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Impulse control disorders in Parkinson's disease: background and update on prevention and management

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SUMMARY

Given that impulse control disorders (ICDs) have been identified among a considerable minority of Parkinson's disease (PD) patients, these conditions have gained increased clinical and research attention in the past decade. Dopamine-replacement therapies, taken to ameliorate PD symptoms, have been associated with ICDs in PD. Unfortunately, there are relatively sparse empirical data regarding how best to address ICDs in PD patients. Conversely, progress has been made in understanding the clinical, neurobiological and cognitive correlates of ICDs in PD. Some of these findings may inform possible courses of action for care providers working with PD patients with ICDs. The literature on ICDs in non-PD populations may also be informative in this regard. The goals of the present article are to outline important clinical characteristics of ICDs in PD, briefly review relevant neurocognitive and neurobiological studies and discuss possible ways to prevent and manage ICDs in PD.

Parkinson's disease (PD) is a progressive neurological disorder typified by motor and non-motor features. Tremors at rest, rigidity, akinesia or bradykinesia (i.e., difficulty with/slowness of movement) and postural instability are considered to be key features [1]. Among other neurological changes, PD progression is characterized by degeneration of dopamine production in the substantia nigra [2,3], and this degeneration may contribute to various neuropsychiatric, cognitive, motor and autonomic impairments seen in PD patients [4,5]. Dopamine deficiency may also contribute to a lack of responsiveness to rewarding stimuli, overall inhibition, apathy and anhedonia (i.e., insensitivity to pleasure) experienced by many PD patients [2,6–8]. A considerable minority of PD patients meet criteria for impulse control disorders (ICDs) [9]. In a large multisite study in the USA and Canada, 13.6% met criteria for one or more ICDs [10]. Prevalence of ICDs in PD patients exceeding that of the general population has also been reported in uncontrolled studies conducted in countries such as China [11], Finland [12] and Italy [13]. A considerable number of patients are affected [10,14] and these disorders can be debilitating [15].

Multiple factors have been associated with ICDs in PD [16]. Data have indicated the association of ICDs in PD with factors predating the onset of PD, including a familial

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history of alcoholism [4,10] or an ICD prior to PD onset [17]. These findings suggest that a common underlying element (e.g., an intermediary phenotype or endophenotype) may underlie this association. Indeed, measures of elevated impulsivity have been associated with ICDs in PD [4,18]. Mental health factors including a personal history of depression and/or anxiety have also been linked to ICDs in PD [11,12,18,19]. Other factors seemingly unrelated to PD (e.g., geographic location and marital status) have also been associated with ICDs in PD [10], suggesting important environmental contributions to the development of these conditions. Other data suggest that certain aspects of disease progression may lead to ICD symptoms or impulsive tendencies [10,20–22]. For example, early age of PD onset has been associated with ICDs in PD [10,11,19,23–25]. Dopamine-replacement therapies (DRTs), taken to ameliorate PD symptoms, have also been linked to ICDs in PD in multiple studies [9,11,13,21,22,25]. Two primary classes of DRTs are levodopa, a biochemical precursor to dopamine [26], and dopamine agonists (DAs; e.g., pramipexole and ropinirole). Deep-brain stimulation (DBS) of the subthalamic nucleus, which has been associated with the reduction of PD motor symptoms in uncontrolled studies [27,28] and a recent open-label, randomized clinical trial [28], allows for the reduction of DRTs when effective and, thus, may indirectly lead to reductions in ICD symptoms in PD patients [29,30]. However, data also suggest that DBS may contribute to ICD behaviors [29,31–33].

Given the number of PD and non-PD factors associated with ICDs in PD, the relative frequencies of ICDs and the frequencies of therapeutic interventions in PD, DRTs [34] or DBS [29,30] alone are probably not sufficient factors for generating ICDs. Research testing genetic risk factors for ICD in PD is in its infancy. In a recent small study, no significant differences were found between PD patients with and without ICDs in the frequency of several allelic variants pertaining to dopamine expression [35]. In a large sample by PD standards (n = 404), marginal relationships were found between a variant of a serotonin receptor gene and impulse control and repetitive behaviors among Korean PD patients, particularly among those taking lower doses of DRT [36]. Given the likelihood of environmental contributions generating epigenetic contributions, it is unclear the extent to which genetic testing may lead to clinical prevention efforts in the near future.

