REVIEW ARTICLE

Drug Safety 2009; 32 (6): 475-488
0114-5916/09/0006-0475/$49.95/0

Behavioural Adverse Effects of Dopaminergic Treatments in Parkinson's Disease

Incidence, Neurobiological Basis, Management and Prevention

Angelo Antonini[1] and *Roberto Cilia*[1,2]

1 Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy
2 Department of Neurology, University of Milan-Bicocca, San Gerardo Hospital, Monza, Italy

Contents

Abstract

Treatment of Parkinson's disease has traditionally focused on the management of motor disability while behavioural disturbances have received less attention. Recently, impulse control disorders and aberrant repetitive behaviours have surged to clinical relevance as they occur during dopamine replacement treatment (mainly with dopamine agonists) and worsen patient and caregiver quality of life. Patients are unable to adequately estimate the negative consequences of their actions and are prone to entertain compulsive reward-seeking activities.

This review aims to summarize current evidence on the epidemiology of behavioural disturbances in Parkinson's disease, recent insights into their neurobiological basis and to discuss strategies for management and prevention. Studies from 1990 through to December 2008 were retrieved via searches of the Cochrane Database of Systematic Reviews and PubMed.

The mechanisms underlying the development of behavioural disturbances in Parkinson's disease are debated but current evidence points to specific risk factors: male sex, young age at onset, underlying personality traits

characterized by high impulsivity and novelty seeking, and personal or family history of addictive disorders. Specifically, in predisposed individuals dopamine replacement therapy leads to overstimulation of dopamine receptors within the mesocorticolimbic pathways and in turn to the development of addictive behaviours, such as impulse control disorders and compulsive medication intake. Since these disturbances affect individuals who have often unremarkable psychiatric history and no cognitive impairment, their identification and management is complex. Compulsive medication intake (described as 'hedonistic homeostatic dysregulation' or 'dopamine dysregulation syndrome') is commonly associated with fluctuations in advanced disease, while impulse control disorders frequently occur in early Parkinson's disease and within normal-range medication dosages.

Management primarily requires reduction of dopaminergic therapy but psychosocial support is often required. Use of selective serotonin reuptake inhibitors in the dose used for obsessive compulsive disorders may help, while benefit from atypical antipsychotics is limited in most cases. Deep brain stimulation should be considered with caution in these subjects. Prevention is based on the identification of at-risk individuals and active monitoring. Given the social and potentially medical-legal consequences of these behaviours, we encourage treating physicians to discuss risks with patients before treatment is initiated.

Parkinson's disease is a neurodegenerative disorder presenting with a variety of motor and non-motor features. Most literature focuses on the motor aspects of Parkinson's disease, but there is increasing awareness about the contribution of non-motor problems to patient disability and quality of life. In particular, behavioural disturbances such as depression and anxiety are common, with a prevalence of 40–60%.[1,2] Recently, deficits in impulse control and compulsive behaviours have also surged to clinical relevance in relation to dopaminergic replacement therapy (DRT)[3-22] [table I].

Impulse control disorder (ICDs) are listed among obsessive-compulsive spectrum disorders similar to 'behavioural' addictive disorders.[23-29] Impulsivity is a goal-directed behaviour in the attainment of different rewards, such as sex, food, money or addictive drugs.[30-32] Compulsions are defined as uncontrollable thoughts or impulses to perform an act; however, there are differences between obsessive-compulsive disorders (OCD), ICDs and substance use disorders. Repetitive behaviours in OCD are aimed to reduce or prevent anxiety (negative reinforcement) and the performance of a specific act is associated with stress relief and not pleasure or gratification (positive reinforcement) as in ICDs and substance use disorders.[33]

The aim of this review is to summarize current evidence on the epidemiology of behavioural disturbances in Parkinson's disease, recent insights on their neurobiological basis and to discuss strategies for management and prevention.

Studies were retrieved via searches of the Cochrane Database of Systematic Reviews and PubMed. Searches were conducted from 1990 through December 2008 using the keywords and subjects 'Parkinson's disease', 'impulse control disorders', 'pathological gambling', 'dopamine dysregulation syndrome', 'behaviour' and 'dopamine'. Further articles and abstracts were found using the reference citations from articles identified.

1. Epidemiology

ICDs are defined in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR) as 'the failure to resist an impulse, drive, or temptation to perform

Table I. Dopaminergic medications in studies reporting medication-induced behavioural disorders in Parkinson's disease

Study (y)	Behavioural disorder (number of patients)	Medication [type of DA (number of patients)]	Study Population
Molina et al.[3] (2000)	Pathological gambling (12)	Levodopa + DA (12)	NA
Giovannoni et al.[4] (2000)	DDS (4), hypersexuality (2)	Levodopa + DA [apomorphine (4), bromocriptine (2), pergolide (1)]	NA
Gschwandtner et al.[5] (2001)	Pathological gambling + DDS (2),	Levodopa + DA [pergolide (1), ropinirole (1)]	NA
Montastruc et al.[6] (2003)	Pathological gambling (1)	Levodopa + DA [bromocriptine]	NA
Driver-Dunckley and Samanta[7] (2003)	Pathological gambling (9)	Levodopa + DA [pramipexole (8), pergolide (1)]	1884
Avanzi et al.[8] (2004)	Pathological gambling (2)	Levodopa + DA [ropinirole (1), cabergoline (1)]	NA
Kurlan[9] (2004)	Pathological gambling (2), punding (4)	Levodopa + DA [pramipexole (2)], levodopa monotherapy (4)	NA
Dodd et al.[10] (2005)	Pathological gambling (11)	Levodopa + DA [pramipexole (9), ropinirole (2)]	NA
Klos et al.[11] (2005)	Hypersexuality (13)	Levodopa monotherapy (1), DA monotherapy (12) [pramipexole (6), ropinirole (4), pergolide (2)]	NA
Weintraub et al.[12] (2006)	Pathological gambling (6), hypersexuality (4), compulsive shopping (1)	Levodopa + DA [pramipexole (6), ropinirole (4), pergolide (1)]	272
Voon et al.[13,14] (2006)	Pathological gambling (10), Hypersexuality (7), compulsive shopping (2)	Pathological gambling: DA monotherapy (1), levodopa + DA [ropinirole (4), pramipexole (3), pergolide (2)] Hypersexuality: levodopa monotherapy (1) levodopa + DA [pramipexole (5), ropinirole (1)] Compulsive shopping: levodopa + DA [pramipexole (1), ropinirole (1)]	297
Grosset et al.[15] (2006)	Pathological gambling (17)	DA monotherapy (8); levodopa + DA (9) [pramipexole (9), ropinirole (7), pergolide (1)]	388
Pontone et al.[16] (2006)	Pathological gambling, hypersexuality, compulsive shopping (9 in total)	DA monotherapy [pramipexole (1)]; levodopa + DA [pramipexole (6) ropinirole (2)]	100
Imamura et al.[17] (2006)	Pathological gambling (6)	DA monotherapy (2); levodopa + DA (4) [pramipexole (4), ropinirole (1), cabergoline (1)]	NA
Drapier et al.[18] (2006)	Pathological gambling (6)	Levodopa + DA [pergolide (2), bromocriptine (2), ropinirole (1), selegiline (1)]	NA
Nirenberg and Waters[19] (2006)	Binge eating, pathological gambling and hypersexuality (7 in total)	DA monotherapy [pramipexole (5)]; levodopa + DA [pramipexole (2)]	NA
Voon et al.[20] (2007)	Pathological gambling (21)	DA monotherapy (1); levodopa + DA [ropinirole (8), pergolide (7), pramipexole (5)]	NA
Wong et al.[21] (2007)	Pathological gambling (8)	Levodopa + DA [ropinirole (3), cabergoline (3), pergolide (2)]	NA
Isaias et al.[22] (2008)	Pathological gambling, hypersexuality, compulsive shopping (20 in total)	NA	50

