Impulse control disorders in patients with Parkinson’s disease receiving dopamine replacement therapy: evidence and implications for the addictions field

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ABSTRACT

Aims  To describe the prevalence, phenomenology and correlates of ‘impulse control disorders’ (ICDs) in patients with Parkinson’s disease (PD) treated with dopamine replacement therapy (DRT); to assess the strength of the evidence that DRT plays a contributory causal role in these disorders; and to highlight the implications of these disorders for research in the addiction field. Methods  PubMed and Web of Science databases were searched and the reference lists of papers examined. Results  The prevalence of ICDs in Parkinson’s patients using DRT varied between 3.5% and 13.6%, depending on the severity and range of disorders assessed. PD patients with ICDs were: generally younger; had an earlier onset of PD; had a personal or family history of substance abuse or an ICD; and were more likely to be treated with dopamine receptor agonists (DA agonists) than levodopa (L-dopa). There is reasonable evidence that dopaminergic medications play a causal role in ICDs in that they occur at a higher rate in an otherwise low-risk population of adults, begin after initiation of DA agonist therapy and cease upon its discontinuation. A causal relationship is biologically plausible, but the role of other factors (such as concurrent mood disorders) remain to be clarified by better-controlled studies. Conclusions  Impulse control disorders among patients with Parkinson’s disease receiving dopamine replacement therapy may provide a unique opportunity for addiction researchers to study the neurobiology of impulsive forms of behaviour (such as problem gambling) that appear to be caused, in part, by the therapeutic use of dopamine receptor agonists.

Keywords  Behavioural addictions, dopamine agonists, gambling, hypersexuality, impulse control disorders, Parkinson’s disease, substance abuse.

INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder associated with a loss of dopaminergic neurones in the substantia nigra and ventral tegmental area (VTA) [1]. A reduction of dopamine activity in the dorsal striatum and frontal cortices contributes to significant and progressive motor and non-motor dysfunction, including tremor, stiffness, loss of dexterity, gait and balance disturbance, mood changes, autonomic symptoms and cognitive problems. These symptoms are treated most often with drugs that compensate for this loss, referred to as dopamine replacement therapy (DRT). They include the dopamine precursor levodopa (L-dopa) and dopamine receptor agonists (DA agonists) such as bromocriptine, cabergoline, pergolide, pramipexole, ropinidine and rotigotine. DRT reduces the Parkinsonian motor and some non-motor impairments, but may be associated with a number of significant side effects such as involuntary movements (dyskinesias) and fluctuations in motor and non-motor symptoms (‘on’ and ‘off’ responses) as the disease progresses [2,3]. These side effects are particularly...
common with l-dopa, and DA agonists are often used in younger-onset PD patients in an attempt to slow their development [4,5].

In the last decade there have been increasing reports of an association between DRT and impulse control disorders (ICDs) [6,7]. ICDs are defined by ‘a failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or others’ [8]. They include: pathological gambling, compulsive eating, hypersexuality and compulsive shopping. Problem gambling (PG) is the most commonly reported ICD in the general population [9]. It is characterized by a preoccupation with gambling, gambling increasing amounts of money, unsuccessful attempts to control or stop gambling and the persistence of these behaviours despite negative impacts upon relationships, work or education [10]. There are no validated diagnostic criteria for hypersexuality, which is more difficult to assess than problem gambling [9]. Patients typically report increased preoccupation with sexual thoughts, making excessive demands for sex from their partners, increased use of pornography, seeking out prostitutes, engaging in exhibitionism and paraphilia [9]. Compulsive eating involves eating greater amounts of food than necessary to alleviate hunger, often producing harmful weight gain [11]. Compulsive eating may also include binge eating: the impulsive consumption of large quantities of carbohydrate or fat-rich foods in a short period of time. Compulsive buying or shopping can be defined as uncontrollable excessive buying of goods that can lead to psychological distress and substantial debt [12].

There is at present no effective treatment for DRT-induced ICDs other than reducing or changing dopaminergic medication, a pharmacotherapy that is necessary to relieve the debilitating symptoms of PD. A number of pharmacological agents have been tried, including atypical antipsychotics, selective serotonin uptake inhibitors (SSRIs) and naltrexone (an opioid antagonist used in the treatment of alcohol and opioid addiction and trialled in pathological gambling), but the findings have been inconsistent [13]. Given the similarity between DRT-induced behaviours and some behavioural-based addictions, and the role that dopamine may play in both [14,15], addiction researchers may make an important contribution to the diagnosis and treatment of ICDs in PD.

