Review

Dopamine dysregulation syndrome, addiction and behavioral changes in Parkinson’s disease

Doron Merims, Nir Giladi

Movement Disorders Unit, Department of Neurology, Tel-Aviv Sourasky Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Received 4 December 2006; received in revised form 24 September 2007; accepted 24 September 2007

Abstract

Degeneration of the dopaminergic system in Parkinson’s disease and longstanding exposure to dopaminergic drugs may cause reward system malfunction. This may manifest as addiction to L-dopa and behavioral disturbances associated with the impulse control system. These disturbances include: gambling, excessive spending (shopping), hypersexuality and binge eating. We included one such patient’s personal story to emphasize the devastating consequences of these potentially reversible phenomena: the patient describes in his own words how gambling induced by an exposure dopamine agonist therapy significantly worsened his disease-related difficulties.

© 2007 Elsevier Ltd. All rights reserved.

Keywords: Dopamine dysregulation syndrome; Parkinson’s disease; L-Dopa; Dopamine agonist; Gambling

Contents

1. Dopamine and addiction ........................................................................................................273
2. Gambling ..................................................................................................................................274
3. One patient’s story—gambling .................................................................................................275
4. Hypersexuality ..........................................................................................................................275
5. Excessive shopping ....................................................................................................................276
6. Compulsive eating .....................................................................................................................276
7. Other addiction-like behaviors ................................................................................................276
8. Risk factors for the development of behavioral changes in PD .............................................276
9. Parkinson’s disease and addiction to levodopa ......................................................................277
10. Conclusions .............................................................................................................................278
Acknowledgment .........................................................................................................................278
References ......................................................................................................................................278

1. Dopamine and addiction

Dopamine plays a key role in reward, signaling and addiction [1–3]. Measurement of the levels of released endogenous dopamine in healthy people during a video game (goal-directed motor task) showed increased release and binding of dopamine to its receptors in the striatum [4]. Playing a video game is one of many examples of anticipatory or motivated behavior where dopamine is involved in the learning of predicted reward. In particular, the nigro-mesolimbic dopaminergic pathway has been implicated in the addictive properties of many drugs of abuse, including: cocaine, heroin, amphetamine, alcohol and nicotine. These agents are known to increase...
extracellular dopamine levels in the nucleus accumbens, partly via blockade of the specific dopamine reuptake channels [1,5–7]. It has been suggested that the dopamine D3 receptor, which is highly enriched in nucleus accumbens, plays an important role in reinforcement and reward. The potential cellular mechanism underlying D3 receptor functions is possibly via D3 receptor activation that suppresses the efficacy of inhibitory synaptic transmission by increasing the phospho-dependent endocytosis of GABA receptors [8].

Experiments that tested the efficacy of selective D3 receptor antagonists in rat models suggest that selective D3 receptor antagonism constitutes a possible pharmacotherapeutic approach to the treatment of nicotine and cocaine dependence [9,10]. Animal studies have identified specific genes that can alter genetic susceptibility to dependence and response to novelty. The mechanisms underlying these two factors are complex, but it is well recognized that genetics play a significant role in the transition from substance use to dependence and from chronic use to addiction [11]. For example, higher than average novelty-seeking score tests (tridimensional personality questionnaire—TPQ) were reported to be significantly associated with a 7 repeat allele in the locus for the D4 dopamine receptor gene [12]. Dopamine D4 receptor knockout mice were also reported to exhibit reduced exploration of novel stimuli [13]. In a recent study, Pogorelov et al. [14] found that disruption of the dopamine transporter gene (Dat1) by increasing the level of extracellular dopamine in mice, led to a reduction in anxiety and novelty seeking. Goal-directed behavior is believed to involve interactions of prefrontal cortical and limbic inputs in the nucleus accumbens, and their modulation by mesolimbic dopamine seems to be of primary importance in the function of the nucleus accumbens. Dynamics of dopamine release regulate the balance between limbic and cortical drive through activation and inactivation of dopamine receptor subtypes in the nucleus accumbens, and this regulates goal-directed behavior [15]. Evans et al. [16] used positron-emission tomography (PET) to show that patients with Parkinson’s disease (PD) who were compulsive drug consumers exhibited enhanced levodopa-induced ventral striatal dopamine release compared to controls. The sensitized ventral striatal dopamine neurotransmission produced by levodopa in these individuals correlated with self-reported desire for the drug.