DA = dopamine receptor agonist; **DDS** = dopamine dysregulation syndrome; **NA** = not available.

an act that is harmful to the person or to others'.[34] The DSM-IV-TR lists as ICDs, intermittent explosive disorder (failure to resist aggressive impulses), pyromania, trichotillomania, kleptomania (failure to resist urges to steal items) and pathological gambling (failure to resist the impulse to gamble despite severe personal, family, or vocational consequences). Binge-eating disorder, hypersexuality and compulsive buying are classified separately in the DSM-IV-TR.[34-36]

In Parkinson's disease, the development of repetitive and/or reward-seeking behaviours is

attributed to stimulation associated with DRT.[12,14] There is debate whether reward-seeking behaviours are associated with individual dopaminergic drugs. Initial observations have linked ICDs to dopamine receptor agonists with preferential activity on dopamine D_3 receptors due to their high expression in brain limbic areas, particularly pramipexole and ropinirole.[10,19] However, methodological observations have been raised suggesting that variables such as different prescribing practices or dosing may be confounding factors.[14,16] Accordingly, a meta-analysis demonstrated no significant association between ICDs and individual dopamine agonists, showing similar odds ratios between pramipexole and ropinorole as well as between ergot and non-ergot derivatives.[37] More recently, a large, cross-sectional, multicentre study of over 3000 Parkinson's disease patients reported a 2- to 3-fold higher odds of presenting with at least one ICD in patients treated with dopamine agonists compared with the non-treated group (17.1% vs 6.9%). This effect was associated with dopamine agonists irrespectively of the concomitant use of levodopa. More importantly, the effect was class specific and confirmed that ICDs are not due to a specific medication[38,39] as previously hypothesized.

It appears that about 80% of ICD cases may develop during the first years of therapy, largely dependent on the pre-morbid personality, with dose and duration of DRT as secondary factors.[10,40] This condition may occur under standard therapy or in the context of 'hedonistic homeostatic dysregulation' or 'dopamine dysregulation syndrome',[4,36] an addictive behaviour that is characterized by overuse of dopaminergic medications. Patients persist in taking rapidly increasing drug doses through self-medication (typically medications with rapid onset of action like apomorphine or levodopa) to feel the 'high' similar to addictive disorders.[4,41]

Literature data on ICDs vary widely, both in terms of prevalence and time to onset. Their mean prevalence in Parkinson's disease is 6–7%, up to 14–17% in patients on dopamine agonist therapy.[14,37,42] The mean prevalence in the general population has been estimated at between 0.25%[40] and 3%,[43] up to 10.6% in studies performed among adults in medical settings.[44] We recently evaluated the relative frequency of ICDs in a selected cohort of Parkinson's disease patients and healthy controls and found it around 10% of all examined subjects.[22] In a recent large study by Weintraub et al.,[42] the most common ICD was compulsive buying (7.2%), followed by pathological gambling (6.4%), binge eating (5.6%) and compulsive sexual behaviour (4.4%). The prevalence of dopamine dysregulation syndrome is estimated at between 3 and 4%.[4]

Specific clinical features are associated with higher risk of developing ICDs or dopamine dysregulation syndrome, including young age at Parkinson's disease onset, impulsivity traits and pre-morbid impulsive behaviours, depression, family history of gambling problems[42] or personal and family alcohol and/or substance abuse.[12,20,22,36,37,42,45,46] Sex differences may account for different ICD profiles in Parkinson's disease patients, i.e. hypersexuality and pathological gambling are mostly reported in the male population.[14,37]

Reward-seeking behaviours may result in severe distress, impairing social and occupational functioning with serious consequences for patient, family and even for the treating physician (legal implications).[47] Nevertheless, the condition is probably still under-diagnosed, often because patients do not appreciate the connection with their Parkinson's disease medication or do not perceive behavioural changes as adverse effects. Moreover, they are not inclined to discuss this condition with the caregivers or the treating neurologist.

2. Neurobiological Basis

2.1 Neurodegeneration and Dopamine Replacement Therapy in Reward-Related Processes

The neurodegenerative process in Parkinson's disease involves not only the nigrostriatal dopaminergic neurons, but also the ventral tegmental area projecting to the nucleus accumbens, amygdala and hippocampus (i.e. the mesolimbic dopaminergic pathways) as well as orbitofrontal, anterior cingulate and prefrontal cortices (i.e.

the mesocortical dopaminergic pathways).[48,49] These regions are involved in the modulation of reward, positive versus negative reinforcement learning, motivation, memory, inhibitory control and decision-making,[50-54] and are thus closely implicated in impulse control and modulation of reward-seeking behaviours.

