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Impulse control disorders and related behaviors in Parkinson's disease: risk factors, clinical and genetic aspects and management

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Abstract

Purpose of review: To review recent findings and research directions on impulse control disorders and related behaviors (ICDRBs) in Parkinson's disease (PD).

Recent findings: Longitudinal studies found that prevalence increases during PD progression, incident ICDRBs being around 10% per year in patients treated with dopaminergic therapies. Screening tools and severity scales already developed have been validated and are available in several countries and languages. Main clinical risk factors include young age, male gender, type, doses and duration of the dopaminergic therapy, PD motor severity and dyskinesia, depression, anxiety, apathy, sleep disorders and impulsivity traits. Genetic factors are suspected by a high estimated heritability, but individual genes and variants remain to be replicated. Management of ICDRBs is centered on dopamine agonists decrease, with the risk to develop withdrawal symptoms. Cognitive behavioral therapy and subthalamic nucleus deep brain stimulation also improve ICDRBs. In the perspective of precision medicine, new individual prediction models of these disorders have been proposed, but they need further independent replication.

Summary: Regular monitoring of ICDRB during the course of PD is needed, particularly in subject at high risk of developing these complications. Precision medicine will require appropriate use of machine learning to be reached in the clinical setting.

Keywords: impulse control disorders, Parkinson's disease, dopamine agonists, dopamine replacement therapy, prediction medicine

Introduction

Impulse control disorders (ICDs) are behavioral disorders are common complication in Parkinson's disease (PD) treated by dopamine replacement therapies (DRT). Related behaviors, such as hobbyism and dopamine dysregulation syndrome (DDS), have also been reported. These disorders negatively impact the quality of life of the patients and caregiver [1].

This article reviews previous and recent findings on ICDs in PD regarding their frequency, phenomenology, screening tools, and risk factors (Figure 1). The current and future strategies to manage these behaviors are also discussed.

Definition and description of impulse control disorders

PD is a frequent neurodegenerative disorder, affecting over 6 million patients worldwide [2]. Apart from the characteristic motor symptoms of PD, a wide variety of non-motor symptoms have been described, among which impulse control disorders and related behaviors (ICDRBs). ICDRBs are characterized by impairment in behavioral self-control with a failure to resist an urge to an enjoyable activity, that can lead to harmful situations and interfere with various areas of daily life when performed excessively. Despite the possible negative consequences, the behaviors are repeated without control, defining those behaviors as impulsive and compulsive. ICDRBs have shown to negatively impact life and social-occupational functioning of PD patients and their caregivers [1,3–7]. Among available dopamine replacement therapies (DRTs), dopamine agonists (DA) are the main treatment and risk factor associated with the occurrence of ICDRBs.

Description of ICDRBs reported in PD

The wide variety of ICDRBs reported in PD are summarized in Table 1 and Figure 1.

The main ICDs are pathological gambling, binge eating, compulsive shopping and hypersexuality. Pathological gambling is defined as recurrent and persistent dysfunctional patterns of gambling behavior leading to clinically significant distress or impairment [8]. Binge eating is characterized by recurrent episodes of high food intake in a short span of time [8]. Compulsive shopping is defined as excessive shopping and buying behavior that leads to distress or impairment [9]. Hypersexuality is characterized by recurrently or persistently present sexual or erotic thoughts or fantasies and desire for sexual activity [8,10]. Repetitive behaviors such as, punding, hobbyism, walkabouts and hoarding and, as in DDS, the compulsive use of DRT medication, have also been described as related behaviors [11–16]. Punding results in repetitive, purposeless behaviors focused on specific activities or motor tasks such as unnecessary repetitive home repair or assembling and disassembling objects repetitively. Hobbyism pertains to more complex repetitive behaviors such as arts, sports or online gaming. Walkabouts are excessive, aimless wanderings. In hoarding, patients collect a large number of items with little objective value, without being able to discard them, leading to impaired living conditions.

Assessment and diagnosis

Given their potentially devastating consequences, prompt identification of these disorders is important, especially as the patients may not be aware, or hide, their behaviors. Several screening tools and scales have been developed to screen, diagnose or assess severity of ICDs in PD (Table 1).

