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# A systematic review of treatments for Impulse Control Disorders and related behaviours in Parkinson's disease



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## ABSTRACT

Impulse Control Disorders (ICDs) are a set of behaviours characterised by impulsivity despite known harm. Related to ICDs is the dopamine dysregulation syndrome (DDS), which is characterised by an addiction-like consumption of dopaminergic medication and punning. These behaviours all have an increased prevalence in Parkinson's disease (PD). The aim of this review is to identify treatments available for patients suffering from ICDs, DDS and punning in PD. Searches of The Cochrane Controlled Trials Register, Embase, Medline and PsychInfo were conducted, using the entire timescale available. Seven out of the 688 papers retrieved met the inclusion criteria and were considered in this systematic review. One class I study, one class II study, and five class IV studies were identified. All studies demonstrated a positive effect on ICDs in PD. Research in this field is still in its early stages. At present, there is insufficient evidence to recommend any treatment over another. There is a need for more methodologically robust research, using larger, more generalisable samples, randomisation and meaningful follow-up periods. In addition, the use of a validated outcome measures should be implemented in future research efforts.

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## 1. Introduction

Parkinson's disease (PD) is primarily a neurodegenerative disorder characterised by a loss of dopaminergic neurons in the nigrostriatal pathway, resulting in a classic repertoire of motor symptoms: i.e. bradykinesia, resting tremor, rigidity, and postural instability. These motor symptoms have long been the hallmark of both diagnosing and treating PD with treatment aimed at providing symptomatic relief by attempting to replace the lost dopamine. This is predominantly managed either with dopamine agonists or by using Levodopa, a dopamine precursor. Neurodegeneration of the nigrostriatal contributes to both motor and non-motor symptoms (e.g. sleep disorders, autonomic dysfunction, and neuro-endocrinal problems; Chaudhuri and Schapira, 2009; Politis et al., 2008). These symptoms can be broadly classified into neuropsychiatric problems (including disturbances in cognition and mood), sleep disturbances and autonomic symptoms. These non-motor symptoms commonly dominate the clinical picture in severe PD and, as such, have a significant impact on quality of life and disability (Rahman et al., 2008). The pathophysiology of these symptoms remains poorly understood.

This, coupled with the emphasis placed on the motor symptomatology of PD, has led to the non-motor complications gaining a relatively late entry into the field of treatment research. Notwithstanding this, in the past few decades a greater emphasis has been placed on non-motor symptoms with new treatment avenues being identified (Wood et al., 2010).

### 1.1. Impulse–Compulsive Behaviours

For the purpose of this review, Impulsive–Compulsive Behaviours (ICBs) will be used as an umbrella term to include Impulse Control Disorders (ICDs), Dopamine Dysregulation Syndrome (DDS) and punning. ICDs are defined as a set of behavioural disorders characterised by repetitive, maladaptive, and disinhibited behaviours that an individual engages in despite being aware of their potentially harmful consequences to the self or others (Association, 2000). The most common ICDs in PD include pathological gambling (PG), hypersexuality (HS), compulsive eating (CE), compulsive buying (CB), kleptomania, trichotillomania (repetitive hair pulling), intermittent explosive behaviour (recurrent outbursts of aggression), and pyromania (deliberate fire-setting). DDS is characterised by a compulsive use of dopaminergic medication, in a similar manner to substance addiction (Giovannoni et al., 2000), dopaminergic medication hoarding, continual self-medication despite the onset of severe

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dyskinesia, and hypomania (Giovannoni et al., 2000). Punding is defined as a compulsive, repetitive, and purposeless behaviour (which the patient recognises as being meaningless), usually causing isolation, social withdrawal, and irritation for the individual when the behaviour is interrupted (Evans et al., 2004). ICBs are common neuropsychiatric complications seen in PD. The DOMINION study, an epidemiological study looking at the incidence of ICBs in PD across movement disorder centres in USA and Canada, reported a prevalence of 13.6% compared to 1% in the general population (Ferris et al., 1996; Weintraub et al., 2010a). However, the actual incidence may be higher as a result of underreporting due to the stigma and shame attached to many of these behaviours (Weintraub et al., 2006).

## 1.2. Pathophysiology

The mechanism underlying the development of these behaviours has not been fully elucidated, although the use of dopamine agonists has been identified as a risk factor (Voon et al., 2006; Weintraub et al., 2010a) with studies showing the reversal of symptoms on dopamine agonist discontinuation (Mamikonyan et al., 2008). In addition, several papers have identified associations between ICBs and polymorphisms of genes involved in metabolising dopamine and dopamine receptors, indicating a genetic predisposition to ICBs (Cormier et al., 2013; Eisenecker et al., 2010). Other risk factors for ICBs in PD include being male, developing PD at a younger age, having a personal or family history of addictive behaviour, experiencing depressive symptoms, and having a novelty seeking personality (Pontone et al., 2006; Voon et al., 2006; Weintraub, 2009). Despite the pathophysiology of ICBs in PD being unclear, the mesolimbic pathway of the brain has been implicated in its development (Cilia et al., 2008), along with the ventral striatum and prefrontal cortex, where alterations in the responsiveness to reward and punishment are thought to occur (Reuter et al., 2005).

