as compulsive use of dopaminergic medication, particularly levodopa (LD) [9,13]. DDS demonstrates similarities with drug addiction, including withdrawal syndromes following medication cessation or reduction [9,14]. Punding, which is defined as the frequent performance of repetitive, stereotyped behaviors, such as collecting or hording, internet use, and sorting and reordering of items, is an example of another pattern of behaviors possibly related to ICDs [4,10].

There is overlap in the diagnostic criteria [11] for ICDs and addictions, consistent with ICDs being described as 'behavioral addictions' [15]. For example, individual inclusionary criteria for both drug dependence and PG exist that target continued engagement despite negative consequences, tolerance, withdrawal and repeated unsuccessful attempts to cut back or quit [11,15]. Evidence has also shown parallels

in the neurotransmitter dysfunction and patterns of limbic and cortical activity typified by addictions and ICDs such as PG [15,16]. For these reasons, PG and possibly other ICDs (e.g., problematic internet use or internet addiction) are being considered for reclassification as addictive disorders in the forthcoming DSM-V [17].

Impulse control disorders may occur more commonly among PD patients than in the general public. In a sample of 554 consecutive PD patients at an outpatient movement disorders clinic in Turkey, 5.9% were found to have an ICD [1]. In a larger, multisite study, a significant percentage of PD patients (13.6%) met criteria for an ICD [2]. Regarding specific disorders, 2.9% met criteria for PG and 5.7% met criteria for compulsive buying in this study. While the compulsive buying frequency is comparable to the rate in the US general population (i.e., 5.8%; [18]), the PG frequency is higher than in the US general population, where the prevalence is approximately 1% in adults [19]. However, elevated frequencies of PG have been observed in association with multiple medical conditions. For example, among a sample of 389 medical and dental patients, over 15% met study criteria for PG and approximately another 10% met criteria for having a gambling problem [20]. Thus, in addition to the specific factors associated with PD, multiple more generalized factors (e.g., the impact of having a significant medical condition and the associated stressors) should be considered when investigating the etiologies of ICDs in PD.

Possible etiologies of ICDs in PD

It has been hypothesized that dopamine deficiencies occurring during the progression of the disease [5,6] may lead PD patients to be less responsive to reward and more responsive to punishment [8,21]. Such a lack of reward responsiveness related to disease progression may lead to a loss of pleasure, which may in turn lead some PD patients to seek extrinsic stimulation, in some cases in the form of impulsive behaviors [9]. Similar neurobiological dysfunction has been described in substance dependence. Continued drug seeking and use may be perpetuated, in part, by reduced numbers of dopamine D2-like receptors in the brain (particularly in the striatum), and these alterations may influence dopamine signaling, feelings of reward or pleasure, reinforcement of behaviors and reward-based learning [22].

Aspects of cognitive decline associated with PD progression (e.g., decrements in working memory [23]) may also predispose PD patients toward impulsive behavior. Tendencies toward response perseveration, a feature sometimes associated with ICDs and addictions, have been found in PD patients and may not be closely linked to anti-Parkinson's medications [23]. Utilizing functional MRI, Rowe *et al.* found with patients both on and off anti-Parkinson's medication that there was less intense anterior cingulate activation during the prospect of reward in a continuous performance task among those with more severe PD [24]. By contrast, activation in response to actual rewards increased with disease severity. These findings suggest that lack of reward responsiveness in more severe PD patients may be associated specifically with weaker anticipation of reward rather than a lack of responsiveness to actual reward receipt. This pattern of response may be related to greater delay discounting (i.e., a preference for more immediate, smaller rewards rather than delayed, larger rewards [25]), which is considered to be an aspect of impulsivity [26].

These findings suggest that disease progression may lead to impulsive tendencies. Data also suggest that dopamine replacement therapies (DRTs), including LD (a biochemical precursor to dopamine) [27] and particularly dopamine agonists (DAs; e.g., pramipexole and ropinirole) are associated with ICDs [2,3]. Another anti-Parkinson's treatment that has been discussed as a possible risk factor for impulsive behavior and ICDs is deep-brain stimulation (DBS) of the subthalamic nucleus [28,29].

