Freezing of gait: a practical approach to management

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Freezing of gait is a common and disabling symptom in patients with parkinsonism, characterised by sudden and brief episodes of inability to produce effective forward stepping. These episodes typically occur during gait initiation or turning. Treatment is important because freezing of gait is a major risk factor for falls in parkinsonism, and a source of disability to patients. Various treatment approaches exist, including pharmacological and surgical options, as well as physiotherapy and occupational therapy, but evidence is inconclusive for many approaches, and clear treatment protocols are not available. To address this gap, we review medical and non-medical treatment strategies for freezing of gait and present a practical algorithm for the management of this disorder, based on a combination of evidence, when available, and clinical experience of the authors. Further research is needed to formally establish the merits of our proposed treatment protocol.

Introduction

Freezing of gait is a common and incapacitating symptom that occurs in patients with Parkinson's disease, and even more frequently in patients with most forms of atypical parkinsonism. Additionally, freezing of gait can occur in isolation in patients with primary progressive freezing of gait; this disorder is often a prelude to later development of progressive supranuclear palsy (PSP) or another tauopathy. In Parkinson's disease, freezing of gait is associated with disease severity,[1] although it can be seen early in the course of the disease. However, if freezing of gait is (one of) the first presenting signs, atypical forms of parkinsonism should be suspected.[2] Freezing is not restricted to gait, and can occur in alternating repetitive movements of the fingers[3,4] and during speech.[5] Whether these other motor blocks have the same pathophysiological substrate as freezing of gait is unclear.

Freezing of gait is characterised clinically by sudden, fairly brief episodes of inability to produce effective forward stepping that typically occur during gait initiation or turning while walking.[6,7] These gait blocks greatly interfere with daily life. Importantly, freezing of gait is now recognised as one of the main risk factors for falls (because, during walking, the trunk keeps moving while the feet become stuck).[8] This risk is compounded by the fact that freezing of gait often co-occurs with substantial balance problems[9] and cognitive (mainly frontal executive) deficits.[10]

Treatment of freezing of gait is perceived by clinicians as a very challenging task. The need for a treatment protocol with a clear decision algorithm is widely acknowledged, but such a protocol does not exist. In this Personal View, we provide an overview of the medical and non-medical management of freezing of gait, including use of drugs and surgical approaches, non-pharmacological therapies, and treatment of co-morbidities. We first discuss the need for careful history taking and clinical assessment to accurately diagnose freezing of gait and to assess its (subjective) severity; we then present an algorithm for the practical management of freezing of gait. All recommended interventions are based on evidence when available (classified according to their level of evidence in table 1). Otherwise, our recommendations reflect practice-based evidence supported by our clinical experience.

History taking and clinical assessment

Several papers provide a detailed description of both history taking and clinical provocation of freezing of gait;[47,48] here, we provide a brief summary. Simply asking the patient whether freezing has occurred is usually insufficient to identify whether or not freezing of gait is present. Instead, we recommend asking whether the patient has ever experienced the characteristic feeling of the feet being glued or pasted to the floor, or being stuck to the floor, as if attracted by an invisible magnet. To ascertain that the patient really understands what freezing of gait is, it can help for the examiner to stand up and imitate a freezing of gait episode or, preferably, to show a video of a typical freezing of gait episode in a patient. Investigation of circumstances during which freezing of gait occurs is necessary (eg, during turning, or under time constraints). Moreover, frequency, intensity, and duration of freezing of gait episodes should be discussed. The new freezing of gait questionnaire can be helpful to assess the subjective severity of freezing of gait and effects on daily life.[49] Additionally, the subjective effect of (dopaminergic) medication should be assessed by asking whether freezing occurs predominantly, or even exclusively, when the medication has worn off (the so-called off-state), or whether freezing of gait occurs in both the off-state and the on-state (characterised by improvement of other symptoms compared with the off-state). Answers to these questions usually provide an accurate portrayal of the treatment response to dopaminergic medication. Finally, asking about the presence of falls can be helpful, since freezing of gait episodes are recognised as a major cause of falls in patients with Parkinson's disease.[8] Fall types typically related to freezing of gait include falling while turning, and apparently spontaneous falls (often the patient has missed a brief freezing of gait episode that preceded the fall). Freezing of gait is an unusual gait disorder because of its episodic character. Provocation of freezing of gait during neurological assessment is therefore difficult. The patient's extra attention to gait during clinical

examination can probably temporarily suppress freezing. Additionally, freezing of gait is less likely to occur in a widely spaced hospital corridor, which is unlike the sometimes tight quarters in the patient's own living space. To provoke freezing of gait, asking the patient to make full and rapid turns in both directions (video),[48] or to walk with short steps as rapidly as possible can help.[50]

