Diagnosis and treatment of impulse control disorders in patients with movement disorders

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Abstract: Impulse control disorders are a psychiatric condition characterized by the failure to resist an impulsive act or behavior that may be harmful to self or others. In movement disorders, impulse control disorders are associated with dopaminergic treatment, notably dopamine agonists (DAs). Impulse control disorders have been studied extensively in Parkinson's disease, but are also recognized in restless leg syndrome and atypical Parkinsonian syndromes. Epidemiological studies suggest younger age, male sex, greater novelty seeking, impulsivity, depression and premorbid impulse control disorders as the most consistent risk factors. Such patients may warrant special monitoring after starting treatment with a DA. Various individual screening tools are available for people without Parkinson's disease. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease has been developed specifically for Parkinson's disease. The best treatment for impulse control disorders is prevention. However, after the development of impulse control disorders, the mainstay intervention is to reduce or discontinue the offending anti-Parkinsonian medication. In refractory cases, other pharmacological interventions are available, including neuroleptics, antiepileptics, amantadine, antiandrogens, lithium and opioid antagonists. Unfortunately, their use is only supported by case reports, small case series or open-label clinical studies. Prospective, controlled studies are warranted. Ongoing investigations include naltrexone and nicotine.

Keywords: Impulse control disorders, Parkinson's disease, restless leg syndrome, parkinsonism, dopamine agonist, non-motor complication, neurobehavioural

Impulse control disorders: definitions and phenomenology

The hallmark of impulse control disorders (ICDs) is a 'failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others' according to the American Psychiatric Association's *Diagnostic and Statistical Manual* – fourth edition text revised (DSM-IVTR) [American Psychiatric Association, 2000]. The most common ICDs are pathological gambling (PG), hypersexuality (HS), compulsive shopping (CS) and compulsive eating (CE). Two large epidemiological studies conducted in North America inform us that PG is a relatively rare disorder with a prevalence of 0.42–1% in the general population [Ferris *et al.* 1996; Petry *et al.* 2005] and a nationwide study on CS reported a lifetime prevalence of 5.8% in the adult US population [Koran *et al.* 2006].

The DSM-IVTR [American Psychiatric Association, 2000] defines PG as a 'persistent and recurrent maladaptive gambling behavior' (see Table 1). To date, a formal schema for diagnosis of hypersexuality does not exist. A definition of HS based on DSM format has been proposed in a prevalence study in Parkinson's disease (PD) [Voon *et al.* 2006] (Table 1). A definition to be included in the upcoming DSM-V was recently published [Kafka, 2010]. CS is characterized by a frequent preoccupation with shopping or intrusive, irresistible, 'senseless' buying impulses that exceed what is needed or can be afforded, and causes distress or significant interference with work or social functioning [McElroy *et al.* 1994] (Table 1). CE is characterized as uncontrolled binge eating without emesis or laxative abuse in a working definition of the DSM-IVTR. It is often, but not always, associated with obesity symptoms [American Psychiatric Association, 2000].

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Table 1. Diagnostic criteria for common impulse control disorders.

Pathological gambling (DSM-IV)

Preoccupation with gambling:

- Needs to gamble with increasing amounts of money in order to achieve the desired excitement
- Repeated unsuccessful efforts to control, cut back or stop gambling
- Restlessness or irritability when attempting to cut down or stop gambling
- Gambling as a way of escaping from problems or of relieving a dysphoric mood
- Returning to gamble to 'get even' after losing money gambling
- Lying to family members, therapists or others to conceal the extent of involvement with gambling
- Committing illegal acts such as forgery, fraud, theft or embezzlement to finance gambling
- Jeopardizing or losing a significant relationship, job or educational or career opportunity because of gambling
- Relying on other to provide money to relieve a desperate financial situation caused by gambling

The gambling should not be during a manic episode. The DSM-V will incorporate other behavioral addictions and thus these definitions may be in flux over the next few years. Persistent and recurrent problematic gambling behavior as indicated by four (or more) of the following in a 12-month period

Hypersexuality [Voon et al. 2006]

The sexual thoughts or behaviors are excessive or an atypical change from baseline marked by one or more of the following:

- Maladaptive preoccupation with sexual thoughts
- Inappropriately or excessively requesting sex from spouse or partner
- Habitual promiscuity
- Compulsive masturbation
- Telephone sex lines or pornography
- Paraphilias

The behavior must have persisted for at least one month

The behavior causes at least one of the following*:

- Marked distress
- Attempts to control thoughts or behavior are unsuccessful or result in marked anxiety or distress
- Are time consuming
- Interfere significantly with social or occupational functioning

The behavior does not occur exclusively during periods of hypomania or mania

If all criteria, except *, are fulfilled, the disorder is subsyndromal

[Kafka, 2010]

