A range of behaviors presumed to be related to aberrant or excessive dopaminergic medications are being increasingly recognized in Parkinson disease. These behaviors are linked by their incentive- or reward-based and repetitive natures and include pathological gambling, hypersexuality, compulsive shopping, compulsive eating, hobbyism, and compulsive medication use. Such behaviors can have potentially devastating psychosocial consequences and are often hidden. Whether these behaviors are simply related to dopaminergic medications interacting with an underlying individual vulnerability or whether the primary pathological features of Parkinson disease play a role is not known. We reviewed the literature on these behaviors in Parkinson disease, including definitions, epidemiological and potential pathophysiological features, and management. The study of these behaviors allows not only improved clinical management but also greater insight into a biologically mediated complex behavioral model.

Parkinson disease (PD) is a neurodegenerative disorder characterized by motor and nonmotor features that include cognitive, neuropsychiatric, and autonomic disturbances. Neuropsychiatric symptoms are common and include mood fluctuations, anxiety fluctuations, apathy, depression, psychotic symptoms, anxiety disorders, cognitive deficits, and dementia. These nonmotor features may be related to the primary underlying pathological features in PD or may be secondary to compensatory mechanisms, treatments used (medical and surgical), unrelated comorbid disorders, or underlying individual vulnerabilities (hereditary, biological, or psychological).

An intriguing set of behaviors presumed to be related to aberrant or excessive dopaminergic stimulation is being increasingly recognized in PD. These behaviors include pathological gambling,^{1-3} hypersexuality,^{2,4} compulsive shopping,^{2,4} compulsive eating,^{5} hobbyism,^{6,7} and compulsive medication use^{8,9} (Table). Such behaviors can have potentially devastating psychosocial consequences, with one study reporting a mean loss of more than $100,000 resulting from pathological gambling behaviors.^{1} These disorders often occur without subjective distress and are frequently hidden or unnoticed by patients. Whether these behaviors are simply related to the presence of dopaminergic medications interacting with an underlying vulnerability or whether the primary pathological features of PD play a role is unknown.

There is much disagreement surrounding the classification of these behaviors. The behaviors likely exist on a spectrum and may be idiosyncratic to an individual's susceptibility, hence complicating any phenomenological classification. Classification within psychiatric categories, which include obsessive-compulsive behaviors, impulse control, and addiction processes, is further confounded given the overlapping cognitive processes underlying

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### Table. Definitions of Impulse Control and Repetitive Behaviors in PD