Presently, there is a lack of evidence regarding how best to address ICDs in PD patients [37]. Fortunately, progress has been made in understanding the clinical, neurobiological and cognitive correlates of ICDs in PD [38]. Some of these findings may inform clinical decision-making by care providers working with PD patients with ICDs. The literature on ICDs in non-PD populations may also help inform clinical decision-making. In a previous review, the authors provided background on ICDs in PD, summarized evidence from relevant studies utilizing neurocognitive tasks and neuroimaging procedures and suggested clinical implications [16]. The focus of the present review is on clinical implications, including important clinical characteristics and possible ways to prevent and manage ICDs in PD. The neurocognitive and neuroimaging evidence that was the central focus of the prior review has been summarized more briefly in this article, in support of the discussion of clinical implications. The present review also includes updated literature published since the previous article.

Methods of review

While papers cited in the prior review of ICDs in PD were considered [16], the focus of this article is on papers published since then. Regarding content, this article focuses on clinical issues pertaining to ICDs in PD, including clinical characteristics and issues involved in the management of treatment. Given these goals, during February 2012, searches were conducted in the Medline and Google Scholar databases for papers published since 2010. Both PD and ICD were covered in every literature search. For PD, the keyword `Parkinson*'

was utilized and for ICDs, the keywords `impuls*' and `impulse control,' along with keywords for particular ICDs including `gambling' were used. Multiple literature searches were conducted with one keyword for each topic in every search. Subsequently, the topic of management/treatment to PD and ICD was added in the next set of literature searches. In these searches, the keywords `manag*' and `treat*' were used. Key papers cited in the papers found as a result of these literature searches were also located. Given the brevity of the present review, the objective is to present the recent papers viewed as the most relevant to clinical issues surrounding ICDs in PD and not to present a comprehensive review of the literature.

Clinical characteristics

ICDs represent a heterogeneous group of disorders characterized by repeated, excessive performance of behaviors that are typically hedonic, at least at their onset [39]. These disorders are categorized as `ICDs not elsewhere classified' in the Diagnostic and Statistical Manual, fourth edition (DSM-IV) [40]. Specific ICDs within the DSM-IV include pyromania, trichotillomania, kleptomania, intermittent explosive disorder and pathological gambling (PG), with PG being the most well-studied ICD overall and among PD patients [16,39,41,42]. The ICD category in the DSM-IV also includes a `not otherwise specified' subcategory, which is used to diagnose other conditions that have been observed relatively frequently in PD: compulsive eating, hypersexuality disorder and compulsive shopping [39]. PD research has investigated other patterns of behavior and conditions besides ICDs [43] that are also typified by excessive, repetitive activities (e.g., dopamine dysregulation syndrome and punding). These conditions may share common neurobiologies with ICDs in PD and possibly result from similar underlying vulnerabilities [23]. One example is dopamine dysregulation syndrome, defined as the compulsive use of dopaminergic medications, particularly levodopa, with proposed similarities to drug addiction [5,23]. Another example is punding: frequent performance of repetitive, stereotyped behaviors such as the collecting, sorting and reordering of items [4,39]. There are similarities between punding and obsessive—compulsive tendencies, notably the performance of stereotyped, ritualistic behaviors. However, there are a number of important differences in the clinical presentations of the two conditions [44]. Accordingly, PD patients with punding tendencies did not report significantly more obsessive—compulsive symptoms than PD patients without punding [44].

There is an overlap in diagnostic criteria for ICDs and addictions [40]. For example, there are a number of common diagnostic criteria between substance dependence and PG, including continued engagement despite negative consequences, withdrawal, tolerance and repeated unsuccessful attempts to quit or cut back [40,42,45]. Accordingly, PG and possibly other ICDs are being considered for reclassification as addictive disorders in the forthcoming DSM-V [46].