The aim of this review is to describe the phenomena of impulse control disorders and to highlight their potential relevance to the addiction field. This review aims to answer the following questions:  
1 Which ICDs have been described in PD patients?  
2 How common are they?  
3 What factors are correlated with their occurrence?  
4 Is there sufficient evidence to conclude that DRT is a contributory cause of ICDs?  
5 What are the possible implications of these disorders for theories of addiction and addiction research, and for the treatment of ICDs in PD?

**MATERIALS AND METHODS**

A literature search was conducted using the Web of Science and PubMed databases until March 2010. Articles were identified using the following search terms: (Parkinson*, dopamine agonist, l-dopa, DRT, dopamine replacement therap*, pramipexole, ropinirole, pergolide, amantadine, apomorphine, OR bromocriptine) AND (impulse control, gambling, hypersexuality, compulsive, over-eating, binge eating, obesity, intermittent explosive disorder, excessive spending, kleptomania, pyromania, OR trichotillomania). Reference lists were scanned for additional articles. Studies were included if they: (1) were in English; and (2) reported primary research on ICDs in PD patients receiving DRT.

**RESULTS**

**Literature search**

The articles retrieved comprised retrospective, cross-sectional and case–control studies. Case–control and cross-sectional studies (see Tables 1 and 2) are discussed in more detail because they provide the strongest evidence on the relationship between DRT use and ICDs, and the best estimates of the prevalence of these disorders and their clinical and other correlates. Data from larger case series were included only for ICD onset and resolution, characteristics not reported routinely in case–control or cross-sectional studies (see [16] for a review of case studies). Nineteen studies met the inclusion criteria, assessing a total of 7336 PD patients.

**Study characteristics**

Prevalence data on ICDs were predominately collected via retrospective reviews of medical records. ICD diagnoses were sometimes corroborated by telephone or face-to-face clinical interviews. Assessment tools used to identify ICD behaviour varied between studies and assessed various degrees of impulsivity, from small increases in impulsivity to pathological behaviour.

