INTRODUCTION

Dopamine agonists are used for the treatment of Parkinson’s disease for many years, regardless of clinical benefits dopamine agonists can result in serious side effects. We evaluated 6 patients after dopamine agonist withdrawal. Patients became disable after reduction or discontinuation of pramipexole, despite compensatory increases in levodopa doses. The exact mechanism underlying the profound and persistent gait freezing after D2 agonist withdrawal experienced by our patients remains to be determined.

The usage of oral dopamine agonists for the treatment of Parkinson’s disease dates back to the 1970s when bromocriptine was launched. Despite their beneficial effects, dopamine agonists can result in serious side effects, such as orthostatic hypotension, hallucinations, and impulse control disorders (including pathological gambling, compulsive eating, compulsive shopping/buying, and hypersexuality). The most effective way to alleviate these side effects is to taper or discontinue dopamine agonist therapy.

Here, we present a series of patients who became wheelchair-bound after reduction or discontinuation of pramipexole, despite compensatory increases in levodopa doses. To our knowledge, this has not been reported previously.

CASE 1

A 61-year-old man was referred to the movement disorders clinic because of inability to walk.

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Fourteen years earlier, Parkinson’s disease was diagnosed on the basis of bradykinesia, and levodopa resulted in clear benefit. After 4 years, pramipexole 0.7 mg/day and amantadine 200 mg/day were added. His disease progressed, but he continued to be able to walk with a walker. In the week before we first saw him, pramipexole was discontinued abruptly because of severe lower limb edema. Subsequently, his bradykinesia worsened, and within 2 days, he had several falls and became wheelchair-bound. He denied a history of hallucinations and impulse control behaviors, but he had insomnia and depression. He had diabetes and was taking metformin 1500 mg/daily and glibenclamide 5 mg/daily.

When we first saw him, 1 week after pramipexole was discontinued, he had severe bradykinesia and rigidity and was unable to stand without help. He was taking levodopa/carbidopa 200/50 three times a day. Pramipexole was restarted and increased gradually to 0.7 mg/day but his bradykinesia responded only slightly, he still could not walk and severe pedal edema recurred. Reducing the pramipexole dosage decreased the edema, but he again became more bradykinetic. Increasing levodopa improved his bradykinesia slightly, but he remained wheelchair-bound after 10 months of follow-up despite taking levodopa/carbidopa 200/50, 8 tablets a day, and 0.7 mg/day Pramipexole, unfortunately, he died after 11 months due to disease severity and complications. (Table S1).

3 | CASE 2

A 65-year-old woman was seen in our movement disorders clinic because of PD, beginning at the age of 50 taking levodopa/benserazide 200/50, four times a day, and pramipexole 0.18 three times a day. She complained of visual hallucinations and severe edema in the lower extremities but walked without assistance. She was well apart from her Parkinson’s disease. Pramipexole was tapered 0.09 mg/week; however, after 1 month, she returned to the clinic on pramipexole 0.09 mg/BID and could not walk due to severe freezing of gait (FOG) that happened during the second week and progressed afterward and made her wheelchair-bound. Pramipexole was increased, but she failed to improve, and after 6 months of follow-up when she was taking 1200 mg of levodopa-B and 0.18 mg/TDS of pramipexole, she remained unable to walk.

4 | CASE 3

A 62-year-old previously well woman was referred to our movement disorder clinic for management of a 6-year history of tremor dominant PD. She was treated with trihexyphenidyl 2 mg/daily, levodopa-carbidopa-entacapone 100 mg QID, levodopa/carbidopa 250/50 mg five times a day, amantadine 100 mg BID, and pramipexole 0.7 mg /TDS (the latter for 2 years). Due to severe dyskinesia, trihexyphenidyl was tapered and the patient improved, but still had dyskinesia. Levodopa-carbidopa-entacapone was decreased to a TDS schedule, and levodopa 125 mg was added to the morning dose. However, this resulted in severe wearing off, and so pramipexole was tapered 0.18 mg/monthly and LD increased. Her walking ability deteriorated gradually, and after discontinuation of pramipexole, she became wheelchair-bound, and despite a further increase of levodopa dosage and restarting pramipexole, she remained wheelchair-bound after 18 months of follow-up at that time when she taking on levodopa-C 2000 mg /daily and pramipexole 0.7 mg/ TDS.