The exact role played by the neurodegeneration in the mesolimbic and mesocortical pathways in the development of ICDs is debated. In untreated Parkinson's disease there is a different pattern of cerebral activation in response to monetary reward compared to healthy controls, suggesting an abnormal reward response due to reduced dopamine availability in the mesolimbic and mesocortical dopamine pathways.[55-57] The effects of DRT on cognitive functioning are closely associated with basal dopamine levels in distinct brain regions, so that medication doses compensating for the most depleted dorsal striatum may over-stimulate relatively spared ventral regions.[58-60] The 'overdose hypothesis' would explain the dysfunction in neural networks underlying cognitive and behavioural functions relevant to the development of ICDs in Parkinson's disease patients taking medication, such as increased impulsivity,[61] sensitivity to reward,[56] as well as deficit in reversal learning and response inhibition.[62] Moreover, baseline dopamine levels strongly influence learning processes in Parkinson's disease, since patients not taking medication learn better how to avoid choices possibly leading to a negative outcome, while patients taking medication are more sensitive to positive rather than negative feedback.[51,63] Accordingly, it has been recently suggested that ICDs may be associated with greater ventral striatal neuronal sensitivity to the outcome prediction error teaching signal, in particular positive feedback.[64] The pattern of dopamine release within the mesolimbic pathway is critical to the reinforcing properties shared by different drugs with potential for abuse as well as rewarding behaviours (i.e. eating, sex and gambling). It is conceivable that intermittent and chronic stimulation of the mesocorticolimbic dopaminergic pathways induced by pulsatile dopaminergic medication disrupts the physiological patterns of dopamine release (both tonic and phasic), producing abnormalities of the mesocortical dopaminergic pathways with plastic adaptive changes within the reward circuit. Pathologically increased saliency attribution to a particular reward produces irresistible and increasingly compulsive drive toward the reward as well as loss of inhibitory control similar to substance abuse.[32,65,66]

The preference of immediate rewards over delayed rewards of larger value (delay discounting) is associated with impairment of decision-making and impulsivity, a common feature of ICDs and substance abuse.[67-69] Neuroimaging studies demonstrated that patients undergoing the Iowa Gambling Task (IGT) activate the neural circuitry that is critical in decision-making under uncertainty, particularly when subjects perceive the risk of their decision.[70] In healthy subjects the anticipation of risk may be addictive as well, as it is associated with phasic dopamine release in the nucleus accumbens. Therefore, chronic exposure to risky behaviours involving rewards (such as money or sex) may trigger adaptive changes in the reward system and, in susceptible individuals, become addictive. Indeed, there is an inverse relationship between decision-making and global cognitive performance in Parkinson's disease, namely patients performing worst at the IGT performed best at memory and frontal lobe testing.[71] Impaired decision-making in Parkinson's disease patients taking medication is also associated with inability to learn from negative reinforcement.[51,71] Therefore, preserved cognitive function would enable Parkinson's disease patients to entertain reward-linked behaviours during dopaminergic therapies, in the presence of specific personality traits (high impulsivity) and/or genetic polymorphisms linked to the mesocorticolimbic dopamine system (figure 1). We recently reported that pathological gambling in treated Parkinson's disease patients is associated with resting state overactivity within a right-sided network, including the ventral basal ganglia, the orbitofrontal cortex, the amygdala, the insular cortex and the hippocampus/parahippocampal gyrus, without areas of relative hypoactivity.[72] These data would also explain the development of ICDs in patients with restless legs syndrome

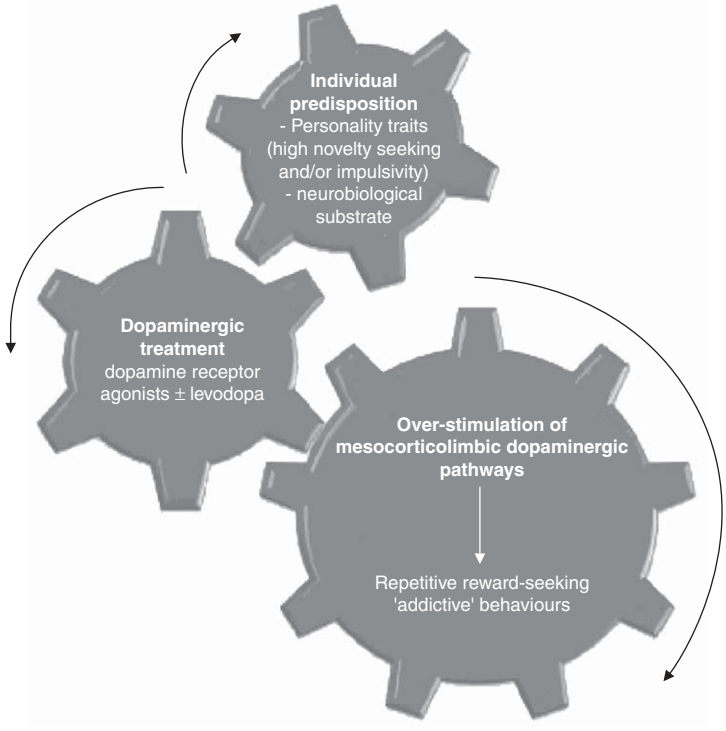

Fig. 1. Putative mechanisms underlying the development of impulse control disorders in patients with Parkinson's disease on medication. According to our hypothesis, addictive behaviours occur in vulnerable individuals with specific pre-morbid personality traits (such as high novelty seeking or impulsivity) and/or predisposing genetically-determined neurobiological features (i.e. high ventral striatum activity) as a result of abnormal overstimulation of the mesocorticolimbic dopamine system by dopaminergic medications.

treated with dopaminergic drugs without cognitive impairment or mesolimbocortical pathway neurodegeneration.[73,74]

2.2 Individual Predisposition

ICDs, in particular pathological gambling, develop in susceptible patients as a consequence of a complex interaction between DRT and underlying individual vulnerability.[36] Most evidence suggests contribution of genetic and neurobiological features lowering the threshold of 'exposure to reward' needed for switching from occasional to repetitive reward-seeking behaviours.[32] Individual differences in trait reward sensitivity are also reported in subjects with binge-eating disorder and substance use disorders, suggesting common neurobiological factors related to the mesocorticolimbic network.[75,76]

Indeed, rats with baseline elevated activity of the ventral tegmental area dopaminergic neurons showed enhanced motivation to drug self-administration and increased drug-seeking behaviour in response to a novel environment. Interestingly, plastic changes were associated with decreased functional activity of pre-synaptic impulse-regulating D_2 autoreceptors.[77] According to this model, it is hypothesized that either spontaneously present (inherited vulnerability) and/or environment-induced (i.e. differential impact of long-term dopaminergic drug use) increased dopaminergic neuron activity may determine long-term adaptive changes in the neuronal firing pattern of the reward circuit, facilitating the development of addictive disorders.[41] In line with these data, some authors observed that individual hyper-reactivity of the ventral striatum and its connected structures in humans are

associated with increased impulsivity, novelty seeking and high risk of addictive behaviours.[69,78]

3. From Neurobiological Basis to Clinical Management

3.1 Recognition of Impulse Control Disorders in the Clinic

The first and most important step in the clinical management of ICDs is the diagnosis. Recognition is difficult mostly because patients are reluctant to discuss the development of unusual behaviours or because clinicians fail to screen for it.[47] In our clinic we have recently started proposing psychological support along with detailed assessment of impulsivity as well as scales for ICD and obsessive-compulsive behaviours to all newly diagnosed Parkinson's disease patients. This may help early recognition of these problems so that at-risk subjects can be monitored. Moreover, clinicians should be aware that impulse control disorders occur with different timing in the course of Parkinson's disease and their relationship with medications depends on motor and cognitive status (figure 2).