The Movement Disorder Society Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) includes an item entitled *Features of dopamine dysregulation syndrome* in the part assessing non-motor aspects of experiences of daily living (part I) [17]. This single item encompasses impulse control disorders, DDS, hobbyism, and punding.

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) was developed as a screening instrument for ICDRBs, structured to be consistent with diagnostic criteria as described in the fourth edition of Diagnostic and Statistical Manual (DSM) of Mental Disorders [18]. Its three sections focus on (i) the four most common ICDs, (ii) punting and hobbyism, and (iii) compulsive medication use. A rating scale version of the QUIP, the QUIP-RS, assess their frequency [19] and has been validated in several countries [20–22]. The QUIP can be used for screening for ICDRBs, while the QUIP-RS can be used for both screening and severity rating of ICDRBs [23].

The Ardouin Scale of Behavior in PD (ASBPD) consists of eighteen items addressing psychological and behavioral symptoms, grouped in four parts: general psychological evaluation, apathy, non-motor fluctuations and hyperdopaminergic behaviors [24]. This scale was validated in comparison to other scales and is particularly useful for the assessment of the severity across the range of ICDRBs [23,25].

The Scale for Outcomes in PD – Psychiatric Complications is a screening and severity scale with a 7-item questionnaire [26]. Each item score ranges from 0 (no symptom) to 3 (severe symptoms). Two items are related to ICD: one for compulsive shopping and pathological gambling, and another for hypersexuality [23]. This scale is only recommended for the evaluation of these three ICDRBs [23].

The Minnesota Impulsive Disorders Interview (MIDI) was originally developed in 2008 for the diagnosis of compulsive buying, trichotillomania, kleptomania, pyromania, intermittent explosive disorder, pathological gambling, and compulsive sexual behavior [27,28]. The original version was revised to match the changes made in the fifth edition of the DSM of Mental Disorders [27]. This semi-structured interview is used to assess the impulsive aspect of a compulsive behavior.

This large number of screening tools and scales may introduce heterogeneity in the assessment of ICDRBs in PD, which is already inherently high because of socio-cultural differences. So far, the QUIP-RS seems the most prominent tool given its validation in several languages. For severity rating across the range of ICBs, the QUIP-RS and the ASBPD are recommended [23]. Further testing of established scales against gold standard diagnostic criteria is required for all individual ICDRBs in PD, in the perspective of studies focusing on a specific subtype of ICD for instance, and such as the South Oaks Gambling Screen (SOGS) for gambling.

Frequency

ICDRBs are common in PD, the prevalence ranging from 14 to 33% in cross-sectional and longitudinal studies [3,29–36]. The prevalence increases during disease progression, incident ICDRBs being around 10% per year in patients treated with DRT [29,37]. The frequency and severity seem higher in specific subpopulations such as PD patients with *Parkin* mutations or *GBA* variants [38,39]. A recent review focused on the geographical analysis of ICD prevalence in PD, in regards to the socio-cultural aspects that may influence their occurrence [40]. The overall prevalence in European and American countries (20.8%) was significantly higher than in Asian countries (12.8%). The relative frequency of each subtype of ICDs also varied across countries. Binge eating was reported as the most frequent in European countries and American states, followed by hypersexuality and compulsive buying; whereas hypersexuality seems the most frequent in Asian countries, followed by pathological gambling. Studies in Turkey and India reported very low pathological gambling prevalences [41,42], possibly explained by the fact that gambling is prohibited in Turkey and heavily restricted in India.

Regarding ICD-related behaviors, less characterized, prevalence data are scarcer. Punding prevalence rates vary from 1.4% to 14% [12,13,43] depending on the clinical profile

of patients such as higher dosage of treatment. The prevalence of hoarding has been estimated at 12.2%, although in a specialized PD clinic, hence possibly overestimated [44]. DDS prevalence rate has been reported at 2.3% [45].

Pharmacological, clinical and genetic risk factors

Many risk factors of ICDs in PD have been reported, including demographic, PD-related, pharmacological and genetic risk factors.

