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Impulse Control Disorders in Parkinson's Disease:Management, Controversies, and Potential Approaches

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Abstract

Impulse control disorders in Parkinson's disease are a group of impulsive behaviors most often associated with dopaminergic treatment. Presently, there is a lack of high quality evidence available to guide their management. This manuscript reviews current management strategies, before concentrating on the concept of dopamine agonist withdrawal syndrome and its implications for the management of impulse control disorders. Further, we focus on controversies including the role of more recently available anti-parkinsonian drugs, and potential future approaches involving routes of drug delivery, non-pharmacological treatments (such as cognitive behaviour therapy and deep brain stimulation), and other as yet experimental strategies.

Introduction

Impulse control disorders (ICDs), including hypersexuality, pathological gambling, compulsive shopping and binge eating, the dopamine dysregulation syndrome (DDS) and punding, are related but somewhat different impulsive behavioral disorders associated with dopaminergic treatment in Parkinson's disease (PD) (and less often in other disorders such as restless legs syndrome). Accompanying manuscripts[1–3] in this issue discuss the clinical features and propose underlying neurobiological substrates for these disorders. In this manuscript, our aim is to discuss currently accepted management strategies for ICDs, and then to describe areas of controversy, the concept of dopamine agonist withdrawal syndrome (DAWS) and its implications for the management of ICDs, the role of more recently available anti-parkinsonian drugs and routes of delivery, and non-pharmacological treatments. Given the limited high quality data and treatment choices that currently exist, we also discuss potential future strategies that could have promise as therapy. Topics were reviewed using Pubmed/Medline searches. In selected cases where only preliminary data were available from presentations at international meetings, material was included if the abstracts were available via a journal online. A specific start year was not set for the searches. For the most up to date reports, full articles known to be in press were also included. Our emphasis is on ICDs but where appropriate, we will provide additional commentary on the related impulsive behaviors. Table 1 provides a summary of the options discussed in this manuscript. (Table 1).

a) Pharmacologic Management

Current practice

There is a remarkable paucity of high quality evidence available to guide the management of ICDs in PD. Indeed there are only two randomized controlled clinical trials (RCTs) evaluating different drugs and the remaining evidence is largely experiential. Recognizing the dominant role of dopamine agonists inducing or triggering ICDs, typically the first pharmacologic management is to reduce the oral dopamine agonists. It is widely appreciated that withdrawal of the dopamine agonist usually resolves the problem and in a proportion of patients, dose reduction without withdrawal will successfully eliminate the problem. Why some patients respond to simple dose reduction and others require drug withdrawal is not known.

Dopamine agonist reduction/withdrawal may be complicated by 2 distinct clinical consequences: (i) worsening of motor function and (ii) in some cases by DAWS (see below). If motor symptoms increase, then addition or increase of levodopa, cathechol-O-methyl transferase (COMT) inhibitors, or monoamine oxidase inhibitors (MAO-I) may be necessary.[4–6] When additional anti-parkinsonian medications are required for motor control, their potential to induce ICDs also needs consideration. There is no clear evidence of an association of ICDs with use of anti-cholinergic drugs or COMT inhibitors. Rare studies have suggested that MAO-I can induce ICDs.[7, 8] The role of amantadine in alleviating or inducing ICDs is unclear due to few published data and conflicting opinions.[9–11] A small randomized, placebo-controlled, cross-over study involving 17 patients demonstrated benefit from amantadine (200 mg/day) for pathological gambling[9]. However, in the largest clinic-

based study of over 3000 patients that evaluated 420 patients with ICDs, amantadine was associated with a significantly higher proportion of ICD cases[11, 12].