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Criteria</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Gambling</td>
<td>Pathological gambling (DSM-IV definition)</td>
<td>A. Persistent and recurrent maladaptive gambling behavior as indicated by ≥ 5 of the following:</td>
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<tr>
<td></td>
<td></td>
<td>1. Preoccupation with gambling</td>
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<td>2. Increasing amount of money wagered</td>
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<td></td>
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<td>3. Repeated unsuccessful attempts to control</td>
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<td>4. Restlessness or irritability when cutting down</td>
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<td></td>
<td></td>
<td>5. Gambles to escape from problems or to relieve dysphoric mood</td>
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<td></td>
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<td>6. Chases losses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Lies to others about gambling</td>
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<td></td>
<td></td>
<td>8. Performs illegal acts to finance gambling</td>
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<td></td>
<td></td>
<td>9. Jeopardized relationship, work, or education</td>
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<td></td>
<td></td>
<td>10. Relies on others for money</td>
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<tr>
<td></td>
<td>B. Does not occur exclusively during periods of hypomania or mania</td>
<td>Similar to pathological gambling but with 3-4 criteria</td>
</tr>
<tr>
<td>Problem gambling</td>
<td>(various definitions)</td>
<td></td>
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<tr>
<td>Hypersexuality</td>
<td>Proposed operational diagnostic criteria</td>
<td>A. The sexual thoughts or behaviors are excessive or an atypical change from baseline marked by ≥ 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>(Voon et al)</td>
<td>1. Maladaptive preoccupation with sexual thoughts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Inappropriately or excessively requesting sex from spouse or partner</td>
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<tr>
<td></td>
<td></td>
<td>3. Habitual promiscuity</td>
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<td></td>
<td>4. Compulsive masturbation</td>
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<td></td>
<td></td>
<td>5. Calls to telephone sex lines or viewing of pornography</td>
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<tr>
<td></td>
<td></td>
<td>6. Paraphilias</td>
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<td></td>
<td>B. The behavior must have persisted for at least 1 mo</td>
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<td></td>
<td>C. The behavior causes ≥ 1 of the following:</td>
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<td></td>
<td></td>
<td>1. Marked distress</td>
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<td></td>
<td>2. Attempts to control thoughts or behavior that are unsuccessful or result in marked anxiety or distress</td>
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<td></td>
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<td>3. Becomes time consuming</td>
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<td></td>
<td>4. Significant interference with social or occupational functioning</td>
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<td></td>
<td>D. The behavior does not occur exclusively during periods of hypomania or mania</td>
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<td></td>
<td>E. If all criteria except E are fulfilled, the disorder is subsyndromal</td>
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<tr>
<td>Compulsive eating</td>
<td>Binge eating (DSM-IV research diagnostic criteria)</td>
<td>A. Recurrent binge eating characterized by eating large amounts in a discrete period, along with a loss of control</td>
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<td></td>
<td>B. ≥ 3 of the following:</td>
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<td></td>
<td></td>
<td>1. Rapid eating</td>
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<td></td>
<td></td>
<td>2. Feeling uncomfortably full</td>
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<td></td>
<td></td>
<td>3. Eating large amounts when not hungry</td>
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<td></td>
<td></td>
<td>4. Eating alone because of embarrassment over amounts</td>
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<td></td>
<td></td>
<td>5. Feeling disgusted or guilty after overeating</td>
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<tr>
<td></td>
<td>C. Marked distress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. Occurs 2 d/wk for 6 mo</td>
<td></td>
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<tr>
<td></td>
<td>E. Does not occur with compensatory behaviors or during anorexia or bulimia nervosa</td>
<td>Uncontrollable consumption of a larger amount of food than normal in excess of that necessary to alleviate hunger</td>
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<tr>
<td>Compulsive eating</td>
<td></td>
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<tr>
<td>Punding</td>
<td></td>
<td>An intense fascination with complex, excessive, repetitive, non-goal-oriented behaviors. The behaviors include less complex acts, such as shuffling papers, reordering bricks, or sorting handbags, or more complex acts, such as hobbyism (gardening, painting), writing, or excessive computer use</td>
</tr>
<tr>
<td>Compulsive medication use (hedonistic homeostatic dysregulation)</td>
<td>A. Clinical diagnosis of levodopa-responsive PD</td>
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<td></td>
<td></td>
<td>B. Need for increasing dopamine replacement therapy in excess of that required for motor signs and symptoms</td>
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<td></td>
<td></td>
<td>C. Pathological use despite severe behavioral disturbances and drug-induced dyskinesias</td>
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<td></td>
<td></td>
<td>D. Social or occupational impairment</td>
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<tr>
<td></td>
<td></td>
<td>E. Development of a dopaminergic withdrawal state with dose reduction</td>
</tr>
</tbody>
</table>

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); PD, Parkinson disease.
these behaviors. Furthermore, which cognitive processes are dysregulated in these behaviors in PD is poorly understood. For instance, punding, which appears as habitual behaviors, likely differs from but overlaps with pathological gambling, which may have a more prominent reward or incentive component.

This review uses the term repetitive behaviors to avoid any reference to the underlying pathophysiological component. We herein review the literature on these behaviors in PD, including definitions, epidemiological and potential pathophysiological features, and management.

DEFINITIONS AND PREVALENCE

The overall definition of these behaviors encompasses repetitive actions with or without urges and with associated negative consequences. The inclusion of consequences allows for clinical differentiation from “normal” behavior, although subsyndromal forms can also occur (Table).

In this review, prevalence rates from studies that used systematic screening and diagnostic criteria only are included. All studies were performed in movement disorder clinics. The term prevalence represents prevalence rates after initiation of medication therapy or sometime during PD.

Pathological gambling is classified within the impulse control disorders in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV). The definition overlaps with substance use disorders, suggesting a behavioral addiction. The prevalence of pathological gambling in PD in systematic clinical studies in North America, Italy, and the United Kingdom has been reported as 3% to 8%. This compares with the lifetime prevalence of pathological gambling of 1.7% among the North American general population. An Italian study found a prevalence of pathological gambling of 6.1% in PD clinics compared with 0.25% in general medical clinics. Hypersexuality is classified under the impulse control disorders and paraphilias in the DSM-IV. The prevalence of hypersexuality in PD has been reported to be approximately 2.5%. The prevalence of compulsive shopping in PD has been reported to be 0.4% to 1.5%.

