Chapter 4
Impulse Control Disorders

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Introduction

Impulse control disorders (ICDs) or behavioral addictions in Parkinson's disease (PD) are commonly associated with dopaminergic medications occurring in 14 % of patients and can potentially have marked consequences. These behaviors include pathological gambling (PG), hypersexuality, binge eating, compulsive shopping, punding, and excessive dopaminergic medication use. Diagnostic criteria for these behaviors have been previously described [1] and broadly are defined as repeated urges and compulsive actions with associated negative consequences. The disorder of PG has now been classified in the newly published DSM-5 into the category of "Substance-Related and Addictive Disorders" and will be renamed as "gambling disorder." The reclassification is based on epidemiological, clinical, and neurobiological factors suggesting overlapping similarities with substance use disorders [2]. This chapter focuses on the epidemiology and associated factors and mechanisms including cognitive and imaging studies and treatment studies in ICDs in PD.

Epidemiology

The largest epidemiological study is the multicenter, cross-sectional North American, DOMINION study ($N = 3{,}090$ patients) reporting an ICD prevalence of 13.6 % [3] (PG 5.0 %, compulsive sexual behavior 3.5 %, compulsive buying 5.7 %, and binge eating disorder 4.3 %). ICDs were more common with dopamine

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agonists (17.1 % vs. 6.9 %) with an odds ratio of developing an ICD on dopamine agonists at 2.72 (95 % CI 2.08–3.54). There were no differences in the frequencies of ICDs on pramipexole and ropinirole (17.7 % vs. 15.5 %, odds ratio 1.22; 95 % CI 0.94–1.57).

Although the behaviors are more common on dopamine agonists and levodopa, whether ICDs in PD and/or restless legs syndrome (RLS) subjects on dopaminergic medications occur more frequently than in the general population is less clear. In a study assessing "new-onset heightened interest or drive" of 203 PD patients compared with 190 healthy controls, 14 % of PD patients had a "heightened interest" in ICD behaviors with 3 % in gambling, whereas 0 % was reported in healthy volunteers [4]. In another Italian sample of 98 PD patients and 392 general hospital control patients, 6.1 % vs. 0.25 %, respectively, were identified with PG [5]. However, in a comparison of 115 PD patients with 115 matched healthy controls, there were no differences in the frequencies of PG (0.85 % vs. 0.85 %) [6]. Larger sample sizes and appropriate screening tools are likely required to adequately compare groups. The frequencies of these disorders are also sensitive to the setting screened. For instance, the populations of PD screened for ICDs are commonly assessed in tertiary subspecialized movement disorder centers in which more complex cases and younger populations may be referred. Along this line, the frequency of PG in PD (PG 2.9 % and problem gambling 2.1 % in North America) identified in the DOMINION study [3] may not be fully comparable to population-based frequencies of PG (PG 1.14 % and problem gambling 2.8 % based on a meta-analysis of North American reports published in 1999) [7]. The prevalence rates of ICDs in community studies in the PD population may possibly be lower and more comparable to the prevalence rates of population-based community surveys of PG in the general population. Another important issue may be that the comparison of incidence rates as new-onset ICDs without any previous history of the same age group in the general population may indeed be lower.

ICDs also occur in a diverse range of non-PD patients treated with dopaminergic medication, such as restless legs syndrome [8], progressive supranuclear palsy [9], and multiple sclerosis [10]. Furthermore, the fact that PD patients display a greater frequency of pathological gambling than patients with amyotrophic lateral sclerosis suggests that ICDs are unlikely to be caused by a chronic neurological condition [11].

Pathophysiology

That observation that ICDs only occur in a subset of PD patients argues for a role for an interaction between other factors and dopaminergic medication [3], suggesting that dopamine agonists play only a partial or interactive role and are not sufficient by themselves to result in the onset of ICDs [1, 12, 13]. Thus, other factors are likely to play a role in mediating and influencing the association between dopamine agonists and ICDs. Factors that might interact with dopamine agonists can be subdivided into

(i) the agonist preparation, the dose, and/or coadministered medications; (ii) a possible role for PD itself; and (iii) individual susceptibility [1, 12] as discussed below. This issue of interacting factors addresses the question of why one person with PD given the same medication type or dose might develop an ICD but others with PD exposed to the same drug and dose might not develop an ICD.