Recurrent and intense sexual fantasies, sexual urges or sexual behaviors in association for at least 6 months with three or more of the following:

- Time consumed by sexual fantasies, urges or behaviors repetitively interferes with other important (nonsexual) goals, activities and obligations
- Repetitively engaging in sexual fantasies, urges or behaviors in response to dysphoric mood states
- Repetitively engaging in sexual fantasies, urges or behaviors in response to stressful life events
- Repetitive but unsuccessful efforts to control or significantly reduce these sexual fantasies, urges or behaviors
- Repetitively engaging in sexual behaviors while disregarding the risk for physical or emotional harm to self or others
- There is clinically significant personal distress or impairment in social, occupational or other important areas of functioning associated with the frequency and intensity of these sexual fantasies, urges or behaviors
- These sexual fantasies, urges or behaviors are not due to the direct physiological effect of an exogenous substance such as a drug of abuse or medication

Abnormal behaviors are different from previous behavior and include excessive masturbation, using pornography, sexual behavior with consenting adults, cybersex, telephone sex, strip clubs, use of sex trade workers

Table 1. (Continued)**Compulsive shopping [McElroy *et al.* 1994]**

Maladaptive preoccupation with buying or shopping, or maladaptive buying or shopping impulses or behavior, as indicated by at least one of the following:

Frequent preoccupation with buying or impulses to buy that is/are experienced as irresistible, intrusive or senseless

Frequent buying of more than can be afforded, frequent buying of items that are not needed, or shopping for longer periods of time than intended

The buying preoccupations, impulses, or behaviors cause marked distress, are time consuming, significantly interfere with social or occupational functioning or result in financial problems (e.g. indebtedness or bankruptcy)

The excessive buying or shopping behavior does not occur exclusively during periods of hypomania or mania

Impulse control disorders in Parkinson's disease

In movement disorders, ICDs have been studied mainly in PD. The next section will cover the brief literature available on ICDs in other movement disorders.

Initial studies of ICDs in PD [Pontone *et al.* 2006; Weintraub *et al.* 2006; Grosset *et al.* 2011; Isaias *et al.* 2008; Singh *et al.* 2007; Voon *et al.* 2006] reported a prevalence of 2.2–28.0% for PG [Weintraub *et al.* 2006; Isaias *et al.* 2008], 2.0–11.0% for HS [Voon *et al.* 2006; Singh *et al.* 2007], 0.4–6.4% for CS [Voon *et al.* 2006; Weintraub *et al.* 2009] and 1–4.5% for CE [Zahodne *et al.* 2011; Weintraub *et al.* 2009]. It is important to recognize that these estimates were obtained with heterogeneous study designs, sample sizes, diagnostic criteria and ascertainment methods. For example, a patient-rated questionnaire on HS documented a lifetime prevalence of 2.4% [Voon *et al.* 2006], while a clinician-rated survey conducted in the same PD population reported a lifetime prevalence of 8.4% (unpublished data from authors). The prevalence of active HS was similar, with 2.0 % for the patient-rated questionnaire [Voon *et al.* 2006] and 1.9% for the clinician-rated survey (unpublished data from authors).

The largest epidemiological study on ICDs in PD, the DOMINO study, reported a 6-month prevalence of any ICDs of 13.6%, including PG (5.0%), HS (3.5%), CS (5.7%) and CE (4.3%) [Weintraub *et al.* 2010a].

Other repetitive behaviors have been recognized as part of the spectrum of ICDs in patients with PD, including walkabouts, that is, excessive, aimless wandering [Giovannoni *et al.* 2000; Quinn *et al.* 1983] reported by 3.2% of patients [Weintraub

et al. 2009], hoarding [O'Sullivan *et al.* 2010b], kleptomania [Bienfait *et al.* 2010], impulsive smoking [Bienfait *et al.* 2010], reckless generosity [O'Sullivan *et al.* 2010c] and reckless driving [Avanzi *et al.* 2008].