The role of dopamine in the non-motor late complications observed in PD goes far beyond its association with psychotic symptoms. Dopamine may be involved in behavior and even play a role in sculpting the parkinsonian patient’s personality. PD patients have an introverted premorbid personality type [17]. Their premorbid personality traits differed from those of controls in that they were more “quiet,” “generous,” “cautious,” and “even-tempered,” and less “flexible” [18]. Even before they manifest symptoms of the disease, people who develop PD show less novelty-seeking behavior than do control populations [19–23]. Until recently, many researchers questioned whether smoking really protects against PD or if the lower incidence of smoking among PD patients is due to their unique non-hedonic personalities [24–26]. The effect of dopamine on the reward system may partly explain the “addiction” to levodopa (see below).

The behavioral changes described in PD have been called dopamine dysregulation syndrome (DDS). DDS is a neuropsychiatric behavioral syndrome associated with substance misuse and behavioral disturbances that can resemble a hypomanic state or disturbances in the impulse control system resulting in an uncontrolled urge or drive to perform certain acts. Pezzella et al., who first developed a questionnaire for DDS [27], later established the criteria for this syndrome [28]. The criteria address increased dopamine replacement therapy (DRT) consumption in addition to the presence or history of mood disorders, i.e., depression, anxiety and hypomanic state. Mood disorders may accompany and parallel in intensity behavioral disorders such as gambling, obsessive shopping, hypersexuality, aggression and social isolation.

Another optional criterion is alteration of the perception of the “on” state, walkabouts and stereotypies [28]. The syndrome typically develops in male patients with early onset PD, and can occur with orally and subcutaneously administered DRT [29–32]. Pezzella et al. [28] screened 202 PD patients for DDS: 7 subjects fulfilled the DDS criteria. The analysis of this case-control study showed a significant correlation between DDS and a previous history of mood disorders and the use of DRT, especially dopamine agonists (DA), either as monotherapy or in combination. Similar results have recently been reported by our group [32]. Comparing 193 PD patients to 190 age-matched normal controls, we observed that new or heightened interest or drive for being involved in gambling, sexual activity, overeating (with weight gain) and excessive money spending (mainly shopping) were reported by 27 patients (14% vs. 0% for controls, \( p < 0.001 \)). A younger age at PD motor symptom onset (OR = 0.99, \( p = 0.0172 \)), male gender (OR = 1.10, \( p = 0.0576 \)) and longer duration of treatment with DAs (OR = 1.18, \( \geq 6 \) years vs. never treated, \( p = 0.0459 \)) contributed additively to the risk of developing one or more of these behaviors [32].

2. Gambling

Gambling is classified as an impulse control disorder according to the DSM IV criteria [33]. Historical records and archeological evidence reveal that gambling has existed throughout the ages and as part of the culture of most civilizations. Betting on horses began as soon as the animals were domesticated. Today, gambling is available online in the Internet, producing a multitude of options for the gambler to lose money and to suffer the financial, psychological and family consequences.
Molina et al. [34] were the first to describe the association between PD and pathological gambling in 12 patients. Gambling behavior appeared more often in the “on” periods of motor fluctuations and it began after the onset of PD in most of their patients, worsening with levodopa therapy. In that same year, Seedat et al. [35] reported a similar single case report. Their patient’s gambling behavior was controlled with risperidone treatment. Evidence for the association between PD and gambling has been accumulating since then [32,34–40]. Imamura et al. [41] raised the possibility that combined dopamine receptor stimulation increases the risk for the development of pathological gambling compared with monotherapy with either DA or levodopa carbidopa. In contrast, several other papers have associated DA treatment alone with pathological gambling [32,42].

A database from the Food and Drug Administration Adverse Event Reporting System (ARES) addressing the gambling phenomenon in PD was recently published. This database contains more than 2.5 million voluntary reports of adverse drug events that had been collected since 1968. Among more than 4400 drugs in the ARES, DRT that included DAs and levodopa were found to share the top reported higher-than-expected drug ratio for gambling. The first in this list was pramipexole (N = 39 reported cases), followed by bromocriptine (N = 6), levodopa with or without carbidopa (N = 10), ropinirole (N = 8) and pergolide (N = 4) [40].