Pathological ICD diagnoses were made using standardized instruments such as the South Oaks Gambling Screen (SOGS, with score > 5) for PG or interviews assessing patients against criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [17]. Other practitioner-constructed screening tools, such as the Minnesota Impulse Disorders Interview (MIDI), were used to assess problematic ICD behaviours (e.g. problem gambling, shopping and...
<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Subjects</th>
<th>Exclusion criteria (n excluded)</th>
<th>Total number included</th>
<th>ICD measured and severity</th>
<th>Screening/criteria tool</th>
<th>Assessment method</th>
</tr>
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<tbody>
<tr>
<td><strong>[36]</strong> Italy (1 Parkinson’s Disease and Movement Disorders Unit of Neurological Division, Hospital of Capri, tertiary)</td>
<td>PD subjects: PD on DRT Controls A: Age- and sex-matched non-PD patients Controls B: Age- and sex-matched PD patients without an ICD</td>
<td>Clinical (DSM-IV-TR) diagnosis of dementia (excluded NA)</td>
<td>PD subjects: 98 Controls A: 392 (age- and sex-matched non-PD from files of 6 GP’s in same region) Controls B: 98 (age- and sex-matched PD patients without ICDs)</td>
<td>Pathological: gambling</td>
<td>DSM-IV-TR criteria for PG; SOGs (score ≥ 5 for PG)</td>
<td>Interview (patient accompanied by caregiver 90%)</td>
</tr>
<tr>
<td><strong>[18]</strong> Israel (1 tertiary care movement disorders clinic of a university-affiliated municipal hospital, tertiary)</td>
<td>PD subjects: PD Controls A: Age- and gender-matched healthy controls Controls B: PD patients without an ICD</td>
<td>Dementia; MMSE &lt; 25; OCD History of medicated psychiatric illness prior to PD onset Prior ICD (10 excluded)</td>
<td>PD subjects: 193 Controls A: 190 age- and gender-matched healthy controls Controls B: 166 PD patients without ICDs</td>
<td>Increases in behaviour: gambling, hypersexuality, shopping, eating</td>
<td>Increases in behaviour: gambling, hypersexuality, shopping, eating</td>
<td>General neurological interview and MMSE regarding competency: own criteria for new onset impulsive behaviours “increased drive” or “heightened interest”</td>
</tr>
<tr>
<td><strong>[37]</strong> Canada (1 out-patient tertiary clinic, tertiary)</td>
<td>PD subjects: Idiopathic PD Controls A: PD patients without an ICD Controls B: PD patients without PG from previous study</td>
<td>Dementia; PD subjects: DSM-IV defined dementia Controls: excluded if PG, HS, CS or ODS</td>
<td>PD subjects: 21 Controls A: 42 Controls B: 286</td>
<td>Pathological: gambling, hypersexuality, shopping</td>
<td>Alcohol Use Disorders Identification Test; Drug Abuse Screening; BDI, Beck Anxiety Inventory, MMSE</td>
<td>Patient-rated scales for ICDs; PG: DSM-IV criteria; CS: McKay’s criteria; HS: clinician-designed criteria; Follow-up clinical interview if positive for ICD</td>
</tr>
<tr>
<td><strong>[33]</strong> Canada (1 university-affiliated movement disorder clinic)</td>
<td>PD subjects: clinically diagnosed PD patients Controls A: healthy controls from Canadian population (&gt; 45 years old) Controls B: PD patients without an ICD</td>
<td>Dementia</td>
<td>PD subjects: 140 Controls A: 27,848 Controls B: 108</td>
<td>Pathological and problem: gambling</td>
<td>Surveys and medical chart review</td>
<td>Surveys and medical chart review</td>
</tr>
<tr>
<td><strong>[38]</strong> USA (1 Division of Movement Neurology clinic, tertiary)</td>
<td>PD subjects: PD Controls: Age- and sex-matched PD patients without PG</td>
<td>History of PG; secondary PD; no responsiveness to l-dopa</td>
<td>PD subjects: 11 Controls: 37</td>
<td>Pathological: gambling</td>
<td>International Classification of Diseases</td>
<td>Retrospective medical database review</td>
</tr>
<tr>
<td><strong>[19]</strong> Italy (NA)</td>
<td>PD subjects: Idiopathic PD Controls: Healthy, age- and gender-matched; randomly selected relatives of hospital employees Controls B: PD patients without an ICD</td>
<td>PD subjects: dementia; antipsychotic or depressant medication; &gt;6 months on DRT; treated with more than one DA agonist Controls: no substance abuse or neurological/psychiatric history</td>
<td>PD subjects: 50 Controls A: 100 Controls B: 36</td>
<td>Pathological: gambling</td>
<td>MIDI; SOGS; Barratt Impulsiveness Scale; Maudslay Obsessional-Compulsive Inventory; Geriatric Depression Scale</td>
<td>Clinical assessment (not clearly specified)</td>
</tr>
<tr>
<td><strong>[39]</strong> Italy (1 university movement disorders unit)</td>
<td>PD subjects: Idiopathic PD; DSM-IV pathological gambling, ‘on’ state Controls: age-, gender- and educational level-matched PD patients without an ICD</td>
<td>No dementia or intellectual decline</td>
<td>PD subjects: 15 Controls: 15</td>
<td>Pathological: gambling</td>
<td>Italian version of SOGS (score ≥ 3 for problem gambling; ≥ 5 for PG); MMSE</td>
<td>Interview with patients and separately with caregivers for PG diagnosis</td>
</tr>
<tr>
<td><strong>[23]</strong> China (1 hospital)</td>
<td>PD subjects: PD on DRT Controls: A: spouses of PD patients Controls B: PD patients without an ICD</td>
<td>Atypical/secondary PD; cognitive abnormality (8/8 did not return questionnaire)</td>
<td>PD subjects: 312 Controls A: 132 Controls B: 301</td>
<td>Pathological: gambling, hypersexuality, shopping Problem: hypersexuality</td>
<td>CS: Lejoyeux’s compulsive shopping Questionnaire; HS: hypersexuality questionnaire; DSM-IV criteria for binge eating, drug addiction, and internet addiction</td>
<td>Self-report screening questionnaires; phone follow-up clinical interview if positive for ICD</td>
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</table>