Treatment of mild freezing of gait

The first step in our treatment algorithm (figure) is to decide whether or not freezing of gait is troublesome to the patient. Troublesome is operationally defined here as interfering with the patient's mobility or quality of life—eg, when freezing of gait is associated with social embarrassment or fear of falling, or actually leads to (near) falls. For some patients, and certainly in early stages of development, freezing of gait can be mild and not interfere with daily function. Importantly, even mild symptoms of freezing of gait need to be taken seriously, because mild freezing almost inevitably progresses to troublesome freezing of gait. Therefore, regular assessment of its effect on the patient is needed.

Troublesome freezing of gait should always be treated aggressively. However, all patients, including those with mild freezing, should be educated about freezing of gait, especially about the risk of falls, various provoking circumstances, and possible preventive measures (table 2). In patients with mild freezing of gait, we therefore always recommend physiotherapy. Physiotherapy includes both dedicated strategies (cues) that can assist patients to overcome freezing of gait episodes (eg, conscious movement strategies to increase step amplitude, retaining stepping rhythm, making lateral weight shifts, directing attention to gait, and making wide arcs when turning) and the recommendation to maintain sufficient exercise levels.[44,51] Although no evidence exists that exercise can prevent or decrease freezing of gait, stimulation of physical activity in patients with Parkinson's disease is generally regarded to be important. Cycling can be advised, at least in countries in which outdoor cycling is prevalent, such as the Netherlands or Japan, because patients rarely experience freezing of gait during cycling.[52,53] A tricycle or stationary bicycle at home can be considered for patients who are not used to cycling (eg, in countries in which outdoor cycling is not part of the culture), or who have difficulty mounting or dismounting owing to balance problems.

Several additional measures can be considered for patients with mild freezing of gait. One consideration is to prescribe monoamine oxidase B inhibitors, such as rasagiline and selegiline, because clinical trials have shown that these are associated with reduced risk of future freezing of gait (for both drug-naive patients and patients already receiving other dopaminergic drugs).[16,54] Freezing of gait was not the primary outcome in these clinical trials, so this finding might have been incidental; future studies with freezing of gait as a primary outcome are needed to further validate this strategy. This strategy aims to prevent possible development of freezing of gait, and not to symptomatically treat overt freezing of gait. We have tried symptomatic treatment of freezing of gait, with very limited success.

	Effect	Level of evidence*
Dopamine-responsive freezing of gait		
Levodopa	Improvement	Level B[11–13]
Dopamine agonist	More new freezing of gait episodes compared with levodopa; effect of dopamine agonist *vs* placebo on freezing of gait has not been investigated	Level A2[14]†
	Expert opinion: dopamine agonists can both worsen and improve freezing of gait	Level D
Monoamine oxidase B inhibitors (rasagiline or selegiline)	Reduced risk of developing freezing of gait	Level A2[15,16]†
STN stimulation	Improvement	Level C[17,18]
GPi stimulation	Effect on freezing of gait needs to be investigated	..
Methylphenidate	Improvement in patients after STN stimulation, but no improvement in general	Level B[19,20]
Intraduodenal levodopa gel	Improvement	Level C[21]
Apomorphine	Effect on freezing of gait needs to be investigated	..
Amantadine (either oral or intravenous)	Inconsistent data	Level C[22–25]
Electroconvulsive therapy	Insufficient data	Level D[26]
Transcranial direct current stimulation	Insufficient data	Level D[27]
PPN stimulation	Inconsistent data	Level C[28–30]
Botulinum toxin injections	No improvement	Level B[31–33]
Dopamine-resistant freezing of gait		
Droxidopa plus entacapone	Insufficient data	Level C[34]
Intraduodenal levodopa gel	Improvement	Level D[35]
STN stimulation	No improvement	Level C[36,37]
Amantadine	No improvement	Level B[38]
Dopamine-induced freezing of gait		
Reduction in levodopa	Improvement	Level D[39]
STN stimulation	Improvement	Level C[40]
All types of freezing of gait		
Physiotherapy		
Rhythmic auditory cues and visual cues	Improvement	Level B[41–44]
Walker or stick projecting a laser line on the floor	Improvement	Level C[45]
Psychoeducation	Improvement	Level D
Occupational therapy		
Home adjustment; help with daily planning	Improvement	Level D[46]