Voon et al reported the overall prevalence of pathological gambling, hypersexuality, or compulsive shopping in patients with PD (hereinafter referred to as PD patients) to be 5.9%, with a point prevalence of 4.2%. The prevalence of those disorders with levodopa treatment alone was 0.7%, whereas with dopamine agonists it was 13.5% (P < .001). In these studies, PD patients were screened using patient-rated questionnaires (the South Oaks Gambling Screen, a clinician-designed screening hypersexuality questionnaire, and Lejoyeux’s Compulsive Shopping Questionnaire). Pathological gambling was defined using DSM-IV criteria; hypersexuality, using a clinician-designed working diagnostic criteria; and compulsive shopping, using the McElroy criteria (Table).

Weintraub et al reported similar prevalence rates of 6.6% for problem gambling, hypersexuality, and compulsive shopping in PD patients, with a point prevalence of 4.0%. These authors used systematic but unstructured clinical interview screening and diagnostic criteria based on the Minnesota Impulsive Disorders Interview. Despite the screening and definitional differences, the prevalence rates of both studies were similar.

Nirenberg and Waters described a case series of compulsive eating in 7 PD patients receiving dopamine agonists. Prevalence rates were not reported.

Punding behaviors are often related to an individual’s previous occupation or interests (ie, prepotent habits) but can occur de novo. A video of punding can be viewed in the online version of the article by Evans et al. Using a structured clinician interview, Evans et al reported a 14% point prevalence of punding in a tertiary referral center. In contrast, Miyasaki et al used a patient-rated adaptation of that structured clinician interview and found a 1.5% point prevalence in a clinic with community-based referrals. These differences were suggested to be related to the clinician- vs patient-rated questionnaires, the referral base, and the potential for the short-acting dopamine agonist apomorphine hydrochloride to accentuate these behaviors; greater availability and use of apomorphine in the United Kingdom than in Canada may account for the differences.

The prevalence of compulsive dopaminergic medication use, also known as dopamine dysregulation syndrome or hedonic homeostatic dysregulation, has been reported to be 3.4% to 4.0%.

PATHOPHYSIOLOGICAL FEATURES

Neuroanatomy and Theories on Addiction Processes

Although differences exist between these behaviors, they are linked by their reward- or incentive-based and repetitive natures. The rewards are learned (pathological gambling and compulsive shopping), intrinsic (hypersexuality and compulsive eating), and drug related (compulsive medication use).

The neuroanatomical regions implicated include the ventral tegmental area; its ventral striatal, limbic, and prefrontal cortical projections; and the ventral and dorsal striatum and associated frontostriatal circuitry.

Several proposed theories on addiction are relevant to these behaviors. For instance, Everitt and Robbins suggest that drug-seeking actions, like habits, start out as explicit behaviors but become implicit, automatic, or overlearned stimulus–response behavioral processes in the dorsal striatum. Alternatively, Robinson and Berrie suggest that drugs of abuse alter nucleus accumbens–related circuitry engaged in incentive processes (ie, the process of wanting rather than the process of liking, as seen in reward or hedonic tone). Behavioral sensitization (ie, an increase in behavioral drug effects with repeated exposure) occurs with psychostimulants, particularly with high or escalating doses and intermittent administration, and is associated with neuronal changes in the nucleus accumbens and prefrontal cortex. The compulsive pursuit of drugs (eg, neutral stimuli such as drug cues becoming salient out of proportion with other stimuli) is suggested to occur through pavlovian stimulus–stimulus associations and adaptations of accumbens-related circuitry. Finally, aberrant prefrontal cortex functioning observed in drug abuse may also be associated with loss of cognitive inhibitory control over prepotent tendencies, thus resulting in impulsive behaviors.
acting agonists such as apomorphine.8 However, these one case series has suggested an association with short-association with the dopamine agonist dose in 2 studies1,12 but comparison studies, pathological gambling was not asso-
ciations along with comparisons with PD control sub-
jects, pathological gambling, hypersexuality, and comp-
ulsive shopping in PD were robustly associated with
the use of dopamine agonists as a class but not with any specific agonists.1,2,4,12,13