3. One patient’s story—gambling

The following paragraphs are part of a letter that was sent to NG after the patient heard him talking at a conference. We thank this patient for sharing his experience and raising our level of awareness to the devastating influence of gambling in PD. He graciously consented to the publication of this letter, and only his name and the name of the DA he was taking have been omitted from the original text.

My family was the poster family. I was just a typical guy living the American Dream. My wife and I found out that I had Parkinson’s disease in May of 1991. Eldepryl and Sinemet initially controlled the symptoms. In early 1997, a DA was added to my treatment with good symptomatic effect. My gambling problem began to manifest itself in July of 1997. I soon became obsessed with riverboat casinos and then instant lottery tickets (spending 4–6 hours a day scratching off tickets). I had never been involved in any gambling activity prior to that year. In a two-year period I spent approximately $30,000 on cards. In January of 2000 my wife threatened me with divorce and I attempted suicide. Up until this time, my position at work was rock solid as a key player in the company. By April of 2000 I took disability retirement. I just could not stop gambling. My pattern was about every 2–3 weeks—I had to gamble. Then I realized that the DA I was taking was suspected of causing addictive gambling. My neurologist was unaware of gambling being a problem with the drug. He took me off it and I no longer experienced any desire to gamble. I am pleased to say it has now been over 2 years and I have had no inclinations toward any types of addictive gambling. This six-year time frame, 1997–2003, during which I was on this DA cost me over $400,000. It depleted all my 25 years of savings and has left me over $300,000 in debt. The pain and suffering from this dreaded Parkinson’s disease is sometimes unbearable, but does not begin to compare with the devastation this drug has had on my family, my character, my reputation and my financial future.

4. Hypersexuality

The behavioral terms “sexual addiction,” “sexual compulsivity,” “sexual impulsivity,” “increased interest in sexual activity” and “hypersexuality” may overlap and all have been used. The definition of when an individual’s sexual behavior is not within normal limits is sometimes very difficult to determine and may vary among different populations and among different couples. The change from “normal” to “hypersexuality” is based on a comparison between premorbid behavior to that following some kind of intervention. Sex addictive behavior was reported to be more common among depressed or anxious people [43]. There is no validated tool for the assessment of this phenomenon in PD. The Sexual Compulsivity Scale was validated for the assessment of compulsive sexual behavior in HIV carriers [44] and in heterosexual college students [45], but its use in PD patients has never been validated.

Hypersexuality in PD was first described by Vogel and Schiffer [46]. The behavioral manifestations of hypersexuality include increased libido, increased in erection frequency and increased sexually demanding behavior sometimes accompanied by aggressiveness and compulsive masturbation [29,30,32,47–50]. Other changes in sexual behavior have also been documented in patients with PD. One such case was reversible transvestic fetishism in a patient who had PD for 37 years and was newly treated with selegiline [51]. Hypersexuality is considered a manifestation of enhanced libido and inappropriate frontal inhibition [52]. The combination of low self-esteem due to motor and autonomic disturbances on one hand, and the limited social activity and paranoid thoughts toward the spouse, on the other hand may drive the patient to more aggressive and sexually demanding behavior. Klos et al. [50] described 13 patients with PD who exhibited hypersexuality; 2 patients were subsequently diagnosed clinically with multiple system atrophy (MSA). These authors reviewed the literature and found that 26 of 29 patients with hypersexuality (90%) were treated with DAs.
There are known risk factors for hypersexuality in the general population, among them substance abuse and smoking [53]. There are several potential theoretical explanations for the development of increased libido as a result of disturbances in the impulse control system. One such explanation is a primary degeneration of the reward system, and another is functional and possibly structural changes secondary to long-term, continuous, non-physiological, stimulation of the dopaminergic system with medications. It is possible, however, that the combination of the two leads to the clinical syndrome. Alternatively, hypersexuality might develop, in part, due to other neurotransmission irregularities. It was recently reported that lamotrigine (an anti-epileptic drug that decreases glutamate release in the synapse) was the cause of dose-dependent hypersexuality [54]. Shapiro et al. [55] described two cases of early onset PD who experienced paraphilia and hypersexuality when selegiline was initiated, and later developed obsessive–compulsive and punding behavior with the addition of DAs.

