

Managing impulse control behaviours in Parkinson's disease: practical guidelines

Impulse control behaviours are increasingly recognized as serious complications of dopaminergic therapy in Parkinson's disease. This article outlines a set of practical guidelines for management of these behaviours which have been developed by five experts from neurology, psychiatry and care of the elderly.

Parkinson's disease is a progressive neurological condition characterized by degeneration of neurons in the substantia nigra and depletion of the neurotransmitter dopamine. Parkinson's disease is increasingly recognized as a neuropsychiatric disorder as well as a motor disorder (Weintraub and Burn, 2011). Dopaminergic medication used to treat the motor symptoms can lead to the development of neurobehavioural syndromes, including impulse control behaviours, which encompass impulse control disorders, dopamine dysregulation syndrome and punding (Voon et al, 2011a). Devastating financial, psychological, legal and social consequences may ensue. This article provides practical guidance for the management of such impulse control behaviours.

Impulse control behaviours Impulse control disorders

Impulse control disorders are a group of psychiatric conditions that have been recognized in the *Diagnostic and Statistical Manual* (American Psychiatric Association, 2000). These disorders are reward-based and involve repetitive and compulsive acts. Impulse control disorders are characterized by 'a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others'. This can result in distress and impaired social and occupational functioning.

The impulse control disorders commonly associated with Parkinson's disease are pathological gambling, hypersexuality, compulsive shopping and compulsive eat-

ing (also known as binge eating). Other behaviours have also been reported, including hoarding, compulsive smoking, kleptomania and reckless driving.

Impulse control disorders are associated with depression, novelty-seeking behaviours, impulsive choice, anxiety and obsessive symptoms (Voon et al, 2011a). There is debate about whether these behaviours should be categorized as behavioural addictions or as obsessive compulsive disorders (Okai et al, 2011). Whereas obsessive compulsive disorder is driven by attempts to reduce anxiety, behavioural addictions are based on the pursuit of pleasure, arousal or 'need'. Both demonstrate failure to resist immediate reinforcement, despite long-term negative consequences.

Impulse control disorders have been linked with a number of other neurological disorders, including restless legs syndrome and amyotrophic lateral sclerosis (Evans and Butzkueven, 2007; Wicks and Macphee, 2009). The greater severity and different character of impulse control disorders in Parkinson's disease compared with those in amyotrophic lateral sclerosis suggests impulse control disorders are not caused simply by response to a chronic neurological disorder (Wicks and Macphee, 2009).

Punding, hobbyism and dopamine dysregulation syndrome

Punding is characterized by stereotyped, repetitive, aimless behaviours, which can be simple (e.g. rearranging objects or shuffling papers) (Spencer et al, 2011) or, in the case of hobbyism, involve more complex acts associated with a specific activity or hobby (Evans et al, 2004).

The activity often relates to a previous occupation or interests and may be associated with a 'soothing' effect. The behaviour may interfere with medication, food and sleep, and insight into the disruptive and harmful nature of the behaviour may be lost. Attempts by caregivers or partners to interfere with the activity are often met with irritability or anger.

Dopamine dysregulation syndrome describes the compulsive use of dopaminergic medication in Parkinson's disease patients (usually short-acting levodopa or apomorphine injections), where dosage is escalated by the patient beyond that required to adequately control motor symptoms. It is often associated with ballistic dyskinesias (Ceravolo et al, 2010). Common mechanisms may underlie impulse control disorders and dyskinesia (Voon

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et al, 2011a). Patients with dopamine dysregulation syndrome often report a craving, or 'wanting', rather than a 'liking' for drug therapy, and they may be driven by an attempt to avoid the dysphoria of 'off' periods.

Punding, hobbyism and dopamine dysregulation syndrome have a degree of overlap with impulse control disorders. Compulsive shopping can be part of hobbyism, and gambling, hypersexual behaviour and binge eating may be seen in dopamine dysregulation syndrome. An umbrella concept of 'disinhibitory psychopathologies' has been proposed for these behaviours in Parkinson's disease patients (Okai et al, 2011). Criteria for defining distinct impulse control behaviours are reviewed by Voon and Fox (2007). Overlap and multiple coexisting impulse control behaviours are common in clinical practice.

