

CASE REPORTS

Increased Frequency and Range of Sexual Behavior in a Patient with Parkinson's Disease After Use of Pramipexole: A Case Report

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ABSTRACT

Introduction. Several recent reports have linked the use of dopamine agonists (DAs) to a variety of compulsive behaviors in patients with Parkinson's disease (PD). These inappropriate behaviors may include pathological gambling, compulsive shopping, and hypersexuality.

Aim. To report the case of a patient with increased range of sexual behavior after use of pramipexole, a DA.

Methods. A 67-year-old man with a 7-year diagnosis of PD treated with levodopa and pramipexole presented with a dramatic change in sexual behavior after an increase in DA dose.

Results. The patient, who historically was a very shy and conservative person, started to present increased frequency of sexual intercourse with his wife, during which he began speaking obscenities with an extreme preference for anal intercourse, preferences never requested before. After pramipexole was withdrawn, complete remission was observed with return to his usual sexual behavior.

Conclusions. Hypersexuality and paraphilic behaviors are complications not uncommonly found in patients with PD under dopaminergic treatment. Further studies are needed for the understanding of this complex complication, and particularly the most prevalent relationship between pathological hypersexuality and use of DAs. **Munhoz RP, Fabiani G, Becker N, and Teive HAG. Increased frequency and range of sexual behavior in a patient with Parkinson's disease after use of pramipexole: A case report. J Sex Med 2009;6:1177–1180.**

Key Words. Parkinson's Disease; Hypersexuality; Dopamine Agonist; Pramipexole; Anal Intercourse

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms that include at least two of four classical cardinal signs (resting tremor, rigidity, bradykinesia, and postural instability) [1]. However, during the disease course, most patients also present with several nonmotor features, including cognitive, behavioral, and autonomic disorders, including sexual dysfunction. In most of such cases, men present with erectile and ejaculation dysfunction, while women may have anorgasmia [1,2].

Additionally, treatment with dopamine agonists (DA) in PD may induce forms of compulsive behaviors [3] currently defined in the literature as

impulse control disorders (ICD) that include pathologic gambling, binge eating, compulsive shopping, punting (complex, repetitive, excessive, nongoal oriented behaviors) [4], and pathologic hypersexuality. The latter usually manifests as an increase in libido and inappropriate penile erections, but it may also involve inadequate behavior with exhibitionism, excessive use of sex phone in lines, prostitution services, and sex shops, including reports of frotteurism, zoophilia, and pederasty. These complications are probably the result of abnormal dopaminergic stimulation, often referred to as dopamine dysregulation syndrome (DDS) [3–9]. Table 1 lists the most common drugs used for the treatment of PD, risk, and type of sexual dysfunction related to each drug class.

Table 1 Drugs commonly used for the treatment of Parkinson's disease, risk and type of abnormal sexual behavior (ABS)

Drug class—mechanism of action	Generic name	Risk of ASB	Type of ASB
Dopamine precursor	Levodopa	0.9% [10]	Hypersexuality/paraphilias
Ergot/Nonergot DAs	Bromocriptine, pergolide, cabergoline, apomorphine, pramipexole, ropinirol, rotigotine	2.4% [4]	Hypersexuality/paraphilias
MAO-B inhibitors	Selegiline, rasagiline	Unknown*	Hypersexuality/paraphilias
NMDA receptor antagonists	Amantadine		
COMT inhibitors	Entacapone, tolcapone		
Anticholinergics	Trihexyphenidyl, biperiden, benzatropine, procyclidine	1.9% [11]	Delayed or retrograde ejaculation/anorgasmia

*Frequency of sexual dysfunction related to selegiline has not been formally estimated. Case reports are listed in the Reference section.
DA = dopamine agonist; MAO-B = monoamine oxidase B; NMDA = N-methyl-D aspartate monoamine oxidase; COMT = cCatechol-O-methyl transferase.

In this report, we describe an elderly patient with PD who developed hypersexuality with significant changes in his range of sexual behavior after use of pramipexole.

Case Report

A 67-year-old, right-handed man with a 7-year diagnosis of PD. His symptoms started as left-sided resting tremor, rigidity, and bradykinesia, and he was initially started on selegiline (5 mg bid). After 1 year, levodopa-carbidopa was started and gradually increased up to 100/25 mg qid. Four years later, selegiline was withdrawn and pramipexole was started up to 1 mg tid. He remained relatively stable for another 2 years when levodopa-related motor fluctuations (wearing-off and on-off phenomena) were reported. DA dose was further increased, reaching 1.5 mg tid. After 4 months on this regimen, the patient's wife called the office stating that her husband had recently developed disturbing and unusual sexual behavior changes. She confirmed that, historically, the patient was a very shy and conservative person, engaging in sexual intercourse once a week. After the last adjustment in DA dosage, there was a profound change in his sexual behavior with increased frequency of sexual activities (daily), during which he began speaking several forms of unusual obscenities, associated with an extreme preference for anal intercourse, preferences never requested before, during more than 40 years of marriage. She was asked to bring the patient to an appointment, in which he initially denied any abnormality. After his wife confronted him describing his recent sexual behavior changes, the patient assumed that his requests were unusual to his previous experiences with his wife, but assumed that these were practices that he secretly desired when he was younger but never felt comfortable enough to open up to her. He confirmed that now he felt somehow less ashamed to put his desires into practice.

