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Review Article

Dopamine-Induced Nonmotor Symptoms of Parkinson's Disease

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Nonmotor symptoms of Parkinson's disease (PD) may emerge secondary to the underlying pathogenesis of the disease, while others are recognized side effects of treatment. Inevitably, there is an overlap as the disease advances and patients require higher dosages and more complex medical regimens. The non-motor symptoms that emerge secondary to dopaminergic therapy encompass several domains, including neuropsychiatric, autonomic, and sleep. These are detailed in the paper. Neuropsychiatric complications include hallucinations and psychosis. In addition, compulsive behaviors, such as pathological gambling, hypersexuality, shopping, binge eating, and punding, have been shown to have a clear association with dopaminergic medications. Dopamine dysregulation syndrome (DDS) is a compulsive behavior that is typically viewed through the lens of addiction, with patients needing escalating dosages of dopamine replacement therapy. Treatment side effects on the autonomic system include nausea, orthostatic hypotension, and constipation. Sleep disturbances include fragmented sleep, nighttime sleep problems, daytime sleepiness, and sleep attacks. Recognizing the non-motor symptoms that can arise specifically from dopamine therapy is useful to help optimize treatment regimens for this complex disease.

1. Neuropsychiatric

Hallucinations and psychosis have long been known to be associated with dopaminergic therapy. Psychosis in PD refers to the combination of chronic hallucinations and delusions occurring in the setting of otherwise clear senses. Hallucinations can involve various sensory modalities; however, visual hallucinations are the most common. Some may be benign and nonbothersome, while others can be terribly frightening to patients. Risk factors for developing hallucinations include older age, longer duration of PD, history of sleep disorder, depression, and coexisting cognitive impairment [1, 2]. Interestingly, there has been no evidence that increased dose or specific dopaminergic drug class (agonists versus L-dopa) is related to this problem [1, 3], and it is clear that hallucinations and psychosis are not just mere side effects of treatment. The likely pathogenesis is multifactorial involving pharmacologic mechanisms in conjunction with disease-related elements. Treatment for chronic hallucinations includes reduction of dopaminergic medications and discontinuation of anticholinergics or other drugs. If needed, antipsychotic medications may be used. Clozapine has demonstrated efficacy in a double-blind placebo-controlled trial [4]; however, in clinical practice quetiapine is preferred, despite the fact that, it has not been proven more effective than placebo in clinical trials [5–7].

Dopaminergic medications, particularly dopamine agonists [8], are known to be associated with impulse control disorders, with no differences seen between specific drugs [9, 10]. The prevalence of any ICD in PD patients on dopamine agonists ranges from 13.7 to 17.1% [11]. The formal definition for impulse control disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) is a group of psychiatric disorders characterized five stages of symptomatic behavior. Essential to this is "a failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others." Patients feel an increasing sense of tension or arousal before the act, experience pleasure, gratification, or relief while committing the act, and finally feel a sense of relief from the urge after the act. Individuals may or may not feel regret, self-reproach, or guilt about these activities [12]. Pathological