In our experience, increased interest in sexual activity is the most common behavioral change seen in PD patients. It is more common in males and is generally underreported [32]. The patient will frequently deny the existence of a problem and the spouse is often the source of information. It is important to detect and treat hypersexuality early because a delay in diagnosis and treatment can lead to considerable and often an unspoken tension within a family that is already dealing with the difficult consequences of PD.

5. Excessive shopping

Compulsive buying is defined by the presence of repetitive impulsive and excessive buying leading to personal and family distress. Patients with this disorder also suffer from a mood disorder in 50–100% of the cases studied, and antidepressants help to decrease the frequency and the severity of uncontrolled buying. In most cases, the behavior is associated with other impulse control or dependence disorders and a high level of impulsivity [56]. Compulsive buying is more frequent in patients with an obsessive–compulsive disorder than in normal individuals. Patients presenting with the combination of obsessive–compulsive disorder and compulsive buying will more frequently experience depression. In addition, they are often extremely interested in and satisfied with the items they are buying but once they possess them frequently express disappointment and lose interest in them [57].

Maia et al. [58] published the first report on uncontrolled buying in PD. We observed an excessive drive to spend money among 3.1% of our patients [32] and, in most cases, when questioned directly the patient had no good explanation why he or she bought a particular item.

6. Compulsive eating

Nirenberg and Waters [59] described seven patients with a compulsive eating disorder that had developed in the context of treatment with pramipexole. All the affected patients had significant, unwanted weight gain; four had other comorbid compulsive behaviors. The dose of pramipexole was either lowered or the DA treatment was discontinued in five of the patients, whereupon the behavior ceased and there was no further weight gain.

We observed a new, excessive and uncontrolled drive to eat with the subsequent undesired and frustrating weight gain in 3.6% of our patients [32]. Our patients reported experiencing this drive particularly at night and in some cases the refrigerator had to be locked as a drastic solution to the bulimic behavior.

Weight gain has also been reported in patients with PD who were treated with deep brain stimulation (DBS) [60–63].

This weight gain may be the result of decreased energy expenditure due to subsidence of chronic tremor or dyskinesia. It is our experience, however, that bulimic behavior as a result of postoperative changes in the reward system could be another reasonable explanation for the observed behavior.

7. Other addiction-like behaviors

In addition to the above-mentioned addictive-like behaviors, there are many more variations, which are probably related to an individual’s premorbid preferences or personality. One very common behavior is excessive use of the Internet. Surfing the Internet becomes such a magnet for some patients to the extent that they are unable to leave the computer, forget to sleep or demand to eat while in front of the computer. Participating in sporting activities of all kinds is another type of activity where individuals frequently lose control. Some of our patients spend 10–12 h a day, 7 days a week participating in different sports and they characteristically develop all the withdrawal symptoms one can expect from an addiction when obliged to cease the activity for a defined period of time. Both these examples are similar to other behavioral disturbances, i.e., hard to diagnose and to define at what point they become pathological in nature. It is especially difficult when taking part in sports and exercise programs is advocated by all physicians and patients frequently claim that they are just following their doctors’ recommendations.

8. Risk factors for the development of behavioral changes in PD

The most striking observation in terms of provocative factors for DDS is its association with DA treatment [25,30,32,49,58]. A recent study by Giladi et al. [32] demonstrated that it is the exposure to DAs and not
levodopa that is associated with the development of addiction-like behavior [32]. They also reported for the first time that the relationship between changes in behavior with DA treatment was dose-dependent and longer treatment duration (but not dosages) with DA drugs (over 6 years) significantly increased the risk for behavioral changes. The question why DAs can provoke these behavioral disturbances more than levodopa is still unanswered, but a different receptor profile is a tempting possible explanation that warrants study. At a time when many young patients are exposed to DAs in high dosages as a strategy for delaying the use of levodopa, the potential development of behavioral problems should certainly be taken into an account when prescribing them.

Other potential risk factors that have been suggested are younger age at PD motor symptom onset and being a male [32]. The role of age at PD motor symptom onset is similar to the well-accepted observation regarding dyskinesias, which also appear earlier and more aggressively in younger patients [64]. It would appear that the younger sick brain is more sensitive to dopaminergic treatment at the level of the basal ganglia (dyskinesias) but also at the level of the nucleus accumbens–limbic system-prefrontal cortex circuit [65].

