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CURRENT OPINION

Impulse Control Disorders in Parkinson's Disease: An Overview of Risk Factors, Pathogenesis and Pharmacological Management

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Abstract

Impulse control disorders in Parkinson's disease are relatively common drug-induced addictive behaviours that are usually triggered by the dopamine agonists pramipexole, ropinirole and rotigotine. This narrative review aimed to provide a comprehensive overview of the current knowledge of impulse control disorders in Parkinson's disease. We summarised the prevalence, clinical features, risk factors and potential underlying mechanisms of impulse control disorders in Parkinson's disease. Moreover, recent advances in behavioural and imaging characteristics and management strategies are discussed. Early detection as well as a tailored multidisciplinary approach, which typically includes careful adjustment of the dopaminergic therapy and the treatment of associated neuropsychiatric symptoms, are necessary. In some cases, a continuous delivery of levodopa via a pump or the dopamine D_1 receptor agonist, apomorphine, can be considered. In selected patients without cognitive or speech impairment, deep brain stimulation of the subthalamic nucleus can also improve addictions. Finding the right balance of tapering dopaminergic dose (usually dopamine agonists) without worsening motor symptoms is essential for a beneficial long-term outcome.

Key Points

Impulse control disorders are a relatively common side effect of dopamine receptor agonists in patients with Parkinson's disease.

Additional neuropsychiatric comorbidities are common in those with impulse control disorders, which further negatively impacts the quality of life of patients and their families.

The underlying mechanisms involved are not entirely clear, although a relatively preserved nucleus accumbens causing a dopaminergic over-stimulation of the ventral striatum seems to play a pivotal role.

Management of impulse control disorders is challenging and requires a reduction and often cessation of dopamine agonists.

1 Introduction

Impulse control disorders (ICDs) are defined as a "failure to resist an impulse, temptation, or drive to perform an act that is harmful to the person or others" [1]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) includes oppositional defiant disorder, intermittent explosive disorder, conduct disorder, kleptomania and pyromania as ICDs [2]. The DSM-V also lists nine types of substance addictions that include alcohol, caffeine, cannabis, hallucinogens, inhalants (such as nitrous oxide, amyl nitrite and volatile solvents including paint removers and cleaning products), opioids, sedatives, hypnotics, anxiolytics, stimulants and tobacco. Moreover, gambling disorder is now included in the chapter on Substance-Related and Addictive Disorders [2]. This change was performed to highlight the similarities between gambling disorder and drug addiction: in both conditions, an anticipatory craving, a decrease of anxiety, and the feeling of euphoria following gambling or intake of the drug may occur. Additionally, both gambling disorder as well as drug addiction frequently co-occur [3]. According to the DSM-V criteria, ICDs occur in five stages. Typically, ICDs begin with an increased sense of tension, followed by a failure to resist an urge to act. During the act, the arousal peaks and as the

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Table 1 Proposed criteria for compulsive sexual behaviours in Parkinson's disease (adapted from Voon et al.) [36]

(A) The sexual thoughts or behaviours are excessive or an atypical change from baseline marked by ≥1 of the following:
Maladaptive preoccupation with sexual thoughts;
Inappropriately or excessively requesting sex from partner;
Habitual promiscuity;
Compulsive masturbation;
Using telephone sex lines or viewing pornography;
Paraphilias.
(B) The behaviour must be persistent for ≥1 month.
(C) The behaviour causes ≥1 of the following:
Marked distress;
Attempts to control thought or behaviour are unsuccessful or result in marked anxiety or distress;
Are time consuming;
Interfere significantly with social or occupational functioning.
(D) No occurring exclusively during (hypo)manic periods.
(E) If all criteria except C are fulfilled, the disorder is subsyndromal.

act is completed a sense of relief or release is felt. Finally, patients may feel remorse or guilt for their behaviour [2].

Impulse control disorders and related disorders are seen as comorbidities in neurodegenerative diseases, such as progressive supranuclear palsy [4, 5], multiple system atrophy [6, 7] and frontotemporal dementia [8], and are most common in patients with idiopathic Parkinson's disease (PD) [9]. Moreover, addictive behaviours can also occur in patients without clear evidence of neuronal/nigrostriatal degeneration as a direct consequence of dopamine agonist therapy in patients with fibromyalgia [10], patients with restless legs syndrome (particularly in those who have in addition augmentation) [11] and in patients with endocrine diseases (such as pituitary adenomas) [12]. Furthermore, ICDs and related disorders have been described in patients with frontal lobe dysfunction such as Gilles de la Tourette syndrome [13], and in patients with attention-deficit hyperactivity syndrome [14]. In the majority of patients diagnosed with PD, these addictive behaviours emerge following the start of dopaminergic therapy, mainly dopamine agonists.

Regardless of the underlying comorbidity, patients with ICDs and related disorders typically continue their addiction despite negative consequences. Any attempt to discontinue the behaviour frequently leads to dysphoria, anxiety and depression, similar to withdrawal symptoms after drug abuse [15].