Pharmacological variables

DRT, especially dopamine agonists (DA), has been strongly associated with ICDs. Ever use, longer cumulative duration, and higher cumulative dose of DAs have been correlated with ICDs [29]. Lifetime average daily dose and duration of treatment by DA were reported as independently associated with ICDs with significant dose-effect relationships [29,33,34,46]. The six DA approved by the US FDA (pramipexole, ropinirole, bromocriptine, cabergoline, rotigotine, and apomorphine) have all been associated with ICDs [47]. The strongest associations were reported for DA with a preferential affinity for D2-like receptors (D2 and D3 receptors) [48], and were higher with oral short-lasting DA than oral long-lasting or transdermal DA suggesting that pharmaceutical formulation and delivery route may also be important [49,50]. To a lesser extent, associations with levodopa [36,46] and amantadine [36] have been reported. Associations of ICDRBs with zonisamide, istradefylline, monoamine oxidase inhibitors but also antidepressants and sleep inductors were also suggested [33,35,51]. ICDRBs have been reported in drug-naïve PD patients with the same prevalence as in the general population, and in patients with restless leg syndrome (RLS) treated by DA [52–56], suggesting that ICDRBs are not related to PD only, but rather to the DRTs. The lack of association found between a PD genetic risk score and ICDRBs in PD supports this hypothesis [57].

Demographic features

A younger age, younger age at PD onset and male sex have been associated with ICDRBs [36,45,46,58–60]. Differences between sexes depending on ICDRBs subtypes were observed, with women developing more compulsive buying and eating disorders and men developing more pathological gambling and hypersexuality disorders [61,62], although the same differences have been reported in the general population [63]. A personal pre-PD history of an ICD and personal or family history of substance abuse are also risk factors for ICDRBs [64].

Personality traits

The most associated personality trait is impulsivity, with studies reporting higher impulsivity scores [64,65] and greater choice impulsivity [65]. PD patients with ICDs show a higher level of neuroticism and lower levels of agreeableness and conscientiousness [58], particularly among PD patients with pathological gambling [66] or hypersexuality [10]. Such patients are also reported to have ineffective coping skills [67], premorbid personality (novelty seeking and harm avoidance) [60], and anxiety [68].

Psychiatric disturbances

Symptoms and a history of depression [58,62,64,66,69–72], and a history of or higher scores of anxiety [10,46,64,72,73] have been reported as associated with ICDs. A recent study reported that the majority of PD patients with ICDs also suffered from clinically significant apathy and more than a third of apathetic PD patients suffered from ICDs [74].

Cognition

The relationship between ICDRBs and cognitive decline is not clear yet. A recent study reported higher prevalence and severity of all ICDRBs in PD patients with dementia than without dementia [75] whereas others reported less common ICDs in PD demented patients, but they were older, and less treated by DAs [59].

Worse set-shifting and reward-related decision-making were reported in PD patients with ICDs [70]. They may show different neuropsychological profiles depending on ICD subtype, with distinct dysexecutive or memory impairments [13,76]. But these alterations may be reversible modifications, only subsequent to DRT use [77,78].

Sleep disturbances

PD patients with ICDs have been reported to have an increased prevalence of sleep disturbances, including worse sleep efficiency, RLS symptoms, and daytime sleepiness [46,79–82]. Recent results suggest a common phenomenology of urge to move between RLS and ICDs [83]. PD patients with RLS develop more ICD, especially compulsive eating disorders, and show a different psycho-behavioral profile with more hyperdopaminergic behaviors on the ASBPD scale [82]. A strong association has been reported between ICDs, especially pathological gambling, and rapid eye movement sleep behavior disorder (RBD) both in early PD and longitudinally [68,82,84–88], although some recent findings did not reproduce this association [88,89].

PD-related factors

Several PD-related factors have been associated with ICDs such as younger age at PD onset [46,58,61,90], longer disease duration [46,58,61], and higher motor impairment [34,58,73]. A negative association between motor fluctuations or dyskinesias and ICDs has been reported [87], but others reported a positive association between dyskinesia and ICDs [91]. A higher

MDS-UPDRS Part I score, assessing non-motor disturbances of daily living, was reported [65,92], but one of the MDS-UPDRS Part I items concerns DDS.