3.2 Therapeutic Options

3.2.1 Evidence in Parkinson's Disease

Dopaminergic Medication

The first observations linked these behavioural abnormalities to taking high-dose levodopa[3] or dopamine agonists,[12] although more recently ICDs were reported in patients with medications in the standard dose range.[36] There may be a benefit from lowering or discontinuing implicated medications, particularly dopamine agonists.[19,79] However, reduction of the dopamine agonist dose may worsen mobility even when levodopa is increased. Moreover, patients with ICDs should be assessed for symptoms of dopamine dysregulation syndrome[4] as they are at greater risk of addictive-like behaviour and thus may refuse to comply. In these cases, adjunctive psychiatric medications may help. A follow-up study investigated behavioural and motor outcome in Parkinson's disease patients who developed ICD during DRT.[79] The authors described at 29-month follow-up, 15 Parkinson's disease patients with ICDs who had shown remission or significant reduction of ICD without worsening motor symptoms after discontinuing or decreasing the dose of dopamine agonists, balanced by an increase in levodopa treatment to obtain a similar total equivalent dosage.

It is worth mentioning that hypersexuality and other ICDs have also been described in patients treated with monoamine oxidase inhibitors.[80,81]

Role of Deep Brain Stimulation

Subthalamic nucleus deep brain stimulation (STN-DBS) has been proposed in patients with Parkinson's disease and ICDs because it allows reduction in medication dosage.[82-85] The main

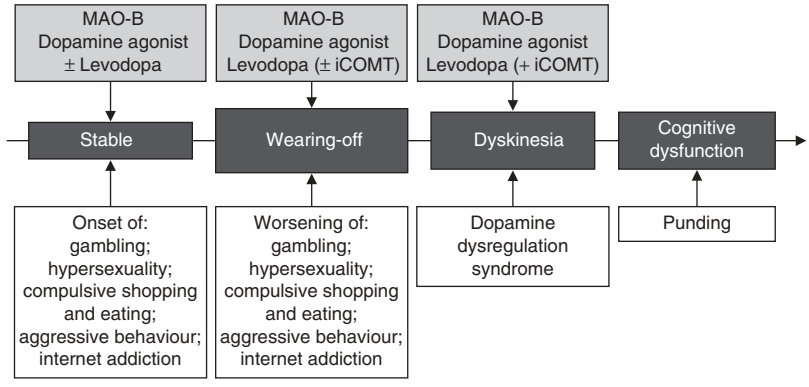

Fig. 2. Timing for development of impulse control disorders in patients with Parkinson's disease and their relationship to motor status and medications. **iCOMT** = inhibitor of catechol methyltransferase; **MAO-B** = monoamine oxidase type B inhibitor.

findings of studies examining STN-DBS-associated behavioural disturbances are summarized in table II.

Ardouin and colleagues[83] recently described seven patients with advanced Parkinson's disease and preoperative active pathological gambling from a total of 598 patients who underwent STN-DBS. Six patients had non-motor fluctuations and four had a diagnosis of dopamine dysregulation syndrome. After surgery, the improvement in motor symptoms allowed a 74% reduction in medication dose. The reduction of total levodopa equivalent daily dose determined the resolution of pathological gambling, and improved non-motor fluctuations and dopamine dysregulation syndrome in all patients after a variable period of time.

However, STN-DBS may also induce transient mania or worsen behavioural symptoms, such as pathological gambling,[83,87,89] hypersexuality[86,87] and compulsive medication intake.[87] It is still unclear whether reward-seeking behaviours are due to effective stimulation of the limbic area of the STN or secondary to surgery lesion effects.[82,87,90-92] The former hypothesis is supported by evidence of STN stimulation-induced enhanced impulsivity during decision conflict,[92] while the latter is suggested by case reports of STN lesion-induced enhanced drive towards sex[90] or food[91] in rats and humans. Interestingly, case reports describe patients who developed disturbance in sexual behaviour following globus pallidus surgery (in particular after right-sided pallidal lesions)[93,94] as well as a case of 'morphine-like' feeling of pleasure (similar to 'sexual climax') leading to compulsive self-stimulation after right STN stimulation.[88] A prevalent right-sided hemispheric involvement has also been recently suggested in pathological gamblers with Parkinson's disease.[72]

It should be highlighted that behavioural complications often occurred in patients with undetected abnormal pre-surgical neuropsychological/psychiatric features, i.e. initial cognitive impairment[89] or personal history of mood disorders, compulsive behaviours or even past substance abuse.[83,86,87,95] Contrasting results about the incidence of non-motor complications after DBS likely reflect insufficient knowledge on past psychiatric and/or behavioural disorders in subjects who underwent DBS. Current recommendations are that DBS should be proposed only to selected patients with behavioural/psychiatric treatment-related complications, and the consequences of surgical treatment should be carefully assessed by

Table II. Behavioural disorders and deep brain stimulation: onset of clinical symptoms, therapeutic management and outcome in Parkinson's disease patients

Study (y)	Behavioural disorder (number of patients/total)	Onset	Management and outcome
Witjas et al.[82] (2005)	DDS and hypersexuality (2)	Pre-surgical	Improvement after DRT reduction/withdrawal
Ardouin et al.[83] (2006)	Pathological gambling (7/7), DDS (4/7)	Pre-surgical	Long-term improvement of pathological gambling and DDS in all patients after DRT reduction. Transient post-operative worsening in 2/7 patients
Bandini et al.[84] (2007)	Pathological gambling (2/2), DDS (1/2)	Pre-surgical	Improvement after DRT withdrawal
Knobel et al.[85] (2008)	DDS	Pre-surgical	Improvement after DRT reduction
Romito et al.[86] (2002)	Transient mania and hypersexuality (2)	Post-surgical	Spontaneous resolution
Houeto et al.[87] (2002)	DDS and hypersexuality (2/2), Pathological gambling (1/2), self-stimulatory behaviour (1/2)	Post-surgical	Not reported
Morgan et al.[88] (2006)	Self-stimulatory behaviour (1)	Post-surgical	Resolution after amplitude reduction/stimulator turn off
Smeding et al.[89] (2007)	Pathological gambling (2)	Post-surgical	Improvement after parameters changed and pergolide withdrawal

DDS = dopamine dysregulation syndrome; **DRT** = dopamine replacement therapy.

a team of specialists (neurologist, neuropsychologist and/or psychiatrist).[83]

3.2.2 Alternative Pharmacological Options

Several studies are available in individuals without Parkinson's disease and a wide range of drugs have been tested, based on the observations of phenomenological similarities between ICDs, obsessive-compulsive and addictive disorders. This evidence may also help to define treatment strategies for Parkinson's disease patients with similar disorders.