Medication Effects

Multiple but not all studies suggest an association between higher dopamine agonist dose and an increased risk of ICD in both subjects with PD and restless legs syndrome (RLS) [14–16]. The multicenter DOMINION study shows that "on univariate analysis the median dopamine agonist LEDD (levodopa-dose equivalent daily dose) in ICD and non-ICD patients was numerically the same (300 mg) but the interquartile range was higher for ICD patients (200–450 mg vs. 150–400 mg, overall $P = 0.002$)" [3]. That a decrease in dopamine agonist dose appears to be effective in improving ICDs in many subjects also suggests a role for dose effects [17]. To adequately address the issue of the role of dopamine agonist dose, longitudinal studies are needed, many of which are underway.

The majority of PD patients are on co-medications including levodopa [3] or amantadine [18]. Both dopamine agonist (odds ratio 2.72 (95 % CI: 2.07–3.57), $P < 0.001$) and levodopa use (odds ratio 1.51 (95 % CI: 1.09–2.09), $P = 0.01$) were independently associated with ICDs with a higher odds ratio for dopamine agonists [3] in the DOMINION study. Coadministration of dopamine agonist and levodopa has also been shown to increase the risk of ICDs as compared to dopamine agonist monotherapy. A higher levodopa dose has also been shown to be associated with a greater risk of ICDs [3].

The association with amantadine, which has a weak antagonist effect on NMDA glutamate receptors and dopamine release, is less clear as an 8-week crossover randomized double-blind placebo-controlled trial of amantadine in 17 PD patients with PG demonstrated efficacy on symptom resolution [19]. However, amantadine was more likely to be associated with ICDs (17.6 % vs. 4.2 %, $p < 0.001$) in the DOMINION study [18]. Similarly, another study also demonstrated a higher association of PG with amantadine users than nonusers (2.4 % vs. 0.6 %, $p = 0.006$) in their assessment of PG frequency in 1,167 PD patients using the Minnesota Impulsive Disorders Interview [20]. Thus, the association with amantadine is less clear.

In recent congresses, the comparative frequencies of long-acting and continuous stimulation dopamine agonists and ICDs were presented [21]. 52/373 (13.9 %) of ICD cases were documented with a lower frequency on both rotigotine delivered as a transdermal patch (5.3 %) and long-acting pramipexole (6.3 %) compared to that of short-acting pramipexole (13.4 %) and ropinirole (14.9 %). The long-acting nature of the formulation may be less likely to act in a nonphysiological manner or result in sensitization effects and hence be associated with a lower risk of ICDs.

Rotigotine acts as an agonist at dopamine receptors with binding affinities at D3 and D2 receptors 2,600 and 53 times higher than dopamine (D3 > D2 > D1) [22] but is administered as a transdermal patch as a continuous delivery system (CDS) suggesting the predominant issue is that of the continuous delivery formulation rather than D3 receptor mechanisms. However, the results are not completely clear as long-acting ropinirole (14.7 %) had a similarly elevated risk. Whether the CDS nature of rotigotine is less likely to be associated with ICDs requires further confirmatory studies.

The Role of Parkinson's Disease

The role of PD in the onset of ICDs is not yet completely established. There are two possibly conflicting theories underlying a role PD might play as either facilitating or protective [1]. That ICDs occur in non-PD disorders treated with dopaminergic medications such as restless legs syndrome [8, 23, 24] suggests that PD is not absolutely necessary to onset of PG. One study that directly compared the frequency of ICDs in RLS and PD suggested that the frequency of reward-seeking behaviors was higher in PD, an effect that was no longer significant after controlling for dose differences [25]. This was suggested to be a function of higher dopaminergic medication dose in PD and the pattern of administration. Furthermore, two studies investigating the frequency of ICD in new-onset PD did not demonstrate any differences in frequency from the general population suggesting that PD by itself does not increase or decrease the frequency of ICDs [26, 27]. These observations however do not rule out a potential role for PD in facilitating or interacting with dopaminergic medications in the onset of ICDs. For instance, a recent rodent study demonstrated that a parkinsonian rodent model had greater sensitivity to rewarding effects but not motor effects of pramipexole [28]. Thus, although PD by itself is not associated with an increased expression of ICD, a factor related to PD might still interact with dopamine agonists to result in an enhanced expression of ICD. The following are examples of possible mechanisms in which PD may play a role in influencing the relationship between dopamine agonists and PD.