Genetic data

Heritability of ICDRBs was estimated at 50-60% both in non PD twin studies and PD studies [93,94].

Studies reporting associations of genetic variants with ICDs in PD usually performed candidate gene analyses. Associations were reported with variants in genes encoding receptors or enzymes from dopamine, norepinephrine, serotonin, glutamate and opioid pathways in PD: *DAT1* [95], *DRD1* [96,97], *DRD2* [93,97], *DRD3* [98–100], *DDC* [93,101], *GRIN2B* [97,100], *HTR2A* [93,102], *OPRK1* [93], *ANKK1* [103], *OPRM1* [95], and *SLC22A1* [104] and in the general population [105]. Several of these associations were not always confirmed [95,106], most of these studies being underpowered in PD and without independent replication. The reader can refer to a recent review for a more extensive list of variants investigated in ICDRBs [107].

Exome sequencing suggests genes implicated in signaling pathways linked to G protein-coupled receptors such as the “Adenylate cyclase activating” pathway could participate to genetic susceptibility to ICDs in PD [108].

Management

There is no specific pharmacological agent approved for the management of ICDRBs [107]. Nonetheless, several strategies to manage these disorders have been investigated.

Since DA use is the most important risk factors to develop ICDRBs in PD, a common approach is to reduce the dose or withdraw DA use, with reports suggesting ICDRB resolution or improvement after a few weeks to several months [1,78,109,110]. DA withdrawal may

however have significant drawbacks, including DA withdrawal syndrome with anxiety and depression [111], and may precipitate motor complications. Some patients may require low doses of DA over a large span of time to prevent psychological disorders, but persistence of ICDRBs also occur [112].

Pharmacological agents, including naltrexone [113], citalopram [114], amantadine, and atomoxetine [115,116], have been trialed with modest results and no definitive demonstration of efficacy.

Cognitive behavioral therapy has been investigated to manage ICDRBs, with encouraging results. A randomized controlled trial reported improvement in ICDRBs as well as anxiety and depression levels for 28 patients enrolled in a cognitive behavioral therapy in comparison to 17 wait-listed controls [117], who also demonstrated beneficial response to therapy six months later [118].

Subthalamic nucleus deep brain stimulation (STN-DBS) seems to possibly improve ICDRBs in most reported cases [119] and in prospective observational studies, possibly related to DA medication decrease [120–122]. Yet, worsening of ICDRBs, no change, and development of de novo ICDRBs after STN-DBS have also been reported [119,122].

Prediction

Given the difficulties to screen for ICDs in clinical practice, and the limited treatment strategies to manage ICDs in PD, developing predictive tools would be of great interest. Although risk factors are useful clinical clues, they still cannot reach prediction medicine level for individual risk prediction, which would require machine learning approaches, applied in a few recent studies.

Studies that investigated the predictability of ICDs in PD [93,96,101] trained and evaluated a logistic regression model with clinical and genetic variables as inputs, each in a

different cohort. Adding genetic variables input increased the predictive performance of the models.

These studies have important limitations as they included a single cohort in their analyses, and none of the studies performed cross-validation to evaluate the predictive performance of their models. The same dataset was used as the training set but also as the test set. The predictive performances of these models may thus be highly overestimated. None of the three studies evaluated the performance of their models on an independent replication cohort, which would help estimate the generalizability of the models. Some publicly available cohorts could be used in the next studies to train algorithms on one dataset and evaluated them on another dataset.

Conclusion

Since the first reports of ICDRBs in PD in the early 2000s, dedicated clinical cohorts allowed to determine the frequency and risk factors of ICDRBs, and screening tools and severity scales have been validated. Genetic liability of ICDRBs remains mostly unknown, and larger genetic association studies with independent replication are still needed. The clinical management of ICDRBs includes the decrease in DA use, cognitive behavioral therapy, and eventually STN-DBS. Preliminary studies have proposed predictive models of ICDRBs in the perspective of precision medicine development. Further discoveries on the pathophysiology and predictability of these disorders will likely integrate the use of deep-learning approaches to combine clinical and genetic risk factors for a potential application in the clinical setting.