Neurocognitive & neurobiological studies

Neurocognitive and neurobiological studies have contributed to our understanding of the cognitive mechanisms and neural pathology underlying ICD behaviors in PD. Findings from these studies also suggest possible treatment targets, in terms of impulsive and risk-taking cognitive tendencies one would hope to diminish throughout treatment and in terms of brain function and neurotransmitter activity that, if altered, could lead to an abatement of ICD behaviors among PD patients. In this section, recent examples of research on underlying cognitive mechanisms and neurobiological dysfunction that may typify ICD behaviors in PD are outlined. More extensive treatment of research findings on pertinent cognitive

mechanisms (both in terms of executive function and decision-making) and neurobiological dysfunction may be found in a number of recent reviews of the literature [16,47].

Cognitive mechanisms

Dopamine deficiencies resulting from PD progression [2,6] may contribute to some patients being hyper-responsive to punishment and hypo-responsive to reward [7,8]. Recent research has suggested that in some PD patients, DRT use may be implicated in a reversal of this pattern (i.e., a shift toward hyper-responsiveness to reward and hypo-responsiveness to punishment) [7,8], which has manifested itself as a risky pattern of decision-making on neurocognitive tests [48,49] (see [50] for negative results). Similarly, recent studies have shown stronger tendencies toward impulsive and risky decision-making in PD patients with ICDs compared with those without ICDs [26] (see [51] for negative results) and, furthermore, that these tendencies may be amplified with DRT use [3,18,26,52], albeit perhaps differentially. These patterns of findings have implications for the types of impulsive, risk-taking behaviors that some PD patients may display while taking DRTs, particularly among those meeting diagnostic criteria for one or more ICDs. It should be noted that many of these studies have utilized relatively small samples, and larger studies should help to delineate further neurocognitive contributions to ICDs in PD and their relationships to clinically relevant individual-difference variables. Apathy and behavioral disturbances indicative of ICDs have been proposed as opposing ends of a behavioral continuum among PD patients [53]. Supporting this conclusion are findings of opposing associated factors for the two, with an older age at PD diagnosis and less DA use being associated with apathy and the opposite being observed for ICDs [19].

Neurobiological dysfunction

Overview & comparison with ICDs in the general population—Research suggests that the ventral striatum and the prefrontal cortex are two important regions with respect to alterations in reward and punishment responsiveness in PD patients. The ventral striatum and parts of the prefrontal cortex such as the ventromedial prefrontal cortex have also been implicated in addictions and ICDs, such as PG in the general population [42,54]. For instance, substance-dependent individuals have been found to release dopamine in the ventral striatum in response to their drug of choice [41,55,56]. Individuals with PG have shown diminished activity in the ventral striatum during simulated gambling [57] and during reward processing [58]. Recent studies involving participants with PD have shown evidence of hypoactivity in the prefrontal cortex. Regarding ventral striatal activity, recent studies have not converged on a clear conclusion with PET studies suggesting hyperactivity and functional MRI (fMRI) results suggesting hypoactivity among participants with PD.

Evidence suggestive of hyperactivity—ICD behaviors have been proposed to reflect `dopamine overdosing' in the ventral striatum as a result of DRT use by PD patients [4,59,60]. While dopaminergic loss initially involves the dorsal striatum, the ventral striatum is less affected in the early stages of PD and thus may be vulnerable to overstimulation due to DRT use. Regulation of reward responsiveness and motivational drives may be affected by DRT use, given the role of the ventral striatum in these processes [50,61]. PET studies in PD suggest greater dopamine release in the ventral striatum among PD patients with PG than without during a gambling task [61] and in response to general rewarding cues during levodopa challenge [62]. Greater dopamine D_2-like receptor availability in the ventral striatum was also observed in the former study among the PD/ICD group at baseline, suggesting nongambling-task-related dysfunction in the PD/ICD group [61].

Evidence suggestive of hypoactivity—Evidence of ventral striatal dysfunction among PD patients with ICD has also come from fMRI studies showing lower activity during risk-

taking tasks compared with PD patients without ICDs [18,51]. Greater activation of the ventral striatum during reward processing (i.e., during reward anticipation) has been linked to ventral striatal dopamine release in healthy volunteers [63], which may suggest that ventral striatal dysfunction in ICDs may relate to less dopamine release. Relatively decreased ventral striatal activation has also been observed in PD/ICD in association with DA administration, whereas the opposite was observed in individuals with PD alone [18].