5 | CASE 4

A 43-year-old woman, otherwise well, with 6-year history of PD treated with trihexyphenidyl 2 mg/TDS, pramipexole 0.7 mg /QID (for 3 years), levodopa/benserazide 100/25 mg four times a day, and amantadine 100 mg/ BID was referred to our movement disorder clinic. Trihexyphenidyl was tapered over the following year because of cognitive decline, and after that, due to severe dyskinesia, pramipexole was tapered 0.18 mg/monthly and levodopa-B was increased concurrently. During tapering, walking ability worsened gradually, and when pramipexole was completely discontinued, she experienced severe (FOG) and became wheelchair-bound despite taking 1200 mg levodopa. Pramipexole was restarted and increased gradually up to 0.7 mg four times a day, and LD-B was increased to 1600 mg/daily but without any benefit after 12 months of follow-up.

6 | CASE 5

A 49-year-old gentleman with a 7-year history of PD was treated with selegiline 5 mg/BID, pramipexole 0.18 mg /TDS, and half of levodopa-C 250/25 four times a day. He did not have any other systemic illness. Because of obsessional paranoid thinking, pramipexole was tapered half of 0.18 mg/monthly and levodopa increased, but when pramipexole was stopped completely, he became wheelchair-bound because of severe FOG.

Increasing dose of levodopa to 1500 mg and restarting pramipexole to 0.18 mg/TDS failed to provide benefit after 1-year of follow-up.
CASE 6

A 59-year-old man with a 5-year history of PD was on trihexyphenidyl 2 mg/BID, selegiline 5 mg/BID, pramipexole 0.7 mg/BID, and levodopa/carbidopa 250/25 mg five times a day. Trihexyphenidyl was tapered over the next year because of hallucinations, but because these did not improve, pramipexole was tapered by 0.18 mg/month. When he reached a dose of 0.18 mg/TDS of pramipexole, he experienced severe FOG that he did not respond to increasing the dose of pramipexole to 0.7/TDS and increasing levodopa to 1750 mg/daily after 8 months of follow-up.

DISCUSSION

Freezing of gait, defined as episodic inability to start effective steps, is one of the debilitating symptoms of PD that affects around 7% of people with early disease and over half of patients with advanced PD.\(^3,4\) The underlying pathogenesis of FOG is not well understood. Growing evidence shows that FOG may be driven by missing or abnormal connectivity between multiple brain areas central to movement control including posterior parietal cortex, the premotor cortex, the supplementary motor area, and deeper brain structures including basal ganglia and brain stem as well as disturbances of visual perception, and cognitive and affective state.\(^5,6\) The increasing dose of dopaminergic medication required to control FOG over the disease progression confirms a central role of dopamine in this variant of FOG. However, the observation of dopaminergic unresponsive FOG and “on” FOG has unveiled the complex nature of this symptom\(^7\) and implies the probable role of other neurotransmitters and pathways, including GABA, glutamate, noradrenaline, serotonin, acetylcholine, and adenosine which are currently under investigations.\(^6,8,9\)

To the best of our knowledge, there are no reports of FOG and severe disability after dopamine agonist dose reduction or withdrawal despite returning to the pre-reduction dosage as well as increasing levodopa dosage.

8.1 | The hypothetical mechanisms which may explain this variant of FOG

8.1.1 | Disease progression and dopaminergic treatments

The frequency and duration of FOG episodes are positively correlated with disease severity.\(^10\) Moreover, it is accepted that long-term treatment with levodopa\(^10\) and dopamine agonists (DAs)\(^11,12\) especially in pulsatile regimens is positively correlated with the development of FOG. It has been hypothesized that long-term treatment with levodopa impairs compensatory upregulation of postsynaptic dopamine receptors and therefore increases the thresholds of postsynaptic membranes to respond to dopamine.\(^13\) Moreover, consistent with the pharmacological fact that chronic agonist treatment will desensitize and downregulate postsynaptic receptors, imaging studies in PD patients treated with levodopa or DAs show that chronic treatment with DAs, but not levodopa, suppresses striatal D2 receptor (D2R) expression,\(^14\) which in turn will increase the threshold of response to dopaminergic treatments. Therefore, PD patients with greater disease severity, especially with a history of long-term levodopa and pramipexole treatment, may experience more frequent and severe FOG. However, the unexpected phenomenon of unresponsiveness to re-treatment with DAs and increased doses of levodopa seen in our patients remains unexplained; further studies to evaluate the half-life and reversibility of DA-induced postsynaptic changes after treatment discontinuation might shed light on this observation.