Key points

- Impulse control disorders and related behaviors are frequent in Parkinson's disease, with an incidence estimated to 10% per year in patients treated with dopamine replacement therapy
- The main risks factors are the dose and duration of the dopamine replacement therapy, a younger age and male gender, motor and non-motor features of Parkinson's disease profile, and potential genetic factors that remain to be explored
- Management relies on the decrease of the dopamine agonist doses with the risk of withdrawal symptoms, cognitive behavioral therapy, and eventually deep brain stimulation in eligible patients
- Clinical-genetic models to predict patients at high risk of developing these disorders would be ideal, but are in need of further development with accurate deep-learning approaches and replication

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Figure legend

Figure 1. Overview of the frequency, screening tools, risk factors, clinical and genetic aspects, management and predictive models of impulse control disorders and related behaviors in Parkinson's disease.

Abbreviations: ASBPD, Ardouin scale of behavior in Parkinson's disease; DD, disease duration; ICDs, impulse control disorders; ICDRBs, impulse control disorders and related behaviors; MAO, monoamine oxidase; MDS-UPDRS, Movement Disorders Society revision of the unified Parkinson's disease rating scale; MIDI, Minnesota impulsive disorders interview; PD, Parkinson's disease; QUIP, questionnaire for impulsive-compulsive disorders in Parkinson's disease; QUIP-RS, questionnaire for impulsive-compulsive disorders in Parkinson's disease – rating scale; RBD, rapid eye moment sleep behavior disorder; RLS, restless leg syndrome; SCOPA, scales for outcomes in Parkinson's disease; SOGS, South Oaks gambling screen; STN-DBS, subthalamic nucleus deep brain stimulation.

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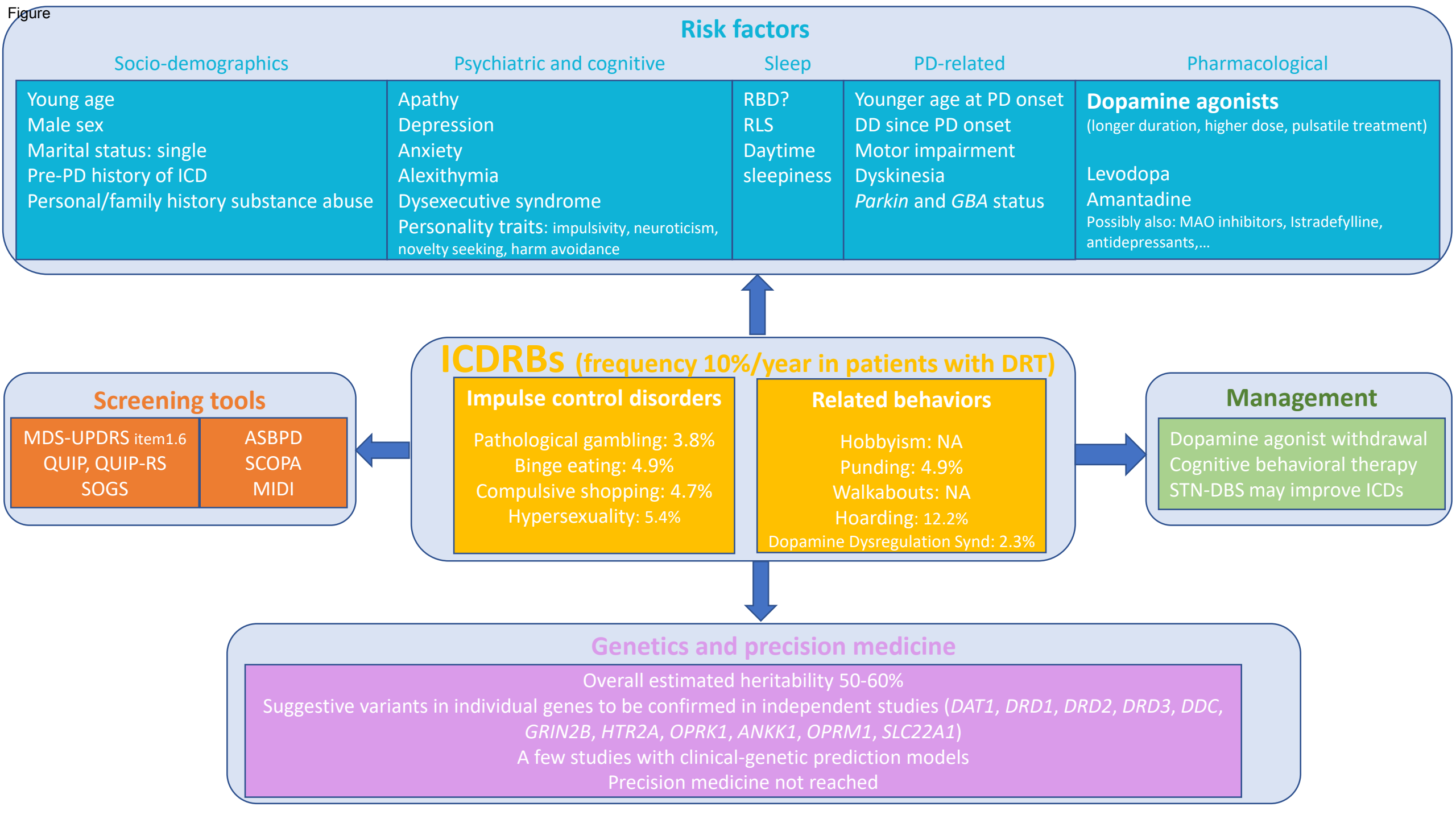
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Figure



