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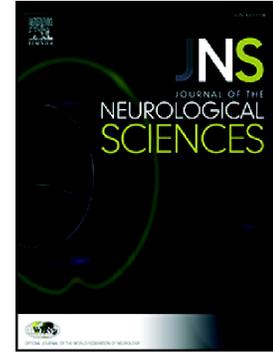
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Title Page

Title: Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical Parkinsonian disorders and non-Parkinsonian populations.

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Abstract

Impulsive-compulsive behaviours are common, quality of life affecting consequences of dopamine replacement therapy which are well recognised in patients with idiopathic Parkinson's disease. Details of the occurrence and nature of these disorders in the atypical parkinsonian neurodegenerative disorders, and in non-Parkinson's patients prescribed dopaminergic stimulation for other disease processes, are slowly emerging. Here we review what is known about the phenomenology, epidemiology and risk factors for impulsive-compulsive behaviours in Parkinson's disease and in other, less well studied, patient groups. By analyzing the available published data, this review identifies potential clues as to the underlying neurobiological mechanism of these disorders, and further identifies critical gaps yet to be addressed.

Key Words

Parkinson's disease, impulsive control disorders, impulsive-compulsive behaviours, atypical Parkinson's, dopaminergic medication

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Conflicts of interest

We have no conflicts of interest to disclose.

1. Introduction

Impulsivity and compulsivity have been defined in various ways in the literature relating to both Parkinson's disease (PD) and to the general population. Impulsivity refers to a behaviour that is performed with little or inadequate forethought and is characterized by a failure to 'resist an impulse'. Compulsivity is characterized as persistent non-goal orientated behavior, often leading to untoward outcomes(1). The major distinction that determines when these traits become disorders is their interference with daily life causing substantial distress or dysfunction(2).

The term impulse control disorder (ICD) generally refers to one of four major disorders; gambling disorder, compulsive shopping, compulsive sexual behavior and compulsive eating, whereas a number of closely related phenomena including punding, hobbyism, hoarding and the dopamine dysregulation syndrome (DDS) are generally classified under the broader heading of impulsive-compulsive behaviours (ICB)(3). It is worth noting that only three of the disorders are included in the DSM-V(4); specifically hoarding is classified under 'Obsessive-Compulsive and Related Disorder', binge eating disorder is classified under 'Feeding and Eating Disorders' and gambling, which has been moved from 'Impulse Control Disorders' to the new category of 'Substance-Related and Addictive Disorders' in the revised DSM V.

The degree of overlap between different ICBs in terms of genetic, biologic and neuroanatomical pathways is incompletely understood. To varying extents, most ICBs have the following features in common: i) repetitive or compulsive engagement in a behavior despite adverse outcomes, ii) diminished control over the problematic behavior iii) an appetitive urge or craving state prior to engagement in the behavior and iv) a hedonic quality during the performance of the behavior(2). However, behaviours such as DDS and punding in addition to other chronic ICBs may lose any initial pleasurable/hedonic qualities as the behaviour becomes more compulsive and automatic.

2. Phenomenology of ICBs seen in Parkinson's disease

2.1 Gambling disorder

Pathological gambling is defined as inappropriate, persistent and maladaptive gambling behavior(4). Pathological gambling was one of the earliest recognized ICBs in PD patients. Prevalence rates amongst cohorts with PD have been reported between 3.4% and 8%(5-7) though prevalence rates vary depending on culture and availability of the practice in the population studied. Prevalence rates were higher among those on dopamine agonist (DA) medication than those not (Voon et al., 2006b; Weintraub et al., 2010). Preferred gambling activities in PD include slot machines, lottery/scratch cards and internet gambling, activities which are repetitive, require little higher cortical processing and have high reward uncertainty(8). PD patients may develop ritualistic behaviours in order to improve winning chances prior to gambling, such a 'lucky charms' or wearing specific 'lucky clothes'(9).

2.2 Compulsive sexual behavior

Voon et al. proposed criteria for the diagnosis of compulsive sexual behavior, in 2006(10). They suggested sexual thoughts or behaviours which are excessive, or a change from baseline, persist for at least one month, and are associated with marked distress and interference with social or occupational functioning. Due to lack of insight or embarrassment, this ICB may be particularly underreported and therefore under diagnosed in PD clinics. The prevalence rate has been estimated at 3.5% of the PD patients, 1.7% for those not taking DA medication and 4.4% for those taking DA(7). Related behaviours such as zoophilia and paraphilia have also been described in PD patients(11, 12).

