Movement Disorders
CLINICAL PRACTICE
CASE SERIES

Clozapine Treatment for Impulse Control Disorders in Parkinson's Disease Patients: A Case Series

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Abstract: Impulse control disorders (ICDs) are nonmotor complications of dopaminergic medications characterized by problems in behavioral self-control. Common management involves discontinuing or lowering dopaminergic medication, often producing motor worsening. We performed a retrospective chart review of Parkinson's disease (PD) patients treated with clozapine for ICDs. Four patients treated with clozapine for ICD were identified. Three patients were men. All 4 took dopaminergic medications at the time that ICDs developed; all received dopamine agonist therapy. ICDs included compulsive shopping, binge drinking, and hypersexuality. All 4 patients had complete resolution of symptoms while taking clozapine (12.5–37.5 mg). Two patients discontinued clozapine because of side effects. Larger studies are needed to further evaluate clozapine's role in treating PD patients with ICD.

Dopaminergic medications are commonly prescribed to treat motor symptoms of Parkinson's disease (PD). Patients on dopaminergic medications, especially nonergot dopamine agonists (DAs), are at increased risk for developing impulse control disorders (ICDs). Almost 40% of patients taking DAs may develop an ICD,[1] and it is reported that patients taking DAs have a 2 to 3.5 times higher odds of developing ICD, compared to those not receiving DAs.[2] Common ICD symptoms include compulsive buying, pathologic gambling, hypersexuality, and compulsive binge eating.[2]

ICDs often have a devastating psychosocial impact on patients and family members; thus, clinicians are compelled to urgently treat when symptoms arise. Management for ICDs predominantly involves discontinuing DAs and lowering levodopa dose. This strategy may fail by worsening motor symptoms and producing psychological withdrawal symptoms. There are no guidelines for optimal management. Various case reports suggested that medications such as atypical neuroleptics, antidepressants, and anticonvulsants may be beneficial.[3] Amantadine and naltrexone were studied in clinical trials. Although amantadine produced a beneficial outcome in one controlled trial, a subsequent study reported that amantadine was associated with ICDs, specifically pathological gambling, compulsive buying, and hypersexuality.[4,5] A recent clinical trial provided class I evidence that naltrexone did not show efficacy for treatment of ICDs in PD.[6] In 1998, a large, multicenter, retrospective review of clozapine in PD reported marked benefit in 2 PD patients with hypersexuality, although it is unclear whether the hypersexuality started after DA initiation.[7] We expand on this literature by reporting on 4 PD patients who developed ICDs and their response to clozapine treatment.

Patients and Methods

We reviewed the patient charts of a psychiatrist working in a movement disorder center to identify patients with PD and ICDs treated from 2007 to 2013. The psychiatrist receives referrals from multiple academic movement disorder practices and works as faculty of a comprehensive movement disorder center, exclusively treating patients with movement disorders. Approximately 70% of patients in this psychiatry practice have PD as the primary diagnosis, 9% of which have comorbid ICD as a clinical problem. Patients were included if: (1) there was no history of ICD before treatment for PD; (2) ICD developed after dopaminergic therapy; and (3) treatment with clozapine was initiated for ICD management and there were no current coexisting symptoms of psychosis. Each patient's psychiatry and neurology clinical charts were reviewed to determine: (1) age of PD onset; (2) disease course; (3) time to ICD onset from medication change; (4) ICD type; and (5) maximal clozapine dose

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used and efficacy. This study was exempt from institutional review board approval.