Pathological gambling has not been associated with the
the dopamine agonist dose in 2 studies4,12 but was associated with the pramipexole dose in 1 study.13 Thus, pathological gambling can be but is not necessarily associated with the dopamine agonist dose. In contrast, hypersexuality was associated with a higher LED, but the dopamine agonist dose was not.4 In a separate study, pathological gambling, hypersexuality, and compulsive shopping assessed as a group were associated with a higher LED.2

The relationship between medications and punding is less clear. Punding has not been systematically assessed for association with medication subtype, but systematic studies have noted an association with a high LED.7 In a case report, punding was reported with the dopamine antagonist quetiapine fumarate, suggesting a nondopaminergic role (given the relatively high serotonin2A receptor–binding affinity of quetiapine) or that these behaviors occurred as a group were associated with a higher LED.2

Compulsive medication use is associated with a high LED but not with dopamine agonists per se,8 although one case series has suggested an association with short-acting agonists such as apomorphine.8 However, these associations with higher LED may be confounded by the presence of compulsive medication use.

Association of Dopaminergic Medications
With These Behaviors

The administration of dopaminergic medications may be associated with aberrant behavior by several mecha-
nisms: (1) interference with the pattern of dopamine release and its normal physiological role as an error-prediction or teaching signal18; (2) stimulation of particular dopamine receptors, thus resulting in aberrant activity of implicated regions; (3) dopaminergic stimulation enhancing the shift from goal-directed behaviors to stimulus response or habit formation; and (4) chronic stimulation resulting in neuronal sensitization of the ventral or dorsal striatal regions, leading to behavioral sensitization. A brief discussion on the first 2 potential mechanisms follows. A more extensive discussion on the pathophysiology can be found in Voon et al.19

Several lines of evidence suggest that phasic release of dopamine from the ventral tegmental area to the nucleus accumbens occurs at the time of anticipation of reward and at the time of receiving an unanticipated reward (ie, reward prediction error).20 Conversely, phasic suppression occurs when a reward is expected but not received. The magnitude of dopamine release varies with the magnitude of the reward. In contrast to phasic release, tonic dopamine release occurs with anticipation of the greatest reward uncertainty (ie, when there is an equal probability or chance of receiving or not receiving a reward).20 This latter observation has been interpreted to suggest that anticipation of conditions of high uncertainty such as gambling may itself be rewarding.20

Levodopa and dopamine agonists have different pharmacological properties, which may result in differences in phasic vs tonic activity. Levodopa is taken up in the presynaptic neuron and converted to dopamine. In the healthy brain or early in the course of PD with intact presynaptic neuronal density, levodopa may be more likely to mimic the physiological role of dopamine. However, with the loss of presynaptic dopaminergic neurons or with excessive doses, levodopa may be converted to dopamine outside the neuron with subsequent loss of normal physiological activity. Hence, excessive doses, appropriate doses in the context of impaired neuronal density, or postsynaptic dopamine receptor stimulation by dopamine agonists may result in loss of the normal physiological pattern of dopamine activity. A person may then anticipate a reward without the feedback teaching signal, indicating the lack of reward.

To illustrate, in a functional magnetic resonance imaging study in healthy individuals, excessive doses of levodopa given in the presence of intact neuronal density increased the reinforcing effect of wins but not losses as measured by ventral striatum blood-oxygen level-dependent activity, a representation of outcome prediction error (Figure 1).21 Thus, in individuals receiving levodopa, approach behaviors would be more likely to be reinforced by rewards than avoidance by punishments, possibly leading to repetitive behaviors.

Alternatively, stimulation of specific dopamine receptor subtypes may be associated with aberrant activity. For instance, D3 receptor–binding affinities may differ between dopamine agonists, in addition to the relative ratio of binding affinities of the D1/D3 or the D2/D3 receptors.22 Unlike the D2 or D1 receptors, D3 receptors are found predominantly in limbic regions and have been implicated in the addiction process.
SUSCEPTIBILITY

The lack of a consistent dose effect and the occurrence of symptoms in only a subset of patients suggest an underlying susceptibility. This susceptibility may be mediated by PD-related factors such as (1) the neurobiology of PD (e.g., pathological features and compensatory mechanisms that may also modulate underlying temperamental traits or cognitive processes), (2) PD-specific medication practices, or (3) individual factors underlying the vulnerability to pathological gambling, addiction disorders, or impulse control behaviors (Figure 2). The latter suggests that dopamine agonists used for non-PD disorders (e.g., restless legs syndrome or depression) may also trigger these symptoms.