Overdose Hypothesis

In PD, neurodegeneration of the substantia nigra pars compacta dopaminergic cells projecting to dorsal striatal or motor regions can affect up to 70 % of dopaminergic cell bodies prior to onset of parkinsonian motor symptoms. The neurodegeneration of the more mesial dopaminergic cells, the ventral tegmental area (VTA), projecting to the ventral striatum or nucleus accumbens and ventromedial prefrontal cortex (regions implicated in limbic processes such as reward, motivation), is much more variable in PD. Thus, in PD subjects who may have greater preservation of

dopaminergic cells projecting to limbic regions (ventral striatal and ventromedial prefrontal) or associative cognitive regions (caudate, orbitofrontal, or dorsolateral prefrontal cortex), treatment with dopaminergic medications targeting degenerated motor striatal regions may result in an "overdose" of otherwise intact limbic and associative regions. This "overdosing" may result in impairment of cognitive and behavioral functioning [1, 29]. The "overdose" hypothesis has been well described and supported by experimental evidence suggesting that functioning of cognition or behavior follows a U-shaped curve. Optimal functioning occurs at an optimal level of dopamine level with either higher or lower dopamine levels resulting in impairments in functioning.

PD-Related Neuropathology

Another possible role for the neurobiology of PD might include greater PD-related neuropathology (deposition of Lewy bodies or neurodegeneration in specific neural regions) related to ICDs. The issue of visual hallucinations in PD gives a very relevant analogy. For instance, visual hallucinations are common in PD occurring in 17–40 % of patients. Although visual hallucinations are clearly associated with the presence of dopaminergic medications, PD is now believed to play a clear role in the onset of hallucinations. For instance, hallucinations are associated with greater Lewy body deposition in limbic regions (amygdala, hippocampus, medial temporal) [30, 31]. Similarly, postmortem studies in PD patients with ICDs may similarly reveal greater deposition of Lewy bodies in limbic regions, thus predisposing the individual toward a greater risk for an interaction with dopamine agonists resulting in ICD symptoms. Specific subtypes of PD may be more likely to be at risk for the development of ICDs. That PG is associated with early-onset PD might also suggest that specific subtypes of PD may have a differential pattern of neurodegeneration or neurobiology [3].

Dyskinesia

A unifying view is that there is a common mechanism of action in the motor and non-motor domains of the corticostriatal circuitry, as evidenced by similarities between ICDs and levodopa-induced dyskinesias [32]. ICDs in PD are associated with an oscillatory theta-alpha activity in the ventral subthalamic nucleus along with electroencephalographic coherence with non-motor prefrontal regions. In contrast, in dyskinesias, theta-alpha activity is associated with a dorsal localization and a coherence with motor regions [33]. PD patients with punding [34] or multiple ICDs [35] also have more severe dyskinesias relative to PD controls. Taken together, this evidence supports potentially unifying neurophysiological mechanisms linking motor and behavioral side effects of dopaminergic treatment.

Apathy

A relationship between apathy (decreased motivation, interest, and emotional response to external and internal stimuli) secondary to PD has been observed with ICDs [36]. Apathy is commonly observed in PD occurring in 17–41 % of patients and is understood to be related to the neurobiology of PD [37]. In a prospective study of subthalamic stimulation in PD patients in which 17 had ICDs, the discontinuation of the dopamine agonist and marked lowering of dopaminergic medication dose was associated with an improvement in ICD in all subjects [36]. However, half of the subjects developed apathy symptoms. The authors suggest a possible relationship between those who develop ICDs on dopaminergic medications and those suffering apathy off dopaminergic medications, implicating abnormalities in ventral striatal dopaminergic functioning. Notably apathy in PD outside of the context of subthalamic stimulation is likely much more complex involving other neurotransmitters including acetylcholine and norepinephrine.