Neurobiology of impulse control disorders in Parkinson's disease

The understanding of the neurobiology that underlies impulse control disorders in Parkinson's disease is evolving rapidly (Ceravolo et al, 2009; Ray and Strafella, 2010). Current evidence suggests that dopamine agonists enhance learning from rewarding stimuli and outcomes and amplify impulsive choice perhaps by interference with the balance between tonic and phasic dopaminergic stimulation. Impulse control disorder patients may also have impaired working memory and impaired inhibition of orbitofrontal influence on enhanced ventral striatal dopamine release to reward anticipation (Voon et al, 2011a). Functional genetic polymorphisms may also contribute to impulse control disorder sensitivity.

Epidemiology of impulse control disorders

The largest multicentre cross-sectional study of impulse control disorders is the DOMINION study from North America. This reported a 6-month prevalence of 13.6% for impulse control disorders (problem and pathological gambling 5%, compulsive sexual behaviour 3.5%, compulsive shopping 5.7%, and binge eating 4.3%), with 3.9% of patients experiencing two or more impulse control disorders (Weintraub et al, 2010a). There was a strong association between impulse control disorders and dopamine agonist use, and a weaker association with higher levodopa dose (but not dopamine agonist dose).

Challenges in the diagnosis of impulse control behaviours

In clinical practice, impulse control behaviours appear to be under-recognized (Weintraub et al, 2009). Often, patients do not disclose behaviours because they are embarrassed or because they do not suspect that their medication is causing the problem. Others may act covertly in the belief that they can manage their behaviours, or because they do not want them treated (Grosset et al, 2006). Nurse specialists often receive information from family members without the patient's knowledge. Detection can be helped by anticipatory care (*Figure 1*).

Risk factors and the role of Parkinson's disease therapy

Parkinson's disease itself may make patients more vulnerable to impulse control disorders, although the extent to which factors such as executive dysfunction in Parkinson's disease contribute to impulse control disorder remains unresolved. Nevertheless, the risk factors associated with development of impulse control disorders in patients with Parkinson's disease are well documented (Voon et al, 2006b, 2007; Weintraub et al, 2010a) (*Table 1*) and highlight the importance of assessing multiple health domains and psychiatric morbidity in patients with Parkinson's disease and impulse control disorders (Voon et al, 2011b).

Impulse control disorders have been reported as a class effect of all dopamine agonists. Generally, the daily doses of dopamine agonists are higher in patients with impulse control disorders than in those without (Weintraub et al, 2006). However, impulse control disorders have also been reported in patients treated with low doses of dopamine agonists in restless legs syndrome that is not associated with Parkinson's disease (Evans and Butzkueven, 2007).

There may be an individual threshold for impulse control disorder behaviour in terms of dopamine agonist dose (Macphee et al, 2009). A study in healthy volunteers found that individual differences in reward-based learning were underpinned by variations in baseline levels of striatal dopamine synthesis (Cools et al, 2009). Dopamine agonist receptor subtypes may also have a role in mediating and controlling risk-based decision making.

Although dopamine agonists have been implicated as a primary risk factor in the development of impulse control disorders in patients with Parkinson's disease, other Parkinson's disease therapies have also been linked to these behaviours, including levodopa and amantadine (Molina et al, 2000; Weintraub et al, 2010b; Walsh and Lang, 2012). Individual cases reporting links between impulse control disorders and monoamine oxidase inhibitors and catechol-O-methyltransferase inhibitors exist but are rare.