PD-Related Factors

Subgroups. First, PD-related factors could be mediated by subgroups of PD patients with a greater risk for behavioral disorders. For example, recurrent psychosis occurs more frequently in patients with the parkin gene, and depression occurs more frequently in early-onset PD. Early-onset PD may also have a greater genetic association. The susceptibility is presumably related to a different distribution and nature of pathological involvement and hence of medication response.

Pathological gambling and compulsive medication use are both associated with an earlier onset of PD, suggesting a potential role for the vulnerability of specific PD patient subgroups to these behaviors. However, this association may be confounded by the relatively greater use of dopamine agonists and higher doses used in early-onset PD.

General Neurobiological Features. Second, aberrant functioning secondary to PD (e.g., neurodegeneration, α-synuclein deposition, or compensatory up-regulation) of relevant neuroanatomical networks may be implicated. This may be due to direct involvement by the neurodegenerative process or to compensatory changes in intact, “unaffected” regions.

The effect of PD and dopaminergic medications on dopaminergic tone may also influence cognitive functions relevant to these behaviors. For instance, PD patients who are “off” medications have been demonstrated to be more sensitive to punishment learning, whereas they are more sensitive to reward learning while “on” medications. Impairments in cognitive flexibility (e.g., reversal learning, attentional set shifting) have also been associated with PD or with medication administration. Which cognitive functions are relevant to these behaviors and how medications and PD affect them are unknown because medications can enhance or impair cognitive function. In PD patients, dopamine influences working memory in a U-shaped curve (e.g., optimal dopamine tone) rather than in a linear fashion. The overdose hypothesis suggests that, in PD patients, relatively preserved functions associated with the ventral striatum and ventral prefrontal cortex (e.g., reversal learning) may be more sensitive to overstimulation and impairment due to dopaminergic medications compared with the dorsal striatum and dorsolateral prefrontal cortical functions (e.g., attentional set shifting and working memory). Untreated PD is associated with impairments in dorsolateral prefrontal cortical functioning (e.g., working memory), which are improved with dopaminergic medications. The cognitive impairments associated with PD are not within the scope of this review but are reviewed elsewhere.

However, an exclusive relationship to general PD-related neurobiological features suggests that the repetitive behaviors should be more common than they seem to be or that, as the disease progresses, the onset or severity may be mediated by disease markers such as stage, duration, and levodopa dose. Voon et al did not find an association between pathological gambling and disease markers, thus arguing that PD-related neurobiological features, rather than playing a primary role, may interact with individual vulnerabilities to increase susceptibility. A weak association between pathological gambling and right-sided PD onset was found, although the implicating factors are not clear.

Medication Practices. Third, compared with other disorders for which dopaminergic drugs are used, PD may involve specific medication practices such as the use of higher doses, the diurnal administration of dopamine agonist, or concurrent levodopa use. Voon et al have suggested that levodopa may play a priming role potentiating the onset of these behaviors. A robust association of pathological gambling with dopamine agonists as an adjunct therapy rather than as monotherapy was observed, although the data were limited by sample size and differences in agonist doses.