**Table 1** Case–control study characteristics.

ID1: Beck Depression Inventory; CE: compulsive eating; CPGI: Canadian Problem Gambling Index; CS: compulsive shopping; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; HS: hypersexuality; MAGS: Massachusetts Gambling Screen; MMSE: Mini State Mental Examination; NPI: Neuropsychiatric Inventory; PG: pathological gambling; SCID: Schedule for Clinical Interview and Diagnosis; SOGS: South Oaks Gambling Screen; NA: not applicable; DA: dopamine receptor agonists; l-dopa: levodopa.
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Subjects</th>
<th>Exclusion criteria (n excluded)</th>
<th>Total number included</th>
<th>ICD measured and severity</th>
<th>Screening / criteria tool</th>
<th>Assessment method</th>
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<tbody>
<tr>
<td>[24]</td>
<td>USA (un-numbered out-patient clinics, research programmes and community outreach centres)</td>
<td>PD subjects: idiopathic PD Controls: PD patients without an ICD</td>
<td>&gt;65 years; dementia; current substance abuse or psychotic disorder; neurosurgical treatment for PD (excluded NA)</td>
<td>PD subjects: 100 Controls: 91</td>
<td>Pathological: gambling, hypersexuality, shopping</td>
<td>DSM-IV-TR; SCID + supplemental questions for ICDs</td>
<td>Clinical psychiatric interview</td>
</tr>
<tr>
<td>[17]</td>
<td>Canada (1 movement disorders clinic)</td>
<td>PD subjects: idiopathic PD Controls: PD patients without PG</td>
<td>Atypical PD; dementia (DSM-IV diagnosis); &lt;1 year motor symptom onset; inability to complete survey (99 excluded; 75% completed survey)</td>
<td>PD subjects: 297 Controls: 286</td>
<td>Pathological: gambling</td>
<td>Modified SOGS; SCID of DSM Axis I psychiatric diagnosis</td>
<td>Patient-rated survey with spousal help; telephone follow-up interview for PG diagnosis and referral for psychiatric assessment</td>
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<tr>
<td>[22]</td>
<td>Canada (1 movement disorders clinic)</td>
<td>PD subjects: idiopathic PD Controls: PD patients without an ICD</td>
<td>Atypical PD; dementia &lt;1 year motor symptom onset; inability to complete survey (99 excluded; 75% completed survey)</td>
<td>PD subjects: 297 Controls: 277</td>
<td>Pathological: gambling (from [17]), hypersexuality, shopping</td>
<td>PG: Modified SOGS, CS: Lejoyeux’s CS questionnaire and HS: specifically designed questionnaire criteria: MC—McElroy’s criteria HS—diagnostic criteria based on DSM-IV, clinical experience and DSM diagnostic formats; SCID of Axis I disorders for psychiatric diagnosis</td>
<td>Patient-rated surveys (SOGS) with spousal help; telephone follow-up interview and assessment referral for ICD diagnosis psychiatric assessment</td>
</tr>
<tr>
<td>[26]</td>
<td>USA (2 university-affiliated movement disorders centres)</td>
<td>PD subjects: idiopathic PD out-patients (mild to moderate severity) Controls: PD patients without an ICD</td>
<td>Inability to consent due to cognitive impairment</td>
<td>PD subjects: 272 Controls: n varied depending on variable being assessed</td>
<td>Problem: gambling, hypersexuality, shopping</td>
<td>MIDI: 15-item Geriatric Depression Scale; MMSE</td>
<td>Unstructured screening interview for ICDs; telephone follow-up with structured interview (MIDI) if screened positive; retrospective review of medical records for ICDs</td>
</tr>
<tr>
<td>Study</td>
<td>PD subjects</td>
<td>Controls</td>
<td>Pathological: gambling</td>
<td>Unstandardized questioning: DSM-IV-TR gambling questionnaire</td>
<td>Verbal survey of current patients (office/telephone); retrospective medical record reviews with follow-up phone survey of past patients</td>
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<td>USA (1 university-based movement disorders unit)</td>
<td>PD on DA agonists prior to the survey: patients with RIS, progressive supranuclear palsy, MSA, diffuse Lewy body disease, essential tremor, vascular PD (20 excluded)</td>
<td>PD subjects: 100 Controls: 242</td>
<td>Increases in behaviour: gambling, hypersexuality, shopping</td>
<td></td>
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</tr>
<tr>
<td>USA (1 referral clinic) (tertiary)</td>
<td>PD not currently taking DA agonist (98 RLS: exclusion from our data extraction)</td>
<td>PD subjects: 211 (207 PD + 4 PD and RLS Controls: 156)</td>
<td>Pathological: gambling Increase in behaviour: gambling, hypersexuality, shopping</td>
<td></td>
<td></td>
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<tr>
<td>USA (1 clinic with patients from 7 rural areas)</td>
<td>PD subjects: probable idiopathic PD Controls: PD patients without an ICD</td>
<td>PD subjects: 267 Controls: 260</td>
<td>Pathological: gambling, hypersexuality Problem: hypersexuality</td>
<td></td>
<td>Clinical interview (patient and family input)</td>
<td></td>
<td></td>
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<tr>
<td>Korea (multi-centre, 6 referral hospitals)</td>
<td>PD subjects: idiopathic PD Controls: PD patients without an ICD</td>
<td>PD subjects: 1167 Controls: 1049</td>
<td>Problem: gambling, hypersexuality, eating</td>
<td></td>
<td>Retrospective review of medical records</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korea (Seoul National University Hospital)</td>
<td>PD subjects: PD patients Controls: healthy spouses of PD patients</td>
<td>PD subjects: 404 Controls: 559</td>
<td>Problem: gambling, hypersexuality, eating</td>
<td>Modified MIDI</td>
<td>Cross-sectional survey; patient-physician interview</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA and Canada (46 movement disorder clinics: n = 3 USA; n = 13 Canada)</td>
<td>PD subjects: treated idiopathic PD Controls: PD patients without an ICD</td>
<td>PD subjects: 3090 Controls: 300</td>
<td>Pathological: gambling, eating Problem: gambling, hypersexuality, shopping</td>
<td>Gambling: MAGS (problem: score of 3–4); PG: score of 5); HS/CS: MIDI; CE: DSM-IV</td>
<td>Semi-structured interview for ICD diagnosis via formal diagnostic criteria, and corroborative information from ‘others’; demographic and clinical data via semi-structured interview with patients with chart review verification</td>
<td></td>
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</tbody>
</table>