Although some experts propose the use of neuroleptics in the management of refractory ICDs, there is no clear evidence that the addition of these or other psychotropic medications (e.g., anti-depressants, anxiolytics, anticonvulsants) without concomitant reduction of anti-parkinsonian medication is effective in resolving ICDs. Typical antipsychotics should not be used in PD since these are very likely to worsen the motor state. The use of some atypical antipsychotics, for example olanzapine[13], risperidone[14] and aripiprazole[15] can worsen the motor state when offered for PD psychosis, so would be expected to also worsen the motor state if offered for ICDs. Further, while the notion that dopaminergic stimulation drives ICDs seems justifiable, there is only sparse evidence that dopaminergic blockade with these agents helps resolve ICDs in PD,[16, 17] and in some cases the offending agonist was simultaneously stopped, confounding interpretation of how the clinical benefit came about. It is also noteworthy that in non-parkinonian impulsive patients, olanzapine did not show benefit to impulsive behaviors[18] and aripiprazole could worsen them[19]. Quetiapine and clozapine have less propensity to worsen the motor state but evidence for their efficacy against ICDs is limited[16, 20, 21], although in the case of a report of benefit with quetiapine, it is noteworthy that the agonist dose was not reduced[21]. There are no clear data to suggest if these few cases can be extrapolated to all forms of ICDs, or if the mechanism of action is via an effect on the dopaminergic system or a relative effect on dopamine receptor subtypes or the serotonergic system. In the absence of rigorous trial evidence for use of atypical neuroleptics for ICDs, there is little to support their use specifically for the management of ICDs. However, psychiatric medications may be used to address other psychiatric symptoms per se if co-existing with an ICD, and may influence the ICD if the other psychiatric symptom is potentially maintaining or driving the ICD. A detailed discussion of the advantages/disadvantages of these and other psychotropic medications in the context of other psychiatric co-morbidity is beyond the scope of this manuscript (for reviews see[6, 22]).

Weintraub and colleagues have recently reported the only other medication – based RCT performed in PD patients with ICDs. Based on the effect of opioid antagonists on impulsive behavior in the primate MPTP model of PD, these investigators conducted an 8 week double-blind placebo-controlled trial of naltrexone 50–100 mg/day (flexible dosing) in 50 PD patients with ICDs. Although their primary outcome measure, the global assessment of response, did not change significantly, the observation of a significant reduction in the PD-specific ICD rating scale (QUIP-RS) scores supports further evaluation of this therapeutic approach[23].

Dopamine agonist withdrawal syndrome (DAWS)

About one-third of patients with ICDs who attempt to taper dopamine agonists can develop a severe syndrome referred to as DAWS, which makes weaning difficult or impossible.[24–27] DAWS does not respond to substitution of levodopa for the dopamine agonist, or to the addition of other medications. The symptoms of DAWS are similar to those of withdrawal from other psychostimulants, and may include anxiety, panic, social phobia, agoraphobia, fatigue, irritability, dysphoria, depression, pain, nausea, vomiting, diaphoresis, orthostatic

hypotension, drug cravings, and suicidal ideation. There is no known effective treatment for DAWS; in many it abates with time but in others the disabling symptoms force a return to the causative agent - but kept at low dose. This underscores the importance of pre-prescription counseling, and the need to identify new treatments for ICDs, as in section (d) of this manuscript.

Other currently available therapies for PD with research potential for effects on ICD: Continuous non-oral dopaminergic drug delivery

There is a notion that continuous, compared with pulsatile, drug delivery might be a potential treatment approach to ICDs. Further study is needed to determine if the nature of drug delivery itself may be relevant. Available data have not systematically addressed the possible beneficial or "ICD-sparing" role of continuous drug delivery utilising non-oral strategies, such as the rotigotine transdermal patch and continuous subcutaneous apomorphine infusion, and these remain under investigation. The speculative rationale would be that PET imaging studies suggest a propensity to release dopamine in an abnormal fashion in the ventral striatum in response to pulsatile dopaminergic therapy both in patients with ICDs and DDS when compared with those without these symptoms.[28–30] However, from a management perspective it may be relevant that while DDS tends to be "driven" by rather short-acting agents such as levodopa and apomorphine (that provide pulsatile stimulation of dopamine receptors), ICDs more commonly occur with longer-acting dopamine agonists, highlighting the need to further investigate the incidence of impulsive behaviors in patients on these agents. Further, clinical practice and the current literature do not allow a clear distinction to be made as to the contribution that each of the following plays in the pathogenesis of ICDs:

total daily dose of drug—The fact that some patients respond well to drug reduction suggests that the propensity of dopamine agonists to induce ICDs is dose related. However, other patients require complete cessation for ICD resolution, suggesting either that these patients are very sensitive to small doses, or that induction of ICDs is related to the presence/absence of the agonist. The precise role of drug dose remains unresolved.