Figure 2. Factors associated with medication-related repetitive behaviors. PD indicates Parkinson disease. *Associated with all behaviors except dopamine agonists not associated with compulsive medication use. ‡Can be but not necessarily associated with pathological gambling, impulsivity, and compulsive shopping; associated with punding and compulsive medication use but may be confounded by excessive use of medications. §Male sex associated with hypersexuality. ¶Associated with pathological gambling. †Associated with compulsive medical use. **Possible association with pathological gambling and hypersexuality.
ever, clinical studies are prone to confounding factors. Studies in normal rodents and primates suggest that pulsatile and long-term administration of psychostimulants results in psychomotor behaviors associated with functional and anatomical changes in the ventral striatum and prefrontal cortex that are presumed to underlie the behavioral sensitization process. Studies in 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)–lesioned marmosets (a nonhuman primate model of PD) have shown that repeated treatment with levodopa results in the development of similar abnormal psychomimetic behaviors; these have recently been proposed to represent psychosislike behaviors. In this model, there is an association between the dose of levodopa and production of psychosislike behaviors. Preclinical studies in unilateral MPTP models of PD further suggest that levodopa administration may result in aberrant D₃ receptor expression, which has been suggested to play a role in the sensitization processes and in the pathophysiological mechanisms of dyskinesias. Exposure to levodopa may thus result in increased susceptibility to the potential of dopamine D₃ agonists to induce repetitive behaviors. Indeed, Dodd et al suggested a link between pathological gambling in PD patients and the use of the dopamine D₃–preferring agonist pramipexole; however, other clinical studies have not shown this link. To try to delineate this further, studies in the MPTP-lesioned primate primed to express psychosislike and compulsive-like behaviors with long-term levodopa administration showed no significant differences among the abilities of levodopa, pergolide mesylate, ropinirole hydrochloride, and pramipexole to induce compulsive-like behaviors at doses with equivalent antiparkinsonian actions. This suggests that dopamine D₃–preferring agonists may be no more likely than levodopa to induce compulsive-like behaviors. However, whether this animal model represents the full spectrum of repetitive behaviors is not known.

**Individual Susceptibility**

In contrast to PD-related factors or in addition to them, individual susceptibility may play a role. This susceptibility can include a predisposition to pathological gambling or other addiction disorders through underlying heritable temperamental traits (eg, novelty or sensation seeking and impulsivity), cognitive processes (eg, in temporal discounting, impulsive choice or action, risk taking, reward or punishment learning, reversal learning, and set shifting), aberrant neural networks (eg, ventral or dorsal striatal, prefrontal cortex, and limbic regions), age, sex, or genetic polymorphisms.

For example, pathological gambling in the general population is associated with the male sex, a history of substance abuse, higher levels of impulsivity and sensation seeking, cognitive impairments in response inhibition and planning, and higher delay discounting rates. Pathological gambling has been associated with aberrant frontostriatal and limbic activity with decreased activation in the ventromedial prefrontal cortex in the Stroop interference task (a measure of the ability to inhibit irrelevant responses) and with decreased activation in the ventral striatum to a forced choice win-vs-loss task. Furthermore, pathological gambling has been associated with increased dopamine function with reduced acute startle prepulse inhibition, increased dopamine metabolites in the cerebrospinal fluid, and a study demonstrating the ability of amphetamine to prime the motivation to gamble.

The published case-control studies that assessed factors associated with repetitive behaviors in PD are reviewed in the following paragraphs.

**Repetitive Behaviors.** Weintraub et al demonstrated that a premorbid history of repetitive behaviors predisposed patients to these behaviors while taking dopamine agonists. Pontone et al demonstrated that depressed mood, increased irritability, disinhibition, and appetite disturbances may be more common in patients with these behaviors, although whether these behaviors predate the use of medications is not clear.

**Compulsive Medication Use.** In keeping with the addiction literature, Evans et al found novelty seeking, depression scores, alcohol intake, and age of PD onset to be independent predictors of repetitive medication use in PD patients. The study did not confirm initial associations with male sex.

In a positron emission tomography study using raclopride tagged with carbon 11 (D₂/D₃ receptor ligand), Evans et al demonstrated increased dopamine release in the ventral striatum in response to a levodopa challenge in PD patients with compulsive medication use. It was suggested that this finding supported the neural sensitization theory leading to the behavior of compulsive drug seeking. Furthermore, the subjective wanting but not the liking of levodopa was positively correlated with the degree of ventral striatal dopamine release. This observation was suggested to reflect an incentive salience for levodopa use rather than a pleasurable or reward-related quality.

**Pathological Gambling and Hypersexuality.** Pathological gambling in the general population has been most consistently associated with male sex, mood and substance use disorders, high sensation seeking, and impulsivity. Voon et al found independent associations of elevated novelty-seeking traits, a personal or family history of alcohol use disorders, and earlier age of PD onset with pathological gambling in PD patients. Using a logistic regression model, these factors accounted for 62% of the variance. Impulsivity scores, particularly planning for long-term consequences, were more weakly associated with pathological gambling. The data, albeit preliminary, suggested that novelty seeking is more likely to be trait related (ie, to reflect an underlying heritable vulnerability), whereas the impulsivity scores may be more state related (ie, related to the presence of dopamine agonist or the state of active pathological gambling).