*Level A1=meta-analysis containing at least some trials with evidence level A2, with consistency in trial results; A2=good quality randomised comparative clinical trials (randomised double-blind controlled trials) of sufficient size and consistency; B=moderate (weak) quality randomised clinical trials of insufficient size or other comparative trials (non-randomised trials, cohort studies, patient-control studies); C=non-comparative trials; D=expert opinion. STN=subthalamic nucleus. GPi=internal globus pallidus. PPN=pedunculopontine nucleus. †Freezing of gait was not the primary outcome measure, but a secondary or fortuitous endpoint.

Table 1: **Level of evidence of interventions for freezing of gait**

See **Online** for video

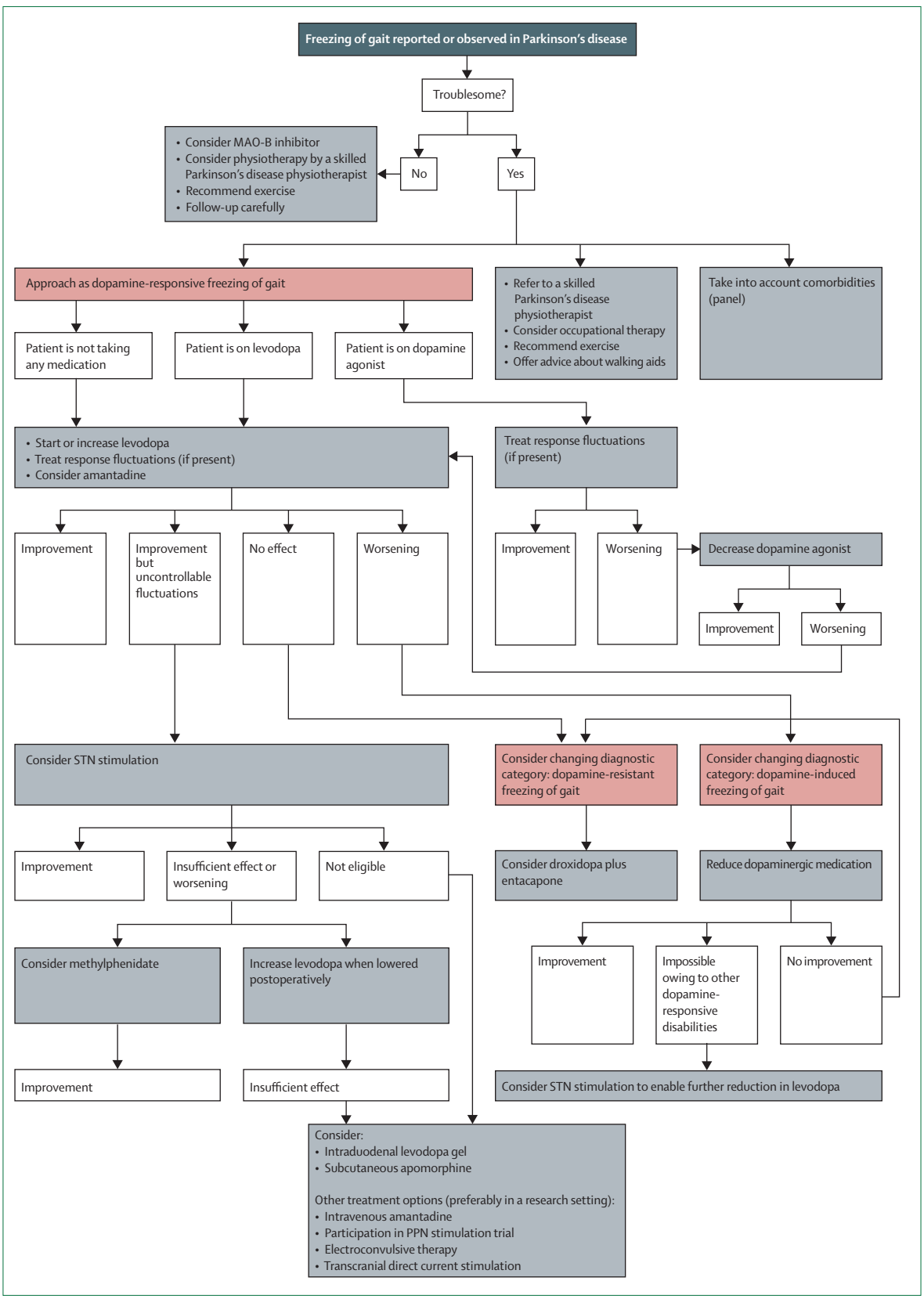

Figure: **Algorithm for the practical management of freezing of gait**
Boxes in grey represent suggested therapeutic interventions; boxes in red represent important classification steps that help to guide the management approach. MAO-B=monoamine oxidase B. STN=subthalamic nucleus.PPN=pedunculopontine nucleus.