gambling (PG) is the most extensively studied ICD in PD, first noted in 2003 by Driver-Dunckley et al. [13] in a retrospective study of 1,884 patients. The essential feature of pathological gambling is that it is a "persistent and recurrent maladaptive gambling behavior that disrupts personal, family, or vocational pursuits" [12]. A recent prospective study of 200 PD patients reported a prevalence of PG to be as high as 7% [14]. Compulsive sexual behavior or hypersexuality as well as compulsive buying are not formally defined in the DSM-IV-TR. However, they are easily identified problems once patients cross the threshold of reasonable urge into compulsions leading to personal, familial, and/or occupational suffering and consequences. Hypersexuality can include not only increased libido, but also exhibitionism, excessive masturbation, phone/internet sex, use of prostitutes, and new sexual orientations. More seriously, criminal behaviors such as rape, pedophilia, and incest have been reported [15]. Hypersexuality can be seen in up to 4% of PD patients [16]. Compulsive buying of items that are unnecessary and go unused (i.e., shirts, shoes, jewelry) has been reported in up to 5.7% of PD patients [17] and often leads to financial distress. These patients tend to have traits of both obsessive-compulsive and impulse control disorders [18]. Binge eating is a proposed diagnosis in the DSM-IV-TR as an eating disorder marked by "uncontrolled eating of food that is larger in amount than most people would eat in a similar period of time under similar circumstances, without emesis or laxative abuse" [12]. Patients have a sense of lack of control over eating during the episode, and some report nocturnal awakening with an extreme sweet craving, eating excessive amounts. This has been reported in 4.3% of PD patients [17]. Punding refers to stereotypic, complex, and repetitive behavior involving meaningless activities (i.e., examining, sorting, collecting, arranging, dismantling objects) sometimes to the point of ignoring basic needs such as eating and sleeping. Patient may be irritable when interrupted, and this behavior can lead to social avoidance and isolation. Interestingly, participating in these activities may or may not be enjoyable for patients. One study involved demonstrated a punding prevalence of 1.4% in an ambulatory PD population [19], but it has been reported to be as high as 14% [20].

Dopamine dysregulation syndrome (DDS), also known as hedonistic homeostatic dysregulation (HHD), is a neuropsychiatric disorder characterized by addiction, self-medication, and escalation of antiparkinsonian medication. It is thought to have a prevalence of approximately 3.4% [21]. Not all patients with DDS have an ICD, although the majority of patients with DDS also exhibit punding [22]. Unlike ICD, DDS is typically associated with levodopa or short-acting dopamine agonist medications (i.e., subcutaneous apomorphine) [23], although it has been described with ergot- and nonergot-derived dopamine agonists as well [24]. These patients often do not have insight into the problem and will often take larger- than-recommended total daily doses, far beyond what is necessary for their motor disabilities. Unfortunately, they do not recognize the harm it is causing to themselves and their loved ones and demand increasing quantities of medication despite the development of complications (i.e., dyskinesia, "off" state dysphoria). Attempts to reduce the dose are met with great resistance, making management quite difficult.

DDS behaviors can be viewed as both a substance dependence disorder and an addiction. In fact, the term hedonic homeostatic dysregulation was coined based on the addiction model that addicts take drugs not only for pleasure but also to avoid unpleasant withdrawal symptoms [25, 26]. Other theories of psychostimulant addiction including pleasure seeking, habit models, and chronic neuroadaptations induced in the ventral striatum and nucleus accumbens may help to explain DDS [24]. Supportive of addiction theories, one study utilizing positron emission tomography (PET) showed that PD patients with DDS had enhanced levodopa-induced ventral striatal dopamine release, perhaps due to sensitization, compared with levodopa-treated patients with PD who did not have DDS [27]. In fact, it has been theorized that the pulsatile stimulation of striatal dopamine receptors inherent in the oral delivery of dopamine may cause changes in the basal ganglia circuitry leading to sensitization [28], leading to motor fluctuations, dyskinesia, and possibly even DDS. Interestingly, patients without PD but treated with dopaminergic therapy for restless legs syndrome have also been reported to have DDS, indicating that drug exposure itself plays a physiologic role, perhaps in triggering these behaviors [13, 29].