2.3 Hoarding

Hoarding is the acquisition of, and failure to discard, a large number of items with little or no objective value(4) and can lead to unsafe or unsanitary living conditions. The prevalence of hoarding among PD patients has been estimated at 12.2%, though this study was based in a specialized PD clinic therefore may be an overestimate of true prevalence(13). Hoarding was seen in association with other ICDs, but the association of hoarding with DA use was not evaluated.

2.4 Binge eating

Binge eating is defined as recurrent episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances with episodes marked by feelings of lack of control, and occur at least once in a week over three months(4). Binge eating has been reported in 4.3% of PD patients in the United States, 1.7% of patients not taking DA and 5.6% of those taking DA. (7).

2.5 Compulsive shopping

The diagnostic criteria for compulsive shopping define a maladaptive preoccupation with buying or shopping, manifested as impulses or behaviours that are experienced as irresistible, intrusive or senseless and result in buying more than can be afforded or items that are not needed, and that the shopping causes marked distress, is time-consuming, significantly interferes with social and occupational functioning or causes financial problems(14). Compulsive shopping has a reported prevalence of 3.4% of the PD population, 2.9% of those not taking DA medication and 7.2% of those taking DA(7).

2.6 Punding

Punding was first described in abusers of amphetamines and is thought to be due to dopaminergic excess(15). Punding is defined as complex stereotyped behavior characterized by an intense fascination with repetitive manipulations of technical equipment, the continual handling, examining and sorting of common objects, pointless driving and walkabouts and the extended engagement in monologues devoid of content(16, 17). In contrast to other ICBs, punding is not driven by pleasure, though patients can get irritable when the behavior is limited. PD patients with punding have been shown to have more obsessive-compulsive traits than controls(16). Because the trait is idiosyncratic and correlates with premorbid hobbies, it is necessary to determine if the behavior interferes with a patient's sleeping or ability to perform daily tasks to make a diagnosis(18). Prevalence rates vary from 1.4% in a Canadian cohort [n=4 of this cohort, all of whom were taking levodopa and DAs(19)] to 14% in a United Kingdom cohort on high (>800mg/day) levodopa equivalent doses(16).

2.7 Dopamine dysregulation syndrome

Diagnostic criteria for DDS, initially termed 'hedonic homeostatic dysregulation', define the need for increasing doses of dopamine replacement therapy in excess of those normally required to relieve parkinsonism with a pattern of pathological use, for example drug hoarding, together with impairment in social or occupational functioning which has persisted for at least six months(20). DDS is more common with L-dopa use than with DAs, in contrast to other ICBs, and punding is frequently a comorbidity in this cohort(21). Estimated of prevalence rates are up to 2.3%(Kim et al., 2013).

2.8 Miscellaneous impulsive behaviours

Reckless generosity(22), compulsive smoking(23), drug addiction(24) and reckless driving(25) have all been reported in PD patients. Recently, a case of recurrent pet killing was reported in a patient with juvenile PD, which resolved on stopping his pramipexole(26).

3. Phenomenology of ICBs seen in non-Parkinson's disease cohorts

DSM-V criteria also describe a number of ICBs not yet specifically reported in PD patients. Trichotillomania involves pulling of hair from the scalp, eyebrows, eyelashes, pubic region or body(4). The exact prevalence is unknown however estimates from university surveys suggest clinically significant hair pulling in 1.5% of males and 3.4% of female students.

Pyromania involves impulsive, repetitive, deliberate fire setting without external reward(4). Lifetime prevalence in the United States has been estimated at 1.7% in men and 0.4% in women(27).

Intermittent explosive disorder is characterized by recurrent episodes of aggressive behavior that is out of proportion to psychosocial stressors or provocation(4). Individuals with intermittent explosive disorder engage in, on average, approximately 65-70 acts of assault and/or property destruction in their lifetime resulting in multiple hospitalizations(28).