BDI: Beck Depression Inventory; CE: compulsive eating; CS: compulsive shopping; DA: dopamine receptor agonists; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; HS: hypersexuality; MAGS: Massachusetts Gambling Screen; MMSE: Mini State Mental Examination; NPI: Neuropsychiatric Inventory; PG: pathological gambling; SCID: Schedule for Clinical Interview and Diagnosis; SOGS: South Oaks Gambling Screen; NA: not applicable.
eating). A special-purpose questionnaire to assess hypersexuality was used in a number of studies. Less stringent criteria were used in several studies to identify ‘increased’ or ‘heightened drive’ to engage in some behaviours [18–21]. These studies were included to provide information on the spectrum of ICD behaviours.

All studies used some type of control group: 14 of 19 used PD patients without an ICD; five of 19 used healthy individuals and PD patients without ICDs.

Gambling behaviour was assessed in 18 studies, hypersexuality in 13, compulsive shopping in 11 and compulsive eating in five. Three studies assessed intermittent explosive disorder.

Prevalence

Prevalence rates for combined ICDs varied (see Table 3) from 3.5% to 9.0% (median 6.1%) for more severe or pathological ICDs [22–24]. The lowest prevalence rate (1.9%) was reported in one study [25] utilizing retrospective medical record review and excluding any PD subjects with symptoms of PG prior to developing PD. Prevalence rates increased to 13.6% when studies assessed problem ICD behaviour [26–28], and to 14–28% (median 22.0%) when more subtle changes in impulsivity were measured [18–21]. Prevalence rates were also higher in patients receiving a DA agonist (10.6–17.1%) [22,25,28]. Of PD patients, 17.1% prescribed a DA agonist displayed ICD behaviour in a survey that assessed pathological and problematic symptoms of multiple ICDs in 3090 PD patients [28]. Estimates based only on medical records almost certainly underestimate the prevalence of these disorders: one study found that clinical charts recorded an ICD in only 27.3% of patients with an active ICD diagnosis by interview [26].

Pathological and problem gambling

DSM-IV-defined pathological gambling rates in PD patients ranged from 1.7% to 6.1% (median 5%) and 8% for patients on a DA agonist [29]. Smaller prevalence figures were reported for PG (0.32%) and problem gambling (up to 1.7%) in PD patients in China and Korea: countries that severely restrict opportunities to gamble and where cultural factors may reduce participants’ preparedness to report these disorders [23,27,30]. The prevalence of problem gambling ranged between 2.2 and 13.3% (median 4.3%) in developed countries with greater access to gambling when these studies were excluded [18,20,21,26,28,31].

Hypersexuality

The prevalence of problematic or pathological hypersexuality ranged from 2% to 11% (median 3.5%) [18,20–23,26–28,30]. The variations in these estimates may reflect a lack of standardized criteria for defining and measuring hypersexuality.

Compulsive shopping

Current prevalence rates varied between 0.4% and 5.7% (median 2.5%) [22,26–28,30] overall and 7.2% for patients on a DA agonist [28]. Rates of less severe compulsive shopping ranged from 3.1% [18] to 9% [20]. Fan et al. [23] found no cases of compulsive shopping in a Chinese sample.

Compulsive eating

Binge eating was reported in 4.3% of PD patients in one study [28] and only 0.32% in a Chinese PD population [23]. An increased drive to eat was found in 3.6% of PD patients in an Israeli study [18]. Compulsive eating was found in 3.4% [27] to 5.9% [30] of Korean PD patients.