Concerning the role of the prefrontal cortex, dopamine stimulation from DRTs may affect gating mechanisms, which help people to distinguish between the stimuli they should attend to and the stimuli they should ignore [59]. Reward receipt, particularly when it is unanticipated, is tied to phasic dopamine release and signaling, whereas nonreceipt of expected rewards is associated with pauses in dopaminergic neuronal firing. Enhanced dopaminergic activity from DRTs has been proposed to alter pauses that may facilitate normative response inhibition [50]. PET research has suggested lower activity in impulse control and response inhibition areas, such as the lateral orbitofrontal cortex and rostral cingulate, following DA administration among PD patients with PG compared with patients without PG [64]. Relatively reduced activity was also shown in the orbitofrontal cortex and anterior cingulate in PD patients with ICDs during a risk-taking task [18].

Summary—Patients with PD and ICDs show differences in brain function from PD patients without ICDs at baseline and during risk-taking tasks. These differences may be accentuated with DRT administration. The prefrontal cortex and ventral striatum appear to be two important regions with respect to these functional differences. Studies concurrently using fMRI and PET are needed to further investigate the nature of dopamine function and regional brain activation differences related to ICDs in PD. Recent studies have identified other possible types of neurobiological dysfunction in PD patients with ICD (e.g., loss of gray matter [65]), and further research is needed to understand the ways in which clinically relevant individual differences may relate to brain structure and function among those with ICDs in PD.

Prevention & management of ICDs in PD

Prevention & potential risk factors

Given that there are no established, empirically supported means of treating ICD behaviors in PD [9,37], it is important to take steps to prevent ICD in PD patients. Following PD diagnosis, clinicians should discuss the potential for ICDs with their patients as early as possible. With the patient's permission, potential caregivers and family members should be involved early on in discussions regarding possible ICD behaviors that may result from treatment. These parties should be advised to be vigilant in observation of patients in order to detect possible changes in behavior and limit access to cash and credit cards should ICD symptoms develop [22]. Subsequently, in anticipation of possible problems with ICD behaviors, contact information for resources such as helplines and other clinical outlets should be offered. Given that features of PD are often distressing and disabling, it is important to discuss risks and benefits of various treatments with patients carefully (see [66] for discussion of these issues).

Clinicians should consider factors associated with ICDs in PD (see Table 1 in our prior review of ICD in PD [16]). For patients reporting multiple factors associated with ICDs, levodopa may be a more appropriate initial option than DAs [22]. Although levodopa treatment has been associated with ICDs [10,67], odds ratios for ICDs in PD related to levodopa were lower than those related to DAs in a large cross-sectional study [10]. These findings agree with results from small, uncontrolled studies that have also suggested stronger associations between DAs and ICDs than between levodopa and ICDs [68–70]. As

individuals on DAs will often be taking levodopa concurrently, it can be challenging to fully disentangle the influence of the respective medications.

Regarding DAs, multiple studies have found no significant differences with respect to specific DAs (e.g., ropinirole and pramipexole) and their relationships to ICDs [7,17,23,69]. However, findings suggest that DRT dose should be carefully considered with regard to ICDs. Recent results from a multicenter case—control study indicated that PD patients with ICDs had significantly higher levodopa equivalent daily doses of DRTs than those without ICDs [18], although there have been negative findings [69].

Screening & diagnosis

Clinicians should assess patients for behaviors and symptoms associated with ICDs in PD at every appointment as this information may influence treatment recommendations [22]. Fortunately, there is a brief screening measure entitled the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) [43] that clinicians can administer at each appointment. The QUIP is comprised of 30 binary (yes/no) items in three sections pertaining to the following: each of the four ICDs most commonly reported in PD: gambling, sex, buying and eating; related behaviors (i.e., hobbyism, punding and walkabout); and compulsive medication use. Any affirmative response for a given condition is considered a positive screen for that condition. The standard version queries patients regarding all related behaviors since PD onset that have lasted at least 4 weeks, although a version pertaining to current behaviors is also available. The QUIP was found to have strong specificity for individual disorders and strong sensitivity to detect a disorder collapsing across individual disorders [43]. Agreement between patient and informant versions has only been moderate-to-fair [25,71]. A short 13-item version (the QUIP-S) was found to have sensitivity similar to the full version. In addition to the original, a rating-scale version (QUIP-RS) has since been developed including items rated on 5-point Likert scales as to the severity of each behavior [72]. The QUIP-RS was found to have enhanced sensitivity in the assessment of individual conditions, while maintaining good specificity. The QUIP-RS was also found to have good test—retest and inter-rater reliability when completed by interviewers as compared with patients. Regarding validity, treatment responders in an ICD intervention study showed a significant decrease in QUIP-RS scores over time, whereas nonresponders did not [72]. Given that the primary purpose of the QUIP is screening, while negative scores provide confidence that no notable ICD behaviors are present, positive scores should be followed by a thorough diagnostic interview [71]. Given that PD patients have often been described as relatively inhibited [24,73], especially when not on DRTs [4,7], a low threshold for ICD diagnosis may be needed [74]. Owing to shame, denial, motivations to continue the behaviors or other reasons, ICD symptoms may be under reported.