Compulsive sexual disorder (see Table 1), gambling disorder (see Table 2), compulsive shopping (see Table 3) and compulsive eating are the most commonly described ICDs in PD [9]. Other related addictions in patients with PD include dopamine dysregulation syndrome (DDS, sometimes also called Lees syndrome), where patients hoard drugs, self-medicate with a larger amount of levodopa against the physician's advice to avoid off-periods (for diagnostic criteria, see Table 4) and exhibit punding, which is the urge to perform senseless activities repeatedly (such as assembling and disassembling, collecting or sorting objects in brackets) [16–18]. Other phenomena include hobbyism (a pathological pursuit in common hobbies, such as excessive fishing, writing or Internet use) reckless generosity [19], excessive hoarding [20], walkabouts [21] and drug addiction [22]. Although the name ICD implies an inability to resist an urge, these heterogeneous behaviours are sometimes complex, sometimes habitual, non-goal oriented and stereotyped. Therefore, ICDs also have impulsive and compulsive aspects that have been mentioned in several studies [23–25]. Similar to the general population, it is believed that the impulsive component, together with the feeling of joy and gratification may be responsible for the initiation of the addiction, while a more habitual and compulsive component may be the culprit of persistence [26].

In line with this, patients with PD with ICDs and DDS often report a feeling of euphoria, mania or pleasure; while punding is a more peculiar addictive behaviour in PD, not driven by pleasure [27]. Previously, it was thought that a gambling disorder was the most frequent ICD and increased libido would occur less frequently [9] but results of several studies suggest that compulsive sexual behaviour (for proposed diagnostic criteria see Table 2) is one of the most, if not the most common addiction in male patients with PD [28, 29]. Multiple addictions are also common if an ICD or related disorder has been detected [9], particularly in those with compulsive sexual disorder [29].

While ICDs in PD have been described more thoroughly within the last few decades, these side effects of dopaminergic medication are not new and had been reported in the

Table 2 Diagnostic and Statistical Manual of Mental Disorders, fifth edition, diagnostic criteria for gambling disorder [2]

(A) Persistent and recurrent problematic gambling behaviour leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:
Needs to gamble with increasing amounts of money in order to achieve the desired excitement;
Is restless or irritable when attempting to cut down or stop gambling;
Has made repeated unsuccessful efforts to control, cut back or stop gambling;
Is often preoccupied with gambling (e.g. having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble);
Often gambles when feeling distressed (e.g. helpless, guilty, anxious, depressed);
After losing money gambling, often returns another day to get even ("chasing" one's losses);
Lies to conceal the extent of involvement with gambling;
Has jeopardised or lost a significant relationship, job, or educational or career opportunity because of gambling;
Relies on others to provide money to relieve desperate financial situations caused by gambling.
(B) The gambling behaviour is not better accounted for by a manic episode.

Table 3 Diagnostic criteria for compulsive shopping [37]

(A) Maladaptive preoccupation with buying or shopping that is manifested as impulses or behaviours that:
1. Irresistible, intrusive and/or senseless experiences;
2. Result in frequent buying of more than can be afforded, items that are not needed or a longer period of time than intended.
(B) Cause marked distress, are time consuming, significantly interfere with social and occupational functioning, or result in financial problems.
(C) Not occurring exclusively during (hypo)manic episodes.

Table 4 Diagnostic criteria for dopamine dysregulation syndrome [21]

(A) Parkinson's disease with documented levodopa responsiveness.
(B) Need for increasing doses of DRT in excess of those normally required to relieve parkinsonian symptoms and signs.
(C) Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being "on", drug hoarding, drug-seeking behaviour, unwillingness to reduce DRT, absence of painful dystonias.
(D) Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence of work, loss of job, legal difficulties, arguments or difficulties with family.
(E) Development of hypomanic, manic or cyclothymic affective syndrome in relation to DRT.
(F) Development of a withdrawal state characterised by dysphoria, depression, irritability and anxiety on reducing the level of DRT.
(G) Duration of disturbance for at least 6 months.

DRT dopamine replacement therapy

1960s and 1970s, a few years after the introduction of levodopa [30–32]. The true prevalence of these behaviours in PD is unknown, as patients likely conceal or under-report these side effects because of shame or denial. The general consensus is that ICDs and related addictions occur somewhere between 14% and 30% [9, 28] and are likely much higher in patients with a younger disease onset [33] with a 5-year cumulative incidence of 46% [34]. Because of the increased awareness and change in prescribing dopaminergic therapy, ICDs and related addictions are currently possibly declining again, although some suggest that the COVID-19-induced lockdowns and thus an increase in environmental stress may have caused again a rise of these addictive behaviours [35].

The objective of this narrative review is to provide a comprehensive overview of risk factors, potential mechanisms, diagnosis and the management of ICDs and related disorders in patients with PD.

2 Behavioural Aspects of Patients with PD with ICDs and Related Disorders

Not surprisingly, studies found that patients with PD with addictive disorders report higher impulsivity scores, had higher levels of neuroticism, lower levels of agreeableness and conscientiousness, as well as lower working memory

capacity than patients with PD without ICDs and related disorders [38–40]. Furthermore, these patients have higher schizotypy scores (which measures the risk of psychosis) compared with controls [41].