extended versus immediate release formulation of the same daily dose of agonist—No studies to our knowledge have formally compared whether the formulation itself impacts the development of ICDs. This issue could be clarified by studies directly comparing the rates of ICDs in patients receiving continuous dopaminergic delivery via an extended release formulation vs intermittent dosing (usually three times/day) of immediate release formulation of the same agonist. It is, however, noted that ICDS still occur in patients who are taking extended release agonists, thus showing that patients who receive their therapy by continuous drug delivery are also susceptible to ICDs.

equivalence of dopaminergic doses with different drug delivery methods—Switching from one agonist to another - but also using a different method of delivery - adds further difficulty in interpretation. When an oral agonist is changed to either transdermal rotigotine or subcutaneous apomorphine, the new drug may be prescribed at a lower equivalent dose, potentially leading to less (but acceptable) motor improvement and also

fewer ICDs. Under these circumstances, it may be that an improvement of the ICD has simply occurred as a consequence of less dopaminergic stimulation, rather than to an alteration in the mode of delivery - that is, the benefit occurred as a result of dose reduction, rather than from continuous drug delivery.

Careful assessment of ICDs in future drug studies is necessary to clarify these important issues. These options are discussed below, noting that the evidence for their success at influencing ICDs, or mechanism of action, is currently weak.

(i) Rotigotine—This is a non-ergolinic, lipid-soluble dopamine agonist which is distributed using a silicone-based transdermal patch allowing continuous drug delivery with a linear absorption profile. Two open-label, prospective, multicenter studies have reported lower rates of ICDs with rotigotine compared to oral dopamine agonists[31] and some patients might potentially be switched to rotigotine with attenuation of ICD symptoms without the development of DAWS[32]. However, a recent report suggested a relatively high (21%) rate of ICDs developing with rotigotine in RLS patients.[33] Further, properly designed controlled studies are required to evaluate this issue. Apart from more continuous dopaminergic stimulation, other factors to consider include differences in dopamine agonist potency and dopamine receptor stimulation profile.

(ii) Continuous subcutaneous apomorphine infusion—No major studies have explored the relationship between apomorphine and ICDs. A large retrospective multi-centre study of 82 patients on chronic apomorphine infusion therapy,[34] followed for a mean of 19.9±16.3 months, reported only 1 patient with severe hypersexuality (8%) and one recent open label, prospective study detected 4 de novo cases in 43 patients treated during 6 months of follow-up.[35] Other preliminary open-label studies, some reported only in abstracts,[36–38] also suggest the possibility of a lower rate of development of ICDs in moderate to advanced PD with apomorphine infusions. Further large scale studies are required to validate these pilot observations.

(iii) Continuous levodopa intestinal infusion—Data on the effect of levodopa infusion in ICDs is generally lacking. Enteral infusion of levodopa/carbidopa gel formulation has been shown to provide more continuous plasma levels when compared to oral administration, with reduction of both dyskinesia and off time.[39] Theoretically, this method might be one strategy to permit the elimination of dopamine agonists in patients with problematic motor complications who are experiencing ICDs. However, there is limited published experience with its use in such patients, or on its impact DAWS. A recent open-label study, lacking validated evaluative tools, reported improvement in behavioral complications in 8 patients (6 with ICDs, 3 with DDS and 5 with punding) with advanced PD and motor complications who were switched from oral to continuous jejunal levodopa infusion.[40] Four patients had successfully withdrawn previously from dopamine agonists and 4 could not due to worsening motor complications. Similarly, 4 patients' ICDs resolved on starting intrajejunal infusion in the open-labeled prospective study.[35] There are major limitations in these reports, though the results may have research relevance given the few reliably effective treatment options. Other cases with similar outcome have been reported suggesting that pulsatile receptor stimulation may indeed play an important pathogenic

role.[41] In a recently published randomized double-blind trial (evaluating the efficacy and safety of levodopa duodenal infusion compared to optimized, oral levodopa)[42], the Minnesota Impulsive Disorder Interview (MIDI) questionnaire was used to screen for ICDs and no cases were reported. However, the observation period was just 3 months and severe ICD patients may have not been enrolled, meaning that continuous delivery is still an unexplored strategy for the treatment of ICDs.

b) Cognitive Behavioural Therapy (CBT)

Not all patients with impulsive behaviours can tolerate or adhere to adjustments in medication, and the alternative unproven medical treatments (discussed above) and possible surgical options (see below) may not be available or acceptable for all patients. While impulsive behaviours in PD appear to be strongly biologically determined, this does not rule out psychological approaches as an alternative or adjunct to medical or surgical management. There is a potential influence of risk factors such as prior learned behaviour (e.g., premorbid gambling), primary biological drivers and more psychological factors that maintain problem behaviours once established, even after the primary driver is reduced. Psychological approaches have demonstrated value in the management of pathological and problem gambling in the general population.[43] Similar approaches might help in the management of these problems in PD through addressing two potential targets. Firstly, by seeking to reduce the frequency and/or intensity of the behaviour itself, and secondly by addressing the psychological processes that pose obstacles to drug reduction or withdrawal.