Antidepressants

The serotonin system is associated with ICD and treatment with selective serotonin reuptake inhibitors (SSRIs) may lead to fewer thoughts on reward, less participation in behaviour, and improved social and occupational functioning.[96] However, data from double-blind, randomized, pharmacotherapy trials of SSRIs, although promising, have been inconclusive. In particular, studies using fluvoxamine showed contrasting results,[97,98] while others failed to consistently demonstrate the efficacy of paroxetine[99,100] and sertraline[101] in treating pathological gambling. Two open-label trials on the safety and efficacy of escitalopram in small cohorts of patients with pathological gambling showed promising results, reporting an improvement of 61–74% in the Yale-Brown Obsessive Compulsive Scale, Modified for pathological gambling (PG-YBOCS).[102,103] SSRIs are commonly used in the treatment of binge-eating disorders with positive outcome, in particular fluoxetine.[104,105]

Improvement after antidepressant therapy is reported in sporadic Parkinson's disease cases with pathological gambling[3] or hypersexuality,[11] but no controlled study has been performed so far. Because SSRIs are used extensively in depressed patients with Parkinson's disease they may also be considered for the treatment of ICDs. More importantly, we recently found that both Parkinson's disease patients and controls with ICDs had higher scores for depression, suggesting a contribution to the development of abnormal behaviours in Parkinson's disease.[22]

Mood Stabilizers and Opioid Receptor Antagonists

Lithium reduced gambling urges, thoughts and behaviours in patients with bipolar disorder.[106,107] A randomized, single-blind study investigating safety and efficacy of lithium versus valproate in the treatment of pathological gambling evidenced significant improvement of both mood stabilizers in mean score on the PG-YBOCS.[35] There is also evidence on the efficacy of topiramate in the treatment of pathological gambling.[97] Case reports suggested positive results from lithium, valproate and topiramate in the treatment of kleptomania.[108-110] Lithium was ineffective in a case of dopamine dysregulation syndrome aggravated after STN-DBS[87]

Opioid receptor antagonists have been tested as a possible treatment for pathological gambling[111] since their efficacy in the treatment of addictive disorders involves opioidergic modulation of mesolimbic dopamine circuitry[112] by reducing dopamine release in the nucleus accumbens and gambling-related craving.[113] The use of the opioid receptor antagonists naltrexone and nalmefene has shown positive results in the treatment of pathological gambling.[111,114]

However, neither mood stabilizers nor opioid receptor antagonists have been tested so far in large populations of patients with Parkinson's disease and ICDs, and their use should be considered with caution.

Atypical Antipsychotics

In individuals without Parkinson's disease, olanzapine was ineffective in the treatment of pathological gambling,[115,116] while clozapine and olanzapine induced recurrence or worsening of food craving and binge-eating disorders in two large studies.[117,118]

Although the mechanisms underlying medication-induced addictive behaviours in Parkinson's disease probably involve dopamine receptors within the mesocortical and mesolimbic pathways, the benefits of atypical antipsychotics are only effective in individual cases. In particular, Parkinson's disease patients with pathological gambling responded to low-dose risperidone,[119] quetiapine,[11,120] and olanzapine,[11] while clozapine may reduce hypersexuality in Parkinson's

disease[121,122] but was ineffective in pathological gambling.[83] In another case report, compulsive medication intake and hypersexuality was aggravated after STN-DBS.[87] Olanzapine has been used in behavioural disorders involving self-control deficit and/or aggressiveness but its use in Parkinson's disease is limited because of the worsening of motor symptoms. Quetiapine and clozapine are better tolerated in Parkinson's disease but are not actually indicated in non-psychotic behavioural disorders.

Anti-Glutamatergic Drugs

Glutamate mediates reward-seeking behaviour within the nucleus accumbens.[78,123] Experimental studies demonstrated that the stimulation of inhibitory metabotropic glutamate receptors by acetylcysteine reduces reward-seeking compulsive behaviours and decreases cravings in rats with cocaine dependence.[124] These data are confirmed in clinical trials in humans with cocaine addiction.[125]

Recently, Grant et al.[126] assessed the efficacy of acetylcysteine in 27 pathological gambling subjects during an 8-week open-label trial followed, in those who met responder criteria (defined as a >30% reduction in PG-YBOCS), by a 6-week, double-blind phase of double-blind acetylcysteine or placebo. At the end of the open-label phase, 59% of subjects were considered responders and more than 80% of those assigned to acetylcysteine still met responder criteria at the end of the double-blind phase, compared with only 29% of those assigned to placebo.

Behavioural Therapies

A recent systematic review and meta-analysis[127] of all randomized, controlled trials of psychological treatments for pathological gambling identified only four studies, with small numbers of participants and poor methodological quality features. Behavioural or cognitive-therapy seems more efficacious than control interventions,[127] with similar positive outcomes from both behavioural therapies and Gamblers Anonymous.[128]

Currently, the role of counselling and supportive psychotherapy in Parkinson's disease patients with addictive behaviours (ICDs and dopamine dysregulation syndrome) is limited to a few cases with variable outcomes.[5,7,9,21,83,87] However, in our experience this is helpful and we are currently offering support to all patients who present at-risk personality traits.

4. Prevention

Recent studies suggest that specific clinical features, including male sex, young age at Parkinson's disease onset, impulsivity traits and premorbid impulsive behaviours, depression and history of personal and family alcohol and/or substance abuse are associated with a higher risk of developing addictive behaviours.[12,22,36,37,45,46] Clinicians should identify vulnerable Parkinson's disease patients and monitor behavioural features during treatment with dopaminergic medication, particularly if dopamine agonists are used. The Barratt Impulsiveness Scale and Minnesota Impulsive Disorders Interview may be useful in the identification of at-risk subjects before treatment initiation.[12,22]

5. Conclusions

ICDs and other addictive disorders occur in susceptible Parkinson's disease patients during dopaminergic therapy, particularly in association with dopamine agonists. Management should involve consideration of the reduction or discontinuation of the dopamine agonist, use of an SSRI and possibly psychosocial support and counselling. DBS should be proposed with caution as the potential benefit of achieving motor control with lower medication doses may be counterbalanced by the unpredictability of stimulation-induced behavioural effects.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest to declare that are directly relevant to the content of this review.