Clinical studies

■ Factors associated with ICDs in PD

Dopamine replacement therapies improve motor function and may influence cognitive flexibility [8,30,31]. ICDs in PD have been associated with DRTs [2,32–35]. In an international study involving over 3000 PD patients, 17.1% of patients taking DAs had ICDs compared with 6.9% of PD patients not taking a DA [2]. LD use was also associated with ICDs in this study, although the association was not as strong as for DAs. Of the small minority of PD patients in this sample who received neither LD nor DA treatments (n = 59), only 1.7% met criteria for an ICD.

The relationship between medication use and ICD does not appear to be straightforward and may reflect an underlying vulnerability. While a considerable number of PD patients are affected,

those who develop an ICD nonetheless represent a minority of the PD patients who take medication [36]. Several factors may influence the likelihood of developing an ICD **(Table 1)** [3,4]. ICDs in PD have been associated with factors related directly to PD (e.g., age at PD onset and functional impairment related to PD) and its treatment (e.g., DBS, DAs, LD and amantadine). In addition, ICDs in PD have been associated with factors seemingly unrelated to PD, including mental health disorders (e.g., personal and/or familial histories of alcoholism, gambling problems and

Table 1. Factors associated with impulse control disorders in Parkinson's disease patients.

Factor	Author (year)	Ref.
Amantadine treatment	Weintraub *et al.* (2010)	[63]
Trait anxiety	Voon *et al.* (In Press)	[60]
Deep-brain stimulation	Ballanger *et al.* (2009)	[28]
	Frank *et al.* (2007)	[72]
	Lim *et al.* (2009)	[29]
Depression	Gallagher *et al.* (2007)	[13]
	Voon *et al.* (In Press)	[60]
Dopamine agonist treatment	Ardouin *et al.* (2006)	[32]
	Bostwick *et al.* (2009)	[73]
	Driver-Dunckley *et al.* (2003)	[33]
	Gallagher *et al.* (2007)	[13]
	Giladi *et al.* (2007)	[74]
	Pontone *et al.* (2006)	[75]
	Voon *et al.* (2006)	[34]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2010)	[2]
Family history of gambling problems	Weintraub *et al.* (2010)	[2]
High functional impairment related to Parkinson's disease	Voon *et al.* (In Press)	[60]
Impulse control disorders history before onset of dopamine agonist treatment	Weintraub *et al.* (2006)	[35]
Impulsivity	Voon *et al.* (In Press); motor and rapid decision	[60]
	Voon *et al.* (2007); nonplanning	[38]
Levodopa equivalent daily dose	Voon *et al.* (In Press)	[60]
Levodopa treatment	Weintraub *et al.* (2010)	[2]
Male sex	Gallagher *et al.* (2007)	[13]
	Giladi *et al.* (2007)	[74]
	Kenangil *et al.* (2010)	[1]
Medication-induced hypomania	Voon *et al.* (2007)	[38]
Novelty/sensation seeking	Bodi *et al.* (2009)	[8]
Obsessive–compulsive symptoms	Voon *et al.* (In Press)	[60]
Personal or family history of alcoholism	Voon *et al.* (2007)	[38]
	Weintraub *et al.* (2010)	[2]
Residing in the USA	Weintraub *et al.* (2010)	[2]
Tobacco smoking	Weintraub *et al.* (2010)	[2]
Unmarried	Weintraub *et al.* (2010)	[2]
Younger age/younger age of Parkinson's disease diagnosis/onset	Gallagher *et al.* (2007)	[13]
	Giladi *et al.* (2007)	[74]
	Voon *et al.* (2006)	[34]
	Voon *et al.* (2007)	[38]
	Weintraub *et al.* (2006)	[35]
	Weintraub *et al.* (2010)	[2]