Several studies have assessed the acute behavioural changes following dopaminergic administration in PD so far. Unmedicated patients with PD showed enhanced learning from negative feedback while medicated patients learned better from positive feedback [42–44]. This has been shown in drug-naïve patients with PD ($n = 26$) who were treated for 12 weeks with an oral dopamine agonist (pramipexole $n = 14$, ropinirole $n = 12$) and tested on feedback learning. This was done using a computer-based probabilistic classification task, where a reward-learning task, a punishment-learning task and a no-feedback outcome were inter-mixed. Untreated patients had intact negative feedback learning but impaired positive feedback learning whereas this behaviour changed to impairment of negative outcomes with normal reward learning following 12 weeks of dopamine agonist therapy [45]. These studies led us to the hypothesis that patients with PD with ICDs have increased positive feedback learning and/or diminished negative feedback learning, which may then facilitate the development of addictive behaviours in PD. However, several studies prior to and following dopaminergic therapy did not show differences in feedback learning in a two-choice probabilistic discrimination task in patients with PD with ICDs and related disorders compared to healthy volunteers [40, 41, 46]. In contrast, one other study with a two-choice probabilistic discrimination task with three conditions (gain, loss, neutral) showed that patients with PD with ICDs and related disorders ($n = 14$) had better reward learning [47], in another study, patients with PD with ICDs and related disorders ($n = 16$) were worse in negative feedback learning [48]. Furthermore, patients with PD with ICDs and related disorders had a heightened reward sensitivity to reward-related cues measured by pupillary dilatation both in the "off" as well as in the "on" state, whereas patients with PD without ICDs and related disorders only had this reward sensitivity after dopaminergic medication [49]. Other factors that may likely contribute to the development of ICDs and related disorders include risk taking. Two studies observed patients with PD prior to and after dopaminergic therapy; patients were tested with a forward and backward digit span test, an instrumental learning task, a gambling task in one study [40] and with the Balloon Analogue Risk Task (a computerised decision-making task used to assess risk-taking behaviour) in the other study. Both studies found increased risk-taking behaviour in patients with PD with ICDs following medication intake [40], particularly dopamine agonists (either pramipexole or ropinorole) [50].

Mixed results have been also reported on inhibitory control. In one study, patients with PD ($n = 52$) were worse than healthy controls in the Stroop task prior to dopaminergic medication intake, with no difference between patients with PD with addictive behaviours ($n = 28$) and those without ($n = 24$). After dopaminergic medication, both patients performed as well as healthy volunteers with no group differences [51]. In line with this, patients with PD with addictions did not perform worse on the Simon task (a task to assess impulsive choice) than PD controls following dopamine agonist intake. In fact, those with ICDs and related behaviours made fewer fast impulsive response errors than PD controls, which suggests that addictive behaviours in PD are less related to motor impulsivity [52]. However, preliminary results from an eye-tracking study showed increased error rates on the anti-saccade task [53]. In the anti-saccade task, participants are asked to fixate a central cross on a screen. As soon as it disappears, a peripheral cue appears on the horizontal plane randomly on the right or left; here participants are asked to not perform a saccade towards the cue, but rather in the opposite direction. Successful inhibitory control depends on intact frontal cortical function as well as an intact frontal eye field and normal function within the thalamo-cortico-cerebellar network [54]. In line with this, a functional magnetic resonance imaging (MRI) study with a double-blind, randomised, crossover design on male volunteers ($n = 16$) receiving placebo and pramipexole has shown that pramipexole reduces striatal interaction with the prefrontal cortex [55]. These data further dovetail with the hypothesis of a dysfunction of prefrontal cortical inhibition in patients with PD with ICDs and related disorders.

Impulsivity has several facets and it is likely that in contrast to motor impulsivity, temporal discounting (the preference of a smaller immediate reward rather than a larger delayed reward) and reflection impulsivity (tendency to make decisions without considering available information) may play a bigger role in the development of addictive behaviours in PD. Patients with PD with ICDs and related disorders ($n = 35$) had a steeper discounting of future rewards on medication compared with their off state [56] and had increased temporal discounting in their on medication state compared with non-impulsive patients with PD ($n = 55$) [41, 43, 57]. In particular, patients with PD with a gambling disorder and those with compulsive shopping seem to have greater temporal discounting than patients with PD with other ICDs, such as compulsive sexual behaviour and binge eating disorder [38]. The orbitofrontal cortex seems to play a critical role in encoding temporal discounting. For example, lesions to the medial part due to a stroke caused increased discounting for money, suggesting that the orbitofrontal cortex is necessary for optimal weighting of future outcomes during decision making [58].

Furthermore, patients with PD with ICDs and related disorders made premature decisions and jumped to conclusions with little evidence in a study comparing patients with PD with ICDs ($n = 6$), patients with PD without ICDs ($n = 27$), patients with a gambling disorder ($n = 23$) and patients with

substance abuse ($n = 13$) using the bead task [59]. This poor information sampling is sometimes also called "reflection impulsivity" and is likely caused by dopamine agonist medication but not levodopa or deep brain stimulation (DBS) [60].

Another typical feature of patients with PD with ICDs and related disorders is enhanced novelty seeking [38], which could also be shown in a probabilistic learning task [61].

Taken together, these studies show that ICDs and related disorders likely affect impulsivity in the decisional domain, with impairment in temporal discounting, poor information sampling, novelty seeking and increased risk taking, and less difficulties in the motor domain, such as response inhibition.