References

1. Zesiewicz TA, Gold M, Chari G, et al. Current issues in depression in Parkinson's disease. Am J Geriatr Psychiatry 1999; 7 (2): 110-8

2. Antonini A, Colosimo C, Marconi R, et al. The PRIAMO study: background, methods and recruitment. Neurol Sci 2008; 29 (2): 61-5
3. Molina JA, Sáinz-Artiga MJ, Fraile A, et al. Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? Mov Disord 2000; 15 (5): 869-72
4. Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry 2000; 68 (4): 423-8
5. Gschwandtner U, Aston J, Renaud S, et al. Pathological gambling in patients with Parkinson's Disease. Clin Neuropharmacol 2001; 24: 170-2
6. Montastruc JL, Schmitt L, Bagheri H. Pathological gambling behavior in a patient with Parkinson's disease treated with levodopa and bromocriptine. Rev Neurol (Paris) 2003; 159 (4): 441-3
7. Driver-Dunckley E, Samanta J. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. Neurology 2003; 61 (3): 422-3
8. Avanzi M, Uber E, Bonfà F. Pathological gambling in two patients on dopamine replacement therapy for Parkinson's disease. Neurol Sci 2004; 25: 98-101
9. Kurlan R. Disabling repetitive behaviors in Parkinson's disease. Mov Disord 2004; 19 (4): 433-69
10. Dodd ML, Klos KJ, Bower JH, et al. Pathological gambling caused by drugs used to treat Parkinson disease. Arch Neurol 2005; 62 (9): 1377-81
11. Klos KJ, Bower JH, Josephs KA, et al. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. Parkinsonism Relat Disord 2005; 11: 381-6
12. Weintraub D, Siderowf AD, Potenza MN, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol 2006; 63 (7): 969-73
13. Voon V, Hassan K, Zurowski M, et al. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. Neurology 2006; 13 (11): 1750-2
14. Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology 2006; 67 (7): 1254-7
15. Grosset KA, Macphee G, Pal G, et al. Problematic gambling on dopamine agonists: not such a rarity. Mov Disord 2006; 21 (12): 2206-8
16. Pontone G, Williams JR, Bassett SS, et al. Clinical features associated with impulse control disorders in Parkinson disease. Neurology 2006; 67 (7): 1258-61
17. Imamura A, Uitti RJ, Wszolek ZK. Dopamine agonist therapy for Parkinson disease and pathological gambling. Parkinsonism Relat Disord 2006; 12 (8): 506-8
18. Drapier D, Drapier S, Sauleau P, et al. Pathological gambling secondary to dopaminergic therapy in Parkinson's disease. Psychiatry Res 2006; 144 (2-3): 241-4
19. Nirenberg MJ, Waters C. Compulsive eating and weight gain related to dopamine agonist use. Mov Disord 2006; 21 (4): 524-9
20. Voon V, Thomsen T, Miyasaki JM, et al. Factors associated with dopaminergic medication-related pathological gambling in Parkinson disease. Arch Neurol 2007; 64 (2): 212-6
21. Wong SH, Cowen Z, Allen EA, et al. Internet gambling and other pathological gambling in Parkinson's disease: a case series. Mov Disord 2007; 22 (4): 591-3
22. Isaias IU, Siri C, Cilia R, et al. The relationship between impulsivity and impulse control disorders in Parkinson's disease. Mov Disord 2008; 23 (3): 411-5
23. Hollander E, Wong CM. Obsessive-compulsive spectrum disorders. J Clin Psychiatry 1995; 56 Suppl. 4: 3-6
24. Blaszczynski A. Pathological gambling and obsessive-compulsive spectrum disorders. Psychol Rep 1999; 84 (1): 107-13
25. Holden C. 'Behavioral' addictions: do they exist? Science 2001; 294 (5544): 980-2
26. Blanco C, Moreyra P, Nunes EV, et al. Pathological gambling: addiction or compulsion? Semin Clin Neuropsychiatry 2001; 6: 167-76
27. Grant JE, Potenza MN. Compulsive aspects of impulse-control disorders. Psychiatr Clin North Am 2006; 29 (2): 539-51
28. Potenza MN. Should addictive disorders include non-substance-related conditions? Addiction 2006; 101 Suppl. 1: 142-51
29. Petry NM. Gambling and substance use disorders: current status and future directions. Am J Addict 2007; 16 (1): 1-9
30. Moeller FG, Barratt ES, Dougherty DM, et al. Psychiatric aspects of impulsivity. Am J Psychiatry 2001; 158: 1783-93
31. Vitacco MJ, Rogers R. Predictors of adolescent psychopathy; the role of impulsivity, hyperactivity, and sensation seeking. J Am Acad Psychiatry Law 2001; 29: 374-82
32. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry 2003; 160 (6): 1041-52
33. Koob GF, Ahmed SH, Boutrel B, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. Neurosci Biobehav Rev 2004; 27 (8): 739-49
34. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., text revision. Washington, DC: American Psychiatric Association, 2000
35. Pallanti S, Quercioli L, Sood E, et al. Lithium and valproate treatment of pathological gambling: a randomized single-blind study. J Clin Psychiatry 2002; 63 (7): 559-64
36. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. Arch Neurol 2007; 64 (8): 1089-96
37. Gallagher DA, O'Sullivan SS, Evans AH, et al. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. Mov Disord 2007; 22 (12): 1757-63
38. Lu C, Bharmal A, Suchowersky O. Gambling and Parkinson disease [letter]. Arch Neurol 2006; 63 (2): 298
39. Fox S. Dopamine receptor pharmacology and impulse control disorders in PD. Mov Disord 2008; 23 (9) 1333-4
40. Avanzi M, Baratti M, Cabrini S, et al. Prevalence of pathological gambling in patients with Parkinson's disease. Mov Disord 2006; 21: 2068-72

41. Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet Neurol 2003; 2 (10): 595-604
42. Weintraub D, Koester J, Potenza M, et al. Dopaminergic therapy and impulse control disorders in Parkinson's disease: top line results of a cross-sectional study of over 3000 patients [abstract]. Mov Disord 2008; 23 Suppl. 4: 38
43. Shaffer HJ, Hall MN, Vander Bilt J. Estimating the prevalence of disordered gambling in the United States and Canada: a research synthesis. Am J Public Health 1999; 89: 1369-76
44. Morasco BJ, Vom Eigen KA, Petry NM. Severity of gambling is associated with physical and emotional health in urban primary care patients. Gen Hosp Psychiatry 2006; 28: 94-100
45. Potenza MN, Fiellin DA, Heninger GR, et al. Gambling: an addictive behavior with health and primary care implications. J Gen Intern Med 2002; 17 (9): 721-32
46. Evans AH, Lawrence AD, Potts J, et al. Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease. Neurology 2005; 65 (10): 1570-4
47. Grant JE, Levine L, Kim D, et al. Impulse control disorders in adult psychiatric inpatients. Am J Psychiatry 2005; 162 (1): 2184-8
48. Javoy-Agid F, Agid Y. Is the mesocortical dopaminergic system involved in Parkinson's disease? Neurology 1980; 30: 1326-30
49. Ouchi Y, Yoshikawa E, Okada H, et al. Alterations in binding site density of dopamine transporter in the striatum, orbitofrontal cortex, and amygdala in early Parkinson's disease: compartment analysis for β-CFT binding with positron emission tomography. Ann Neurol 1999; 45: 601-10
50. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997; 275: 1593-9
51. Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004; 306 (5703): 1940-3
52. Girault JA, Greengard P. The neurobiology of dopamine signaling. Arch Neurol 2004; 61 (5): 641-4
53. Schultz W. Behavioral dopamine signals. Trends Neurosci 2007; 30 (5): 203-10
54. Volkow ND, Fowler JS, Wang GJ, et al. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol 2007; 64 (11): 1575-9
55. Künig G, Leenders KL, Martin-Sölch C, et al. Reduced reward processing in the brains of Parkinsonian patients. Neuroreport 2000; 11 (17): 3681-7
56. Czernecki V, Pillon B, Houeto JL, et al. Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 2002; 40 (13): 2257-67
57. Goerendt IK, Lawrence AD, Brooks DJ. Reward processing in health and Parkinson's disease: neural organization and reorganization. Cereb Cortex 2004; 14 (1): 73-80
58. Kulisevsky J, Avila A, Barbanoj M, et al. Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels. Brain 1996; 119: 2121-32
59. Frank MJ. Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. J Cogn Neurosci 2005; 17 (1): 51-72
60. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006; 30 (1): 1-23
61. Cools R, Barker RA, Sahakian BJ, et al. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003; 41 (11): 1431-41
62. Cools R, Lewis SJ, Clark L, et al. L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. Neuropsychopharmacology 2007; 32 (1): 180-9
63. Dagher A, Robbins TW. Personality, addiction, dopamine: insights from Parkinson's disease. Neuron 2009; 61: 502-10
64. Voon V, Pessiglione M, Brezing C, et al. Dopamine agonist-induced gambling and shopping is associated with enhanced reward learning mediated via dopaminergic ventral striatal prediction error teaching signal [abstract]. Mov Disord 2008; 23 Suppl. 14: 35
65. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993; 18: 247-91
66. Hyman SE. Addiction: a disease of learning and memory. Am J Psychiatry 2005; 162 (8): 1414-22
67. Bechara A, Damasio AR, Damasio H, et al. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 1994; 50: 7-15
68. Alessi SM, Petry NM. Pathological gambling severity is associated with impulsivity in a delay discounting procedure. Behav Processes 2003; 64 (3): 345-54
69. Hariri AR, Brown SM, Williamson DE, et al. Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. J Neurosci 2006; 26 (51): 13213-7
70. Fukui H, Murai T, Fukuyama H, et al. Functional activity related to risk anticipation during performance of the Iowa Gambling Task. Neuroimage 2005; 24 (1): 253-9
71. Pagonabarraga J, Kulisevsky J, Llebaria G, et al. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord 2008; 23 (7): 998-1005
72. Cilia R, Siri C, Marotta G, et al. Functional abnormalities underlying pathological gambling in Parkinson's disease. Arch Neurol 2008; 65: 1604-11
73. Tippmann-Peikert M, Park JG, Boeve BF, et al. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology 2007; 68 (4): 301-3
74. Evans AH, Butzkueven H. Dopamine agonist-induced pathological gambling in restless legs syndrome due to multiple sclerosis. Mov Disord 2007; 22 (4): 590-1
75. Wang GJ, Yang J, Volkow ND, et al. Gastric stimulation in obese subjects activates the hippocampus and other regions involved in brain reward circuitry. Proc Natl Acad Sci USA 2006; 103 (42): 15641-5