Dopamine dysregulation syndrome (DDS) and punding are related behaviors. DDS or hedonic homeostatic dysregulation is defined by a compulsive use of dopaminergic medication with drug hoarding regardless of the patient being 'on' and experiencing excessive and significant dyskinesias. It can be associated with a hypomanic state and symptoms consistent with a withdrawal syndrome [Giovannoni *et al.* 2000]. Estimated prevalence for DDS ranges from 0.6 % to 3.4–4% [Weintraub *et al.* 2009; Giovannoni *et al.* 2000; Pezzella *et al.* 2005]. Levodopa and short-acting DAs are the main culprits and DDS is associated, in at least 88% of the cases, with severe off-period dysphoria, disabling dyskinesias and co-occurrence of punding [Evans *et al.* 2005]. It is worth emphasizing that the reverse does not happen, with primary punders manifesting less often a DDS [Evans *et al.* 2005]. Punding corresponds to an intense fascination with meaningless movements or activities that are repeated in an endless fashion. It was first used to coin stereotyped motor behaviors in amphetamine and cocaine addicts [Rylander, 1972]. Based on surveys conducted in tertiary outpatient movement disorders centers, the incidence of punding ranges between 1.4% and 13.8% in PD [Evans *et al.* 2004; Miyasaki *et al.* 2007; Weintraub *et al.* 2009]. Punding behaviors encompass repetitive manipulations of technical equipment, handling and sorting common objects, grooming, cleaning, gardening, writing, artistic drawing or craft-making, singing or playing a musical instrument, playing cards, fishing and excessive computer use [Lim *et al.*

2008]. The patient typically will have difficulty in completing projects, is aware of creating chaos while punning and will resist to disengage from the activity, continuing punning overnight or manifesting irritability if interrupted [Evans *et al.* 2004]. Hoarding and walkabouts have been included in a spectrum of punning, though other authors study these phenomena separately [Weintraub *et al.* 2009]. The first description of punning in PD was associated with L-dopa [Friedman, 1994]. Later, a small case series documented the association of punning with the use of DAs [Fernandez and Friedman, 1999]. Hobbyism is considered a complex form of punning related to a specific activity or hobby (e.g. coin collection, repairing or dismantling things, computer use) that frequently corresponds to a premorbid activity or hobby. Hobbyism is reported to occur in 14.6% of patients with PD [Weintraub *et al.* 2009] and rarely (3.8 %) co-occurs with punning [Weintraub *et al.* 2009].

Impulse control disorders in other movement disorders

The clinician should be aware that ICDs are reported in other movement disorders using dopaminergic medication for treatment. These include restless legs syndrome (RLS) [Evans and Stegeman, 2009; Quickfall and Suchowersky, 2007], progressive supranuclear palsy (PSP) regardless of the clinical variant (Richardson's syndrome *versus* PSP Parkinsonism) [Kim *et al.* 2008; O'Sullivan *et al.* 2010a] and multiple system atrophy [Klos *et al.* 2005; McKeon *et al.* 2007].

The literature is limited to case reports or case series with the exception of RLS. A case-control study reported that the frequency of any ICDs in a RLS-treated group was 17%, based on a questionnaire followed by a phone interview [Cornelius *et al.* 2010]. The latency between initiation of treatment and onset of any ICD was 9.5 months [Cornelius *et al.* 2010]. The frequency of individual ICDs was 11% for CE, 9% for CS, 7% for punning, 5% for PG and 3% for HS [Cornelius *et al.* 2010]. In another study of ICDs with 140 patients, screening through patient-completed questionnaires and confirmation by psychiatric interview revealed 80% of the patients had multiple ICDs [Voon *et al.* 2011a]. The prevalence of any ICDs was 11% and included CE (4.3%), CS (3.6%), PG (2.1%), punning (2.1%) and HS (1.4%) [Voon *et al.* 2011a]. DDS was not reported [Voon *et al.* 2011a], though it has been recognized

in a single patient with RLS [Leu-Semenescu *et al.* 2009]. In addition, ICDs were associated with a higher DA dose, younger age of onset of RLS, history of experimental drug use, female sex and a family history of gambling disorders [Voon *et al.* 2011a]. Recently, a case series of 27 patients with RLS undergoing treatment with rotigotine reported a prevalence of 21% for single ($n = 4$) and multiple ($n = 2$) ICDs. Regardless of occurrence of ICDs, all patients showed an increase of impulsivity measured by the Zurich Screening Questionnaire for ICD [Schregermann *et al.* 2012]. Other studies, controlled for the cofounder of medication, reported that patients with RLS without dopaminergic treatment have an impairment of executive function with worse performance in the Wisconsin Card Sorting Test for patients with frequent symptoms [Fulda *et al.* 2011], reduced decision-making abilities under ambiguity but not risky conditions [Bayard *et al.* 2010] and deficits in short-term attention and verbal fluency [Fulda *et al.* 2010] compared with matched controls. These features can also be associated with secondary manifestations of sleep deprivation or depression in RLS [Bayard *et al.* 2010], but it leads to a hypothesis in need of further testing that the executive dysfunction found in patients with RLS may predispose them to ICDs.

ICDs were also reported in a patient with secondary RLS due to multiple sclerosis [Evans and Butzkueven, 2007].