Treatment of troublesome freezing of gait

For patients with troublesome freezing of gait, management consists of three pillars: medical treatment (drugs and deep-brain stimulation); non-pharmacological therapies; and assessment and treatment of comorbidities.

Pharmacological and surgical treatment options

The first crucial step in treatment of troublesome freezing of gait is a detailed assessment of when freezing occurs with respect to medication dosages. In this assessment, identification of which of three types of freezing of gait is present is important: dopamine-responsive (ie, related to loss of central dopamine); dopamine-induced (ie, caused by administration of dopaminergic medication); or dopamine-resistant (ie, related to presence of non-dopaminergic brain lesions). A detailed diagnostic approach to differentiate between these types of freezing of gait has been presented;[39] we give a summary here, with recommended therapeutic strategies.

Dopamine-responsive freezing of gait

We recommend that freezing of gait should always be approached first as dopamine-responsive, because this is the most common phenotype of freezing of gait, especially in early disease stages of Parkinson's disease (video).[6,39] Indeed, many patients first experience freezing of gait exclusively when medication wears off. A careful assessment of this possibility and management of early response fluctuations (ie, the patient's variable response to dopaminergic medication, as reflected by transitions between a patient's relatively good motor performance when the dopaminergic medication is effective and a more prominent parkinsonian state when the dopaminergic medication has transiently lost its effect) often alleviates or even resolves the problem, at least initially. A typical feature is that episodes of freezing of gait are more common and more prolonged during the off-state than during the on-state.[11] Adequate treatment of dopamine-responsive freezing of gait seems to need higher doses of dopaminergic medication than does suppression of other cardinal signs of Parkinson's disease, such as bradykinesia and rigidity.[39] This means that one can encounter patients whose upper body signs—and particularly the fine hand movements—seem to be in an on-state, while the legs continue to manifest freezing of gait. A tempting conclusion would be that such patients have on-state freezing of gait, but in our experience many patients have improved walking when increased levodopa doses are tried, sometimes at the expense of upper body dyskinesias.

The first step in the drug treatment of freezing of gait is to assess the effect of levodopa (in treatment-naive patients), or to increase the dose in patients already treated with levodopa, to at least 1000 mg/day if needed. If freezing of gait only partly responds to such high doses of levodopa, and if the patient is not hindered by dose-limiting adverse effects, then dosage can potentially be increased further to improve control of freezing of gait. If freezing of gait occurs mostly when medication has worn off (which is often the case), patients can benefit from well known strategies to alleviate response fluctuations (eg, reduction of time intervals between the subsequent medication intakes).[55] Patients who experience freezing of gait when getting up at night to go to the bathroom might benefit from controlled-release preparations before sleeping to reduce night-time off-periods. Levodopa is our first choice in treatment-naive patients, because an incidental observation in a clinical trial[14] suggests that dopamine agonists are associated with a greater risk of development of freezing of gait than is levodopa. Specifically, freezing of gait was more common in the agonist group than in the levodopa group, but this finding must be interpreted with caution because freezing of gait was not the primary outcome in this trial. Moreover, dopamine agonists are more weakly effective than levodopa, so patients with freezing who were given an agonist might have simply been undertreated. However, in our experience, agonists (irrespective of which) occasionally worsen or even induce freezing of gait, which then disappears when the agonist is discontinued and does not return when levodopa is subsequently introduced (see below).

When we encounter a patient who has developed freezing of gait while being treated with a dopamine agonist (either as monotherapy or as part of polypharmacy), we first assess whether freezing of gait occurs mostly when medication has worn off. A first step should be to treat the response fluctuations, which could include increasing the dose of the dopamine agonist if the dose is fairly low (note that patients with so-called agonist-induced freezing of gait usually do not have any response fluctuations). However, we would be inclined to recommend not increasing the dopamine agonist as the first step, but rather to start levodopa or increase the levodopa dose or one of the other established strategies to treat the response fluctuations. If freezing of gait worsens despite successful reduction of response fluctuations, we assess the effect of reduction of the dopamine agonist and perhaps stop the agonist altogether.