Comparison with the general population prevalence rates

With the exception of PG, there are no large epidemiological studies of the life-time prevalence of most ICDs in the general population with which to compare PD

<table>
<thead>
<tr>
<th>ICD</th>
<th>Lower estimate (%)</th>
<th>Upper estimate (%)</th>
<th>Median (%)</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological gambling</td>
<td>1.7</td>
<td>6.1</td>
<td>5.0</td>
<td>[17,20,21,29,31,36]</td>
</tr>
<tr>
<td>Problem gambling</td>
<td>2.2</td>
<td>13.3</td>
<td>4.3</td>
<td>[18,20,21,26,28,31]</td>
</tr>
<tr>
<td>Hypersexuality*</td>
<td>2.0</td>
<td>11</td>
<td>3.5</td>
<td>[18,20–23,26–28,30]</td>
</tr>
<tr>
<td>Compulsive shopping*</td>
<td>0.4</td>
<td>9.0</td>
<td>3.1</td>
<td>[18,20,22,26–28,30]</td>
</tr>
<tr>
<td>Compulsive eating*</td>
<td>0.3</td>
<td>5.9</td>
<td>3.6</td>
<td>[18,23,27,28,30]</td>
</tr>
<tr>
<td>Pathological ICDs: 1 or more</td>
<td>3.5</td>
<td>9.0</td>
<td>6.1</td>
<td>[17,23,24]</td>
</tr>
<tr>
<td>Problem ICDs: 1 or more</td>
<td>4.0</td>
<td>13.6</td>
<td>7.6</td>
<td>[26–28]</td>
</tr>
<tr>
<td>Increased impulsivity: 1 or more</td>
<td>14.0</td>
<td>28.0</td>
<td>22.0</td>
<td>[18–21]</td>
</tr>
</tbody>
</table>

*Includes behaviours along the whole ICD spectrum (increases in behaviours to pathological ICDs).
prevalence rates. For PG, the estimated life-time prevalence in the general population was less than 0.5% in a large epidemiological study [32]. Other studies report life-time and 12-month prevalence of PG in the general population of less than 1.0% in the United Kingdom [33], Denmark [34], Sweden and New Zealand [35]. The median estimate for PD patients is at least six times greater than the prevalence in the general population. This finding is supported by case–control studies where ICDs were more common in PD patients treated with DRT than controls [18,19,23,31,36].

**Correlates of ICDs**

*Patient characteristics*

Males were more likely to report ICDs in most (e.g. [19,21–23]), but not all, studies [17,20,24,25,29,31,36–38]. Weintraub et al.’s [28] study of 3090 PD patients reported an increased risk of HS and PG in males, but greater risks for compulsive shopping and eating in females.

PD patients with ICDs were generally younger than those without ICDs [20,21,25–29,31]. Weintraub and colleagues [28] found a higher prevalence in younger PD patients, even when taking into account the higher use of DA agonists in these patients. Early PD onset was correlated with a higher rate of ICDs [17,20,22,27,30,37], and the association persisted after adjustment for confounders in the largest study [18]. A longer duration of PD has been associated with ICDs in some [26,27,30], but not all, studies [18,21,23,24,29,31,38,39]. No significant association has been found between severity of PD and ICD [19,24,27,28,30,31,37,39]. The personality traits of novelty seeking and disinhibition have been associated with increased rate of ICDs in PD patients on DRT [19,24,37].

*Substance use*

A family or personal history of alcohol or substance abuse has been reported in 30% (137 of 451) of PD patients with ICDs [22,28,37]. In the large multi-centre study [28], PD patients with ICDs were more likely to be current smokers or have a family history of alcohol abuse.

In the four studies in which comorbid substance addictions and drug abuse (predominantly tobacco and alcohol) were assessed, 51% (235 of 459) of patients with ICDs reported these disorders [23,25,28,37]. Fan et al. [23] reported a higher frequency of alcoholic users among patients with ICDs. Bostwick et al. [25] also found a higher frequency of ICDs in PD smokers [odds ratio (OR) 1.70; 95% confidence interval (CI) 1.07, 2.70].

**Psychiatric disorders**

Anxiety and depression were found in patients with an ICD [17,19,24,37], although anxiety and depression are more common in PD than in the general population. These conditions and the drugs utilized to treat them can also be associated with behavioural changes. The relationship between ICD and comorbid psychiatric conditions remains to be clarified.

**Prior history of impulsive behaviour**

A history of impulsive behaviour has been reported in approximately one-third (19 of 64) of patients with an ICD [23,25,26,31,39]. This was most often occasional or frequent gambling. Weintraub et al. [26] found that a prior history of ICD symptoms was the strongest predictor of an ICD in a multivariate analysis (OR 10.73; 95% CI 1.54, undefined). In their large sample [28], they also reported a greater rate of compulsive gambling, shopping and eating in patients who had current and familial history of gambling problems (OR 2.08; 95% CI 1.33, 3.25) (see Table 4).