Pramipexole was discontinued and entacapone (200 mg tid) was started. After 30 days, the patient's sexual behavior returned to his usual pattern, as previously described. On a recent follow-up, when asked to recall his recent change in sexual behavior, the patient demonstrated some insight into how now those practices seem inadequate and unacceptable considering the couple's background.

Discussion

The first case of hypersexuality induced by dopaminergic medications in PD was published in 1983, describing a patient treated with levodopa and bromocriptine [12]. Previously, studies evaluating psychiatric complications of levodopa therapy in PD had already reported hypersexuality in up to 1% of patients [10]. Later, PD treatment with levodopa, selegiline, and particularly DAs, has been implicated in several pathological sexual behaviors [8,9,12,13–16]. Berger et al. [13], for instance, reported two legal cases of PD patients treated with DAs presenting with sexual delinquency, one with hypersexuality and exhibitionism related to high-dose ropinerol, and the second with increased libido and pederasty using levodopa and bromocriptine. The authors believe that increased sexual impulsiveness in these patients may be underestimated and highlight the devastating impact that these side effects may have on social and legal aspects. Cannas et al. [8] also described a case with serious legal consequences in a cognitively intact patient using a different DA, pergolide, who developed a frotteurism and delusional jealousy. This case was successfully treated with pergolide dosage reduction and use of quetiapine. Shapiro et al. [14] published the report of two cases of hypersexuality and paraphilia induced by selegiline, both later complicated by obsessive-compulsive and punding behavior after the addition of DAs. Selegiline was also the agent related

to the case of reversible transvestic fetishism reported by Riley [15]. Klos et al. [16] reported 15 patients, 13 with PD and two with multiple system atrophy (MSA), presenting pathological hypersexuality linked to DA therapy, showing that in most cases, these complications are typically early features starting within 8 months after introduction of this form of therapy. Of importance, this series included four subjects on DA monotherapy. Additionally, nine (60%) of their cases also had additional compulsive or addictive behaviors. Jiménez-Jiménez et al. [9] described a case of possible zoophilia in a 74-year-old man with PD treated with levodopa and bromocriptine.

Risk factors described in previous studies include: male gender, younger age at assessment and younger age at PD motor symptoms onset [17,18]. Most series did not support a differential association between specific DAs and this form of complication, suggesting a class effect. On the other hand, two case series implicated pramipexole as the agent most likely to cause ICDs [4]. Neither of these series however, accounted for the relative frequency of pramipexole use in comparison with other DAs. These same series also suggested that the greatest risk might involve DA doses at the high end of the therapeutic range. Longer duration of treatment with DAs was implicated in some but not other studies [4,17,18]. One of the earliest studies describing this complication also described dose as a risk factor but did not find that prior sexual profile, history of psychiatric illness and brain damage were predisposing factors. This particular paper speculated about the possibility that hypersexuality in these cases was secondary to inhibition of prolactin secretion [19].

Our report describes one elderly patient with PD who developed sexual behaviors that were previously considered unusual after use of high doses of pramipexole. This patient had a profound modification in his sexual approach with his wife, including an increased frequency of sexual activity associated with an extreme preference for anal intercourse. When pramipexole was discontinued and entacapone was started, the patient's sexual behavior returned to his usual pattern. Pontone et al. [5] showed that generally, a psychiatric comorbidity might play a role in the development of ICD, including hypersexuality, in patients with PD using dopaminergic drugs. The case presented here, however, had no evident previous psychiatric history, as well as no such signs or symptoms before the DA dosage was increased. DAs as a cause of pathological hypersexuality are not exclu-

sive for PD, and include cases of atypical parkinsonism (two patients with MSA, mentioned above) [13] and restless legs syndrome [20].

The mechanisms responsible for the occurrence of these abnormal sexual behaviors in humans have not been firmly established, but theoretical and animal studies point to the interactions between anti-parkinsonian agents, particularly dopamine agonists and levodopa, and the D₃ dopamine receptor (DD₃R). In PD, the DD₃R is expressed in the ventral striatal area. Animal studies have shown that long-term levodopa treatment results in ectopic induction and sensitization of the DD₃R receptor in the dorsal striatum, an integral component of a reward circuitry involved in the control of motivated behavior [5]. An additional factor would be the inhibition of prolactin secretion induced by the stimulation of the D₂ dopamine receptor [19].

Other aspects of the interference of dopaminergic agents in sexual function are the use of DAs in the management of erectile and female orgasmic dysfunction (particularly the nonergot DA apomorphine) [21,22] and sexual side effects (usually expressed as decreased libido and/or delayed orgasm/ejaculation) found in up to 60% of subjects treated with selective serotonin-reuptake inhibitors. This complication is even referred in the literature as "dopamine-dependent," reflecting how effective the use of DAs or bupropion, a dopamine reuptake inhibitor, is in such patients [23].

Further studies are needed for the understanding of this complex complication, and particularly the most prevalent relationship between pathological hypersexuality and use of DAs in PD patients.

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