	Preventive measures
Gait initiation	Shift weight to one leg before swinging the other leg forward
Narrow turns	Take a wide turn, step over a line or companion's foot
Tight quarters	Create wider spaces (home visit by occupational therapist)
Time pressure	Behavioural modification
Crowded situations	Anxiety control
Dual tasking	Focus attention to gait

The preventive measures listed are based on expert opinion.

***Table 2*: Provoking circumstances and preventive measures for freezing of gait**

In addition to dopaminergic medication, we consider oral administration of amantadine in patients with dopamine-responsive freezing of gait, although the supporting evidence is inconclusive[23–25] and further studies are needed. We recommend a trial of amantadine, undertaken judiciously (100 mg/day) in view of its common side-effects, especially in elderly patients. However, if tolerated, amantadine doses as high as 600 mg total per day could be used, if no dose-limiting side-effects occur.

Levodopa treatment is often complicated by dose-limiting side-effects, resulting in suboptimal treatment of dopamine-responsive freezing of gait. In such cases, deep brain stimulation of the subthalamic nucleus (STN) can be considered, especially when several reasons exist to move towards surgery. Studies of the effect of STN stimulation on dopamine-responsive freezing of gait are fairly small (the largest number of patients to be treated with STN stimulation is 20)[17] and have a fairly brief follow-up (on average 1 year after surgery). The limited evidence suggests that STN stimulation can reduce the occurrence of dopamine-responsive freezing of gait, as measured with freezing of gait questionnaires.[17,18] Additionally, several studies have reported beneficial effects of STN stimulation on spatiotemporal gait characteristics and improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores of postural instability and gait disability (UPDRS-PIGD scores).[56] STN stimulation and dopaminergic therapy combined can result in further improvement of UPDRS-PIGD scores and spatiotemporal gait characteristics compared with STN stimulation alone.[57–60]

No studies have directly investigated the effect of deep brain stimulation of the internal globus pallidus (GPi) on occurrence of dopamine-responsive freezing of gait. The effect of GPi stimulation on spatiotemporal gait characteristics has been investigated,[61–63] with beneficial effects on step length, but inconclusive effects on other parameters such as cadence, velocity, and double support time (the time during which both feet are on the ground). Additionally, beneficial effects on UPDRS-PIGD scores have been reported.[56] Because the effect of GPi stimulation on dopamine-responsive freezing of gait occurrence has not been formally documented, we prefer STN stimulation to GPi stimulation. However, future work is needed because GPi stimulation has been suggested to offer an improved long-term perspective for gait and balance deficits compared with STN stimulation.[64–66] These future studies should closely monitor for potential worsening of freezing of gait after GPi stimulation because stimulation-induced freezing of gait has been reported as an adverse effect of GPi stimulation in patients with dystonia.[67]

Some patients develop or have worsened freezing of gait and other axial motor problems several years after deep brain electrodes have been implanted, possibly as a result of natural disease progression.[40,68,69] In such patients, we recommend increasing levodopa dose because dopaminergic medication is typically lowered substantially after implantation of the STN electrodes (thereby effectively unmasking dopamine-responsive freezing of gait). Another option is to adjust the stimulator settings;[70] beneficial effects have been described when stimulation frequency is decreased to as low as 60 Hz,[71,72] when stimulation voltage is lowered,[73–75] or when left–right asymmetry in stimulator settings is minimised.[76] In our experience, adjustment of stimulator amplitude should be the first step, and sufficient time after the adjustment should be allowed to fully judge the effect; adjustment of the frequency or symmetry of stimulation are secondary steps. If a patient with optimally tuned STN stimulation (plus adequate levodopa treatment) continues to manifest freezing of gait, we recommend a judicious trial of methylphenidate (1 mg/kg per day), because beneficial effects have been reported in this specific subgroup of patients.[19] Effects of methylphenidate for patients with freezing of gait who have not undergone surgery are not convincing.[20] Further large-scale randomised trials are needed to understand the role of methylphenidate in patients with advanced Parkinson's disease with troublesome freezing of gait, and to examine its mechanism of action (eg, direct effect on freezing of gait, or possibly an indirect effect via increased alertness).