Cognitive Deficits

Cognitive deficits in PD may facilitate the onset of ICDs [38, 39]. PD patients without ICDs were shown to have elevated delay discounting scores (tendency to select immediate smaller rewards over delayed larger rewards) both on and off medications [39]. Elevated delay discounting is associated with ICDs in the general population [40, 41], and three studies of PD patients with ICDs, particularly PG or compulsive shopping, demonstrated elevated delay discounting compared to PD controls without ICDs [35, 42, 43]. Delay discounting is a known predictive risk factor for cocaine dependence in rodents. Rodents who have higher delay discounting at baseline are more likely to escalate into cocaine acquisition and compulsive drug-seeking behaviors than those with lower delay discounting scores at baseline [44, 45]. Thus, the facts that elevated delay discounting (i) is a known predictor for substance dependence, (ii) is increased in ICDs in the general population and in ICDs in PD, and (iii) is increased in PD patients at baseline might suggest a potential interaction between a cognitive deficit in PD and dopamine agonists in the development of ICDs [38].

Individual Susceptibility Factors

There are multiple known factors that contribute to the pathophysiology of PG in the general population that have also been demonstrated to be associated with PG in the PD population. The papers reporting associated factors with PG in the general population have been systematically assessed and ranked for level of evidence in a review by Johansson et al. in 2009 [46]. In this review, associated factors for PG in the general population are ranked by level of evidence (well established: more than two studies to support conclusions; probable: 1–2 studies). The following discusses the

identified factors associated with PG in the general population as discussed in this review and compared evidence from the literature on factors associated with PG in the PD population. That the associated factors are similar between PG in the general population and in PD suggests a similar underlying individual vulnerability.

Age and Gender

PG in the general population is associated with younger age and male gender (2:1 male to female ratio) based on level 1 supportive evidence [46]. Similarly, PG in PD is associated with younger age in multiple studies and definitively demonstrated as an independent associated factor for PG in PD in the DOMINION study [3]. Although there were no gender differences in PG in PD in the DOMINION study, males were more likely to express hypersexuality and women to express binge eating and compulsive shopping [3].

Depression

Depression is identified as a probable risk factor for PG in the general population [46] with a genetic link postulated between the two disorders [47]. In a survey of 7,869 individuals from the Vietnam Era Twin Registry (middle-aged men), the odds ratio for major depression was elevated for PG (OR 4.06). Thirty-four percent of the genetic variance for each disorder contributed to that of the other with the best-fitting model estimating that 100 % of the overlap between PG and MD was genetic [47]. Furthermore, the likelihood of major depression predicting the onset of PG has been reported at 6.6 based on data from the US National Comorbidity Survey Replication study [48]. Similarly, the DOMINION study identified higher depression scores in both the cross-sectional and case-control study as an independent risk factor in the association of ICDs in PD patients [3, 35].

Substance Use Disorders

Alcohol and other substance use disorders have level 1 evidence to support an association with PG in the general population [46] with a genetic link postulated between alcohol use disorders and PG [49]. Substance use disorders such as alcohol or drug abuse, alcohol or drug dependence, or nicotine dependence have an odds ratio predicting the onset of PG of 5.4, 8.8, and 1.9, respectively, based on the US National Comorbidity Survey Replication study [48]. In a twin study of genetics, 12–20 % of the genetic variation and 3–8 % of the non-shared environmental risk for PG was accounted for by the risk for alcohol dependence [49].

Although the DOMINION cross-sectional study identified an increased association with a family history of alcohol use disorder with PG, following multivariate analysis this factor was not identified as an independent risk factor

suggesting that it is closely linked to another associated factor (e.g., current smoking or family history of gambling) [3, 12]. In a smaller study of 21 PD and PG patients compared to 42 PD controls, a personal or immediate family history of alcohol use disorders (rather than current alcohol use) was assessed. This factor along with novelty seeking and younger age of PD onset predicted PG at 83.7 % and accounted for 62 % of the variance [50]. Current alcohol use as measured using the alcohol-use disorders identification test (AUDIT) was not associated with PG in either the cross-sectional or case-control arms of the DOMINION study. In contrast, current cigarette smoking was identified as an independent factor associated in PG in both arms of the DOMINION study [3, 12]. In a study of restless legs syndrome and ICDs, a premorbid history of experimental drug use was also highlighted as an independent associated factor [23].