It is very reasonable to look for premorbid personality traits, which might be of importance to the development of DDR and behavioral changes in patients with PD. There are no published data to support an increased risk among specific personality types. A recent pilot study by our group found that PD patients with premorbid obsessive–compulsive behavioral features were at a greater risk to develop DDS, which was independent of other known risk factors (unpublished data). Due to the difficulties in obtaining reliable retrospective data on premorbid behavioral features, however, one should view these preliminary observations with caution.

The effect of subthalamic nucleus (STN) DBS on addiction in PD remains to be investigated in depth. The postoperative motor improvement resulting from STN DBS makes it possible to reduce significantly the DRT dosages, which may lead either to an improvement or DBS makes it possible to reduce significantly the DRT postoperative motor improvement resulting from STN addiction in PD remains to be investigated in depth. The observations with caution.

features, however, one should view these preliminary (unpublished data). Due to the difficulties in obtaining DDS, which was independent of other known risk factors [64]. It would appear that the younger sick brain is more sensitive to dopaminergic treatment at the level of the basal ganglia (dyskinesias) but also at the level of the nucleus accumbens–limbic system-prefrontal cortex circuit [65].

It is very reasonable to look for premorbid personality traits, which might be of importance to the development of DDR and behavioral changes in patients with PD. There are no published data to support an increased risk among specific personality types. A recent pilot study by our group found that PD patients with premorbid obsessive–compulsive behavioral features were at a greater risk to develop DDS, which was independent of other known risk factors (unpublished data). Due to the difficulties in obtaining reliable retrospective data on premorbid behavioral features, however, one should view these preliminary observations with caution.

The effect of subthalamic nucleus (STN) DBS on addiction in PD remains to be investigated in depth. The postoperative motor improvement resulting from STN DBS makes it possible to reduce significantly the DRT dosages, which may lead either to an improvement or worsening in DDS. Witjas et al. [66] described 2 patients with severe DDS who were extremely responsive to STN stimulation. Motor improvement was associated with a complete cessation of the manic and compulsive behaviors. STN DBS may, however, have a direct effect on the reward-seeking brain circuitry and thereby worsen addictive symptoms. Morgan et al. [67] described a patient who did not display addictive behaviors before STN DBS, despite chronic therapy with a DA (pergolide). The patient described receiving a “morphine-like” effect, a sensation similar to “sexual climax,” during DBS adjustments. As a result, his request for DBS programming visits increased significantly. He admitted that he had turned himself “off” and “on” using his magnet on multiple occasions, even when driving.

9. Parkinson’s disease and addiction to levodopa

After an initial period of stable and smooth response to levodopa, the so-called “levodopa honeymoon,” many patients with PD on chronic treatment develop motor response fluctuations. Those are manifested by daily “on” periods of satisfactory clinical benefit, alternating with “off” phases when patients may be slow, rigid, tremulous, dystonic and often unable to move. Many patients with motor response fluctuations are totally dependent on the success of single doses of levodopa for a short-term regain of motor function [68]. The motor oscillations are not the only clinical manifestation of these response fluctuations, since alternation in mood and behavior are also common [69]. The patient is often agitated, depressed and anxious during the “off” period. Prolonged “off” is a common cause of presentation to an ER on the weekend when clinics are closed [70]. These symptoms strikingly resemble withdrawal phenomena commonly experienced by drug addicts. Such mood and behavioral symptoms are also similar to panic attacks, frequently experienced by PD patients [71]. The causes of these symptoms (attacks) are not entirely clear. In fluctuating PD patients, many of these panic episodes are time-linked to their “off” periods, but whether they coincide with, follow, or even precede the “off” event is unclear [71]. In most patients, the “off”-linked panic attacks subside when a motor “on” is induced by a dose of levodopa. One possibility is that the “off”-linked panic simply occurs in reaction to the PD symptoms taking over. Another explanation is that there is a decline in dopamine concentration not only at the level of the striatum but also within other structures, e.g., the limbic system. Alternatively, panic attacks may represent withdrawal phenomena due to recurrent depletions of levodopa and its metabolite, dopamine in mesolimbic regions such as the nucleus accumbens. There are several additional phenomena suggesting “addiction” to levodopa in fluctuating PD patients: they reportedly feel the need to take doses of levodopa regularly, are unable to skip doses and cannot tolerate long “drug holidays” [72–74].