Risk factors of impulse control disorders in Parkinson's disease

The knowledge of risk factors for ICDs in PD enables the clinician to identify patients more prone to develop ICDs. DA treatment is the primary risk factor for ICDs in PD [Weintraub *et al.* 2010b] and ICDs are usually considered a drug class effect. Nevertheless, it is important to recognize that ICDs can occur on a stable dose of dopaminergic treatment, away from the onset of dopaminergic treatment or a change in dose [Cooper *et al.* 2009; Kurlan, 2004].

Though exceedingly rare (~2%), cases exist [Gallagher *et al.* 2007] documenting an association of L-dopa, amantadine and selegiline with ICDs [Fernandez and Friedman, 1999; Shapiro *et al.* 2006; Weintraub *et al.* 2010b]. In addition, in a recent case-control study, the use of DAs [adjusted odds ratio 20.3; 95% confidence interval (CI) 2.70–65.01] but also of monoamine oxidase B inhibitors

(adjusted odds ratio 3.74; 95 % CI 1.11–12.64) stood out among other dopaminergic drug classes as predictors of occurrence of ICDs [Perez-Lloret *et al.* 2012].

Though nearly all patients with PD are being treated with dopaminergic drugs, at least 17% develop ICDs. The incidence of subsyndromal forms of ICDs is not known. Robust epidemiological data provide insight regarding individual variables associated with ICDs. Studies analyzing individual characteristics associated with the occurrence of ICDs in PD [Singh *et al.* 2007; Isaias *et al.* 2008; Pontone *et al.* 2006; Voon *et al.* 2007, 2011b; Weintraub *et al.* 2010b] commonly report younger age, male sex, greater premorbid novelty seeking, impulsivity and depression as risk factors for ICDs. Efforts to identify the contribution of each factor for specific ICDs disclosed that medication-induced mania and adjunctive DA use (*versus* monotherapy) are risk factors for PG [Voon *et al.* 2007] and male sex and early onset of PD onset are more associated with HS [Weintraub *et al.* 2010b; Uitti *et al.* 1989]. A history of ICD symptoms prior to PD was found to be a premorbid characteristic of patients with PD who went on to develop PG, HS or PS [Weintraub *et al.* 2006]. Personal or family history of substance abuse including alcoholism increased risk of ICDs in one cohort [Voon *et al.* 2006]. A history of repetitive behaviors or obesity was associated with CE and weight gain was associated with CS [Nirenberg and Waters, 2006; Rylander, 1972]. Motor complications are more common in patients with ICDs [Solla *et al.* 2011]. Dyskinesias have been found to be significantly present in patients with HS or CS, but not PG or CE [Solla *et al.* 2011]. Multiple ICDs will occur more likely in younger patients with more intense dyskinesias and alcohol use [Voon *et al.* 2011b].

Related behaviors such as DDS share similar risk factors, including the existence of depressive symptoms, alcohol intake, younger age at PD onset, impulsive sensation seeking and novelty-seeking personality traits [Evans *et al.* 2005], but are better predicted by a higher dopaminergic drug intake and greater past experimental drug use [Evans *et al.* 2005]. An increased clinical severity of punding has been associated with higher total daily L-dopa equivalents, younger age, reduced sleep time overnight and average number of daily rescue doses [Evans *et al.* 2004]. Insomnia, previously treated psychosis and excessive libido were commonly reported comorbidities.

Dyskinesias have also been associated with punding behaviors and DDS but not ICDs [Silveira-Moriyama *et al.* 2006].

Screening and diagnostic tools for impulse control disorders in Parkinson's disease

Clinical scales have been created to screen and diagnose different forms of ICDs in the general population. The South Oaks Gambling Screen [Lesieur and Blume, 1987], Pathological Gambling Adaptation of the Yale–Brown Obsessive–Compulsive Scale [Pallanti *et al.* 2005], the Gambling Symptom Assessment Scale [Kim *et al.* 2009] and the Massachusetts Gambling Screen [Shaffer *et al.* 1994] are used for PG. Some of these have been used in PD for specific ICDs. A Buying Questionnaire [Christenson *et al.* 1994] is also found in literature. The Minnesota Impulsive Disorders Interview is a global measurement tool that includes sections for PG, HS and CS, however it is not formatted for diagnosis according to DSM-IVTR and lacks clear instructions for its administration and scoring guidance [Weintraub *et al.* 2012]. These are not validated in PD, but some of the items were incorporated in the Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease (QUIP) (see below) [Weintraub *et al.* 2009]. All of the above scales are designed to be patient completed. However, in addiction research, patient-completed tools are not sufficient as screening or diagnostic tools. As discussed below, informed ‘others’ increase their sensitivity.