Family History of Gambling

Twin studies suggest possible genetic factors underlying PG. In PG-affected subjects, 8 % of first-degree relatives compared to 2 % of first-degree relatives in unaffected controls had a lifetime history of PG [51]. In the Vietnam Era Twin Registry study, 23 % of monozygotic co-twins and 10 % of dizygotic male co-twins had a lifetime history of PG [52] which modeling suggested was attributed to shared genetic rather than environmental factors [49]. In the recent community-based Australian Twin Registry study, the variation in the risk for disordered gambling due to genetic influences was 49.2 %, whereas no evidence for shared environmental influences contributed to the variation in risk [53].

PG in PD patients is also associated with a greater likelihood of a family history of gambling problems as an independent factor predicting the onset of PG in the DOMINION study [3]. Similarly, in a study of RLS and ICDs, a family history of gambling problems was identified as an independent associated factor [23]. These studies highlight the role of genetic and environmental factors in mediating the relationship between dopamine agonists and PG.

Personality and Temperamental Traits

PG in the general population is associated with greater impulsivity and novelty and sensation seeking as probable risk factors [46]. PG is also associated with more personality disorders, specifically antisocial personality disorder, as a probable risk factor [46]. For instance, in a study by Slutske et al. of the Vietnam Era Twin Registry data, subjects with a history of PG had higher prevalence rates of antisocial personality disorder (odds ratio = 6.4) which precedes the onset of PG symptoms [54]. PG is also significantly associated with delinquency, criminal, and illegal activity with level 1 supportive evidence [46]. Similarly, PG and compulsive shopping subjects in the PD population have higher scores on novelty seeking and impulsivity questionnaires as demonstrated in the case-control arm of the DOMINION study [35].

Social Factors

The relationship between marital status and PG in the general population is less clear with both being married and being single identified as associated factors [46]. Proximity and availability of gambling are identified as an associated factor for PG in the general population with level 1 supportive evidence [46]. In the cross-sectional arm of the DOMINION study, ICDs were independently associated with being unmarried and living in the United States as compared to Canada [3]. The latter association may be mediated by greater availability of casinos in the United States or by differences in medication practices. Thus, these individual susceptibility factors may modify the relationship between dopamine agonists and the expression of ICDs in PD.

Neural Mechanisms

The following section discusses possible cognitive, neural, and molecular mechanisms that underlie the expression of ICDs in PD.

Reward Processing

Dopamine mediates reward-related processing playing a role in the initial acquisition and the subsequent craving and compulsive use in substance use disorders. Phasic ventral striatal dopamine is triggered by unexpected receipt of reward and shifts to the cue predicting reward after associative learning [55] and, along with glutamate, underlies formation of conditioned responses. Converging human and primate studies have demonstrated that phasic dopamine encodes discrepancies between rewards received and those predicted, thus acting as a teaching signal signifying a prediction error [55].

In rodents, pramipexole acts similarly to methamphetamine, but not saline control, to promote conditioned place preference or learning to associate a context with a reward [28]. Higher doses of pramipexole were required to achieve the same rewarding effect in sham rodents as compared to the lower doses required in parkinsonian rodents, but there were no differences in locomotor responses. The authors suggested that PD may play a role in enhancing responsiveness to the rewarding but not the motor effects of pramipexole. Dopamine replacement therapy may influence physiological function via either exogenous tonic dopaminergic stimulation or interference with the endogenous, physiological, phasic pattern of striatal dopamine release. In response to conditioned cues or to a gambling task, PD + ICD patients demonstrate increased ventral striatal dopamine release as measured using (^{11}C)raclopride. Similarly, in response to conditioned cues or to unexpected and anticipated rewards, PD + ICD patients demonstrated increased ventral striatal activity [56–58]. DAs in PD patients with

either problem gambling or compulsive shopping were shown to enhance the rate of learning from gain-specific outcomes [56] although not all studies demonstrate this effect [59]. Using a reinforcement learning computational approach that models reward prediction error activity to assess fMRI blood oxygen level-dependent (BOLD) response and indirectly assess phasic dopaminergic activity, DAs were shown to increase ventral striatal activity to prediction error in ICD, signifying a "better-than-expected outcome" and enhanced reward prediction. These results are most consistent with the early acquisition stage and also are relevant to forming learned associations with cues.