There are accumulating clinical observations suggesting that PD patients develop physical and emotional dependence to levodopa, which is beyond the relief experienced bestowed by its beneficial motor effect [73–76]. Such patients need to take their levodopa at regular times. They impatiently wait for ignition of “on” after an oral dose of levodopa, feel the need to take the next dose when the effect of the previous one had worn off and can no longer skip doses. Although such phenomena are reminiscent of addiction, PD patients are generally not regarded as being addicted to levodopa. Their compulsive use of the drug is considered merely as an urge to overcome their incapacitating motor signs and symptoms and not as a phenomenon of psychological craving. One fascinating case report describes a patient with PD who was completely paralyzed due to Guillain–Barre syndrome [73]. This patient continued to ask for his levodopa treatment on regular
intervals although it had no apparent beneficial motor effect. This exceptional case completely isolates the physical/emotional need for levodopa from the known motor relief by the drug. The potential addiction to levodopa has very relevant clinical consequences. Consumption of increasing doses of levodopa may expose some patients to devastating and difficult to control adverse effects, such as severe disabling dyskinesias and psychosis.

10. Conclusions

There is extensive evidence to link dopamine and addiction. PD is a unique human condition in which the homeostasis of dopamine is chronically disturbed. The addiction to levodopa and the “addictive-like behavior” in PD patients may help to elucidate the complex system of reward and addiction. In this review, we tried to combine the personal tragedy of a patient with PD who had an associated uncontrollable drive to gamble with current scientific knowledge on the frequency and type of behavioral changes and the addiction to levodopa.

DDS has appeared in the literature for many years but was somehow ignored until recently when behavioral changes and addiction-like syndromes drew well-deserved attention to these phenomena. Patients do not spontaneously admit their addiction to levodopa, or the presence of behavioral changes, especially not those concerning gambling and hypersexuality. On the contrary, we suspect that there are patients who exaggerate the severity of their functional status in order to convince their doctors to raise the daily dose of dopaminergic drugs. Some patients increase their daily levodopa dose to achieve euphoria and do not mind the resultant side effects, not even enhanced dyskinesias.

Why certain behavioral changes occur in some patients with PD and not in others is an important question whose answer awaits future prospective clinico-pathological and pharmaco-genetic studies. Other complications of PD, such as dyskinesias and hallucinations, represent a classic example of nature vs. nurture, and the answer is most likely a combination of both genetic factors and the effects of drug administration. The genetic profile of the patient is also likely to pre-dispose him/her to the addictive properties of the drug, making him/her more susceptible to behavioral changes. It should be borne in mind that chronic administration of dopaminergic drugs to patients with an abnormal reward system may increase the risk of behavioral changes. As such, clinicians should increase their level of awareness of this phenomenon and specifically ask their patients about their habits in order to prevent serious ramifications of PD drug ingestion, such as bankruptcy or family crisis.

Some topics for future investigation include the identification of special populations at risk for the development of DDS. A screening questionnaire that can identify patients at risk is sorely lacking.

In the most extreme cases, pathological DDS is easy to detect, but there is no validated tool to quantify the severity of DDS behavior. As a result, the actual frequency of DDS in PD and especially the mild or moderate cases are still under-recognized and untreated. Treatment strategies may include avoidance of certain drugs with a high-risk profile, especially for “high-risk” patients. The role of STN DBS in patients with DDS is not clear, but surgery may reduce compulsive drug consumption [77]. STN DBS may also improve symptoms of DDS in association with the reduction of dopaminergic medications [78]. It is also possible that early STN DBS and minimizing the use of the dopaminergic drugs may prevent these potential adverse effects, especially in high-risk patients.

Acknowledgment

DM was supported in part by an educational grant from the National Parkinson Foundation INC (NPF) USA. This review was written with the support of a center of excellence grant by the National Parkinson Foundation (NPF), Miami, USA. The Authors thank Mrs. Ester Eshkol for editorial support and Mrs. Judith Knaani for secretarial support.

References


[55] Shapiro MA, Chang YL, Munson SK, Okun MS, Fernandez HH. Hypersexuality and paraphilia induced by selegiline in Parkinson’s disease.