Table

Table 1. Different types of impulse control disorders and related behaviors in Parkinson's disease, their frequency and the relevant screening and evaluation tools.

Class	Type	Description	Frequency % [range]	Relevant screening tools in PD
Impulse control disorders	Pathological gambling	Addiction to casino games and slot machines, scratch card games, online gambling, with potentially devastating financial repercussions	3.8% [0% - 14.0%]	ABSPD, MDS-UPDRS 1.6, MIDI, QUIP, QUIP-RS, SCOPA, SOGS
	Binge eating	Recurrent episodes characterized by eating, in a small span of time, an excessive amount of food	4.9% [0.3% - 34.8%]	ABSPD, MDS-UPDRS 1.6, QUIP, QUIP-RS
	Compulsive shopping	Excessive shopping and buying behavior that leads to distress or impairment, with devotion of excessive time or money to these behaviors	4.7% [0% - 20%]	ABSPD, MDS-UPDRS 1.6, MIDI, QUIP, QUIP-RS, SCOPA
	Hypersexuality	Persistent or recurrent sexual or erotic thoughts or fantasies and desire for sexual activity	5.4% [0.7% - 23.8%]	ABSPD, MDS-UPDRS 1.6, MIDI, QUIP, QUIP-RS, SCOPA
Other behavioral addictions	Hobbyism	Recurrent and repetitive excessive activities such as physical exercise, gardening, handiwork, taking a stroll on		ABSPD, QUIP, QUIP-RS

		the Internet, painting, sewing, etc.		
	Punding	Intense fascination with repetitive manipulations of technical equipment, and continual handling, examining, sorting common objects	4.9% [0.3% - 14%]	ABSPD, MDS-UPDRS 1.6, QUIP, QUIP-RS
	Dopamine dysregulation syndrome	Intake of large doses of dopamine drugs in excess of that required to control motor symptoms, repetitive requests to physicians for larger doses of dopamine replacement therapy or self-escalation of these doses without medical approval	2.3%	ABSPD, MDS-UPDRS 1.6, QUIP, QUIP-RS
	Walkabouts	Excessive strolling and difficulties to sit still		
	Compulsive hoarding	Procurement of an excessive number of worthless objects that may lead to unsafe living conditions	12.2%	

Abbreviations:

ASBPD, Ardouin Scale of Behavior in Parkinson's Disease; MDS-UPDRS, Movement Disorders Society Revision of the Unified Parkinson's Disease Rating Scale; MIDI, Minnesota Impulsive Disorders Interview; PD, Parkinson's disease; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; QUIP-RS, Questionnaire for Impulsive-

Compulsive Disorders in Parkinson's Disease – Rating Scale; SCOPA, Scales for Outcomes in Parkinson's Disease; SOGS, South Oaks Gambling Screen.