76. Beaver JD, Lawrence AD, van Ditzhuijzen J, et al. Individual differences in reward drive predict neural responses to images of food. J Neurosci 2006; 26 (19): 5160-6
77. Marinelli M, White FJ. Enhanced vulnerability to cocaine self-administration is associated with elevated impulse activity of midbrain dopamine neurons. J Neurosci 2000; 20 (23): 8876-85
78. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005; 162 (8): 1403-13
79. Mamikonyan E, Siderowf AD, Duda JE, et al. Long-term follow-up of impulse control disorders in Parkinson's disease. Mov Disord 2008; 23 (1): 75-80
80. Riley DE. Reversible transvestic fetishism in a man with Parkinson's disease treated with selegiline. Clin Neuropharmacol 2002; 25 (4): 234-7
81. Shapiro MA, Chang YL, Munson SK, et al. Hypersexuality and paraphilia induced by selegiline in Parkinson's disease: report of 2 cases. Parkinsonism Relat Disord 2006; 12 (6): 392-5
82. Witjas T, Baunez C, Henry JM, et al. Addiction in Parkinson's disease: impact of subthalamic nucleus deep brain stimulation. Mov Disord 2005; 20 (8): 1052-5
83. Ardouin C, Voon V, Worbe Y, et al. Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. Mov Disord 2006; 21 (11): 1941-6
84. Bandini F, Primavera A, Pizzorno M, et al. DBS and medication reduction as a strategy to treat pathological gambling in Parkinson's disease. Parkinsonism Relat Disord 2007; 13 (6): 369-71
85. Knobel D, Aybek S, Pollo C, et al. Rapid resolution of dopamine dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): a case report. Cogn Behav Neurol 2008 Sep; 21 (3): 187-9
86. Romito LM, Raja M, Daniele A, et al. Transient mania with hypersexuality after surgery for high frequency stimulation of the subthalamic nucleus in Parkinson's disease. Mov Disord 2002; 17 (6): 1371-4
87. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders: Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002; 72: 701-7
88. Morgan JC, diDonato CJ, Iyer SS, et al. Self-stimulatory behavior associated with deep brain stimulation in Parkinson's disease. Mov Disord 2006; 21: 283-5
89. Smeding HM, Goudriaan AE, Foncke EM, et al. Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. J Neurol Neurosurg Psychiatry 2007; 78 (5): 517-9
90. Absher JR, Vogt BA, Clark DG, et al. Hypersexuality and hemiballism due to subthalamic infarction. Neuropsychiatry Neuropsychol Behav Neurol 2000; 13: 220-9
91. Baunez C, Amalric M, Robbins TW. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. J Neurosci 2002; 22 (2): 562-8
92. Frank MJ, Samanta J, Moustafa AA, et al. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007; 318 (5854): 1309-12
93. Roane DM, Yu M, Feinberg TE, et al. Hypersexuality after pallidal surgery in Parkinson disease. Neuropsychiatry Neuropsychol Behav Neurol 2002; 15 (4): 247-51
94. Mendez MF, O'Connor SM, Lim GT. Hypersexuality after right pallidotomy for Parkinson's disease. J Neuropsychiatry Clin Neurosci 2004; 16 (1): 37-40
95. Burkhard PR, Vingerhoets FJ, Berney A, et al. Suicide after successful deep brain stimulation for movement disorders. Neurology 2004; 63 (11): 2170-2
96. Grant JE, Potenza MN. Impulse control disorders: clinical characteristics and pharmacological management. Ann Clin Psychiatry 2004; 16 (1): 27-34
97. Hollander E, DeCaria CM, Finkell JN, et al. A randomized double blind fluvoxamine/placebo crossover trial in pathological gambling. Biol Psychiatry 2000; 47 (9): 813-7
98. Blanco C, Petkova E, Ibanez A, et al. A pilot placebo-controlled study of fluvoxamine for pathological gambling. Ann Clin Psychiatry 2002; 14 (1): 9-15
99. Kim SW, Grant JE, Adson DE, et al. A double-blind placebo-controlled study of the efficacy and safety of paroxetine in the treatment of pathological gambling. J Clin Psychiatry 2002; 63 (6): 501-7
100. Grant JE, Kim SW, Potenza MN, et al. Paroxetine treatment of pathological gambling: a multi-center randomized controlled trial. Int Clin Psychopharmacol 2003; 18 (4): 243-9
101. Saiz-Ruiz J, Blanco C, Ibanez A, et al. Sertraline treatment of pathological gambling: a pilot study. J Clin Psychiatry 2005; 66 (1): 28-33
102. Grant JE, Potenza MN. Escitalopram treatment of pathological gambling with co-occurring anxiety: an open-label pilot study with double-blind discontinuation. Int Clin Psychopharmacol 2006; 21 (4): 203-9
103. Black DW, Shaw M, Forbush KT, et al. An open-label trial of escitalopram in the treatment of pathological gambling. Clin Neuropharmacol 2007; 30 (4): 206-12
104. Mitchell JE, de Zwaan M, Roerig JL. Drug therapy for patients with eating disorders. Curr Drug Targets CNS Neurol Disord 2003; 2 (1): 17-29
105. Wilfley DE, Crow SJ, Hudson JI, et al. Sibutramine Binge Eating Disorder Research Group. Efficacy of sibutramine for the treatment of binge eating disorder: a randomized multicenter placebo-controlled double-blind study. Am J Psychiatry 2008; 165 (1): 51-8
106. Hollander E, Pallanti S, Allen A, et al. Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? Am J Psychiatry 2005; 162 (1): 137-45
107. Rogers R, Goodwin G. Lithium may reduce gambling severity in pathological gamblers with bipolar disorder [letter]. Evid Based Ment Health 2005; 8 (3): 80
108. Dannon PN. Topiramate for the treatment of kleptomania: a case series and review of the literature. Clin Neuropharmacol 2003; 26 (1): 1-4
109. Grant JE. Understanding and treating kleptomania: new models and new treatments. Isr J Psychiatry Relat Sci 2006; 43 (2): 81-7
110. Nicolato R, Romano-Silva MA, Correa H, et al. Lithium and topiramate association in the treatment of comorbid pathological gambling and bipolar disorder [letter]. Aust N Z J Psychiatry 2007; 41 (7): 628

111. Kim SW, Grant JE, Adson DE, et al. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. Biol Psychiatry 2001; 49: 914-21
112. Ikemoto S, Glazier BS, Murphy JM, et al. Role of dopamine D1 and D2 receptors in the nucleus accumbens in mediating reward. J Neurosci 1997; 17: 8580-7
113. Kim SW. Opioid antagonists in the treatment of impulse-control disorders. J Clin Psychiatry 1998; 59 (4): 159-62
114. Grant JE, Potenza MN, Hollander E, et al. A multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. Am J Psychiatry 2006; 163 (12): 303-12
115. Fong T, Kalechstein A, Bernhard B, et al. A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers. Pharmacol Biochem Behav 2008; 89 (3): 298-303
116. McElroy SL, Nelson EB, Welge JA, et al. Olanzapine in the treatment of pathological gambling: a negative randomized placebo-controlled trial. J Clin Psychiatry 2008; 69 (3): 433-40
117. Gebhardt S, Haberhausen M, Krieg JC, et al. Clozapine/olanzapine-induced recurrence or deterioration of binge eating-related eating disorders. J Neural Transm 2007; 114 (8): 1091-5
118. Kluge M, Schuld A, Himmerich H, et al. Clozapine and olanzapine are associated with food craving and binge eating: results from a randomized double-blind study. J Clin Psychopharmacol 2007; 27 (6): 662-6
119. Seedat S, Kesler S, Niehaus DJ, et al. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. Depress Anxiety 2000; 11 (4): 185-6
120. Sevincok L, Akoglu A, Akyol A. Quetiapine in a case with Parkinson disease and pathological gambling. J Clin Psychopharmacol 2007; 27 (1): 107-8
121. Trosch RM, Friedman JH, Lannon MC, et al. Clozapine use in Parkinson's disease: a retrospective analysis of a large multicentered clinical experience. Mov Disord 1998; 13 (3): 377-82
122. Fernandez HH, Durso R. Clozapine for dopaminergic-induced paraphilias in Parkinson's disease. Mov Disord 1998; 13 (3): 597-8
123. McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J Neurosci 2003; 23 (8): 3531-7
124. Baker DA, McFarland K, Lake RW, et al. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. Ann N Y Acad Sci 2003; 1003: 349-51
125. LaRowe SD, Mardikian P, Malcolm R, et al. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. Am J Addict 2006; 15: 105-10
126. Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry 2007; 62 (6): 652-7
127. Oakley-Browne MA, Adams P, Mobberley PM. Withdrawn: interventions for pathological gambling. Cochrane Database Syst Rev 2007; (1): CD001521
128. Toneatto T, Dragonetti R. Effectiveness of community-based treatment for problem gambling: a quasi-experimental evaluation of cognitive-behavioral versus twelve-step therapy. Am J Addict 2008; 17 (4): 298-303

Correspondence: Professor *Angelo Antonini*, Parkinson Institute, Istituti Clinici di Perfezionamento, Via Bignami 1, 20126, Milano, Italy.
E-mail: angelo3000@yahoo.com