When deep brain stimulation is not appropriate, a few dopaminergic treatment options can be considered for which no meta-analyses or randomised double-blind controlled trials exist (table 1). Intraduodenal levodopa gel and subcutaneous apomorphine infusions provide more continuous dopaminergic stimulation and are associated with fewer response fluctuations than oral levodopa.[77,78] For suitable patient subgroups (those with severe response fluctuations that cannot be controlled with oral medication, and with contraindications for deep brain stimulation), intraduodenal levodopa gel and subcutaneous apomorphine injections or continuous infusion can be considered for management of freezing of gait. Although positive effects can be expected in such patients, only one (fairly small) study[21] has assessed formally the effect of intraduodenal levodopa gel on gait disorders, including freezing of gait, festination, and postural instability. In this retrospective study, clinicians were asked to rate the effect of intraduodenal levodopa infusion on a three-point scale: improvement, no change, or worsening. Gait improved in 46 of 75 patients with Parkinson's disease treated with intraduodenal levodopa infusion, whereas it did not change in 28 patients, and worsened in one patient.[21] For subcutaneous apomorphine infusions, no studies have been done to our knowledge. We therefore recommend preferential use of these therapies in a research setting, but patients who are good candidates (ie, those with a contraindication for deep brain stimulation, or patients who prefer either intraduodenal levodopa gel or apomorphine) can also receive these treatments in daily clinical practice.

Amantadine given intravenously seemed to improve secondary outcomes in a single study, but this is an experimental therapy that should first be studied in more detail.[22] Amantadine could work through the dopaminergic system, but improvement through its known effect on fatigue or on alertness cannot be excluded. In view of the high bioavailability of oral amantadine, the reason for intravenous treatment being superior is not clear, and placebo effects cannot be excluded; this is another area that should be investigated in controlled trials.

(Partly) dopamine-resistant freezing of gait

With disease progression and increased disease duration, partial dopamine resistance develops in most patients with initially dopamine-responsive freezing of gait, partly because dose-limiting response fluctuations make delivery of adequate doses increasingly difficult. Additionally, this dopamine resistance can partly be ascribed to progressive development of non-dopaminergic brain lesions involving, for example, the frontal lobe, adrenergic locus coeruleus,[79] or the cholinergic portion of the pedunculopontine nucleus (PPN).[19] However, freezing of gait that is completely dopamine resistant is uncommon,[39] and we suggest that clinicians should follow the algorithm depicted (figure) before reaching this conclusion.

Non-dopaminergic drugs could potentially reduce freezing of gait occurrence, both for partly and completely dopamine-resistant freezing of gait, but, so far, results have been disappointing, and no meta-analyses or randomised double-blind controlled trials exist. In our opinion, these treatment options should be reserved for research settings. Non-dopaminergic treatment options have been investigated mostly in patients who initially presented with dopamine-responsive freezing of gait, and are therefore listed under that category in table 1. One approach focuses on correction of deficits in adrenergic circuits, including treatment with the combination of droxidopa and entacapone. This approach is listed under the category dopamine-resistant freezing of gait, because beneficial effects on freezing of gait were reported in this patient group.[34] However, whether the patients in this study were completely, partly, or even apparently resistant to levodopa is not clear. Another approach focuses on correction of deficits in cholinergic pathways, which seem to contribute to dopamine-resistant freezing of gait.[80] Central cholinesterase inhibitors reduce falls in patients with Parkinson's disease with postural instability,[81] which is potentially interesting because freezing of gait is closely related to falls. However, most patients included in this trial did not experience freezing of gait, and fall rates did not improve in those with freezing of gait. Future studies are needed to investigate the effect of cholinesterase inhibitors on occurrence of freezing of gait. On the basis of our clinical experience, we would not expect striking effects, because patients who receive cholinesterase inhibitors (with the aim of improved cognition) rarely have substantial improvements in freezing of gait.

Patients whose freezing of gait does not respond to dopaminergic therapy will not improve with deep brain stimulation targeted at either the STN or the GPi. Deep brain stimulation of the PPN is one of the non-dopaminergic treatment options that can be considered. However, experience with PPN stimulation is inconsistent,[28–30] with improved scores on freezing of gait questionnaires in one study,[30] but no overall improvement of questionnaire scores in another study.[29] The optimum stimulation target within the large, diffuse PPN has not been investigated, and whether the PPN proper needs to be targeted or whether the cuneiform or subcuneiform nuclei need to be targeted is unknown.[82] Moreover, work is needed to define the best possible treatment candidates. Until such evidence becomes available, PPN stimulation is an experimental procedure that, in our opinion, should be studied only in a research setting.