Many patients with mild impulse control behaviours find their behaviour non-intrusive or non-deleterious (Ondo and Lai, 2008), and others may consider their behaviour their only pleasure, a factor which must be considered before clinical intervention. In Parkinson's disease, a 'continuum' of behaviour, from apathy associated with hypodopaminergic stimulation to impulse control disorder provoked by excess or aberrant dopaminergic stimulation, may be conceptualized. The clinician must carefully assess the impact of impulse control behaviours on daily living and other activities and should review the consequences of the behaviours before intervention. The degree of distress to the patient and family should also be weighed, appreciating that disparity of views (often as a result of lack of insight) may be taxing in determining the most ethical course.

Figure 1 presents an algorithm for the management of impulse control behaviours. The article now reviews strategies for the management of impulse control behav-

ious and provides a brief recommendation on each strategy that reflects the consensus opinion of the authors, acknowledging the paucity of robust evidence. The overall treatment benefit must be determined judiciously; e.g. withdrawal of dopamine agonists or switching therapies may benefit impulse control behaviour but be detrimental to motor symptoms (*Case study 1*).

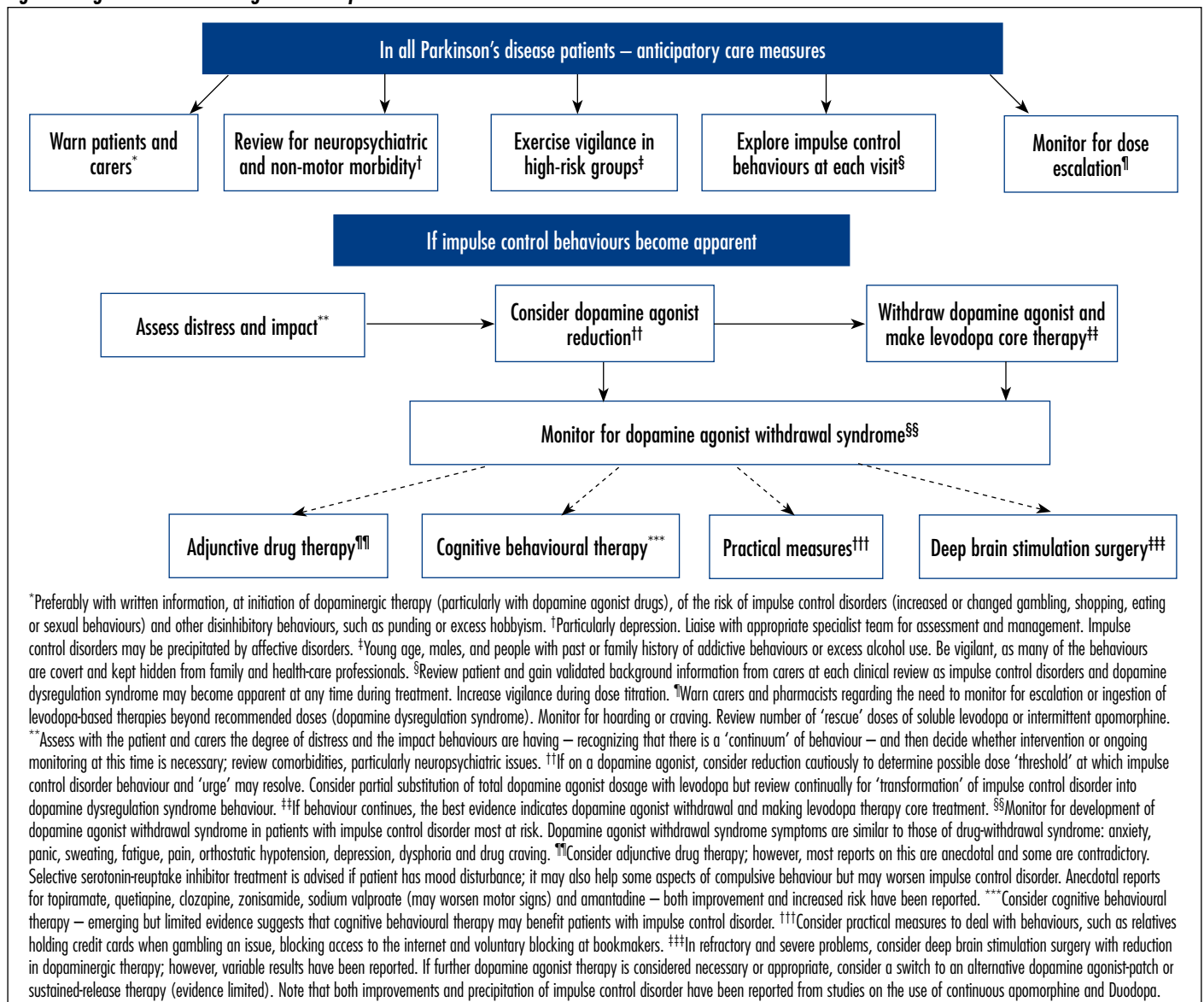
Dopamine dysregulation syndrome should have similar anticipatory care measures as impulse control disorder. Red flags to dopamine dysregulation syndrome include early or severe dyskinesia and reports of ‘running out’ of medication. To minimize excess dosing, patients with dopamine dysregulation syndrome may require surveillance measures such as GP and pharmacy checks and ensuring patients are not obtaining alternative supplies of levodopa (e.g. from the internet or other patients), particularly short-acting preparations such as Madopar dispersible and rescue apomorphine injections.