**Relationship with PD medication**

*Medication type*

DA agonists were associated with an increased rate of an ICD in the majority of studies. In 18 studies, 85% (697 of 818) of ICD cases occurred in patients taking DA agonists. Weintraub et al. [26] found that DA agonist use was the strongest predictor of an ICD after adjustment for all other confounders, including personal and family history of ICDs (OR 10.47; 95% CI 0.04, undefined). Most studies found no difference in the rate of ICDs between the different types of DA agonists [17,19–21,23,26,29–31,36], including the largest study [28].

Studies differed on the possible role of l-dopa. Only five of 120 cases of patients with an ICD (4%) were taking l-dopa alone. Weintraub et al. [28] reported that 7.2% of patients with ICDs in their study were taking l-dopa.
without concurrent DA agonist treatment. The majority of studies, however, did not find a significant association between ICDs and l-dopa use either as an adjunctive or monotherapy [20,21,24,38]. Weintraub and colleagues found a weak association with l-dopa use (OR 1.43; 95% CI 1.03, 2.00) and a marginally higher risk (OR 1.42; 95% CI 1.02, 1.98) of developing ICDs in patients treated with a combination of DA agonist and l-dopa than DA agonist alone.

**Dosage**

The relationship between DRT medication dose and the risk of ICD is also unclear. Higher doses of DA agonists were associated with an increase ICD risk in some studies [20] (OR 1.23; 95% CI 1.05, 1.45) [26,30], but this was not found in the largest study [28]. Paradoxically, Weintraub and colleagues [28] found that the risk of ICD increased with l-dopa dose but not DA agonist dose. Further research is required to clarify this issue.

**Time to onset and resolution of ICDs**

Fewer than half the studies provided information on the resolution of ICDs. Eight case series that used standardized assessments and three follow-up studies provided further information.

**Onset** ICDs have typically been reported after initiation or increase of DRT use [17,22,29,36–39] and most often after initiation of a DA agonist [21,23,25,40–44]. There is limited and conflicting evidence on the length of DRT use prior to onset. Large prospective studies are needed to describe the relationship between duration of DRT use and ICD onset.

**Resolution** Fifteen studies reported significant improvement or total resolution of ICDs with changes to DRT. There was complete resolution upon discontinuation, dose reduction or switching to a different DA agonist in 79% (75 of 95) of patients. The remainder improved [20].

**Follow-up** There was no recurrence of PG in 15 patients 21 months [45] or 30 months [46] after withdrawal of a DA agonist [21].

**DISCUSSION**

ICDs have been reported in a substantial minority of patients with PD who receive DRT. Problem gambling has been the most commonly reported, followed by impulsive sexual behaviour, over-eating and compulsive shopping. This may reflect the frequency with which these disorders have been assessed, as the largest study to date found a similar prevalence of each type of disorder [28].

The prevalence of these ICDs ranged between 4.0% and 13.6%, reflecting, in part, variations in methods of assessment. The rates of PG are higher in PD than in the general population, but there are too few well-controlled comparisons to be confident about the other ICDs. The prevalence rates represent a small but significant proportion of those taking dopaminergic medications. These rates are within the range of dependence risks in individuals consuming alcohol and other drugs [47].

The correlates of developing an ICD while on DRT appear to be similar to those for PG and drug dependence. Some correlates of PG in the general population [48] have also been identified in PD patients: younger age, high impulsivity and personal or family history of ICD or substance abuse. Earlier onset of PD was also correlated significantly. Comorbid substance abuse was not assessed in most studies [16], but the incidence of ICDs was significantly higher in individuals with a personal or family history of drug dependence or addictive behaviour.

ICDs were much more likely to occur in patients treated with the DA agonists, with 85% of cases reported in patients receiving these drugs. ICDs most often started after DA agonist initiation or dose increase. There were high rates of ICD resolution after cessation of or changes to DA agonist medications in the small series of patients that have been followed-up. The role of l-dopa on its own or as an adjunctive treatment is less clear.

**Is the relationship between DRT and ICDs causal?**

In assessing the plausibility of a causal relationship between DRT and ICDs we looked for evidence that:

1. there was an association between DRT use and ICDs;
2. the association was not due to chance;
3. DRT use precedes the outcome; and
4. alternative non-causal explanations of the association are implausible [49].

This assessment found that there is reasonable, although not yet conclusive, evidence for a causal relationship between DA agonists and some ICDs (e.g. gambling).