3 Differences of ICDs and Related Disorders Within Patients with PD

Comparative studies and large studies with differences between the single addictive behaviours are rare. This is likely because of the multiple addictions that frequently co-occur [9]. One large study, however, compared patients with PD with gambling disorders ($n = 54$), compulsive sexual behaviour disorders ($n = 47$), compulsive shopping ($n = 54$) and those with binge eating disorders ($n = 42$). All these patients only had one addictive behaviour. As expected, all patients with PD with ICDs and related disorders had greater depression and all but the binge eating group had higher anxiety scores compared with PD controls ($n = 282$). Interestingly, only patients with PD with compulsive shopping had increased temporal discounting (assessed with the delayed discounting task, a self-report scale used to observe choice impulsivity) compared with PD controls. Novelty seeking was significantly different to PD controls (18.7 on the self-report Temperament and Character Inventory) in patients with compulsive shopping (25.1) with a trend in those with a gambling disorder (22.3) but not in patients with PD with a compulsive sexual disorder (19.1) and patients diagnosed with a binge eating disorder (18.9) [38]. Moreover, patients with PD with single or multiple ICDs had higher levodopa doses (679.9 vs 544 mg/day), were functionally more impaired and had higher scores on depression (Geriatric Depression Scale-15, 4.9 vs 2.8), anxiety (State Trait Anxiety Inventory, 39.9 vs 33.6), obsessive-compulsive (Obsessive Compulsive Inventory, 13.7 vs 8.8), novelty seeking (Temperament and Character Inventory, 21.8 vs 18.7) and impulsivity (Barratt Impulsiveness Scale, 66.6 vs 57.5) compared with PD controls. However, there was no difference between patients with PD with single and with multiple ICDs [38].

There are some characteristics that are probably more commonly seen in patients with PD with compulsive sexual disorders than in patients with PD with other types of addictions. For example, one albeit small study ($n = 111$) reported that multiple ICDs are particularly common in young male patients with PD with a compulsive sexual disorder [29]. Furthermore, psychotic symptoms such as paranoid delusional jealousy (Othello syndrome) have also been more commonly described in those with a compulsive sexual disorder. These patients have the false certainty of the infidelity of their partners [62]. In line with this, one study also found that patients with PD with a compulsive sexual disorder are less agreeable than patients with PD with other ICDs or PD controls using the Neuroticism-Extroversion-Openness Five Factor Inventory [63]. In the Parkinson Progression Markers Initiative cohort, punding behaviours could be predicted by current or antecedent attentional dysfunction in de novo patients with PD and by impairments in activities of daily living [64].

4 Burden of ICDs and Related Disorders in PD

Patients with PD with ICDs and related disorders experience more non-motor symptoms (particularly neuropsychiatric problems) than patients with PD without addictive behaviours. More specifically, depression, a poorer quality of life [28], a reduction in social well-being [65], apathy [66] worse sleep, more anxiety as well as higher mania scores [67], psychosis [68] and a higher frequency of rapid eye movement-sleep behaviour disturbances [69] are frequently seen in these patients. Higher aggressiveness, irritability, disinhibition, poorer insight and denial also occur regularly [70]. Moreover, urinary dysfunction, fatigue, cardiovascular problems [71] as well as poorer working memory [40] negatively impact the quality of life of patients with PD and ICDs.

In addition, patients with PD who develop addictive behaviours have a longer disease duration (i.e. data from the National Danish Patient Registry show a mean disease duration of 9.3 years in patients with ICDs compared with 7.5 years in those without), have more motor complications, and take larger amounts of dopaminergic medication than those without ICDs and related disorders [38, 39, 68, 72, 73].

Apart from the patients' personal disease burden, the burden of relatives caring for patients with PD is already high because of mental, physical and socioeconomic problems [74]. Carers of patients with PD without ICDs and related problems report a far greater burden from mental rather than physical stress, which significantly reduces their quality of life [75]; this strain on the quality of life is even more pronounced in carers of patients with PD with ICDs and related disorders [76]. More specifically, depressive symptoms, apathy and disinhibition in patients with PD with ICDs result in the high caregiver burden [77].

4.1 Illustrative Case

4.1.1 Non-Pharmacological Risk Factors for ICDs and Related Disorders in PD

It is unclear why some patients with PD develop addictive disorders and others do not. It is therefore unlikely that a single mechanism is causative for the development of ICDs. However, it has now been widely accepted that the use of dopaminergic medications (particularly dopamine agonists) in susceptible patients is responsible for the development of an addiction in PD [78] [79]. Several non-pharmacological risk factors have been identified in recent years. The individual vulnerability may consist of striatal density or genetic factors or a combination of both [72]. In line with this, a recent genome-wide association study identified four loci (DAB1, PRKAG2, MEFV and PRKCE) associated with ICDs in a large cohort of 5770 patients with PD, which can distinguish patients with PD at high versus low risk for developing addictions [80].

Other factors include a younger age, younger onset of PD, being single and experiencing more non-motor symptoms than patients with PD without addictions (see Table 5) [38, 68, 72, 73]. Furthermore, higher anxiety scores as well as autonomic and cognitive dysfunction seem to also be risk factors [81]. Sex differences also play a role but are not specific for PD. Compulsive sexual behaviour has been more frequently reported in male patients with PD ($n = 3090$, 5.2% prevalence in men vs 0.5% prevalence in women [9]), while compulsive shopping and binge eating disorders (same study cohort, respectively, 4.5% in men vs 7.8% in women and 3.4% in men vs 5.8% in women) seem to occur more often in female patients with PD [9, 36].