Antipsychotic drugs, such as quetiapine or clozapine, may be required to control dopamine-induced psychosis or mania or, in extreme cases, impactful pathological gambling or hypersexuality.

Anticipatory care and the management of impulse control behaviours

Before prescribing dopamine agonists, patients and caregivers should be advised of the potential for dopamine agonists to cause impulse control disorders and excessive daytime somnolence (Grosset et al, 2010). The Scottish Intercollegiate Guideline Network guidelines (Grosset et al, 2010) recommend written documentation of such conversations and advise signposting patients and carers to validated materials, such as the Parkinson’s UK website. Clearly, a balanced discussion of the benefits and risks of treatment is crucial. Individual patients and carers may differ in their assessment of the benefit:risk ratio,

Figure 1. Algorithm for the management of impulse control behaviours in Parkinson’s disease.



but some can be 'frightened off' therapy by the prospect of impulse control disorders.

Recommendation: before the initiation of treatment patients and caregivers should be warned about the potential for dopamine agonists (and other dopaminergic therapies) to cause impulse control behaviours and provided with written information for future reference.

Detecting impulse control behaviours in patients with Parkinson's disease

It is important that probing for impulse control behaviours is performed at regular intervals because it is difficult to predict when they might emerge. Both patients and their caregivers should be included in this process as this will help the treating health-care professional establish the degree of the patient's knowledge and gauge the impact of the patient's behaviours on the caregivers.

Parkinson's UK developed a simple tool that can be used to assess impulse control behaviours in patients with Parkinson's disease – the 'Impulsive and compulsive behaviour in Parkinson's monitoring and information tool'. This acts as a prompt when talking to patients during a consultation by raising questions relating to impulse control disorders, punding, dopamine dysregulation syndrome and medication use. It also highlights risk factors for impulse control disorders, such as family history of alcohol abuse or gambling; if present, these should increase vigilance in the clinician and be considered when deciding whether dopamine agonists are an appropriate treatment choice. This tool is available to download from the Parkinson's UK website (Parkinson's UK, 2010) and a new version is in development.

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS), which is a development of the QUIP and QUIP-S screening tool (Weintraub et al, 2009), is reliable both in supporting the diagnosis of impulse control behaviours and also in monitoring changes in symptom severity over time (Weintraub et al, 2012). Impulse control behaviours may also be detected using the non-motor symptoms questionnaire (items 17, 18 and 30) (Chaudhuri et al, 2006) or the sexual domain questions in the non-motor symptoms scale (Chaudhuri et al, 2007).