Finally, kleptomania is a disorder in which the individual impulsively steals even though there is no need to do so(4).

While a unifying neurobiological theory of ICB development is still awaited, there is evidence that abnormal functioning within the mesolimbic reward system contributes to their development in PD(29, 30). Furthermore, neuropsychological testing on PD patients have found a significant increase in risk-taking behavior in on state compared to off state(31). It may be that the underlying neuropsychological functioning abnormalities contribute to a tendency to impulsive and compulsive acts, rather than to specific abnormal behaviours and therefore the behaviours described above may yet be reported in PD.

4. Epidemiology of ICBs

ICBs exist in both the general population(32) and in adult psychiatric cohorts(33). In terms of individual ICBs, prevalence rates vary worldwide and are likely influenced by culture. For example, problematic gambling rates in the general population vary between 0.2% in Norway and 5.3% in Hong Kong(34) and 1.9% in the United States(35) and the point prevalence of compulsive buying has been estimated to be 5.8% in the United States(36).

The largest study to date investigating prevalence of ICBs in medicated PD patients included 3090 patients across 46 movement disorder clinics in the United States and Canada(7). This study used three independent diagnostic instruments for the detection of four ICBs, specifically, the Massachusetts Gambling Screen for pathological gambling, the Minnesota Impulsive Disorders Interview for compulsive buying and sexual behavior and the Diagnostic and Statistical Manual of Mental Disorders Forth Edition (DSM-IV) for binge-eating.

At least one active ICB was identified in 13.6% of patients and 3.9% of patients had more than one ICB. Similar frequencies were found of each of the four ICDs studied, specifically, 5% for pathological gambling, 3.5% for compulsive sexual behavior, 5.7% compulsive buying and 4.3% for binge-eating disorder. For all individual ICBs, prevalence was higher in those taking DA medication than those not, see below for further discussion.

Cultural differences play a role in prevalence of specific ICBs among PD patients. A recent study of point prevalence of ICBs among PD patients in South Korea, including those taking and not taking DAs, demonstrated 10% prevalence overall but only 1.3% problematic gambling(37). Similarly, overall ICB prevalence of 35% was found in a Malaysian population, including those taking and not taking DAs,

but with relatively low levels for gambling compared to binge eating, hobbyism and compulsive sexual behaviour(38). Epidemiological studies in Italy(39), Denmark(40) and Finland(41) have estimated the prevalence of ICBs in their PD populations at 8.1%, 14.9% 34.8%, respectively.

Though total ICB prevalence is similar between genders, there are sex differences between specific ICBs; men are more likely to develop compulsive sexual behavior, whereas women were more likely to develop compulsive shopping or binge eating(7) and these gender differences are mirrored in the general population(42, 43).

4. 1 Influence of dopamine

All forms of dopamine replacement therapy have been associated with the development of ICBs, including levodopa, especially at higher doses, amantadine(7) and monoamine oxidase inhibitors(44). However, DAs are particularly strongly implicated, with the odds of having an ICB were 2 to 3.5 times higher on DA than levodopa(7). Whilst higher DA doses have been linked with higher incidences of ICBs(45), the effect of DA was not dose-dependent in all studies(Weintraub et al., 2010). Despite earlier case series implicating pramipexole as being the DA most associated with ICBs(8) no statistically significant difference was found between individual between DAs, in larger studies(Weintraub et al., 2010). Furthermore, the effect of DAs were similar across all four ICBs, suggesting DAs have a class effect for increasing all ICBs rather than a specific ICB(Weintraub et al., 2010). Levodopa taken concurrently with a DA also increases risk(7, 45).

Recently, a study from the United States investigated the adverse drug event reports related to ICBs by determining the proportional reporting ratio, a measure similar to the relative risk(46). A total of 1580 reports of ICBs over a ten year period in the United States and 21 other countries were identified, and a strong signal of association was found between these behaviours and DA medication. Specifically, DAs with preferential affinity for the D3 receptor, pramipexole and ropinirole, had the strongest association. The medications had been prescribed for patients with PD in almost 62% of cases, restless legs in almost 24% of cases and hyperprolactinaemia in 3.5% of cases. Importantly, this supports the evidence that ICBs are not inherently associated with PD pathology, but rather are a consequence of medication used to treat the disease. However, this study also found signals of association for other drugs affecting dopamine availability,

specifically levodopa, carbidopa and entacapone combinations, though dopamine agonists were a concomitant medication in 82.2% of these reports. When cases of concomitant dopamine agonist use were excluded, the association between other drugs affecting dopamine availability and developing ICBs was attenuated but still significant(46). This study did not investigate the risk per mg of DA across different medical conditions and future study of this area may help to elucidate the inherent dose related risk of DAs versus any predisposing risk of neurodegenerative disorders such as PD.