Incentive Salience

The incentive motivation theory hypothesizes that dopamine alters nucleus accumbens sensitivity to incentive processing, such that motivational value is assigned to cues associated with rewards, making them desirable in their own right [60]. Using (^{11}C)raclopride PET imaging, PD patients with mixed ICDs were shown to have a heightened striatal dopamine release to heterogeneous reward-related visual cues as compared to levodopa or neutral cues [58]. Similarly, using fMRI, PD patients with hypersexuality were shown to have greater ventral striatal activity to sexual cues as compared to those without hypersexuality, an effect that correlated with an index of subjective sexual desire or wanting but not liking [61]. These findings were suggested to be in support of an incentive salience process. Similarly, activation of the ventral striatum in response to gambling-related cues was demonstrated in a small fMRI study in PD patients with ICDs [62]. These studies are consistent with studies in cocaine dependence demonstrating greater striatal dopamine release in response to cocaine cues [63].

Risk and Uncertainty

Pathological behavioral choices are associated with both positive and negative financial, social, and occupational outcomes, thus consistent with definitions of risky (with known probabilities) or uncertain (with unknown probabilities) choices. In rodent studies, pramipexole increases probabilistic discounting or the preference for the risky choice. This increase in risk taking occurs irrespective of the presence of the parkinsonian model of 6-OHDA injected in the dorsolateral striatum [64]. Similarly, d-amphetamine impaired task performance on a rodent gambling task modeled on the Iowa gambling task which measures risk taking under uncertainty [65].

Two studies focusing on risk anticipation without outcome demonstrate that DAs increase risk taking in PD patients with ICDs [59, 66]. This risk-taking bias appears to be unrelated to loss aversion and is accompanied by lower ventral striatal, orbitofrontal, and anterior cingulate activity [66]. The lower ventral striatal activity is

consistent with an fMRI study of PD patients with ICDs using the balloon analogue risk task (BART) that examines uncertainty with feedback [67]. Similarly, ICD subjects tested using the BART demonstrate greater risk taking on medication as compared to off medication [68].

A recent study has proposed that the findings of greater reflection impulsivity (or decisions under uncertainty without adequate information sampling) [69], delay discounting (selection of the immediate salient lower reward over the possibly more uncertain delayed reward) [35, 43], and novelty seeking in the context of uncertainty [70] may reflect underlying uncertainty about mapping future actions into rewards [71].

Behavioral Regulation and Impulsivity

Some evidence for impaired "top-down" prefrontal regulation is beginning to emerge. Using H_2O PET, in PD patients with pathological gambling engaged in a probabilistic gambling task, apomorphine challenge was associated with decreased activity in circuits involved in behavioral regulation, including the lateral orbitofrontal cortex and rostral cingulate cortex [72]. Similarly, a resting state single-photon emission tomography (SPECT) study in PD patients with pathological gambling demonstrated decreased functional connectivity between the striatum and the anterior cingulate cortex, the latter being a region involved in negative feedback and conflict detection [73]. Impulsivity, defined as a lack of behavioral inhibition, has motor and decisional subtypes. Impulsive choice is characterized by a preference for small, immediate, rewards, instead of larger, delayed rewards. Enhanced impulsive choice has been demonstrated in PD patients with ICDs using delay discounting tasks with hypothetical long delayed monetary rewards [35, 43] and real-time short delay monetary rewards [35]. In one study, impaired delay discounting with intact reward incentive performance in PD patients with ICDs was interpreted as evidence for a potential impairment in waiting for the delayed reward, rather than an enhanced incentive toward the immediate reward [43]. Alternatively, impulsive choice normally demonstrates a magnitude effect whereby lower impulsive choices accompany increasing reward magnitude. This magnitude effect in delay discounting is less pronounced in PD patients with ICDs, suggesting that dopamine agonists may be associated with greater subjective devaluation of the delayed, higher reward magnitude [35], resulting in greater impulsivity toward the smaller, immediate choice.

With respect to other forms of impulsivity, DAs in PD patients with ICDs appear to enhance the rapidity of decision-making, also known as reflection impulsivity, suggesting that the long-term negative consequences may not be as carefully considered as they otherwise would be [42]. Impulsive PD patients do not perform differently to non-impulsive PD patients on the Stroop color word test [59] that probes inhibition of prepotent responses and response selection associated with anterior cingulate function.