A retrospective report of PD patients receiving CBT for gambling found no difference in outcome from non-PD gamblers, although the sample was small.[44] Okai et al[45] reported a randomized study involving 45 patients with PD with a range of persistent impulsive behaviours despite attempts to optimize dopaminergic treatment. The treatment was based on current approaches for impulsive behaviours in non-neurological conditions in most cases with the target of a reduction in the frequency or intensity of the problem behaviour. Clinician ratings of change identified significant improvement in 75% of the treatment group compared to 29% in the comparator waitlist group. Although this study demonstrated good efficacy, and additional psychiatric and behavioral benefits, as a single site study, with treatment delivered by a single highly skilled therapist, the reliability and generalizability of these findings are limited. While further trials are needed, the study illustrates the potential opportunities offered by CBT approaches in the context of wider management.

In the context of ICDs, patients can experience DAWS even with slow titration. Although there have been no reports to date of CBT approaches to the management of DAWS, the individual symptoms, particularly anxiety and depression, can be responsive to CBT in PD[46], while other symptoms such as fatigue and pain-related distress are amenable to psychological approaches in patients with medical conditions. Therefore, including psychological support to patients during agonist reduction may be an additional valuable tool.

c) Deep Brain Stimulation

There has been considerable interest in the role of deep brain stimulation (DBS) in either inducing or alleviating impulsive behaviors in PD. DBS is effective for the motor symptoms of PD and for the motor complications associated with medical treatment.[47–50] Three main types of DBS have been applied to PD, targeting the subthalamic nucleus (STN), globus pallidus internus (GPi) and thalamic ventral intermediate nucleus (VIM). VIM DBS only reliably improves tremor and its use has declined in recent years. We have not found data concerning the VIM target with ICDs, and VIM DBS will not be considered further here. Most reports have concentrated on bilateral STN DBS as this allows post-operative reduction of anti-parkinsonian medication. Since ICDs are generally drug-induced, it has been suggested that there might be a role for STN DBS in the management of ICDs, although the evidence is somewhat complex and murky.[51, 52]

Early reports of STN DBS suggested that some behavioural disturbances (e.g., mania, aggressiveness, euphoria) can be detected following DBS.[53–56] These behaviors are not typical ICDs, so will not be considered further here. In the description of single ICD cases[57–60], it was not always possible to confirm a direct relationship with DBS. In addition, there are reports of covert impulsive behaviours[61] and dopamine dysregulation syndrome[62] existing pre-operatively but only being declared post-operatively. It is not clear whether such effects are secondary to acute or chronic electrical stimulation of the target itself or of adjacent structures, e.g. the non-motor (ventral) portion of the STN.[63] In keeping with the latter concept, PD patients with ICDs were found to have oscillatory activity in the theta-alpha band in the ventral, associative-limbic portion of the STN with coherence between the STN and frontal cortical regions anterior to the primary motor cortex. This contrasted with patients with dyskinesias who had similar oscillatory activity mainly localized to the dorsal motor STN with cortical-subthalamic coherence involving the primary motor and supplementary motor areas. This suggests an important anatomo-functional role for the associative-limbic region of the STN and its frontal connections in the expression of PD ICDs.[64]

There have been reports on the relationships of DBS to both impulse control behaviours and dopamine dysregulation syndrome, with differing findings.[57, 64–72] Despite these reports, no trials have specifically addressed the use of DBS in impulsive behaviors, and current opinion is therefore based on reports of single cases, case series and reviews. Additionally, in interpreting these results, the location of the active contact is presumed to be near the sensorimotor area of the STN, which is the intended motor target. Further studies on the relationships of DBS and impulsive behaviors would be most helpful if accompanied by information about the precise location of stimulation, but this is technically difficult because of the small structures involved, the electrode artefact on MRI, the processing required for CT-MRI fusion (if used), the theoretical shape of the volume of tissue activated around the active contact, and the varied DBS parameters used. Currently, these factors remain as confounds to the clear interpretation of these relationship of DBS and impulsive behaviours.