Other risk factors include a higher novelty-seeking personality trait, a history of alcohol or smoking, depression, anxiety, insomnia, higher caffeine consumption, and a personal or family history of addictive behaviour [23, 82–84]. Depression and anxiety seem to play an important role, as both of these symptoms occur significantly more often in the off-state and on-state in patients with ICDs compared with those without (depression, 23% vs 13%; anxiety, 9% vs 4%). Moreover, larger changes in depressive symptoms from the off to the on state (identified as the change in the Hamilton Depression Rating Scale) were also observed in the ICD group compared with the PD control group; this was assessed in a cross-sectional study including 159 patients without ICDs and 41 patients with ICDs [85]. Alexithymia, the difficulty to express, define or identify emotions, has been also linked with increased impulsivity in drug-naïve patients with PD [86] and has been proposed as a risk factor for ICDs [86, 87]. In line with this, apathy, a reduction in emotions, interests and motivation which is common in PD, frequently also co-occurs in patients with ICDs [88]. It has been therefore speculated that the hypodopaminergic behaviours, such as depression, anxiety and apathy, which lie on the opposite spectrum of hyperdopaminergic behaviours (ICDs) [89], may share a common behavioural continuum [90, 91].

Table 5 Summary of main risk factors for International Classification of Diseases and related disorders in Parkinson's disease [9, 68, 69, 80]. For each risk factor, the OR for developing International Classification of Diseases-related disorders has been reported

Risk factors	OR
Genetic (single nucleotide polymorphisms)	
DAB1-OMA1 intron	2.1
PRKAG2 intron	0.8
MEVF intron	2.6
PRKCE intron	0.5
Presence of psychotic symptoms	4.3
Dopamine agonist treatment	2.7
Age (≤65 vs >65 years)	2.5
Depression	2.4
Family history of gambling problems	2.1
REM sleep behavioural problem	1.8
Current smoking	1.7
Not married vs married	1.5
Levodopa treatment	1.5
Complexity of fluctuations	1.4

OR odds ratio, *REM* rapid eye movement

4.1.2 Pharmacological Risk factors for ICDs and Related Disorders in PD

It is currently accepted that dopaminergic medication can trigger addiction in PD, as PD itself is not associated with an increased prevalence of ICDs and related disorders. In fact, a case-control study in drug-naïve patients with PD ($n = 168$) showed a similar frequency of ICDs and related disorders (18.5% PD vs 20.3% controls) compared to healthy controls ($n = 143$) [92].

By far the biggest risk factor for developing compulsive sexual behaviour, compulsive shopping, and gambling disorder in PD is the use of dopamine agonist therapy [23]. Gambling disorder in patients with PD has almost always been triggered by dopamine agonists and has been only rarely associated with levodopa monotherapy [93].

Although craving for sweets is common in PD, particularly in those who have ICDs [94], the association of binge eating and dopamine agonist therapy remains unclear. Counterintuitively, dopamine agonist use seems not to be associated with binge eating and food addiction in PD [95]. In fact, a small ($n = 96$ patients with PD) cross-sectional study

Table 6 Synopsis for the management of ICDs and DDS in PD

Prevention	Inform patients and relatives of potential ICDs prior to the start of dopamine replacement therapy
	Continue screening for ICDs by asking patients and family members during each follow-up visit
Management of ICDs and DDS in PD	Limit access to money and Internet
	Consider CBT
	ICDs: reduce/stop dopamine agonists
	DDS: stop fast-acting dopaminergic drugs (dispersible levodopa, apomorphine injections)
	Treat neuropsychiatric symptoms (e.g. psychosis, anxiety, depression)
	Target insomnia
Management of complications	Treat potential withdrawal symptoms (pain, insomnia, irritability, levodopa refractory motor symptoms …)
	To improve motor fluctuations, consider advanced therapies (DBS, continuous levodopa or apomorphine pump therapy)

CBT cognitive behavioural therapy, *DBS* deep brain stimulation, *DDS* dopamine dysregulation syndrome, *ICDs* impulsive control disorders, *PD* Parkinson's disease

identified eight patients with binge eating with DBS being the only predictor for overeating [96].

There have been conflicting reports on whether ICDs correlate with the dopamine agonist dose but the dopamine agonist plasma concentration was similar between those with compared to those without ICDs [97]. However, the lifetime average dose as well as the duration of dopamine agonist therapy seem to be associated with ICDs [34]. Moreover, the combination of a dopamine agonist with levodopa seems to increase the risk of ICDs and related disorders even further possibly owing to an increase of mesolimbic dopamine levels and the synergic effect on dopamine receptors [9, 25, 98–100]. In line with this, dyskinesias (resulting from higher dopaminergic therapy) are significantly more often seen in patients with PD with ICDs and related disorders than in those without [101].

Although addictive behaviours can be triggered with all available dopamine agonists, they are less often seen in patients with PD treated with the transdermal dopamine agonist rotigotine compared with pramipexole or ropinirole [102]. These results have been recently confirmed in a meta-analysis including more than 650 patients with PD. The rotigotine patch was three times less likely to induce addictive behaviours than pramipexole and ropinirole [103]. While rotigotine has high affinities to the dopamine D_1, D_2, D_3, D_4, and D_5 receptors, ropinirole and pramipexole only have high affinities to the D_2, D_3 and D_4 receptors. While these pharmacodynamics may play a role in triggering addictions, it is more likely that the drug delivery (oral vs transdermal) is more relevant. Transdermal drug application may lead to a more continuous drug delivery, avoiding peaks and troughs. While oral dopamine agonist plasma concentrations eventually drop after 6–12 h, plasma concentrations during rotigotine therapy remain stable for up to 24 h. Moreover, transdermal application of rotigotine provides direct access to the bloodstream avoiding the hepatic first-pass effect seen in oral dopamine agonists [103] (see Table 6).