Initial initiatives to produce clinical rating scales specific for ICDs in PD include a hypersexuality questionnaire [Voon *et al.* 2006] and a punding questionnaire [Evans *et al.* 2005]. The first attempt to combine various survey instruments in a clinically usable tool in PD was the QUIP [Weintraub *et al.* 2009]. It is a self-completed screening questionnaire for ICDs and other compulsive behaviors occurring at ‘anytime’ during PD [Weintraub *et al.* 2009]. A short form of the QUIP (QUIP-S) has been recommended for routine use since it has similar psychometric properties to the original version and a shorter median completion time of 3 min [Weintraub *et al.* 2009]. An intrinsic limitation is the requirement of a 12th grade reading level [Weintraub *et al.* 2009]. For the QUIP-S, the ability to identify an individual with any at least one ICD is 0.89 and the discriminant validity for selected cut-offs in the different ICDs was 0.95 (0.84–1.05) for PG, 0.97 (0.93–0.99) for

Figure 1. Ventral striatum. Striatal regions associated with significant reduction in dopamine transporter with single photon emission tomography binding in patients with Parkinson's disease with pathological gambling. Reproduced from Cilia *et al.* [2010], with permission of the authors.

HS, 0.87 (0.72–1.02) for PB and 0.88 (0.72–1.04) for CE. The QUIP is also valid when completed by a patient's informant [Papay *et al.* 2011].

A follow-up study of the QUIP showed a sensitivity of 100% regardless of whether a patient or informant completed the instrument and a lower specificity (~75%) that translated to 40% of patients with a positive QUIP based on either patient or informant reporting not fulfilling criteria for a formal diagnosis of any ICD [Papay *et al.* 2011]. This suggests that a positive screen with QUIP should be followed by a comprehensive psychiatric interview to determine the range and severity of symptoms. In addition, the application of the QUIP documented the existence of subsyndromal ICD symptoms, which likely represent an important window of opportunity for clinicians to act early and prevent more serious consequences of ICDs [Weintraub *et al.* 2009]. The natural history of subsyndromal forms is not known. For example, do subsyndromal forms necessarily progress to ICDs and over what time course? Could subsyndromal forms be stable for long periods of time? What separates those patients experiencing subsyndromal forms compared with full ICDs? Patients often acknowledge subsyndromal forms only after a reduction in their dopaminergic medication and complete resolution of their symptoms [Voon *et al.* 2006]. A new version of the QUIP (QUIP rating scale/QUIP-RS) has been designed to capture a change in the severity of ICD symptoms and thus improve the characterization of

subsyndromal forms. The QUIP-RS was found to be a valid and reliable rating scale for ICDs and related disorders in PD, applicable both for diagnosis and monitoring temporal changes in the severity of symptoms [Weintraub *et al.* 2012]. The QUIP and QUIP-RS have not been validated for other populations at risk for ICD development [Weintraub *et al.* 2009]. A clinical scale with a comprehensive section in impulse control behaviors, including the most common ICDs and related behaviors in PD (PG, HS, PS, punding and DDS), has been created in French [Ardouin *et al.* 2009] but requires further clinimetric validation.

Clues for future approaches to identify patients with PD more prone to developing ICDs are given by imaging data such as positron emission tomography that consistently document a distinct functional state of the brain in patients with PD who developed ICDs (see Figure 1) [Cilia *et al.* 2010; Steeves *et al.* 2009; van Eimeren *et al.* 2010]. The predictive value of these changes in a premorbid condition is yet to be established.

Management of impulse control disorders

The best treatment for ICDs is prevention. Counseling patients and ideally spouses or family members prior to initiating therapy and recognizing premonitory signs of ICDs is mandatory. This includes counseling families to question and report to the physician unexplained absences, secretive behavior, irritability, hiding evidence of

Table 2. Treatment approach for impulse control disorder in Parkinson's disease.

Management steps	Commentaries
Address reversible risk factors	
Reduce or discontinue dopaminergic drug	Most likely effective
Switch dopamine agonist	Less likely effective
Depression	SSRIs, TCA
Psychosocial support	
Family involvement, support groups	-
Cognitive behavioral therapy	Possibly effective
Pharmacological treatment	
Clozapine, quetiapine	Punding, HS, PG
Risperidone, olanzapine	Risk of motor deterioration
Valproate	HS, PG, punding, DDS
Zonisamide	HS, PG, CS, CE
Topiramate	HS, PG, CS, CE
Amantadine	Punding, PG
Naltrexone	PG
SSRIs	Punding, other ICDs
Lithium (+ olanzapine)	HS
Cyproterone	HS
Finasteride	PG
Clomipramine	Nocturnal punding
Donepezil	Patient with cognitive impairment and HS