Improved freezing of gait questionnaire scores and reduced fall frequency were reported in a study of five patients with dopamine-resistant freezing of gait after treatment with 24-hour levodopa-carbidopa intestinal gel (with the night-time rate at 50–80% of the daytime infusion rate).[35] The underlying mechanism needs to be investigated, but might be related to improved sleep quality, resulting in subsequent improved daytime motor performance. A large prospective placebo-controlled study is needed to verify these observations.

Non-invasive brain stimulation techniques might reduce occurrence of freezing of gait in patients with partly dopamine-resistant freezing of gait. Both electroconvulsive therapy[26] and transcranial direct current stimulation[27] reduced the number of freezing of gait episodes in small studies. The underlying mechanism is not known, but might be non-dopaminergic. Dopaminergic mechanisms might also be involved, because electroconvulsive therapy has been suggested to enhance sensitivity of postsynaptic dopaminergic receptors,[26] and transcranial direct current stimulation can induce dopamine release in the basal ganglia.[27]

Treatment with botulinum toxin into calf muscles has been tried to alleviate freezing of gait. However, results of several studies[31–33] have shown that this approach does not improve freezing, and this treatment option is therefore discouraged.

Dopamine-induced freezing of gait

Freezing of gait can occasionally be caused by dopaminergic medication.[39] No properly documented prevalence studies have been done, but in our experience, dopamine-induced freezing of gait is rare (probably less than 5% of cases). Patients with true dopamine-induced freezing of gait generally report walking better at night (when medication has worn off) than during the day—eg, when visiting the toilet because of nocturia, or early in the morning (before

taking their first daily dose of dopaminergic medication). Improved gait during the night or early morning could be a so-called sleep benefit effect,[83] although results of one study suggest that sleep benefit is mostly subjective and does not result in objective motor improvement.[84] In patients with true dopamine-induced freezing of gait, well intended attempts to improve gait with increasing doses of dopaminergic medication only worsen freezing. The mechanism underlying dopamine-induced freezing of gait is unknown. Dopamine-induced freezing of gait can occur in patients treated with levodopa,[39] but as noted above, we have seen clear freezing of gait induced by agonist monotherapy (which disappeared when the agonist was stopped, and did not recur when levodopa was given). This finding suggests a complex interaction between medication and various types of dopamine receptors in the pathophysiology of freezing of gait. Hypothetically, dopaminergic medication might worsen freezing of gait indirectly via its effects on cognitive performance, and particularly via a negative effect on frontal executive functions and alertness; this hypothesis needs to be investigated in future studies. In low doses, dopaminergic medication can improve cognition, but increasing doses can negatively affect cognitive function (U-shaped curve).[85] Executive functions might thus deteriorate in some patients when the dosage of dopaminergic medication is increased, resulting in development or worsening of freezing of gait (eg, because of disturbed motor planning or impaired attention). Monitoring of cognitive functions and alertness in patients with freezing of gait is crucial, both on and off medication.

Dopamine-induced freezing of gait is treated mostly by reducing dopaminergic medication. The agonist should be reduced first, followed by levodopa. Switching to another agonist has not been reported to be successful. When the necessary reduction of dopaminergic medication is impossible owing to unacceptable worsening of other Parkinson's disease-related dopamine-responsive signs, such as severe tremor or rigidity, we consider STN stimulation to be a last resort treatment for dopamine-induced freezing of gait. This intervention does not act directly on dopamine-induced freezing of gait, but only alleviates the problems indirectly by enabling a substantial reduction in postoperative dosage of dopaminergic medication.

Panel: **Comorbidities that negatively affect mobility and falls in freezing of gait**

- Depression (consider treatment with SSRIs or SNRIs)
- Anxiety (consider consultation with psychologist or treatment with SSRIs or SNRIs)
- Disturbed vision
- Cognitive dysfunction, executive dysfunction, or both
- Orthostatic hypotension
- Orthopaedic or muscle problems

Treatment recommendations are based on the authors' experience. SSRIs=selective serotonin reuptake inhibitors. SNRIs=serotonin–norepinephrine reuptake inhibitors.