Treatment for these impulse control disorders starts with recognizing that they exist. It is important for physicians to be aware of these neuropsychiatric side effects of dopaminergic therapy and to actively screen for them, as patients often do not volunteer the information either because they do not have insight into these issues, they are in denial, or they are embarrassed. This is where family/caregiver input can be particularly helpful. One study found that only 25% of PD patients with an active ICD were identified clinically [9]. The risk factor profile of these patients includes male gender, early-onset PD, novelty-seeking personality, history of substance dependence, history of depression, high alcohol intake, and early emergence of dyskinesia [30–32]. Once identified, a thorough review of the patient's mediations is warranted, followed by a systematic reduction or cessation of dopaminergic treatment. For ICDs, this would involve dopamine agonists. If parkinsonism worsens, it may be prudent to concomitantly increase levodopa. In DDS, the strategy is reversed and levodopa is the initial agent to wean, with a subsequent increase in dopamine agonist treatment. However, as previously mentioned, patients with DDS often are not complaint with this, and therefore counseling with both the patients and their families/caregivers is important. As far as additional pharmacologic options, antidepressants for obsessive thoughts and antiandrogens to help decrease hypersexuality may be considered. A recent study found amantadine to be effective in the treatment of pathological gambling in PD [33]. Deep brain stimulation to the subthalamic nucleus may allow dopaminergic drug reduction and therefore improvement in these symptoms [34, 35] although DDS and ICDs may worsen or develop for the first time after DBS surgery [36].

2. Autonomic

Nausea is very commonly associated with dopamineric therapy. It is thought to result from stimulation of the area postrema [37]. Orthostatic hypotension and constipation may be intrinsic to neurodegenerative changes related to PD, but these can clearly worsen with dopaminergic therapy. Higher rates of constipation and nausea have been seen in patients treated with dopamine agonists versus levodopa [38], suggesting that the different pharmacodynamic properties of the various dopamine formulation may contribute to adverse effects. Autonomic symptoms in PD are attributed to the involvement of the central and peripheral postganglionic autonomic nervous system. Constipation in PD may be attributed to Lewy body pathology in the myenteric plexus and colonic sympathetic denervation. These symptoms are exceedingly common. One study found that 60% of patients had orthostatic hypotension early in the course of the disease [39], and 58% of PD patients may experience constipation [40].

In the vast majority of cases, nausea subsides with a slow titration up on dosage, with the addition of carbidopa or domperidone, a peripheral dopamine receptor blocking agent, or taking dopaminergic medications with food.

Conservative measures for the treatment of orthostatic hypotension include increasing salt and fluid intake, elevating the head of the bed (>30 degree incline), and the use of thigh and abdominal compression bands. Patients should be advised to avoid Valsalva maneuvers, warm temperatures, and meals rich in carbohydrates and alcohol, as these may be triggers. Pharmacologic treatments include fludrocortisone, a salt-retaining mineralocorticoid, midodrine, a selective peripherally acting α-adrenergic agent, and droxidopa, an orally active synthetic precursor of norepinephrine [41]. Pyridostigmine has been found to be effective in neurogenic orthostatic hypotension but has not been formally tested in PD [42]. Reduction in dopaminergic medication may be warranted if these medications are not tolerated or if orthostatic hypotension is severe.

Nonpharmacologic treatments for constipation include regular exercise, adequate water intake, and diet including symbiotic yogurts containing *Bifidobacterium*, fructoligosaccharide, and bulking agents (fibers, psyllium, and polycarbophil). A dietary herb extract, Dai-kenchu-to, has been found to ameliorate PD-related constipation [43]. Osmotic laxatives including magnesium sulfate and polyethylene glycol can be effective. Other laxatives include lubiprostone [44] and macrogol [45]. Serotonergic agents such as cisapride [46], mosapride citrate [47], tegaserod [48], and pyridostigmine [49], an acetylcholinesterase inhibitor, have been shown to be beneficial as well. Constipation in PD may be associated with focal dystonia of the puborectalis muscle, and botulinum toxin A injections to the puborectalis muscle have demonstrated clinical benefit [50]. Sacral nerve stimulation has shown some promise [51]; however, it has not been extensively studied and is not widely used. Reduction of dopaminergic medications, amantadine, and anticholinergics should also be considered. Highlighting the complexity of the pathophysiology involved in PD-related constipation, some dopaminergic agents such as apomorphine [52] and intrajejunal continuous infusion of levodopa [53] can improve constipation and bowel dysfunction.