8.1.2 | Pharmacodynamics and kinetics of DAs

Our cases of irreversible FOG all were under treatment with immediate-release (IR) pramipexole that was tapered or abruptly discontinued. Although there are pieces of evidence that pramipexole-IR, pramipexole-extended release (ER), and ropinirole-ER oral formulations provide a broadly comparable benefit and risk in the adjunctive treatment of advanced PD,\(^15\) the importance of the pharmacodynamics and kinetics of different DAs and their formulations should not be neglected. To this regard, it is shown that transdermal patch of rotigotine over a treatment course of 7 months significantly attenuates wearing off FOG, though prolonged-release pramipexole or ropinirole in equivalent doses do not improve or worsen FOG.\(^16\) Moreover, in a 5-year study on patients with early PD, it is observed that ropinirole medication may deteriorate dopamine-responsive FOG.\(^11\) The benefit of rotigotine in treating off time FOG can be attributed to its binding affinity to the D1 (D1/D5) and D2 (D2/D3/D4) family and its 24-h constant plasma concentrations transdermal.\(^16\) Therefore, the irreversible FOG after pramipexole treatment discontinuation, regarding its affinity to only D2 family of dopamine receptors (like ropinirole), can be associated with an imbalance between the function of D1 and D2 family of receptors as well as its non-steady hemodynamics provided by immediate-release formulation.
8.1.3 | The Dopamine agonist withdrawal syndrome: effects on limbic system on brain stem and basal ganglia

The globus pallidus interna (GPI) and substantia pars reticularis (SNr), grouped together as basal ganglia output nuclei, receive inputs not only from the striatum and subthalamic nucleus but also from limbic structures including amygdala and hypothalamus17 and deliver afferents to the thalamus and the brainstem pedunculopontine tegmental nucleus (PPN) providing a robust inhibitory control.18 PPN is mainly considered as the key component in a feedback loop between the limbic system back into the basal ganglia and thalamus,17 and this mutually regulated system is strikingly involved in the control of motor and cognitive processes.19,20

Dopamine depletion in the striatum impairs the proper processing of information from motor, cognitive, and limbic pathways, which in turn results in the overactivity of the inhibitory output of the basal ganglia to the thalamus and PPN leading to a vicious cycle contributing to the typical gait problems of PD.21 According to this model, it is assumed that any increase in processing demands in the striatum, during certain challenging states with an overload of sensory and/or cognitive inputs, may result in or worsen FOG.21,22

In PD patients, DA discontinuation, even after tapering, can cause a withdrawal syndrome similar to narcotic withdrawal in chronic users, with prominent psychiatric manifestations including anxiety, panic attacks, dysphoria, depression, agitation, irritability, and fatigue are all related to limbic system dysregulation. In these patients, this dopamine agonist withdrawal syndrome (DAWS) is usually misdiagnosed as end-of-dose wearing off or inadequate dopaminergic medication,23 although symptoms persist even in the motor on state are refractory to increasing levodopa dose.23,24 Therefore, theoretically the negative affective state of withdrawal could disrupt the functional connectivity between the limbic system, brainstem, and basal ganglia and cause refractory FOG. However, in contrast to DAWS, which typically resolves on reinstatement of DA dosage, the FOG in our patients seemed to be irreversible despite this approach.

The exact mechanism underlying the profound and persistent FOG after D2 agonist withdrawal experienced by our patients remains to be determined. Future animal studies might help to understand precise pathogenesis.

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CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
MS involved in conception, organization, and execution of the research project and wrote the first draft of the manuscript. AEL and LD involved in conception, organization, and execution of the research project and critically reviewed the manuscript. AHH critically reviewed the manuscript. ME involved in conception, organization, and execution of the research project.

DATA AVAILABILITY STATEMENT
Data is available on request.

ORCID
Mehri Salari https://orcid.org/0000-0001-7102-821X
Amir Hasan Habibi https://orcid.org/0000-0001-6896-4779

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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