More recently, a bio-psycho-social model of ICBs has been proposed which purports that impulsive behaviours arise from maladaptive coping mechanisms to deal with the psychological distress of dealing with a chronic condition, especially in a younger population where the disability has a greater impact on quality of life (Delaney et al., 2012). In the proposed model, psychological distress predisposes patients to developing ICBs and dopamine agonists act to multiply the susceptibility to ICBs. If this is above a certain threshold, ICBs arise, offering an explanation as to why only a subset of patients are affected (Delaney et al., 2012).

To date, no evidence-based method has been established for treating ICBs in PD. Management typically consists of dose reduction or discontinuation of dopamine agonists, which can be coupled with an increase in levodopa dose (Mamikonyan et al., 2008), however, there are several limitations to this approach. First, care must be taken to balance ameliorating the ICB symptoms with preventing an increase in motor symptoms. Dopamine agonists have been established as an effective treatment for the motor symptoms of PD (Stowe et al., 2008) and therefore staying on the treatment takes precedent over a non-evidence based method of tackling ICBs. Second, abrupt cessation or dose reduction of dopamine agonists can lead to the development of a dopamine agonist withdrawal syndrome (DAWS; Limotai et al., 2012). DAWS is defined as a group of symptoms, both physiological and psychological, resembling those of other drug withdrawal syndromes. Symptoms such as dysphoria, anxiety, and drug cravings are present and have been shown to occur in a drug-dependent manner (Pondal et al., 2013). In addition, the cravings present can lead to hesitation on the patient's behalf in stopping treatment despite the ongoing ICBs and dyskinesia present with excessive use (Rabinak and Nirenberg, 2010). Furthermore, despite treatment reduction and switching to Levodopa, some patients remain drug refractory and ICBs prevail (Ávila et al., 2011; Bermejo, 2008a;

Kurlan, 2004), indeed levodopa has been identified as a causatory agent (Ávila et al., 2011). The significant impact of ICBs on a patient's quality of life gives rise to the need for treatment without these limitations (Leroi et al., 2011; Nikitina et al., 2013). The aim of this review is to track progress towards an evidence-based treatment for ICBs in PD and to identify future research needs.

## 2. Methods

This systematic review was conducted at Institute of Psychiatry, King's College London, UK using studies retrieved by performing electronic searches of the Cochrane controlled trials register, MEDLINE, EMBASE, and PsychInfo, along with the references of identified papers. The entire timescale was used up to February 2014 (week 8) inclusive. The search strategy employed the following keywords: "Parkinson's disease" and "Impulse Control Disorders" or "Dopamine Dysregulation Syndrome" or "DDS" or "punding", in combination with "management" or "treatment" or "therapeutics" or "CBT" or "pharmacological therapy" or "drug therapy" or "pharmacological interventions". The inclusion criteria were studies: (1) investigating at the effectiveness of any type of treatment on for Impulse Control Disorders in PD; (2) with participants presenting a clinical diagnosis of idiopathic PD currently on medication for PD, including all genders and ages; (3) with participants with no co-morbidities such as dementia (MMSE > 24), psychosis, or any other neuropsychiatric complications; (4) assessing treatment according to DSM-IV criteria (American Psychiatric Association, 1994) or using a validated outcome measure; and (5) utilising all methodological designs (where full-text was available). The exclusion criteria were studies carried out on animals, not available in English, or with retrospective data analysis (i.e. studies needed to be testing an active treatment with the aim of reducing ICBs).

Initially titles were screened and duplicates were excluded. The remaining abstracts were screened and studies were excluded using the inclusion/exclusion criteria. After the first screening, the remaining full text articles were assessed against a quality checklist in consideration of selection, performance, detection, attrition and reporting biases. The following details were collected from each study: bibliographic details (i.e. author, country, and date of study); design of study; number of participants; mean participant age; percentage of male patients; method of assessing ICBs; type of treatment; outcome measures; average follow-up period; methods of statistical analysis; findings and conclusions of authors (see Table 1).

## 3. Results

Six hundred and eighty eight studies were retrieved through the search strategy. Of these, 124 were duplicates and 530 were excluded on abstract review because inclusion/exclusion criteria [studies done on animals (12), not in English (six), not dealing with the clinical condition (178), not looking at treatment of the clinical condition (162) and literature reviews (171)]. Thirty four full-text studies were read and further assessed for eligibility (inclusion/exclusion criteria). These were also subjected to a quality checklist (described above). Twenty seven studies were excluded (10 based on the exclusion criteria and 17 as a result of the quality checklist). Seven studies were included in this systematic review.

### 3.1. Pharmacological treatment

One class I and five class IV trials were identified that evaluated pharmacological treatments for ICBs. All the pharmacological agents reviewed demonstrated positive effects on reduction of ICBs. The class I trial was a double blind RCT looking at the effect of 200 mg/day Amantadine against placebo control lasting 17 weeks and included 17 patients with pathological gambling (Thomas et al., 2010). A combination crossover and open label design was used, with patients switching from intervention to control group (and vice versa) after 2 weeks of treatment (with a 1 week washout period in between) before a final stage where all patients were put on active treatment for 2 weeks. All patients showed a reduction in pathological gambling behaviour, measured using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989) and the Gambling Symptom Assessment Scale (G-SAS; Kim et al., 2009). Emilio Bermejo et al. (2010) reported positive effects of 200 mg/day of Zonisamide (an anticonvulsant) on ICBs, assessed using the

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