The role of D_3 agonism in inducing impulsivity has been further confirmed in a recent pharmacovigilance-pharmacodynamic study. Here, around 3000 ICD reports of impulsivity under dopamine agonists (pramipexole and pergolide) are presented, with data regarding receptor occupancy supporting the role of D_3-induced ICDs [104]. Interestingly, however, there seems to be no difference between the extended-release and standard oral dopamine agonist formulation (pramipexole and ropinirole) [34].

Although much rarer, ICDs and related disorders have been also described with the use of monoamine oxidase B inhibitors [102] and amantadine [9]. Impulse control disorders under the therapy of catechol O methyltransferase inhibitors are rare. The exact frequency is unknown, mainly because most studies report levodopa equivalent daily doses. A post-hoc analysis on the pooled data from two large randomised, double-blind, placebo-controlled trials on opicapone ($n = 517$) shows a low incidence of addictive behaviours (between 0.2 and 0.5%) [105], but importantly the risk of ICDs does not appear to increase with long-term use of opicapone [106]. More recently, ICDs have also been observed with aripiprazole ($n = 97$), which acts as a partial D_3 agonist, bupropion ($n = 56$), a dopaminergic antidepressant and the psychostimulant methylphenidate ($n = 40$) [107–109].

5 Management of ICDs in PD and Pragmatic Treatment

5.1 Experimental Drugs Currently Under Investigation

Naltrexone, an opioid receptor antagonist, which is effective in alcohol addiction, failed to improve ICDs in PD [133]. However, it has been argued that some ICDs such as hobbyism may be more responsive to naltrexone than other ICDs, but further studies are warranted [134]. Clonidine,

an α2-adrenergic agonist, has been shown to significantly reduce impulsivity in a gambling task in abstinent heroin addicts ($n = 53$) [135]. A recent randomised, controlled, double-blind, phase IIb trial in patients with PD with ICDs ($n = 39$) showed, however, that administration of clonidine for 8 weeks resulted only in a non-significant reduction of impulsivity compared with placebo [136]. Although in this study clonidine (75 µg twice daily) was well tolerated, common side effects include low blood pressure as well as dizziness and depression, which may further reduce the quality of life in PD. Nevertheless, the results of this study warrant a longer treatment duration and a larger sample size in a further phase III trial. A crossover, double-blind, placebo-controlled study using atomoxetine (40 mg orally), a noradrenalin reuptake inhibitor, showed reduced motor and reflection impulsivity as well as risk taking. Although this study is promising, the sample size was rather small and none of the patients with PD had ICDs ($n = 33$) [137]. However, evidence from functional MRI shows that atomoxetine may enhance prefrontal cortex connectivity and possibly have a restoring effect on executive functions; this may hold interest in future trials [138].

Currently, a randomised, placebo-controlled, phase II trial (NCT03947216) assessing the effect of pimavanserin, a selective serotonin 5-HT_{2A} inverse agonist, on ICDs is underway and results are expected in 2025. In this trial, patients with PD will be treated with pimavanserin 17 mg or placebo daily for 8 weeks, with the primary outcome measure being the change in ICDs (measured with the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease [QUIP]) after treatment.

Management of ICDs and related disorders in PD is challenging. Thus, the phrase "prevention is better than cure" is particularly important, as there are no consensus guidelines available because of the paucity of randomised controlled trials. Therefore, all patients with PD should be advised about the potential risk of developing behavioural addictions especially following dopamine agonist therapy. This consultation should ideally take place together with family members, carers or close friends who are in regular contact with the patient. Long-term vigilance is required especially in younger patients, those who have a personal or family history of addictive behaviours, or who are single and experience more motor symptoms such as dyskinesias as well as non-motor symptoms [23]. It is also important to highlight that ICDs and related behaviours in PD almost always build up gradually and any change in behaviour, particularly increased irritability, disturbed night-time sleep or increased spending may be harbingers. In line with this, it has been reported that 24% of patients with subsyndromal ICDs (defined as subthreshold behaviours without reaching the formal diagnostic criteria) developed clinically significant ICDs after 1 year [88]. The severity of the addiction is important to take into consideration and sometimes an immediate hospital admission may be required. The QUIP [139] and the QUIP rating scale, which includes the severity of the addiction [24], can be useful to detect an ICD early on.

In contrast, there are rare circumstances where no change of treatment is required in patients with PD with addictive behaviours depending on the patients' disability, financial and social circumstances. However, usually if an ICD or a related disorder is left untreated or ignored, it may have devastating financial and psychological consequences for the lives of patients and their families (see illustrative case).