CE, compulsive eating; CS, compulsive shopping; DDS, dopamine dysregulation syndrome; HS, hypersexuality; ICD, impulse control disorder; PG, pathological gambling, SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

the ICDs and monetary consequences of ICDs. The majority of patients with PD with ICDs may be undetected by their physicians [Weintraub *et al.* 2006; Evans *et al.* 2004]. The normalization of the behaviors associated with dopaminergic treatment induced ICDs improves patients' comfort in disclosing these activities (some patients develop the following behaviors as a result of their treatment). The disparity between patient self report and spouse or family member report continues in the literature. This highlights either lack of insight regarding the impact of behavior or guilt and shame resulting in denying behavior. In addition, the mean latency of onset of PG from onset of DA treatment is 23.0 months (range 1–84 months) [Gallagher *et al.* 2007], which warrants a sustained monitoring of ICDs by the physician. Changes in behavior such as an increasing tendency for insomnia, missing meals, doses of medication and absences from work can be potential red flags for the presence of ICDs (Table 2).

Potential risk factors such as male sex, young age and a history of drug abuse should be taken into consideration. Physicians may wish to counsel

these individuals carefully or avoid the use of DAs. In addition, premorbid gambling, drug use histories and impulsive sensation seeking personality traits may be relevant in identifying at-risk individuals [Gallagher *et al.* 2007].

The following nonpharmacological approaches may be helpful. PG consequences may be mitigated by limiting access to bank accounts, limiting access to travel to casinos, discontinuing credit card accounts and providing a budget for patients. Families and physicians should be aware that increased access to the internet and thus online gambling are particular challenges that facilitate ICDs in subjects with motor disability due to PD [Gallagher *et al.* 2007]. Blocking computer sites for gambling, shopping or pornography is frequently warranted and patients should avoid visits to casinos or places to purchase lottery tickets. Clinicians should discourage patients from taking nocturnal or 'rescue' doses of short-acting dopaminergic agents, although this is not systematically shown to be beneficial in reducing risk. Such practices may reduce the overall levodopa equivalent daily dose and thus reduce the

risk of ICDs. In those more prone to develop DDS/punding or with subsyndromal forms, medication refills should be limited to avoid self-regulation of dosage and hoarding of medications [Ferrara and Stacy, 2008]. Engaged family members are crucial to the success of all these measures. Individuals without strong social support are most vulnerable to unchecked ICDs potentially from multiple factors: despair at isolation, detached relationship patterns and depression, in addition to lack of support to withstand medication reduction and behavior modification.

Cognitive behavioral therapy is helpful in non-PD behavioral addictions and may have a role in PD [Petry and Roll, 2001]. Other authors have not found '12-step' programs helpful in ICDs without medication modification. Such programs may be more successful for those with a family history of alcohol, substance abuse or pathologic gambling as these individuals may have an increased susceptibility to behavioral addictions, even in the absence of dopaminergic stimulation. Identification of the ICD alone may result in resolution or ability to control it [Petry and Roll, 2001].

The mainstay of treatment is the reduction or discontinuation of DAs [Klos *et al.* 2005; Gallagher *et al.* 2007; Nirenberg and Waters, 2006]. Reduction in L-dopa dose may also be required [Gallagher *et al.* 2007; Quinn *et al.* 1983]. One case of spontaneous remission has been reported [Klos *et al.* 2005]. Little is known about the long-term prognosis of treated ICDs. Two studies with a total of 30 patients and a follow-up of 21–29 months showed that an increase in L-dopa after DA withdrawal sufficient to maintain motor symptom control was not associated with recurrence of ICDs, even with higher total daily L-dopa equivalents [Macphee *et al.* 2009; Mamikonyan *et al.* 2008]. Nevertheless, one patient developed DDS [Macphee *et al.* 2009; Mamikonyan *et al.* 2008]. Some case reports suggest that switching from a short-acting DA (ropinirole, pramipexole) to a long-acting DA (piribedil) or treatment with a DA with less D3 receptor agonist action can be effective [Gallagher *et al.* 2007]. Nevertheless, this strategy is rarely used. When changing dopaminergic medication, the following conversion rates can be used: 100 mg L-dopa is equivalent to 1 mg pergolide, pramipexole, lisuride or cabergoline, 6 mg of ropinirole, 10 mg of bromocriptine or apomorphine, 75 mg sustained-release L-dopa, 133 mg L-dopa with entacapone, and 150 mg L-dopa with tolcapone [Tomlinson *et al.* 2010].