It is, however, clear that patients undergoing pre-operative assessment for DBS can have impulsive behaviours or dopamine dysregulation syndrome. Indeed, some have argued that

those patients undertaking a surgical treatment for their PD constitute a more “risk-taking” population on the whole than those not seeking surgery and therefore they may be predisposed to behavioral complications. The prevalence of impulsive behaviours in DBS services is estimated at 16%[70, 73], but has also been reported as a high as 50% depending on definitions and the impulsive behaviours scales used.[68] In the latter study, almost half of the patients had a behavioural disturbance such as nocturnal hyperactivity, excessive eating, creativity, hobbyism, punding, risk-taking behaviour, compulsive shopping, pathological gambling, hypersexuality, or dopamine dysregulation syndrome, which improved following STN DBS and drug reduction. These studies all support the importance of a neuropsychiatric assessment prior to DBS to document the presence or absence of an ICD pre-operatively.

A further important factor is the management of medications around the time of DBS surgery. Some centres stop dopaminergic medications at the time of surgery abruptly, while others taper them slowly. Medication reduction or cessation post-operatively had been reported to successfully lead to resolution of ICDs and dopamine dysregulation syndrome.[57, 67, 68, 71, 74] In contrast, this has also been described to increase the risk of apathy and mood disorders post-operatively.[68] Further, some patients can develop DAWS and may be unable to reduce the dopamine agonists despite good motor control.[62, 75] The immediate post-operative period can also be influenced by surgical effects, (eg insertional oedema) which can lead to a change of behaviour in the short term. For example, transient mania can co-exist with an ICD.[58, 65] In a previous report[65], a gradual reduction of total daily dopaminergic medication to below the level at which the ICD was documented eventually led to cessation of pathological gambling, but transient worsening in 2/7 patients occurred. It is not known if all ICDs can have an analogous outcome following DBS. Compulsive eating may cause weight gain after STN DBS[72], and there is a suggestion that DBS does not alleviate it, may worsen it or lead to de novo cases.

Other reports have reached different conclusions about outcomes of impulsive behaviours in PD after DBS. A retrospective comparison of two groups of patients with and without STN DBS suggested a high frequency of impulsive behaviours in DBS patients despite significant post-surgical reduction of dopaminergic medication[66], although ICDs were not specifically assessed at baseline. Of 159 total surgeries operated in staged fashion, 2/7 patients with pre-existing impulsive behaviours improved, while 2 further patients with pre-existing impulsive behaviours developed a new dopamine dysregulation syndrome after STN DBS, and a small number of new impulsive behaviours developed after either unilateral or bilateral staged STN DBS or GPi DBS.[69] Further, a retrospective postal survey[62] reported the persistence/worsening of impulsive behaviours/dopamine dysregulation syndrome in 71% of 21 patients who had these syndromes pre-operatively.

Current data do not support firm conclusions on the relationships between clinically significant impulsive behaviours and DBS. However, they suggest that pre-operatively, DBS candidates should be assessed carefully for impulsive behaviours (recognizing that some patients may not be fully forthcoming if concerned that knowledge of this behaviour would negatively impact on their surgical candidacy), informed about the possibility of lead misplacement (which might increase risk of impulsive behaviours), be counselled to

anticipate drug reductions post-operatively, and be provided with post-operative surveillance. Until specific prospective studies using uniform definitions of ICDs, DBS targets, drug changes and DBS parameters are available, clinicians wishing to consider DBS for patients (with and without impulsive behaviours) should remain vigilant for their pre and post-operative occurrence.

d) Future Therapeutic Targets: Concepts and Challenges

Until recently, little effort had been aimed at developing novel therapeutics for ICDs in PD. This situation was to some extent due to a perception that there was a simple solution to the problem, i.e., reducing dopaminergic therapy. The last decade has brought significant advances in defining the underlying neural circuitry, developing animal models, and improving clinical trial methodology, thereby enabling increased research and novel hypotheses for therapeutic targets. Generally, three therapeutic approaches can be considered: (i) *novel adjuncts* to current therapy to treat ICDs without reducing anti-parkinsonian benefit, (ii) *non-dopaminergic* drugs to provide anti-parkinsonian benefit without inducing ICDs, and (iii) *novel dopaminergic* drugs that might benefit parkinsonism without inducing ICDs. To date, most efforts have focused on the development of novel adjunctive therapies, as described below. With improved understanding of relevant targets within the ICD circuitry, specifically involvement of the ventral striatum, ventral tegmental area, hippocampus and anterior cingulate/prefrontal cortex for some ICD symptoms,[29, 76–81] novel agents may yet be identified.