Non-pharmacological approaches such as physical exercise, cognitive behavioural therapy or limiting access to credit cards, the Internet or gambling venues should be implemented but are usually not enough on their own [16, 23, 140]. Dopamine agonists should be reduced in patients with gambling disorders, compulsive sexual disorders and those with compulsive shopping and (if possible) completely weaned off. Patients are sometimes reluctant to reduce the dopamine agonist because of low insight but switching from a dopamine agonist to levodopa can improve impulsive behaviour within a few months [141]. However, patients must be informed that anxiety, panic attacks, depression, dysphoria, fatigue, pain and the feeling of being undertreated may occur. These symptoms are known as dopamine agonist withdrawal syndrome and may cause significant psychological distress that may be refractory to levodopa or any other PD medication [142]. Hospital admission may be necessary in these patients to alleviate dopamine agonist withdrawal syndrome.

In patients with DDS, a reduction in levodopa, or a fast-acting apomorphine pen injection is necessary, but these patients often do not tolerate the reduction because of worsening of motor fluctuations, 'off' dystonia or withdrawal symptoms. These heterogeneous non-motor as well as motor symptoms usually subside within a few days or weeks but can also last several months [72]. Again, in these patients, hospital admission and a multidisciplinary approach including a psychiatrist and psychologist may be necessary.

Treatment of the neuropsychiatric comorbidities, such as depression, anxiety and panic attacks, as well as an improvement of potential sleep disturbances may be frequently required regardless of the underlying addictive behaviour [23, 67, 143]. Trazodone and the alpha-2 adrenoreceptor antagonist mirtazapine may help to improve some neuropsychiatric symptoms as well as nocturnal sleep [144]. Additionally, considering that the pathophysiology of depression in PD likely involves several neurotransmitters (dopaminergic, serotoninergic, noradrenergic), depression should be treated with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or a tricyclic antidepressant. Although there are no official guidelines

guiding the therapeutic choice, there is some evidence in favour of the aforementioned drugs, as well as for cognitive-behavioural therapy [145, 146]. If patients have additional psychosis, quetiapine or clozapine may be administered; however, regular blood counts because of the potential risk of agranulocytosis are limitations in those treated with clozapine [146].

The role of DBS of the subthalamic nucleus in patients with PD with ICDs and related disorders is controversial. However, in selected patients with PD who do not experience cognitive impairment, or have any other contraindication for functional surgery, DBS of the subthalamic nucleus can result in improvement of ICDs and related symptoms because of the reduction in dopaminergic therapy [147]. In some patients, however, de novo ICDs can occur, possibly due to misplacement of the electrode, or failure of a dopaminergic drug reduction [16]. Pre-operative but also post-operative psychiatric monitoring is mandatory in patients with PD who undergo DBS, given reports of the increased risk of post-surgical suicide attempts [143].

Dyskinesias have been linked with ICDs in PD [72] and thus, a reduction in dyskinesias by decreasing the overall dopaminergic therapy will often also lead to an improvement of addictive behaviours. In line with this, there is preliminary evidence that continuous delivery of levodopa/carbidopa or the D1 receptor agonist apomorphine can improve ICDs [148, 149].

Overall, a remission of ICDs and related disorders can be achieved in about 40–80% of patients. Not surprisingly, several studies have shown that a reduction in the dopamine agonist dose or ideally a complete discontinuation is linked with better outcomes [34, 150–152].

6 Potential Underlying Mechanisms

In PD, the dorsal striatum is primarily affected and neurodegeneration is more severe than in mesolimbic neurons, which are relatively unaffected [111]. Therefore, one hypothesis is that in patients with PD with ICDs and related behaviours, the nucleus accumbens may still be relatively intact and that the extra dopaminergic medication leads to a local dopamine overdose in the ventral striatum [112]. Importantly the nucleus accumbens shell has strong connections to limbic structures and is therefore believed to have an important role in motivation and addiction. Stimulation of the nucleus accumbens is believed to play a pivotal role in drug addiction, as the iatrogenic dopamine release in this nucleus shares similarities to natural rewards (such as food), but is missing the physiological adaptation (habituation and inhibition by predictive stimuli) [113, 114].

This "overdose hypothesis" has been recently confirmed in a post-mortem immunohistochemistry study in patients with PD with various addictive behaviours ($n = 31$) who were matched to patients with PD without addictions ($n = 29$). Patients with PD with ICDs and related disorders had significantly less alpha-synuclein pathology in the ventral striatum than patients without addictions. This further strengthens the hypothesis that the ventral striatum is indeed better preserved in these patients. Furthermore, and on the surface counterintuitively, patients with ICDs had also lower D_3 receptors [115]. This may be due to down-regulation of the receptors leading to a supersensitivity of the remaining D_3 receptors or a premorbid personality trait making these patients more vulnerable for addictive behaviours [115, 116]. Alternatively, the lower D_3 receptors could also reflect a smaller motor response to dopaminergic medication in patients, which would then lead to higher doses to achieve symptomatic control, causing a dopamine overdose of the ventral striatum [115]. However, as D_1 and D_2 but not D_3 receptors are responsible for the overall best motor response [114], this hypothesis remains speculative.

Dopamine agonists may directly affect the cortico-striatal network. A study with 16 healthy male volunteers shows that pramipexole increases mesolimbic dopamine levels during anticipation of monetary rewards, but at the same time reduces the striatal interaction to the prefrontal cortex [55]. This dopamine agonist induced reduction in "top down control" in addition to the mesolimbic dopamine "overdose" is currently thought to play a key role for developing ICDs and related disorders in susceptible patients [110].