DA dose reduction can be complicated by a highly stereotyped symptom complex, including irritability, anxiety, agoraphobia, dysphoria, depression, drug cravings, fatigue, pain, diaphoresis and orthostatic hypotension. The Dopamine Agonist Withdrawal Syndrome (DAWS) has been characterized in two studies in a total of 390 patients with PD and concurrent use of a DA. The reported prevalence ranges from 15.5% to 19% [Pondal *et al.* 2011; Rabinak and Nirenberg, 2010]. Risk factors for DAWS are the presence of baseline ICDs [Pondal *et al.* 2011; Rabinak and Nirenberg, 2010], a higher baseline DA use and cumulative exposure of a DA, and lower scores on the UPDRS motor score, regardless of disease duration and dopaminergic medication use [Rabinak and Nirenberg, 2010]. Higher L-dopa dose at withdrawal and baseline smoking have also been identified to be more common in DAWS [Pondal *et al.* 2011]. The prognosis is good with full recovery in weeks to months in 61% of patients, though 15% were unable to discontinue the DA [Pondal *et al.* 2011]. Consequently, a point of practice is that DA withdrawal should be slow (over several months to achieve complete discontinuation) to avoid the occurrence of DAWS and close vigilance by the physician. Here again, spouse or family members need to understand the need to discontinue the DA and to encourage the patient to persist to achieve resolution of ICDs.

It is important to recognize that reduction/discontinuation of a DA may not be successful in all patients with PD and ICDs because of persisting ICDs, poor tolerance due to DAWS or significant motor worsening. In a case series of patients with PD with PG and punding, there was a lack of improvement after reduction of dopaminergic medications [Kurlan, 2004] and symptoms persisted in about 80% of patients in a case series of punders, regardless of changes in dopaminergic medication [Avila *et al.* 2011]. For those cases, the pharmacological options are few and there is a lack of robust evidence to inform the clinician. In a recent Movement Disorder Society Evidence-Based Medicine Review, no randomized, controlled trials were found for ICDs in PD [Seppi *et al.* 2011]. Data are extremely limited and most studies are case reports or small case series. Prospective, double-blinded, controlled trials are needed [Galpern and Stacy, 2007]. For ICDs in PD, the need to consider placebo responses when analyzing uncontrolled trials of interventions is further emphasized. The placebo effect is highly significant both in non-PD populations with pathological

gambling or compulsive buying and in patients with PD [Lim *et al.* 2008].

Although the use of neuroleptics reportedly improves ICDs, the use of typical neuroleptics, risperidone or olanzapine will most likely worsen motor function in PD [Gschwandtner *et al.* 2001; Klos *et al.* 2005; Quinn *et al.* 1983]. Kurlan did not find improvement of ICDs with risperidone or olanzapine [Kurlan, 2004]. Quetiapine [Evans *et al.* 2004; Fasano *et al.* 2006; Jimenez-Jimenez *et al.* 2002; Sevincok *et al.* 2007], and clozapine [Fernandez and Durso, 1998; Kurlan, 2004] were used to treat punting, PG and HS without deleterious effects on motor function. Quetiapine is typically used first because clozapine requires long-term hematological monitoring. This advantage has to be weighed against the observation that motor worsening with quetiapine can happen in 32% of Parkinsonian patients and lead to discontinuation in 9% of those patients [Fernandez *et al.* 2003]. Anecdotally, quetiapine in doses of 100–200 mg triggered punting in two patients with PD and psychosis, which resolved with dose reduction [Miwa *et al.* 2004].

A crossover study of 17 patients with PD reported a benefit of amantadine 200 mg/day for the treatment of PG in patients with PD [Thomas *et al.* 2010] and open-label amantadine 100–300 mg/day was beneficial for punting [Fasano *et al.* 2011; Kashihara and Imamura, 2008]. The role of amantadine on ICDs remains controversial, as in the *post hoc* analysis of the largest epidemiological study conducted for ICDs, amantadine was associated with the presence of one or more ICDs, including PG, HS, CE and CS, independent of DA use and L-dopa dose [Weintraub *et al.* 2010b]. Nevertheless, the use of amantadine for the treatment of PG or punting lacks robust evidence, as concluded in a recent Movement Disorder Society evidence-based medicine review [Seppi *et al.* 2011].

The treatment of associated psychopathologies such as depression and mania, known risk factors for ICDs, can be useful for ICDs. The current recommendations for the treatment of depression or depressive symptoms in PD are selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants nortriptyline and desipramine [Seppi *et al.* 2011].

In addition, antidepressants, namely SSRIs, can help reduce ICDs independently of the presence of depressive symptoms [Klos *et al.* 2005; Mamikonyan *et al.* 2008; McElroy *et al.* 2011]. Clomipramine

[Evans *et al.* 2004; Jimenez-Jimenez *et al.* 2002], a tricyclic antidepressant, has been used for nocturnal punting. In a series of six patients with PD, treatment with a diverse range of antidepressants such as citalopram, fluvoxamine, paroxetine, sertraline, imipramine was not successful for PG or punting [Kurlan, 2004].