A high level of novelty seeking has been associated with pathological gambling and is characterized by exploratory approach rather than avoidance behaviors, excitement with novel situations, impulsivity, rapid decision making, extravagance, and greater disorganization. A low level
of novelty seeking has been variably but not consistently associated with PD and is characterized by a reflective, rigid, and slow-tempered temperament. The lowered novelty-seeking level, presumed to be related to the neurobiological mechanisms of PD affecting the ventral striatum, has been suggested to play a role in the lower rates of alcohol, cigarette, and other drug use in the PD population and may play a protective role against these behaviors before the onset of medication therapy.

Medication-induced mania with onset after that of pathological gambling is robustly associated with pathological gambling in PD patients. However, rather than a bipolar diathesis being a risk factor, medication-induced mania may be part of the spectrum of dopamine dysregulation. In contrast to the studies on compulsive medication use and general pathological gambling, there was no association with depression or male sex. However, because pathological gambling in the general population is associated with males more than females in a 2:1 ratio, the lack of an association with sex in PD may be due to limited study power.

Hypersexuality in PD is more likely to be associated with younger onset PD and, in contrast to that of pathological gambling, with males.

Compulsive Eating. In an uncontrolled case series, Nirenberg et al found that PD patients with compulsive eating behaviors who were taking dopamine agonists were likely to have younger-onset PD and premorbid histories of repetitive behaviors or being overweight.

**MANAGEMENT**

Patients should be warned of the potential risk of these behaviors before initiation of treatment with dopamine agonists. The identification of patients at greater risk to allow for closer follow-up would be an ideal component to the ongoing management of PD. With all studies, earlier age of PD onset is associated with these behaviors, although differences in medication practices may mediate the association. Current studies suggest that specific risk factors for pathological gambling may include a personal or family history of alcohol use disorders and increased novelty-seeking traits, whereas impulsivity may be associated but is more likely state related. Specific risk factors for compulsive medication use include increased novelty seeking, alcohol use, and higher depression scores. Hypersexuality is associated with the male sex.

Nonspecific associated factors include a premorbid history of these behaviors, depressed mood, irritability, and appetite disturbances. Higher medication doses can be but are not necessarily associated with these behaviors.

The management of pathological gambling has been described only in anecdotal reports. In patients with compulsive medication use or who take high doses, a decrease in medication dose may be sufficient. Decreasing or discontinuing therapy or switching to a different dopamine agonist may be but is not consistently effective. Antidepressants have not been found to be useful in case reports. External controls (eg, external control of finances) and referrals for gambling treatment have been anecdotally reported to be useful in a proportion of patients.

Ardouin et al described a multicenter retrospective series of PD patients with active pathological gambling before deep brain stimulation targeting the subthalamic nucleus. The pathological gambling symptoms resolved immediately after or over the course of months in parallel with the decrease in the LED. The authors suggest that improvement may be related to (1) dose decreases or discontinuation of dopamine agonist therapy; (2) the relative specificity of deep brain stimulation for motor regions compared with medications; (3) the replacement of pulsatile stimulation with chronic stimulation, which may decrease neural sensitization; or (4) the actions of deep brain stimulation targeting the subthalamic nucleus. Point 4 is exemplified by studies of lesions in the subthalamic nucleus in rodent models of substance abuse. However, that the behaviors can worsen in the early postoperative period suggests that caution be applied in the selection and postoperative management of these patients.

In subjects with compulsive medication use, management includes decreasing doses; external controls of doses; treatment of secondary psychotic, manic, or behavioral symptoms; and management of dopaminergic depressive withdrawal symptoms. Multidisciplinary involvement may be necessary. Similarly, deep brain stimulation of the subthalamic nucleus has been reported to be effective in well-selected patients. Relapse of addictive dopaminergic drug abuse behaviors is not infrequent in these patients.

**CONCLUSIONS**

Medication-induced repetitive behaviors as a group are relatively common and can have devastating psychosocial consequences. The study of these behaviors allows not only improved clinical management but also greater insight into a biologically mediated complex behavioral model.

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**REFERENCES**


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