Results

Patient 1 was diagnosed with PD at 59 years of age; he developed sleep attacks when taking pramipexole. He was switched to ropinirole. He subsequently developed psychosis, including paranoia and auditory/visual hallucinations, and ropinirole was discontinued. He was then treated with trihexyphenidyl (1 mg/day) and carbidopa/L-dopa (300 mg/day). At age 66, carbidopa/L-dopa therapy was increased (up to 750 mg/day) and entacapone (800 mg/day) was added. He developed worsening symptoms of hypersexuality (obsessive thoughts of sex, viewing pornography, and spending thousands of dollars on prostitutes). Sertraline and quetiapine had no impact on symptoms. He was unable to tolerate lowering of the L-dopa dosage as a result of worsening motor symptoms. Clozapine (6.25 mg/day) was started and the patient reported a decrease in impulsive decision making within 1 week. Clozapine was gradually increased to 25 mg/day. He reported decreased sex drive, erectile dysfunction, and markedly reduced pornography viewing. Clozapine was further increased to 37.5 mg/day. He gained insight into his impulses and made reparations with his family. After 6 months on clozapine, improvement continued and he took the initiative to self-enroll into a 12-step sex addiction program.

Patient 2 was diagnosed with PD at 45 years of age and was treated with selegiline (5 mg/day) and pramipexole (3 mg/day). Ten months later, he developed increased sexual thoughts. Over the next 3 years, his hypersexuality gradually worsened and he engaged in extramarital affairs. He developed compulsive urges to call escort services. Quetiapine and venlafaxine extended release did not improve this behavior. Pramipexole was switched to ropinirole extended release (4 mg/day). This did not alleviate sexual thoughts. He also developed compulsive junk food binges. DAs were discontinued and carbidopa/L-dopa/entacapone (300 mg/day) was started without improvement in compulsive behaviors. Clozapine (12.5 mg/day) was started with partial response and eventually increased (to 37.5 mg/day) with sustained remission at 1-year follow-up.

Patient 3 had a family history of substance abuse and a personal history of alcohol-responsive postural tremor beginning in his thirties. At age 57, he developed right-sided rest tremor and decreased right arm swing. Carbidopa/L-dopa (300 mg/day) was started and titrated to higher doses (800 mg/day) within 1 year. He subsequently developed dyskinesias, which resulted in the lowering of L-dopa doses (600 mg/day) and the addition of ropinirole (8 mg/day). The patient developed significant *off* time and L-dopa dosing was subsequently increased (1,000 mg/day). Rasagiline (1 mg/day) was added. By age 62, his motor symptoms were well controlled. However, he developed hypersexual behaviors, including visiting pornographic websites and spending $250,000 on extramarital affairs. Ropinirole was discontinued with no change in compulsive behaviors. He then experienced severe motor fluctuations, alternating between periods of *on* dyskinesia and *off* akinesia. He was started on clozapine (12.5 mg/day) and, 3 weeks later, underwent subthalamic DBS placement. He reported no ICD symptoms 1 week postop, which was pre-DBS programming and 4 weeks after clozapine initiation. On 1-month follow-up, the patient refused to continue clozapine because of fatigue. Compulsive symptoms returned. He reported two episodes of infidelity 4 months after discontinuing clozapine.

Patient 4 had a history of anxiety disorder and presented at 45 years of age with right arm and leg stiffness. Her exam was consistent with PD and she was started on carbidopa/L-dopa (300 mg/day) and pramipexole. She developed compulsive shopping soon after medication was started and spent $40,000 in 2 months. Pramipexole was discontinued and carbidopa/L-dopa was increased (400 mg/day) without further ICDs until age 49, when she developed an uncontrollable craving for alcohol. She drank two bottles of wine nightly. She also developed persistent uncontrollable urges to clean the house. Quetiapine, amantadine, and venlafaxine did not decrease compulsions. She developed freezing of gait and wearing-off symptoms. Attempts to increase carbidopa/L-dopa led to worsening of ICD, which precluded appropriate symptom control. Clozapine (12.5 mg) was started, and at 1-month follow-up, she reported decreased alcohol consumption in addition to cessation of all other compulsions. Clozapine was increased (to 25 mg/day), and at 15-month follow-up, she reported full remission of all ICD symptoms and significant reduction in dyskinesia. Unfortunately, she gained more than 50 pounds while taking clozapine and ultimately discontinued the medication; soon after discontinuation, she resumed excessive alcohol consumption and has had intermittent exacerbations of compulsive shopping.