Lateral Prefrontal Cortex Function

Visuospatial working memory tested "on" medication was impaired in medicated PD patients with ICD compared with those without [42]. Similarly, PD patients with ICD both when "on" and "off" medications have a significantly reduced digit span compared with PD and control groups [59]. These results suggest that dorsolateral corticostriatal circuitry in PD with ICD might be similarly affected by "overdose" from exogenous dopamine when "on" medication and possibly from endogenous dopamine when "off" medication.

Molecular Mechanisms

Dopamine Transporter Levels

Two studies have demonstrated decreased striatal dopamine transporter (DAT) levels in PD patients with ICDs compared to those without [74, 75]. Dopamine reuptake via DAT, a membrane-spanning protein located in the axon terminals, is the primary mechanism by which striatal dopamine is removed from the synaptic cleft and dopamine neurotransmission regulated and terminated. These findings may help explain the observation of enhanced ventral striatal activity and enhanced dopamine release in PD + ICD patients in response to conditioned cues or to unexpected and anticipated rewards [56–58]. Impaired clearance of dopamine may play a role in extending the physiological effect of dopamine at the synaptic terminal.

The binding levels of (^{123}I)FP-CIT may reflect either lower DAT levels or greater dopaminergic nerve terminal degeneration. However, there is no clear clinical evidence for a greater decrease in dopaminergic terminals in PD + ICD patients relative to PD controls [75] suggesting that the lower binding levels might either reflect greater sensitivity to medication-related DAT downregulation or baseline trait differences and hence higher dopaminergic activity. Lower DAT levels with similar nerve terminal density suggest that extracellular dopamine neurotransmission can be enhanced both in distance from the synaptic cleft and duration of action.

Multiple substances of abuse, such as methamphetamine, cocaine, and alcohol, can differentially affect the regulation of DAT. For instance, methamphetamine and alcohol are associated with decreased DAT density as measured using PET imaging and DAT ligands [76, 77] particularly in early abstinence (<6 months) with some degree of recovery after prolonged abstinence (12–16 months) [78, 79] In contrast to the effects of substances of abuse, DAT regulation by Levodopa or dopamine agonists, if any, appears to be modest, and its effect might be dependent on its use in early versus late PD or as monotherapy versus co-therapy. Although any regulation of DAT by antiparkinsonian medications appears to be modest [80–91], PD + ICD patients may be differentially sensitive to regulatory mechanisms of DAT expression (e.g., D2 autoreceptor, TAAR1, protein kinase A and C) [81] compared to PD controls. A mechanism implicating DAT downregulation would also suggest

that symptom improvement following discontinuation of the dopamine agonist would have a delayed time course. This may also play a role in the observation of enhanced dopamine withdrawal symptoms (DAWS) observed following dopamine agonist discontinuation in PD patients with ICDs [82].

D2/D3 Autoreceptor Downregulation and Increase in Gain

Although acute dopamine agonist (pramipexole) administration in rodents has been shown to decrease the proportion of spontaneously firing dopaminergic neurons, chronic dopamine agonists normalize this proportion of firing neurons mediated via D2/D3 autoreceptor downregulation [83]. Furthermore, chronic levodopa administration in a parkinsonian rodent model has been shown to increase the proportion of spontaneously firing dopaminergic neurons, secondary to D2/D3 autoreceptor downregulation [84]. These spontaneously firing dopaminergic neurons are the neurons that are capable of phasic activity in response to a stimulus (e.g., the unconditioned rewarding stimulus, conditioned stimulus, a gambling task) [85]. Thus, increasing the proportion of spontaneously firing neurons effectively increases the gain and proportion of dopamine neurons capable of phasically responding to a stimulus. Preliminary evidence exists that PD patients with ICDs have decreased sensitivity of the D2/D3 autoreceptor in the midbrain as measured using (^{11}C)FLB-457 PET [86]. In this study, PD controls on dopamine agonists demonstrated decreased D2/D3 midbrain autoreceptor binding to a gamble task as compared to a control task, consistent with the feedback regulation of endogenous dopamine released in the gamble task. In contrast, PD patients with ICDs on dopamine agonists failed to demonstrate a difference suggesting decreased sensitivity of the D2/D3 autoreceptor. Thus, the enhanced dopamine levels observed in PD + ICD may be related to impaired regulatory feedback.