First, the incidence of ICDs is higher in the DA agonist–treated PD population than in the general population. The evidence is clearest for PG: rates are much higher in the PD population than the general population. Case–control studies show that PD patients treated with DA agonists are much more likely to have an ICD than healthy controls [18,19,23,31,36].

Secondly, the onset of ICDs in PD patients is related temporally to the use of DA agonists: onset often occurs after the initiation of DA agonist medication or after a significant increase in dose; and disorders often resolve or improve significantly after discontinuation of DA agonist treatment, dose reduction or changing to a different DA agonist.
Thirdly, a causal relationship is biologically plausible in that the development of ICDs in patients treated with long-term DRT is consistent with the neurobiology of stimulant drug addiction and the effects of chronic DA agonist exposure on the brain’s reward system [50,51].

The fact that ICDs do not occur in all individuals with PD who are treated with DRT indicates that DRT is likely to be only a contributory cause of ICDs: a factor that acts in combination with others such as younger age, and a personal or family history of ICD or substance abuse. The fact that the relationship between DA agonists and ICDs remains after controlling for these correlates suggests that people with these characteristics are more likely to develop these disorders when given DA agonists.

Testing alternative explanations of the association

The high prevalence of ICDs in PD patients treated with DRT is unlikely to be attributable to their PD for two reasons. First, PD patients usually have lower levels of the impulsive and sensation-seeking traits associated with compulsive behaviour [14,52]. They are also less likely to use alcohol, caffeine and tobacco than the general population [53]. Secondly, similar ICDs have also been reported in patients with unrelated conditions who were also treated with DRT (e.g. restless legs syndrome (RLS) [54–56], fibromyalgia [57,58] and prolactinoma [59]).

Implications for the addictions field

The evidence for a causal relationship between DRT and ICDs is reasonable, but needs to be strengthened by collaborative studies between addiction researchers and neurologists. Studies to date have been cross-sectional and retrospective, rather than prospective, and have included primarily patients in tertiary hospitals who may not represent PD populations. Prevalence estimates have varied because studies have not generally used standardized methods for diagnosing ICDs. With the exception of Weintraub et al.’s study [28], sample sizes have been small, limiting statistical power for analyses of the effects of possible confounders. There is a need for prospective studies of PD patients initiating DA agonist treatment that use validated assessment and screening tools to assess ICDs. These studies also need to assess substance-based addictions and addictive patterns of DRT use, or dopamine dysregulation syndrome (DDS).

These studies will characterize more clearly the factors associated with the development of these disorders, such as family history of addictive disorders, coexisting depressive and hypomanic disorders and the use of other medications, such as SSRIs, that are often used in patients with PD [60,61]. Better information is needed on the relationships between ICDs and specific types of DRT (dopamine agonists and L-dopa), including the duration of their use, patterns of concurrent use and doses.

We also need better prospective studies of the onset and resolution of these disorders after the discontinuation of DA agonists. Prospective studies should also examine the incidence of substance abuse in an otherwise low-risk population [53]. The results of such research would have important implications for the treatment and management of PD patients.

Given the current paucity of treatments for ICDs in PD, we urgently need studies of interventions to treat these disorders that will permit PD patients to continue on DRT. There are currently no adequate treatments for ICDs and limited empirical data [62]. The addiction field may be able to provide neurologists with more effective psychological and pharmacological treatments of ICDs. A collaborative approach between addiction researchers and neurologists will greatly improve the chances of success in such research.

Studies of these disorders may also improve our understanding of the neurobiology of addictive behaviours. There has been considerable debate about the status of compulsive forms of behaviour, such as gambling, that share some of the features of substance-based addictions. The observation that DRT can induce ICDs that resemble ‘behavioural addictions’ adds some weight to the claim that these behaviours share similar underlying neurobiological mechanisms. This may also lead to more effective therapeutic interventions for both types of disorder.

ICDs in PD patients may also provide a model for better understanding of the neurobiology of addiction. Neuroimaging studies of addicted individuals are often complicated by polysubstance abuse and examine brain changes that occur after years of chronic drug use. It is impossible to determine from such studies whether behavioural or neurobiological changes are a cause or consequence of chronic drug use. The study of ICDs in PD patients may present a novel model to study an addictive behaviour that is less burdened by these limitations and where disorders develop and resolve over a shorter period of time.

The therapeutic use of dopaminergic medications is likely to grow as more disorders are treated by these drugs [54–59]. As the use of dopaminergic drugs increases, so too will the demand for effective treatments and clinical management of ICDs. Early development of tools to reduce the risk and severity of developing these disorders will greatly reduce the personal and economic burden.

Declarations of interest

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