4.2 Demographic risk factors and premorbid personality types

Studies investigating de novo, untreated PD patients, have demonstrated that PD itself does not confer an increased risk for the development of ICBs in the absence of treatment(47, 48). Knowledge of non-PD related risk factors and premorbid personality types associated with ICBs might aid clinicians when determining risk prior to commencing treatment. Patients with an ICB are more likely to be younger, unmarried, smoke cigarettes and report a family history of problematic gambling and alcohol use(7) and to have impulsive or novelty seeking personality traits(49). Recently, Callesen et al.,(40) demonstrated that PD patients with ICBs scored significantly higher for the personality trait of neuroticism and lower for both agreeableness and conscientiousness than patients without ICBs. They also reported significantly more depressive symptoms in their ICB group compared to no ICB group. Furthermore, PD patients with pathological gambling have been shown to have significantly higher depressive and anxious symptoms than patients with other ICBs or no ICB(50). However, whether this fact is a cause or effect of the pathological gambling, or a parallel process has not been elicited.

There has been very little prospective research on the development of ICBs and lifetime prevalence has not been determined. However, one recent prospective cohort study followed outpatients with PD and no ICBs for four years and found that timing of ICB development from DA commencement was highly variable, ranging from 3 to 114 months with a median of 23 month(51). Risk factors for developing an ICB included cigarette smoking, caffeine use, motor complications and higher peak dopamine doses, though cumulative DA exposure was similar between groups.

5. ICBs in atypical parkinsonian neurodegenerative disorders

There has been very little published to date on ICBs in the atypical parkinsonian neurodegenerative disorder population. Two early studies investigating compulsive behaviours by mean of retrospective chart reviews of identified a total of three patients with multiple systems atrophy (MSA) who developed ICBs in relation to dopaminergic medication(52, 53). Specifically, patients reported a combination of ICBs including hypersexuality, hyperphagia and repetitive behaviours such as locking and unlocking doors, which developed after initiation of a DA and resolved on cessation of DA treatment.

There are four cases in the literature of ICBs in patients with progressive supra nuclear palsy (PSP). A single case report in 2008 described an 83 year old man with a clinical diagnosis of PSP who developed pathological hypersexuality following initiation of bromocriptine. The ICB initially resolved on cessation of bromocriptine, however reemerged following commencement of pramipexole(54). Three pathologically proven PSP cases developed ICBs in the context of DA medication(55). Phenomenologically, the ICBs included hypersexuality, binge eating, compulsive shopping and reckless generosity. Though formal neuropsychological testing had not been performed, all three cases had documented MMSE within the normal range at onset of ICB.

To our knowledge, there are no studies to date demonstrating ICBs in patients with corticobasal degeneration or dementia with Lewy bodies. The studies above are case descriptions and no prospective or case control series have investigated the prevalence of ICBs among the atypical PD group. However, this may be particularly difficult among this group where clinical diagnosis is often contrary to pathological diagnosis, even in a specialist movement disorder clinics(56). However, the presence of DA-associated ICBs in these case reports is supportive to the argument that the dopamine agonist rather than an underlying pathology exclusive to PD is the trigger for the behavior.

6. ICBs in non-Parkinsonian disorders

Dopamine agonists have been used in the management of restless legs syndrome (RLS) for decades(57), although average doses are approximately 4-25% and 3-32% of those used for PD for pramipexole and ropinerole, respectively(7, 58). Case reports began to emerge in 2007 describing pathological gambling in patients with

restless leg syndrome (RLS) on DA medication(59, 60). The first case-control study on patients with RLS found statistically significantly higher frequency of compulsive shopping in RLS patients on DA compared to untreated RLS patients(61). A recent study has linked the two major side effects of dopaminergic therapy and found that RLS patients with augmentation had an almost 6 fold risk of developing ICBs (Heim et al 2016).