Recommendation: clinicians managing people with Parkinson's disease should make regular enquiries into non-motor symptoms and impulse control behaviours (particularly overspending and hypersexuality) before further examination. This can be supplemented if needed by a specific questionnaire, such as the QUIP, to measure change and to ensure comprehensive coverage of symptoms.

Dopamine agonist reduction or cessation

Management of impulse control disorders by reduction or cessation of dopamine agonists (with a concomitant increase in levodopa dose, if necessary) has been investi-

gated in three long-term observational studies (Mamikonyan et al, 2008; Macphee et al, 2009; Sohtaoglu et al, 2010). Dopamine agonist reduction or discontinuation was associated with remission or reduction in the majority of impulse control disorders. Motor control did not appear to be significantly affected in most cases following such treatment changes (Mamikonyan et al, 2008).

After any change in medication, careful follow up is important particularly to monitor for the development of new impulse control disorders (*Case study 2*) and dopamine agonist withdrawal syndrome which manifests in patients with baseline impulse control disorders. Symptoms of dopamine agonist withdrawal syndrome resemble those of other drug withdrawal syndromes (Rabinak and Nirenberg, 2010), and include anxiety, depression, panic attacks, fatigue, sweating, drug cravings, orthostatic hypotension and pain. This may pose other challenges to the continuing management of the patient with impulse control disorders as these symptoms may only respond to dopamine agonists and not to levodopa or other medications (Rabinak and Nirenberg, 2010). Patients who manifest impulse control disorder on dopamine agonist may develop dopamine dysregulation syndrome if 'converted' to levodopa-based therapy (Macphee et al, 2009).

Table 1. Risk factors for the development of impulse control disorders in patients with Parkinson's disease

Use of dopamine agonists or levodopa
Smoking
Unmarried
Early-onset Parkinson's disease
Depression
High levels of novelty-seeking behaviour
Family history of gambling or alcohol abuse

From Voon et al (2006a, 2007), Weintraub et al (2010a)

Case Study 1

A 57-year-old man was diagnosed with Parkinson's disease in 1996 and commenced treatment with selegiline and pergolide. Following an episode of paranoid psychosis in 2001, treatment was changed from pergolide to pramipexole. Levodopa was commenced in 2003 and slowly titrated upwards, and entacapone was added in 2004 following some decline in motor symptoms. Later that year, the patient's partner reported problematic hypersexuality. Entacapone was withdrawn, whereupon the patient's behaviour returned to normal. In 2007, the patient's partner discovered that he had significant credit card debts from online gambling. Pramipexole was rapidly down-titrated and stopped, but levodopa monotherapy was continued as the patient needed to remain mobile.

In 2009, the patient described his motor symptoms as intolerable. Rotigotine was commenced with regular reviews. Motor symptoms improved considerably and there was no evidence of impulse control disorders or neuropsychiatric concerns disclosed 8 months later although regular monitoring and review is being undertaken as relapse of behaviour remains possible.

Recommendation: during reduction or cessation of dopamine agonist therapy, patients with impulse control disorders should be closely monitored for deterioration of motor control and the emergence of withdrawal symptoms or the development of other impulse control behaviours, such as dopamine dysregulation syndrome.

Route of dopamine agonist administration

The route and nature of dopaminergic administration may have a role in treatment complications. Evidence from several studies (Honig et al, 2009; Martinez-Martin et al, 2011; Trenkwalder et al, 2011) suggests that continuous dopamine stimulation achieved by continuous drug delivery via intrajejunal levodopa, subcutaneous apomorphine or transdermal rotigotine can improve the non-motor symptoms of Parkinson's disease.