3. Sleep

Sleep dysfunction is very common in PD, seen in 60–98% of patients [54], and if severe enough can lead to decreased quality of life, impaired function, and caregiver burden. Many sleep problems, are intrinsic to PD, such as fragmented sleep, nighttime sleep problems and daytime sleepiness. Complicating matters, all of these symptoms can be associated with dopaminergic medications [55], and these effects are dose related [56]. Dopaminergic medication is thought to have a desynchronizing effect on sleep architecture that causes disruption of sleep continuity [57]. Low-dose dopamine agonists have been associated with insomnia, whereas higher doses can lead to excessive daytime sleepiness (EDS). EDS has been defined as those patients who are experiencing unusually severe sleepiness during the day, sleeping more than 2 hours in the daytime, or falling asleep three or more times a day [58]. "Sleep attacks," sudden transitions from wakefulness to sleep without a prodrome, were first described in patients treated with pramipexole or ropinirole [59]. Sleep attacks may be a severe form of excessive daytime sleepiness, and the prevalence in patients treated with dopaminergic medications has been reported to be as high as 43% [60]. While initially associated with dopamine agonists, they can be induced by levodopa as well. One study showed that levodopa monotherapy carries the lowest risk, and combination therapy with levodopa and dopamine agonists has the highest risk [61] of sleep attacks. Drugs that are not associated with excessive daytime sleepiness/sleep attacks include selegiline, amantadine, and entacapone. Selegiline and amantadine have stimulating properties and therefore can induce problems with sleep initiation. Sleep attacks are important to be aware of because these abrupt sleep episodes can have dangerous implications, particularly when driving; thus, it is important to continuously monitor for this side effect.

Management of these sleep issues first begins with education regarding healthy sleep hygiene. Patients should try to maintain regular sleep/wake schedules, exercise regularly, and minimize the use of alcohol and caffeine. Some PD patients have coexisting sleep disorders, including sleep apnea and restless legs syndrome (RLS), and in these cases, a referral to a sleep specialist may be necessary. Physicians should carefully review medication lists and remove those that may be contributing to sleepiness. Medications that may be stimulating should be given earlier in the day. Dopaminergic medication may need to be reduced or discontinued, particularly in cases involving sleep attacks. The use of prolonged release dopamine agonists should be considered, as a recent study using ropinirole prolonged release demonstrated improved subjective quality of sleep, reduced daytime sleepiness, and disappearance of sleep attacks in some PD patients [62]. Possible pharmacologic therapies for daytime sleepiness that have demonstrated benefit in PD patients include methylphenidate [63], modafinil [64], and sodium

Table 1: Dopamine-induced nonmotor symptoms of Parkinson's disease.

Neuropsychiatric
Hallucinations
Impulse control disorders
Dopamine dysregulation syndrome
Autonomic
Nausea
Orthostatic hypotension
Constipation
Sleep
Fragmented sleep
Nighttime sleep problems
Daytime sleepiness
Sleep attacks

oxybate [65]. For fragmented sleep and sleep initiation, melatonin, a neurohormone produced in the pineal gland at night, has been shown to improve sleep quality and daytime sleepiness [66]. Patients who have undergone deep brain stimulation (DBS) of the subthalamic nucleus (STN) have reported improvements in nocturnal sleep [67]; however, it is not clear how DBS affects daytime sleepiness.

4. Conclusion

The management of dopamine-induced nonmotor symptoms of PD can be challenging, especially as treatment strategies often involve tapering off of these drugs, and such changes to therapy can worsen motor symptoms (Table 1). However, these effects of dopaminergic therapy are important to recognize given the impact they can have on patients' quality of life. Hallucinations and psychosis can be frightening to both patients and their loved ones. ICD and DDS can lead to serious personal, social, and financial consequences, and autonomic and sleep symptoms can often be more debilitating than PD motor symptoms themselves. Thus, it is important to exercise sound clinical judgment when initiating and titrating medication and closely monitor patients with the involvement of family and caregivers.

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