Freezing of Gait and Its Levodopa Paradox

Freezing of gait (FOG) in Parkinson disease (PD) is common and disabling. It has 3 phenotypes, 1 the least common one being akinetic freezing (a lack of discernible leg movements despite an intention to walk). The other phenotypes can be characterized as freezing with attempted but ineffective stepping: one involves alternating-leg trembling with a frequency of 3 to 8 Hz, the other by small, shuffling steps. The underlying pathophysiological substrate remains insufficiently understood. In this Viewpoint, we address this fascinating but hitherto largely neglected paradox: levodopa generally reduces the severity of FOG, but 2 recent observations showed that in patients with parkinsonism who were untreated—even those with severe disease—the ineffective-stepping phenotype of freezing is absent.2,3 Such observations suggest that long-term pulsatile levodopa treatment may contribute to FOG development. Initially, it is difficult to reconcile levodopa’s beneficial symptomatic outcomes with this negative development. We provide a new framework to explain this paradox as a basis for research and treatment.

Several observations suggest that FOG was rare before patients were treated with levodopa. First, not long after the introduction of levodopa in the late 1960s, clinicians began to observe a new phenotype of PD. In 1971, Barbeau4 described patients receiving levodopa treatment starting to experience a new type of walking problem—one we would now refer to as FOG with attempted stepping. In a series5 of 80 patients, freezing typically appeared during the second year of levodopa treatment, and its cumulative prevalence gradually increased to 55% after 6 years of treatment. His observations suggest that long-term levodopa treatment increases the likelihood of FOG occurrence and the FOG phenotype changed after levodopa introduction, with FOG with attempted stepping occurring more often.

It is accepted that long-term levodopa treatment, possibly because of its pulsatile administration, results in a loss of compensatory postsynaptic dopaminergic receptor upregulation and maladaptive plasticity of the striatum via influence on physiological forms of synaptic plasticity (including long-term potentiation and depression). We hypothesize that in patients with FOG, levodopa-induced aberrant plasticity has resulted in increased thresholds of postsynaptic receptors within the motor circuitry connecting the striatum, premotor area, and supplementary motor area, so that increasingly higher dopamine concentrations are required for their activation. This motor circuitry is essential for the fine regulation of gait but needed to control simple steady state gait to a much lesser degree or not at all, so this remains better preserved. However, more complex circumstances requiring greater motor circuitry involvement (eg, gait initiation, turning) become compromised, resulting in FOG. In the off-medication state, it is more difficult to overcome the higher-than-normal stimulation thresholds within the motor circuitry, so FOG is typically more severe in this state than the on-state. But when the levodopa dosage is increased, thresholds are met more easily and FOG will be less severe. In the long term, however, higher levodopa dosages will further stimulate maladaptive plasticity, resulting in even higher stimulation thresholds and consequently greater FOG severity. This calls for still higher dosages of levodopa, inducing a vicious circle. Ultimately, levodopa cannot be increased further because of dosagelimiting adverse effects, contributing to the appearance of levodopa resistance.

To explain the observed increase of FOG with attempted stepping, we must extend our framework. Gait control is not only dependent on the motor circuitry connecting striatum, premotor area, and supplementary motor area but also on cognitive and limbic input.7 In PD, dopaminergic motor loops originating from the substantia nigra pars compacta are denervated more than the dopaminergic limbic and cortical loops originating from the ventral tegmental area (Figure).8 Because levodopa-induced aberrant plasticity is associated with greater dopaminergic denervation,9 the increase in thresholds of postsynaptic receptors is expected to occur disproportionally within motor circuitries. Specifically, there will be relatively less increase in postsynaptic thresholds within the cognitive and limbic loops. We hypothesize that levodopa treatment thus leads to a growing mis-
In untreated Parkinson disease (A), dopaminergic cell loss is greater in the substantia nigra (SN) pars compacta than the ventral tegmental area (VTA), leading to greater dysfunction in the striatal–premotor-supplementary motor area loop compared with cognitive and limbic loops. Postsynaptic dopamine receptor upregulation partially compensates for the dopaminergic cell loss. In these circumstances, dysfunction in the striatal–premotor–supplementary motor area loop may lead to a slow, shuffling gait and occasionally freezing of the akinetic type. After long-term pulsatile levodopa treatment (B), the postsynaptic dopamine receptor upregulation will be lost, and maladaptive plasticity induced by levodopa will disproportionately increase the mismatch between striatal–premotor–supplementary motor area loops on the one hand and the cognitive and limbic loops on the other, resulting in freezing with attempted stepping. Interactions between corticocortical and corticostriatal loops and convergence from cortex to striatum are not shown.

match between activated cognitive and limbic loops (causing a desire to walk) but understimulated motor loops (causing an inability to initiate a desired step). This dissociation between desire and capacity may result in FOG with attempted stepping. In most patients, the dissociation between cognitive or limbic loops and motor loops will mainly occur while medications are in an off-state, when it is more difficult for patients to reach stimulation thresholds within the motor loop. In a small proportion, FOG is more prominent in the on-medication state, presumably because of relatively better dopaminergic influences on cognitive and limbic functioning, so that patients feel capable of initiating large steps but are unable to do so. This would again lead to FOG with attempted stepping.

Testing of this hypothesis is required. Prospective trials with long follow-up should compare patients with early levodopa treatment vs delayed levodopa treatment. Also, future intervention studies could evaluate whether alternatives for the current treatment approach (including the conventional way of administering levodopa in pulsatile doses) may help to reduce the severity of FOG. One conceivable approach is to administer levodopa more continuously from the outset of treatment (using controlled-release preparations or an advanced treatment). Another question worth investigating is whether thresholds within the motor loops can be restored. One option is deep-brain stimulation: subthalamic nucleus stimulation allows for a substantial reduction in dopaminergic medication, and this is associated with reversal of motor and nonmotor sensitization. Accordingly, several studies showed beneficial effects of subthalamic nucleus stimulation on FOG. Another interesting approach is to tackle postsynaptic modifications in N-methyl-D-aspartate receptor firing (e.g., using antagonists such as amantadine). The available evidence is conflicting, and double-blind randomized clinical trials with FOG as primary outcome are needed.

ARTICLE INFORMATION
Published Online: December 16, 2019. doi:10.1001/jamaneurol.2019.4006
Conflict of Interest Disclosures: Dr Bloem reported grants from Netherlands Organization for Scientific Research, Stichting Parkinson Fonds, the Michael J. Fox Foundation, Parkinson’s Foundation, Verily Life Sciences, Horizon 2020, Toppers/Life Sciences and Health, and UCSB outside the submitted work. Dr Nonnekes reported grants from Netherlands Organization for Scientific Research, the Michael J. Fox Foundation, and Gossweiler Foundation outside the submitted work. No other disclosures were reported.

Additional Contributions: We thank Paul Krack, MD, PhD, University Hospital Bern, for his extensive and valuable input. He was not compensated.

REFERENCES