Therapies that do not achieve continuous dopamine stimulation (e.g. levodopa or dopamine agonist) may excessively activate the 'reward centre' (nucleus accumbens), thus sensitizing the reward pathway (ventral striatum). In support of this, Parkinson's disease patients with dopamine dysregulation syndrome have greater ventral striatal dopamine agonist release in response to levodopa stimulation than patients without dopamine dysregulation syndrome (Evans et al, 2006). A similar increase in ventral striatal dopamine was recorded in response to pulsatile dopamine stimulation in a positron emission tomography study in patients with pathological gambling (Steeves et al, 2009). This suggests that using longer acting therapies at the initiation of therapy may reduce the risk of impulse control disorders. Preliminary data from the EUROPAR study (373 patients from several centres across Europe) sug-

gest that, compared with shorter acting dopamine agonists, rotigotine therapy appears to have a low rate of emergent impulse control disorder and discontinuation of therapy (Rizos et al, 2012). Controlled studies are currently underway (A Antonini, personal communication, 2012) but at this stage there is insufficient evidence to make specific recommendations for which preparation should be used when starting dopamine agonist therapy.

Pharmacological management

A number of pharmacological strategies have been studied for the management of impulse control behaviours. Selective serotonin-reuptake inhibitors may be effective in treating impulse control behaviours in non-Parkinson's disease patients (Kim et al, 2002). There is preliminary evidence from two small randomized controlled studies that topiramate and amantadine may assist in the treatment of impulse control behaviours in Parkinson's disease patients (Bermejo, 2008; Thomas et al, 2010) although amantadine has also been implicated in impulse control disorders (Weintraub et al, 2010b).

The opioid antagonist naltrexone has been used to treat pathological gambling in non-Parkinson's disease populations (Kim, 1998; Grant et al, 2008); a phase IV 8-week study has investigated its effectiveness against impulse control disorders in Parkinson's disease patients and the results are awaited (Clinicaltrials.gov, 2013). Assessment and treatment of adjunctive neuropsychiatric disorders, such as anxiety, panic attacks, depression and hypomania, is important as these disorders may 'drive' impulse control behaviours.

Recommendation: there is limited evidence for the use of adjunctive pharmacotherapy in impulse control disorder but detection and treatment of concurrent psychopathology, such as depression, may be helpful in managing impulse control behaviour.

Deep brain stimulation

Over time, dopaminergic therapy may become less effective in treating the motor symptoms associated with Parkinson's disease. Deep brain stimulation, commonly of the subthalamic nucleus, can reduce motor symptoms and permit a reduction in dopaminergic therapy (Demetriades et al, 2011). The evidence regarding deep brain stimulation and impulse control disorders is conflicting. Some studies have reported resolution of impulse control disorders after deep brain stimulation (Ardouin et al, 2006), whereas others have found that impulse control disorders may emerge or worsen after deep brain stimulation (Smeding et al, 2007).

Recommendation: the overall effect of deep brain stimulation on impulse control behaviour is not yet resolved; however, deep brain stimulation can be considered in carefully selected patients for whom pharmacological measures have failed.

Case Study 2

A male patient was diagnosed with Parkinson's disease at 45 years of age and commenced treatment with levodopa. He was prescribed selegiline 1 year later but did not tolerate it, so he was switched to dopamine agonists. The patient was admitted to psychiatric care following an acute psychotic episode, whereupon dopamine agonists were stopped and he was treated with escalating doses of levodopa monotherapy for several years. The patient was unable to tolerate catechol-O-methyltransferase inhibitors.

In 2004, he received an apomorphine challenge and was prescribed intermittent injections, during which time there was a marked improvement in his Parkinson's disease. Intermittent injections soon escalated to seven–eight per day and the patient was switched to an apomorphine pump. In 2007, the patient was changed to Duodopa, which significantly improved his lifestyle and quality of life. However, approximately 1 year later his spouse reported uncontrollable dyskinesias, resulting in weight loss and friction burns. The Duodopa dose was decreased by two-thirds, but Parkinson's disease control was poor. A rotigotine patch was co-administered for overnight control. In 2008, his partner reported compulsive shopping, at which point Duodopa and rotigotine doses were reduced, which relieved this impulse control disorder. However, the patient began to experience compulsive eating, although this was not problematic as the patient had previously lost weight.