Management of ICD symptoms

Pharmacologic interventions—Options for management of ICD symptoms are summarized in Table 1. Presently, the primary approaches to ameliorating ICD symptoms are reductions in the dosage of DAs or outright discontinuation of these medications [9,75–77], sometimes coupled with increases in levodopa dose [70]. The benefits of these approaches have been supported by case studies [78] and small uncontrolled studies [17,21,23,70,79,80]. Evidence from a recent 1-year follow-up in a small uncontrolled study suggested that DA dose reduction was less effective for punding symptoms [80]. Two cautionary notes concern the need to balance amelioration of ICD symptoms with avoiding worsening of PD motor symptoms as DAs have established efficacy for this indication [9], and the possibility of withdrawal upon DA dose reduction or discontinuation [22,77].

A dopamine agonist withdrawal syndrome (DAWS) has been characterized among a minority of PD patients taking DAs following dose reduction or discontinuation [81]. DAWS appears to resemble other drug withdrawal syndromes with features including anxiety, dysphoria and intense drug cravings. DAWS may respond only to DA dose increase and not levodopa or nonpharmacologic interventions. The negative impact of DAWS and its seeming resistance to treatment highlight the importance of clinicians being mindful of potential risk factors that have been associated with ICDs [16] when prescribing DAs to PD patients, and also to be especially careful regarding dosing as patients with DAWS tended to have greater DA exposure than PD patients whose DA doses were reduced but who did not develop DAWS [81].

Alternative treatments may be considered, although there is no substantial evidence supporting any such options [9]. A recent small double-blind, placebo-controlled, crossover trial yielded evidence supporting the efficacy of amantadine – a drug that influences glutamatergic function used to treat motor symptoms during the early stages of PD [82] – for the treatment of recent-onset PG in PD [82]. These findings should be cautiously considered due to the limited sample size, adverse-effect profile and potential for psychosis induction. Furthermore, data from a large multisite cross-sectional study [10,83], a case study [84], a moderate-sized uncontrolled study [25] and a large uncontrolled study [85] suggest that amantadine may be related to increased risk of ICDs. Speculatively, the prodopaminergic action of amantadine could underlie its relationship to ICDs, while its antiglutamatergic action may underlie potential therapeutic effects. Additional research is needed to address these issues [83].

Research addressing other pharmacotherapy options has been limited. A series of three case studies supported valproate [86], an anticonvulsant also US FDA-approved to treat migraine headaches and manic or mixed episodes in bipolar disorder. If efficacious for the reduction of ICD behaviors in PD, its effects may relate to its actions on serotonergic and/or GABAergic systems [86]. Another anticonvulsant, zonisamide, which has efficacy for treating motor symptoms in PD, was tested in an open-label fashion in a small group of patients who had not benefited from DRT reduction and was found to reduce self-reported impulsivity, but had no notable effect on ICD features [87]. In the absence of large randomized controlled trials, results such as these should be approached with caution due to the small number of patients involved, the use of open-label administration and possible reporting bias in favor of positive results.