One approach to identifying potential therapies for ICD in PD is by analogy to impulsivity and addiction not associated with PD, given the similarities in behavioural manifestations and anatomic substrates, although there are limitations in such extrapolations. For instance, non-PD impulsivity or addiction studies in animals, and genetic studies, suggest involvement of mu opioid, cannabinoid, nicotinic and D4 dopamine systems.[82–86] While it is important to recognize that data on pre-clinical efficacy obtained in models with an intact dopaminergic system may not be predictive of ICDs in PD patients who have dopaminergic systems affected by the disease process, these data identify potential therapeutic targets for PD ICDs. Animal models where dopaminergic treatment - on a background of a parkinsonian deficit - drives implusive behaviors may serve as more physiological models for testing potential new drugs. These models include the 5-choice test (5CSRTT) in bilateral 6-OHDA-lesioned rats[87], driven locomotor activity in MPTP-lesioned primate[88] and the object recognition task in the MPTP-lesioned primate[89].

In these models, we can broadly categorise impulsivity into motor impulsivity and decision-making impulsivity. As novel drug acting at these various targets are assessed, we will learn whether these models predict efficacy for the different clinical sub-types of PD impulsivity. Such approaches are critical for the optimal translation of animal model data to clinical drug development. For instance, mu opioid selective antagonists reduce motor impulsivity[90] in the MPTP monkey, supporting the value of the opioid system as a novel target for at least a component of the ICD spectrum. The opioid antagonist naltrexone has already been evaluated in ICDs with some encouraging results in gambling behavior[91] and the study of Weintraub and colleagues[23] begins to define a path from pre-clinical research to clinical

proof-of-concept studies. Although the study was negative for the primary outcome, such Phase II clinical proof-of-concept trials are critical to evaluate the safety, tolerability, and preliminary efficacy of novel agents to allow for well-designed efficacy studies.

In a similar manner, motor impulsivity in the MPTP-lesioned monkey can be reduced via URB597, an inhibitor of endocannbinoid breakdown, highlighting the potential of enhancing the cannabinoid system.[92] Likewise, alpha1 adrenergic antagonists[88], mGlu5 negative allosteric modulators[93] and D4 dopamine receptor antagonists[94] reduce motor impulsivity in MPTP-lesioned monkeys and could all be considered as potential approaches to at least some components of ICDs. Decision-making impulsivity, which may be better assessed in 5-choice or object recognition assays, may have an overlapping but distinct pharmacology, being reduced by both D3[89] and D4[95] dopamine receptor antagonists. As we continue to better understand the biologic underpinnings of the different ICDs in PD, it is expected that more drug targets will be identified and further trials initiated.

Conclusion

The first step in the management of ICDs and related disorders is counselling and surveillance to facilitate early diagnosis and treatment. Dopamine agonist taper and substitution of other classes of PD medications can be highly effective in some patients, but not all patients tolerate this because of DAWS or other clinical factors. When this approach is unsuccessful, then other pharmacological or non-pharmacological approaches can be considered. It is important to recognize, however, that at this time these largely have only anecdotal evidence for efficacy. Advances in the management of these disabling conditions can be made by including ICDs as a specific outcome measure in trials of medical or surgical therapies for PD. Future studies are needed to clarify the underlying pathophysiology of ICDs and identify novel therapeutic targets, to facilitate the development of safe and effective evidence-based treatments for ICDs.

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Table 1

Summary of treatment options for the management of impulse control disorders in Parkinson's disease (PD)

Adjustment of PD medications – and reduction/cessation of dopamine agonists – is the primary treatment at this time; other treatments are unproven but can be considered. The order is not sequential. ICD = impulse control disorder, COMT = cathechol-O-methyl transferase, MAOI = monoamine oxidase inhibitor. DAWS = Dopamine Agonist Withdrawal Syndrome, STN = subthalamic nucleus, VIM = ventral intermediate nucleus, DBS = deep brain stimulation.