Valproate [Klos *et al.* 2005; Hicks *et al.* 2011] and topiramate [Bermejo, 2008] have also been reported to improve ICDs. Valproate can worsen Parkinsonism and cause cognitive deterioration. Both side effects are reversible upon drug discontinuation [Armon *et al.* 1996]. Zonisamide (25–200 mg/day) has been studied in 15 patients with PG, HS, CE or CS in a noncontrolled and open-label design. The study found a marked reduction in the severity of impulsive behaviors without deterioration of the UPDRS motor score and a good tolerance [Bermejo *et al.* 2010].

Naltrexone, an opioid antagonist, has been found to be efficacious in three patients with PG refractory to the discontinuation of DA [Bosco *et al.* 2012]. Donepezil has been used with success in a patient with HS and cognitive deterioration [Ivanco and Bohnen, 2005]. Selegiline discontinuation was necessary to treat punting in one patient [Fernandez and Friedman, 1999] and, in an open-label study, punting and PG were treated with success after the introduction of amantadine [Fasano *et al.* 2011]. The antiandrogen cyproterone has been used in two refractory cases of HS [Evans *et al.* 2004] and finasteride, a 5 α -reductase inhibitor used for benign prostatic hypertrophy, was reported to reduce PG in two patients with PD [Bortolato *et al.* 2012].

Ongoing prospective controlled studies are being conducted for naltrexone [ClinicalTrials.gov identifier: NCT01052831] and nicotine for [ClinicalTrials.gov identifier: NCT01216904] ICDs in PD.

Interventional studies conducted for ICDs in patients without PD open new perspectives in the treatment of refractory ICDs in PD. Memantine [ClinicalTrials.gov identifier: NCT00585169], tolcapone [ClinicalTrials.gov identifier: NCT00927563], ecocipam, a selective dopamine D1 antagonist [ClinicalTrials.gov identifier: NCT01215357] and the opioid antagonists naltrexone [ClinicalTrials.gov identifier: NCT01057862] and nalmefene [Grant *et al.* 2010] are being studied for PG in patients without PD. In addition,

nonpharmacological interventions such as cognitive-motivational behavior therapy [ClinicalTrials.gov identifier: NCT01135264], a combination of behavioral therapy and N-acetylcysteine specifically for smokers with PG [ClinicalTrials.gov identifier: NCT00967005], repeated low-frequency transcranial magnetic stimulation, ClinicalTrials.gov identifier: NCT01560351 and a community reinforcement approach and family training focused on significant others of people with PG are being investigated [ClinicalTrials.gov identifier: NCT 01340274]. Acamprosate, a synthetic analogue of γ -aminobutyric acid approved for the treatment of alcohol abuse has been tested in binge-eating disorder in patients without PD in a randomized, placebo-controlled study showing the partial benefit in the frequency of episodes and weight gain [McElroy *et al.* 2011].

Deep brain stimulation (DBS) has been proposed for ICD treatment. Current understanding is that DBS of the subthalamic nucleus (STN) improves ICDs by allowing a reduction in the levodopa equivalent daily dose or discontinuation of DAs [Ardouin *et al.* 2006]. In surgical case series, ICDs, DDS and punting worsened and persisted after DBS [Lim *et al.* 2009]. One case report documented the *de novo* appearance of PG following bilateral STN DBS without adjustment of medication, which recurred when switching on the neurostimulator [Smeding *et al.* 2007]. A recent chart review in a surgical center reported *de novo* occurrence of DDS after either STN DBS or globus pallidus pars interna (GPi) DBS [Moum *et al.* 2012]. One possible explanation is that improved motor function allowed full expression of the ICD following DBS. Nevertheless, some aspects of DBS in PD can be potentially used to the advantage of a patient with a prior or ongoing history of ICDs proposed for DBS. STN may be a more suitable target compared with GPi as it enables greater dopaminergic medication reduction [Rodriguez-Oroz *et al.* 2005; Volkmann *et al.* 2004]. In some cases, major depression can occur following reduction of dopaminergic medication after DBS, which may worsen pre-existing ICDs or cause the development of new ICDs. At this time, DBS should not be considered treatment for ICDs in PD *per se*. Conversely, ICDs are not a contraindication for DBS, although careful monitoring of patients is required. Psychiatric assessment prior to surgery and following implantation and programming may help avoid worsening or triggering of ICDs.

Conclusion and recommendations

ICDs and related behaviors such as punting and DDS reduce quality of life in a significant minority of patients with PD. Although prevention and reduction of dopaminergic therapy is the mainstay of management, these disorders may be unsatisfactorily treated after such interventions. A variety of other pharmacological treatments used in addiction research has been studied for ICDs in PD. Further well designed clinical trials are required to allow evidence-based treatment of ICDs. The present review emphasizes the need for further research with prospective, controlled studies that will help the physician better manage ICDs in PD and other movement disorders.

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