Evidence is suggestive of neurobiological similarities among substance-use disorders and ICDs with and without PD [42]. For example, diminished ventral prefrontal cortical activation has been observed both in ICDs with and without PD [54,64] and in substance-use disorders [54]. Given evidence suggesting neurobiological similarities, treatments that have been found to be efficacious in ICD patients without PD may have utility for ICDs in PD patients [22]. Direct testing of this hypothesis is warranted, due to potential influences of neuropathology particular to PD. While there are no FDA-approved medications for ICDs, findings from multiple randomized clinical trials support the efficacy of opioid antagonists, particularly for PG [74], and the possibility of their efficacy in ICDs in PD is currently being investigated [201]. In studies of non-PD subjects with PG, findings from four randomized clinical trials support the efficacy of opioid antagonists in diminishing problem gambling severity [88–91] (see [92] for negative results). This effect appears to be particularly robust among those with family histories of alcoholism [89] or strong urges to gamble [89,91]. Early evidence suggests that opioid antagonists may be a better option than selective serotonin reuptake inhibitors (e.g., fluvoxamine and paroxetine), for which clinical findings have been mixed (positive [93,94]; negative [95–97]) or atypical antipsychotics, findings for which have been negative [98,99]. Limited evidence supports possible efficacy for

medications believed to modify glutamatergic neurotransmission, with data coming from a controlled trial of *N*-acetyl cysteine, a glutamatergic nutraceutical [100] and an open-label trial of memantine, a NMDA receptor antagonist [39]. Memantine may also reduce aspects of impulsivity and, potentially, compulsivity in PG [101].

Nonpharmacologic interventions—Limitations in evidence supporting pharmacologic interventions for ICDs in PD highlight the importance of addressing further nonpharmacologic interventions in this population. Possible nonpharmacologic treatments for ICD in PD include DBS, which early evidence suggests may enhance motor function and overall quality of life [102]. Recent evidence supporting DBS for ICDs in PD comes from open-labeled, randomized clinical trials [28] and prospective observational studies [27]. However, there has been a lack of sufficiently powered, randomized controlled trials testing the efficacy of DBS for ICDs in PD [28,102]. It has also been suggested that DBS may improve ICD symptoms in PD patients [29,30]. On the other hand, DBS has been associated with impulsive behavior [8,31], ICDs [29,32] and transient increases in ICD-like tendencies (e.g., loss chasing in a gambling task [33]). There have also been negative findings regarding associations with ICDs [10,30], and the likelihood of ICD behaviors following DBS may be affected by the specific locations that are stimulated [103].

In addition, self-help organizations (e.g., Gamblers Anonymous [104]) or professionally delivered behavioral therapies (e.g., cognitive behavioral therapy [105,106]) that have demonstrated utility in treating ICDs in non-PD populations may help to address ICD behaviors in PD patients. While participation in Gamblers Anonymous has been cited as potentially helpful or as adjunctive to other interventions targeting PG in PD [79,107], evidence is limited and more research is needed to determine its utility. Cognitive behavioral therapy may be well suited for ICDs in PD given cognitive models suggested for impulsive behaviors, dopamine dysregulation syndrome and DAWS in PD [108]. However, given potential cognitive deficits associated with PD, this approach may not work well uniformly, and randomized clinical trials are needed to investigate how well and for whom such approaches may work best.

Conclusion & future perspective

Although a great deal has been gained from recent studies on ICDs in PD, further research is needed [9]. Available evidence suggests that specific ICDs are more common among PD patients than in the general population. PG prevalence among PD patients has been found to be several times higher than in the general population [9] and rates of compulsive buying among PD patients appear to be roughly equivalent to the general population [10]. However, it is difficult to assess the prevalence of other ICDs observed relatively commonly in PD patients (i.e., hypersexuality and compulsive eating) visà-vis the general population due to a lack of solid epidemiologic evidence regarding ICD prevalence in the general population [9,109]. Stronger epidemiologic evidence on ICD prevalence in the general population would advance clinical research on ICDs in general and among PD patients.

Testing pharmacologic and behavioral treatments in large, controlled randomized clinical trials will be critical for identifying safe and efficacious therapies for individuals with ICDs and PD [37]. Presently, given that there are no established empirically supported means of treating ICD behaviors in PD [9,37], it is important to attempt to prevent ICD in PD patients. Clinicians should consider factors associated with ICDs in PD (e.g., personal or family history of alcoholism [16]) when making treatment recommendations. Levodopa may be preferable to DAs for patients with ICD-related factors, and DRT dose should be considered carefully with regard to ICDs [22]. Clinicians should assess patients for behaviors and symptoms associated with ICDs in PD at every appointment as this information may

influence treatment recommendations [22]. At this time, the primary approaches to ameliorating ICD symptoms are reductions in dose or discontinuation of DAs [9,75–77], sometimes coupled with increases in levodopa dose [70]. Alternative treatments may be considered, although there is no substantial evidence supporting any such options and certain treatments, such as amantadine [25,83,85] and DBS [29,31–33], may carry their own risks of ICD symptoms.