		Commentary.
Education, prevention, and surveillance	Patient education, carer education, and surveillance to facilitate early diagnosis and treatment.	Involvement of carers in surveillance for ICDs can facilitate earlier detection. Also, caregivers/family may participate in management when symptoms persist (if refractory or a patient needs to stay on causative drug(s) due to motor worsening or DAWS). Behavioural/environmental approaches, such as the removal of credit cards, limiting money expenditure, monitoring food intake, monitoring internet access, etc, can be considered on an individual basis.
Adjustment of PD medications	Reduce oral dopamine agonist. - Observe for resolution of ICDs - Observe for loss of motor control - Observe for DAWS	As a class effect, dopamine agonists have a strong association with ICDs. Reduction to cessation of dopamine agonists (and substituting other PD medications, as needed) is the preferred treatment for ICD resolution, but may not be optimal for DAWS/motor control. Maintaining a low "sub-threshold" dopamine agonist dose - which might be effective at balancing the resolution of ICDs with worsening of motor control, and/or induction of DAWS - will continue to place a patient at risk of ICDs, with or without the influence of other factors, e.g. if level of supervision decreases, other driving factors co-exits, other anti-parkinsonian medications increase, or covert ICDs are a possibility. All patients who continue dopamine agonist treatment – even at a low dose – need to be closely monitored for recurrent or worsening of ICDs.
	If concomitant loss of motor control occurs as dopamine agonists are reduced, then consider adding a COMT inhibitor to the pre-existing oral levodopa doses, or increasing the levodopa.	The effect of levodopa is also associated with ICDs. No evidence of efficacy against DAWS.
	If concomitant loss of motor control occurs, consider adding a MAOI and observe for re-emergence of ICD	MAOI drugs can be rarely associated with induction of ICDs. No evidence of efficacy against DAWS.
	Amantadine	Conflicting evidence about whether amantadine may be beneficial (for pathological gambling) or deleterious. Its use in ICDs is controversial.
	Consider switching from an oral dopamine agonist to transdermal rotigotine	Evidence is beginning to emerge, but currently is insufficient. Rotigotine has also been associated with induction of ICDs.
	Consider switching from an oral dopamine agonist to subcutaneous continuous apomorphine infusion	Evidence is beginning to emerge, but currently is insufficient. Subcutaneous continuous apomorphine infusion may fail to resolve ICDs and might potentially induce new ICDs.
	Consider switching to continuous intrajejunal levodopa infusion to control motor symptoms.	Evidence is beginning to emerge, but currently is insufficient.
Psychiatric management	Consider addition of: - antidepressants - anxiolytics - atypical neuroleptics	Psychiatric co-morbidity can occur with ICDs. Evidence for efficacy of psychiatric medications for ICDs is controversial. These drugs may help the psychiatric symptoms per se if they co-exist with ICD, and may help the ICD if the psychiatric symptoms are driving the ICD (eg anxiety). Neuropsychiatric referral is suggested.

		Commentary.
	- antiepileptics - naltrexone	Efficacy against DAWS is lacking.
Psychological treatment	Cognitive behaviour therapy	Some evidence of efficacy in ICDs exists. Can also be tried for DAWS but evidence is lacking.
Deep brain stimulation	Consider “levodopa-sparing” types of deep brain stimulation, such as at STN (or VIM if patient is mainly troubled by tremor)	Conflicting evidence as to whether STN DBS can improve ICDs or induce them. No clear conclusions can be drawn. DBS candidates may be inherently at higher risk of impulsivity. Post-operative surveillance for ICD, apathy, DAWS and motor control is required. If ICDs are present post-operatively, consider the possibility of spread of current to adjacent structures, lead misplacement or post-operative drug changes.
Consider the severity of DAWS vs the severity of ICDs	Re-introduce dopamine agonist at the lowest possible dose to avoid DAWS	This will maintain the current ICD, and the future risk of worsening the ICD. Even patients whose ICDs initially improve may develop recurrent ICDs in the future. Marked caution is required. Consider whether ICDs or DAWS symptoms are the more distressing and the level of long-term surveillance required for ICDs.