An overview of the clinical course for the 4 patients is provided in Table 1.

Discussion

Treating ICDs in PD patients is challenging. There is no standard-of-care treatment, and common strategies often lead to worsening motor symptoms. We describe 4 patients with positive response to clozapine.

Clozapine is an atypical neuroleptic with minimal extrapyramidal side effects. It is used by clinicians for PD patients with psychosis and dyskinesias. Clozapine's exact mechanism of action for dyskinesias is unclear. It is hypothesized that the major metabolite of clozapine has partial agonist effect on dopamine D2/D3 receptors, which decreases dyskinesias. It may also regulate the reward pathway and thus treat ICD.[8] Successful use of clozapine in patients with ICD was previously reported: 3 patients with pathological gambling and 2 patients with hypersexuality, 1 with zoophilia.[7,9,10] The latter patient had frequent mood swings and hallucinations; clozapine was initiated and the dose increased to target hallucinations. Our patients did not have concomitant hallucinations and clozapine was targeted solely at ICD. All 3 of our patients with symptoms of hypersexuality had significant observable reduction of sex drive and subsequent behavior modification while taking clozapine.

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TABLE 1 Treatment summary

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	M	M	M	F
Age of PD diagnosis	59	45	57	45
Initial DA medication	Pramipexole[a] Ropinirole[a]	Pramipexole 3 mg/day	Ropinirole 8 mg/day	Pramipexole[a]
Duration on DA	<1 year	10 months	5 years	2 months
Type of ICD	Hypersexual	Hypersexual	Hypersexual	Compulsive buying[b] Compulsive cleaning (Compulsive drinking)
Age of ICD onset	66	46	62	45[b]; 49
Treatment trials				
DA reduction/cessation attempted	—	Yes	Yes	Yes
L-dopa reduction attempted	Yes	Yes	—	Yes
SSRI	Sertraline 100 mg/day	—	—	—
SNRI	—	Venlafaxine XR 225 mg/day	—	Venlafaxine 150 mg/day
Antipsychotic	Quetiapine 50 mg/day	Quetiapine 25 mg/day	—	Quetiapine 12.5 mg/day
Other	—	Amantadine 300 mg/day	Amantadine 200 mg/day	Amantadine 200 mg/day
Clozapine maximum dose	37.5 mg	37.5 mg	12.5 mg	25 mg
Follow-up duration of sustained resolution	6 months	1 year	1 month	15 months
Side effect	—	—	Sedation	Weight gain

[a]Dosing unknown.
[b]Initial ICD, responded to dopamine agonist cessation.
SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline (norepinephrine) reuptake inhibitor.

Alcoholism is not considered as an ICD, but is a recognized comorbid condition with ICD. A personal or family history of alcohol-use disorders are predictive factors for development of an ICD in PD patients taking DAs.[1] Patient 4 developed compulsive shopping shortly after pramipexole was introduced, which resolved with discontinuation of drug, but later developed uncontrollable craving for alcohol. To our knowledge, this is the first report of successful reduction of alcoholism emerging after dopaminergic treatment with clozapine use.

This case series highlights our experience with the off-label use of clozapine in PD patients with ICDs. Clozapine was initiated when changes in dopaminergic treatment failed to improve symptoms. Commonly reported side effects of clozapine include sedation, weight gain, and orthostatic hypotension. It is associated with the rare condition of agranulocytosis and requires regular serum testing and monitoring. None of our patients developed serum abnormalities. Sedation and weight gain were the side effects that led to discontinuation in patients 3 and 4, respectively. Once clozapine was discontinued in these patients, compulsive symptoms returned.

Although the retrospective nature of this study limits our ability to recommend routine use of clozapine for ICDs in PD patients, this case series suggests a possible treatment option in patients who have failed traditional approaches. Randomized studies are warranted to further define the role of clozapine for treatment of ICDs in PD.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

J.L.: 1C, 3A

M.G.: 1A, 1B, 3B

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