7 Imaging in Patients with PD with ICDs and Related Disorders

7.1 Structural MRI

The role of structural imaging in patients with PD with ICDs is inconclusive with some studies showing cortical thinning of the orbitofrontal cortex [117], while others reported an increased cortical thickness of the orbitofrontal cortex [118, 119], and others did not find structural differences compared to PD controls [81, 120]. There are only a few of these studies and they vary in the number of participants observed and their demographics; orbitofrontal cortex thinning has also been associated with other conditions, which may work as confounders when interpreting these results (depression, alcohol dependence). Thus, there is no clear evidence on whether cortical thickness does play a major role in patients with PD with ICDs and related behaviours.

7.2 Functional MRI

Resting-state MRI revealed that patients with PD with ICDs have an increased connectivity within the salience network (anterior insula and dorsal anterior cingulate cortex) and a decreased connectivity within the central executive network (dorsolateral prefrontal and lateral posterior parietal cortex). This altered connectivity of the neurocognitive networks, which is also found in patients with other addiction disorders, may be one neural correlate of ICDs in PD [121].

7.3 Positron Emission Tomography

One of the first positron emission tomography (PET) studies using [^{11}C] raclopride assessed patients with PD with DDS ($n = 8$) and PD controls ($n = 8$) prior to and following the first levodopa dose. Patients with PD with DDS but not PD controls had elevated levodopa-induced ventral striatal dopamine release. This sensitised ventral striatal dopamine release was associated with self-reported compulsive drug "wanting" but not "liking" [122]. Sensitisation (an enhanced response to a stimulus) is — like tolerance, withdrawal and dependence — a hallmark of addiction [123]. In line with this, another PET study using [^{11}C] raclopride showed a higher ventral striatal dopamine release in patients with PD with a gambling disorder during gambling but not in PD controls following dopamine agonist therapy (pramipexole $n = 5$, ropinirole $n = 2$) [124]. Moreover, patients with PD with a variety of different ICDs but not PD controls also exhibited an increased ventral striatal dopamine release following reward-related visual cues after levodopa intake (200/50 mg, scanning acquired 45 minutes after intake) [125]. Another $H_2{}^{15}O$ PET study revealed a reduction in the lateral orbitofrontal cortex, as well as in the amygdala and the rostral cingulum during a card selection game following apomorphine administration only in patients with PD with a gambling disorder ($n = 7$) [126].

A study using the PET radiotracer, [11C] FLB-457, with high affinity for extra-striatal D_2/D_3 receptors, found decreased binding in the midbrain during a gambling task in patients with PD with ICDs ($n = 7$) compared with PD controls ($n = 7$). These results hint towards a wider dopaminergic dysfunction with altered striatal and cortical dopamine homeostasis in patients with PD with ICDs [127]. In line with this, a study using cerebral 18F-fluorodeoxyglucose PET showed that patients with PD with ICDs ($n = 18$) had a dysfunction of a large network including the mesocorticolimbic system, the caudate, the parahippocampus and the orbitofrontal cortex, but also with increased metabolism of the right middle and inferior temporal gyri [128]. It is therefore possible that these temporal regions are involved in the establishment of the mnemonic component of addiction [128].

Several studies have used the [123I] FP-CIT radioligand, which showed a reduction in dopamine transporter (DAT) levels in the ventral striatum of patients with PD with a gambling disorder ($n = 8$) [129] and patients with PD with a variety of different ICDs ($n = 282$) [130]. It is possible that the lower DAT binding reflects lower membrane DAT expression on presynaptic terminals, resulting in a functional reduction of presynaptic reuptake and thus increased dopamine levels within the ventral striatum [129]. In line with these results, a small preliminary study ($n = 31$) [131] and a large ($n = 320$ at baseline; $n = 284$ at year 1, $n = 217$ at year 2, $n = 96$ at year 3) longitudinal study using the data acquired in the Parkinson's Progression Marker Initiative found an association between lower striatal DAT binding and an increased risk of developing ICDs [132]. Thus, these PET studies, combined with the neuropathological results, imply that increased and abnormal mesolimbic dopamine release, due to a relatively intact ventral striatum, in combination with prefrontal cortex dysfunction may trigger behavioural addictions [115, 124–126].

8 Conclusions

Impulse control disorders are relatively common non-motor symptoms that arise in patients with PD being treated with dopaminergic drugs, most commonly with dopamine agonist therapy. The variability on the amount of patients who develop ICDs and also the type of ICDs that may arise depends on several risk factors, which include younger age, higher anxiety traits and a history of addictive behaviours in the past. As ICDs may have devastating consequences in patients' lives both socially and financially, patients being started on dopaminergic drugs should be properly informed of the possibility of ICDs arising, ideally in the presence of a family member or close friend. If an ICD is reported, early treatment is of paramount importance, as the patient's cognition may already be impaired. Management of ICDs requires a reduction, and if possible, a complete discontinuation of dopamine agonist therapy. In patients with DDS, a reduction in fast-acting dopaminergic drugs is necessary. Often patients with PD have to be admitted to hospital to alleviate dopamine agonist withdrawal syndrome. New trials exploring additional therapeutic strategies need to take in account the diverse nature of all disorders falling under the term ICDs and if necessary tailor a therapy for each disorder.

Declarations

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