ICBs have been reported in fibromyalgia patients in a case series that screened 1356 patients exposed to at least one dose of DA and identified 21 patients who positive for an ICB(62). Specifically, compulsive gambling was reported in 33%, compulsive shopping in 40% and a further 27% screened positive for both. Patients were taking average amounts of 4.5 mg of pramipexole at night, which is approximately 1.45 times that used in PD(7, 62). All ICBs resolved on gradual, supervised wean of the dopamine agonist(62). Compulsive eating, cleaning and crafting were also described. However, no accurate prevalence studies have been performed on either patients with RLS or fibromyalgia.

DAs are the gold standard medical treatment for prolactinomas because their use controls hormonal levels and controls tumor growth in about 80% of cases(63). The ergot derived medications cabergoline and bromocriptine are first and second line, respectively,(63) whereas non-ergot derived medications such as pramipexole and ropinerole are more commonly used in PD(64). Initial case reports and case series(65, 66)have been followed more recently with a cross sectional observation study which found that 24.6% of patients on DAs for pituitary adenoma screened positive for an ICB compared to 17.14% of control subjects(67). However, this difference was not statistically significant, though subgroup analysis did demonstrate significantly increased frequency of ICBs among males on DAs. This may be due to lower average dopamine equivalent doses used in this cohort compared to PD groups; 262.5mg per week levodopa equivalent for bromocriptine and 66mg levodopa equivalent per week for cabergoline (using Levodopa equivalent calculations as per(68) compared to, on average, 300mg levodopa equivalent per day in Weintraub's 2010 ICB in PD prevalence study(7). Additionally, this study included patients with either current or past use of a DA and, as we know that ICBs can resolve on cessation of the medication, this may not accurately reflex true incidence in a currently treated population and further research is needed to determine this.

With regard to ICBs among the normal aging population as well as the neurodegenerative dementias, there is a lack of published research. However, the

one epidemiological study published to date has shown that the prevalence rates of ICBs in general decrease with aging(69). The lifetime prevalence in this group of patients over 60 years of age was 22.4 %, with the prevalence rate of ICB within the last month at only 6.6%. As seen in the ICB/PD studies, there was an association of ICB presence with a history of alcohol or substance abuse. This study excluded patients with Mini Mental State Examination of less than or equal to 24 points. However, it is known that physical and verbal aggression is commonly seen in patients with dementia(70). Intermittent explosive disorder was the most common ICB seen in this group. Therefore, a more representative population sample including patients with cognitive impairment, may have had an even higher incidence of this particular ICB and increased the prevalence overall.

With regard to the neurodegenerative dementias, published work to date includes only case reports and case series and is primarily focused on frontotemporal dementia. ICBs described include pathological gambling, compulsive eating, skin-picking and compulsive stealing and in some cases ICB have preceded dementia as the presenting complaint(71-73).

Comparison of hypersexuality among 47 patients with frontotemporal dementia compared to 58 patients with Alzheimer's disease found a prevalence of 13% compared to 0%, respectively, without a significant difference in Mini Mental State Examination scores(74). However, this study was based on retrospective chart review and no prospective or targeted screening study has yet been carried out. While these case reports support functional MRI studies suggesting abnormalities in the neural circuits of the orbitofrontal cortex, the ventral striatum and the cingulate gyrus in the development of ICBs in patients with PD(75, 76), more detailed and targeted neuropsychological testing on these patient groups could provide important clues as to the neurobiological dysfunction underlying ICBs.

7. Conclusion

ICBs represent a spectrum of disorders, which can manifest as different behaviours depending on gender, premorbid personality, interests and geographical presentation. All cases can have significant impact on quality of life for both the patient(77) and their carer(78). While research is ongoing into the neurobiological pathology underlying these diseases, through the study of both PD and non-PD populations, all clinicians dealing with patients potentially at risk need

to be aware of clinical presentation of ICBs in order to comprehensively screen for, and appropriately intervene on, their occurrence.

ACCEPTED MANUSCRIPT

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