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Practice Points

- A considerable minority (13.6% in a recent, large multisite study) of patients with Parkinson's disease (PD) meet criteria for impulse control disorders (ICDs), which can be debilitating.
- Dopamine-replacement therapy, taken to ameliorate PD symptoms, has been associated with ICDs in PD, as have other factors, including individual mental health and the patient's environment.
- Given that empirically supported evidence for treating ICDs in PD is scarce, clinicians should attempt to prevent ICD onset in their patients.
- Clinicians should consider factors associated with ICDs in PD (e.g., age at PD onset, personal or family history of alcoholism, personal history of depression or anxiety, marital status and aspects of the environment) when making treatment recommendations. Levodopa may be preferable to dopamine agonists (DAs) for patients with ICD-related factors. Dopamine-replacement therapy dose should be considered carefully with regard to ICDs.
- Clinicians should assess patients for behaviors and symptoms associated with ICDs in PD at every clinical appointment as this information may influence treatment recommendations. There is a brief screening measure entitled the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease that can be administered at each appointment. There are multiple versions of the instrument that clinicians may opt to administer based on a patient's needs.
- Owing to shame, denial, motivations to continue the behaviors or other reasons, clinicians should be aware that ICD symptoms may be under reported.
- Currently, approaches to ameliorating ICD symptoms include dose reduction or discontinuation of DAs. Clinicians should monitor for possible withdrawal upon considerable reductions in DA dose or medication discontinuation and consider the importance of balancing amelioration of ICD symptoms with avoiding worsening of PD motor symptoms, which can also be debilitating.
- Behavioral interventions, including involvement of family (e.g., spouse) or care providers, as well as those with efficacy in the treatment of non-PD ICDs, warrant consideration.
- Alternative treatments may be considered, although at this point there is no substantial evidence supporting any such options, and certain treatments, such as amantadine and deep-brain stimulation, may carry their own risk of ICD symptoms.

Table 1

Summary of possible pharmacological and brain-based options for the management of impulse control disorder symptoms in Parkinson's disease.

Management option	Proposed mechanism of action	Possible drawbacks	Evidence supporting ICD symptom reduction	Ref.
DA reduction with possible increase in levodopa dose	Reduction of 'dopamine overdosing' in the ventral striatum	Withdrawal; worsening of PD motor symptoms; may be less effective in reducing punding	Case studies and several small, uncontrolled studies	[9,17,21–23,70, 75–81]
Amantadine	Reduction of dopaminergic activity due to its glutamate antagonist properties	May increase ICD behaviors	Small, double-blind, placebo-controlled crossover trial supporting its efficacy for PG severity in PD patients; however, a case study and multiple uncontrolled studies support its association with ICDs in PD	[10,25,82–85]
Valproate	Actions on serotonergic and/or GABAergic systems	Uncertain	Evidence very limited, derived from a series of case studies that favor its utility in reducing ICD symptoms	[86]
Zonisamide	Uncertain, but may involve dopaminergic and nondopaminergic mechanisms	Uncertain	Evidence very limited, derived from findings from a small, open-labeled trial showing reductions in self-reported impulsivity, but not ICD symptoms	[87]
DBS	When effective, reduces PD motor symptoms, thus allowing reduction in DRT use, which may lead to an indirect benefit of ICD behavior reduction	May increase ICD behaviors	Evidence from case histories and uncontrolled studies have shown that DBS may decrease ICD symptoms; however, evidence from other case histories, uncontrolled studies and neurocognitive tasks suggests DBS may be associated with increases in ICD symptoms and tendencies	[10,27–33,102–103]

DA: Dopamine agonist; DBS: Deep-brain stimulation; DRT: Dopamine-replacement therapy; ICD: Impulse control disorder; PD: Parkinson's disease; PG: Pathological gambling.