Practical strategies

Practical measures implemented by the caregiver (and supported by Parkinson's disease specialist nurses) might be initiated at the start of dopamine agonist therapy. These can include monitoring medication compliance, reporting impulse control disorder behaviours and taking control of internet access and the financial affairs of the patient.

Recommendation: practical measures, particularly in relation to finances and internet access, are useful in patients with impulse control behaviours, as is family education and support by Parkinson's disease nurse specialists.

Psychological strategies

Psychological interventions, including cognitive behavioural therapy, may be useful in managing impulse control behaviours in non-Parkinson's disease populations (Dowling et al, 2006; Muller et al, 2013). A randomized controlled proof-of-concept trial of cognitive behavioural intervention to reduce impulse control behaviours and associated problems in patients with Parkinson's disease (ICAADS) has shown encouraging results in reducing impulse control behaviours and associated psychopathology (Okai et al, 2013).

Recommendation: a broad psychosocial approach, including management of psychopathology, carer strain and specific cognitive behavioural therapy strategies to reduce impulse control behaviours, is likely to be beneficial, although more research is needed in this area.

Conclusions

Pathological, personally and socially intrusive impulse control behaviours usually triggered by dopaminergic therapies affect a significant minority of patients with Parkinson's disease and require education and support of patients and families. Warning patients of potential behaviours is mandatory, as is ongoing supervision, as significant psychological, social and legal consequences may ensue. Limited evidence exists for determining the optimal management of impulse control behaviour but it is reviewed and incorporated in the current consensus guidelines and algorithm. [BJHM](#)

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Genus, GSK, Abbott, Teva/Lundbeck, Medtronic and Boehringer-Ingelheim. He is an expert advisor to Parkinson's UK and is a past Chairman of the British Geriatrics Society Movement Disorders Section, which has received support from several pharmaceutical companies. Professor KR Chaudhuri has received honoraria for academic lectures at sponsored symposia from UCB, Britannia, GSK, Abbott, Teva, Medtronic and Boehringer-Ingelheim. He has received educational grants for research from UCB, Abbott, Boehringer-Ingelheim and Britannia. He serves as the European editor of Basal Ganglia, is on the editorial board of Parkinson's and Related Disorders and the Journal of Parkinson's Disease, and is Liaison and PR committee chairman of the Movement Disorders Society. Professor AS David attended the consensus meeting sponsored by UCB, from which this article was partly derived. He has received honoraria from pharmaceutical companies for academic lectures at sponsored symposia on schizophrenia but not on Parkinson's disease. He is the principal investigator on a recently completed study of a psychosocial intervention for impulse control behaviours funded by Parkinson's UK. Dr P Worth has received honoraria for academic lectures and consulting fees from Boehringer-Ingelheim, Teva, Lundbeck, UCB, Britannia and Abbott. He has received research funding from GE Healthcare. Dr B Wood has received honoraria and travel grants from Abbott, UCB, GSK and Boehringer-Ingelheim.

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KEY POINTS

- Impulse control behaviours are increasingly recognized as serious complications of dopaminergic therapy in Parkinson's disease.
- Impulse control behaviours encompass impulse control disorders (such as pathological gambling, hypersexuality, binge eating and compulsive shopping), punding and dopamine dysregulation syndrome.
- Patients with impulse control behaviours may face devastating financial, psychological, legal and social consequences.
- Impulse control behaviours appear to be under-recognized in clinical practice. Detection can be aided by anticipatory care.
- Clinicians managing patients with Parkinson's disease should regularly enquire about non-motor symptoms and impulse control behaviours because these may not be declared to family or health professionals routinely.
- Management by reduction or cessation of dopaminergic therapy should include close monitoring for the deterioration of motor control and the emergence of withdrawal symptoms or the development of other behaviours.
- Other therapeutic management strategies include adjunctive pharmacotherapy and deep brain stimulation, although further evidence is required.
- Practical management strategies (e.g. in relation to finances) and psychological interventions (e.g. cognitive behavioural therapy) may be useful.

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