Dopamine Receptor Subtypes

Dopamine D3 receptors are predominantly expressed in the ventral striatum, and they mediate reward, emotional, and cognitive processes. Pramipexole and ropinirole, two widely used non-ergot DAs, have greater D2/D3 selectivity relative to D1. That concurrent levodopa use with a DA increases the odds of developing an ICD [3] is consistent with a primate study demonstrating that levodopa administration results in ectopic induction of dorsal striatal D3 receptors [87].

Genetic Polymorphisms

Genetic polymorphisms may also contribute to ICD susceptibility. Evaluation of dopamine and glutamate receptors and serotonin transporter gene polymorphisms identified D3 dopamine receptor p.S9G and GRIN2B c.366C > G as a risk factor for ICDs in PD [88].

Diagnosis

Patients and caregivers should be warned about the risk of development of ICDs at treatment onset and actively questioned on follow-up. Patients with a premorbid history of substance or behavioral addiction may be at a greater risk for the development of these disorders. The validated screening tool, questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP), has >80 % sensitivity and specificity and can be completed in 5 min [89]. Given the low positive predictive value (21–59 %), clinical interview should follow a positive screening result. The QUIP is valid also when completed by the patient's informant [90].

Treatment

Pharmacotherapy

Observational follow-up studies suggest that a decrease or discontinuation of the DA, if tolerated, may be efficacious for some patients. PD patients with ICDs will be more sensitive to dopamine agonist withdrawal symptoms (DAWS) [82]. A recent crossover randomized trial demonstrated efficacy of amantadine [19]; however, a contradicting report of increased risk of ICDs associated with amantadine [3] suggests its role is not yet established. Cognitive behavioral therapy has been shown in a randomized wait list control with standard medical care to improve global symptom severity [91]. Naltrexone, an opioid antagonist, which has been shown to be effective in the management of PG in the general population, was effective in a case study involving 3 PD patients with PG [92]. Other case reports have also reported preliminary efficacy with valproate [93] and clozapine [94].

Deep Brain Stimulation

There is as yet no clear consensus regarding the role of DBS for preoperative ICD and compulsive medication use. ICD behaviors have been reported to improve, remain unchanged, or worsen after surgery [95]. De novo onset of ICDs has also been reported [96]. In two retrospective case series, mixed ICD behaviors were reported primarily to remain unchanged or worsen following bilateral STN DBS or unilateral STN or GPi DBS. For instance, in one of the retrospective bilateral STN and GPi DBS case series that included both ICDs and compulsive medication use, postoperative worsening of symptoms was associated with the lack of preoperative recognition of the disorder and high dopaminergic medication dose [95]. In another retrospective unilateral STN DBS case series, only two of seven subjects with preoperative ICD improved, with no clear relationship

to medication dose [97]. That there were no significant changes in medication dosage following the unilateral DBS may be an important limiting factor. Compulsive medication use in 5 patients persisted in the postoperative stage. In this same case series, 17 of 159 patients developed new-onset ICD behaviors, although the exact nature of these behaviors was not reported. In contrast, other small retrospective studies have suggested that ICD can resolve after STN DBS and could become a new indication for surgery in this target [98, 99]. In a prospective study of 17 patients with preoperative ICDs treated with bilateral STN DBS, using systematic preoperative and postoperative evaluation of ICD and systematic discontinuation of dopamine agonists, all ICD behaviors ceased [36]. In this study, however, preoperative overall appetitive behavior changed into an overall more apathetic mode of functioning, which might mitigate the beneficial effect on ICD [36]. Thus, careful preoperative behavioral assessment and management of postoperative medications are crucial.

Overall, although ICDs can occur after surgery, the case reports suggest that their occurrence, particularly that of pathological gambling or compulsive shopping, is rare. This may differ for the behaviors of binge eating and hypersexuality. The existing data suggest that, with careful preoperative and postoperative assessment and management, there is a role for STN DBS in the management of ICD in patients in whom medication changes are ineffective or poorly tolerated. Transient postoperative worsening might occur early in the postoperative stage. STN DBS allows a greater decrease in dopaminergic medication dose relative to GPi DBS and enables a discontinuation of the dopamine agonist. However, patients may be reluctant to decrease their dopaminergic medication. Patients with ICD may also be at greater risk of DAWS, requiring careful titration of medications [100], and of postoperative suicidal behaviors [101].

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