Non-pharmacological therapies

Non-pharmacological therapy includes the same physiotherapy strategies discussed for mild freezing of gait. Additionally, knowing that freezing of gait is affected by constraints in the physical environment, we recommend involving an occupational therapist who can advise about possible domestic adaptations, such as removal of obstacles, optimisation of light, or provision of safety rails.[46] Moreover, freezing of gait can increase during stressful situations, and occupational therapists can assist with planning of daily schedules, aiming to minimise stressful moments. Together with a physiotherapist, occupational therapists can offer advice about assistive walking aids such as light, folding wheelchairs. Walking aids can be useful, but can paradoxically worsen freezing of gait in some patients, so training the patient in use of the walking aid is important. When a walker is necessary, a wheeled walker is preferred.[86] Patients who respond to visual cues can benefit from a walker or stick projecting a laser line on the floor to step over.[45] Guidelines recommend that physiotherapists and occupational therapists should give short consultations, aiming to educate patients and thereby support their independence, rather than offering long-term treatment.[87,88] However, both disciplines should remain available for renewed consultation as disease progresses and potential new problems arise. When prescribing physiotherapy or occupational therapy, we recommend referral to professionals who have received specific training in use of these Parkinson's-disease-specific strategies, and who have a high caseload of patients with parkinsonism.[89–91] Unfortunately, access to physiotherapy and occupational therapy (and particularly to skilled therapists with dedicated expertise in delivery of cueing strategies, for instance) is not available in all countries.

Treatment of comorbidities

The presence of various comorbid disorders (panel) can negatively affect freezing of gait, and these should be treated when possible. As mentioned before, treatment of cognition with cholinesterase inhibitors rarely has a strong beneficial effect on freezing of gait. In our experience, depression and anxiety are better treatment targets than cognition. Anxiety is common in patients with freezing of gait, both as a trigger for freezing of gait events (eg, in crowded places, or during time-constrained situations) and as a result of freezing of gait (including fear of falling). Occupational therapists can assist with planning of daily schedules, aiming to minimise stressful provocative events. If this approach seems to be unsuccessful, or if anxiety strongly interferes with daily life activities, our experience is that an anxiety-lowering strategy offered by a psychologist can be helpful in reduction of freezing of gait. Additionally, selective serotonin reuptake inhibitors can decrease freezing of gait in some patients, especially in

those with comorbid anxiety. However, well designed clinical trials have not been done. Interestingly, improvement of freezing of gait has been reported in a single patient who received duloxetine—a serotonin and norepinephrine reuptake inhibitor—as treatment for his depression,[92] either indirectly (owing to an antidepressant effect) or directly (suppression of freezing of gait via an effect on non-dopaminergic neurotransmitter systems). Replication of this finding in increased numbers and, eventually, in controlled clinical studies is needed.

Ophthalmological disorders are common in patients with Parkinson's disease. These disorders can be caused by the neurodegenerative process underlying Parkinson's disease, be a comorbid feature of older age, or be a side-effect of Parkinson's disease-related pharmaceutical and surgical treatment.[93] The combination of freezing of gait with disturbed vision or oculomotor deficits can potentially have a detrimental effect on mobility and increase risk of falls, especially because many patients with Parkinson's disease depend on visually guided movements to compensate for disturbed automaticity in defective basal ganglia circuits. Disturbed vision and oculomotor deficits are therefore potentially important treatment targets, and referral to an optometrist or ophthalmologist should be considered for these patients.

Orthostatic hypotension negatively affects mobility and contributes to falls in patients with freezing of gait, and is therefore an important treatment target. Several treatment strategies are available (not discussed here).[94] Assessment of whether orthostatic hypotension is a side-effect of medication (such as antihypertensive drugs) is important.

Finally, orthopaedic comorbidity (including traumatic lesions related to falling) can further affect gait and balance—eg, by increasing gait asymmetry, which leads to worsened freezing of gait. Alertness to underlying orthopaedic problems and tailored interventions can reduce freezing of gait and improve general mobility.

Freezing of gait in atypical parkinsonism

Owing to a paucity of well designed clinical trials, the extent to which freezing of gait in patients with atypical parkinsonism improves with dopaminergic medication is unclear. Our experience suggests that a trial of adequately dosed levodopa is justified. High doses of levodopa are often needed to achieve some benefit. Additionally, amantadine could be considered in patients with PSP, because improved scores on freezing of gait questionnaires have been reported after treatment with amantadine.[95] A placebo-controlled trial in patients with multiple system atrophy[96] showed no effect of amantadine on UPDRS-III gait subscores, but this study did not focus specifically on freezing of gait. Whether amantadine is effective for patients with other forms of atypical parkinsonism is unknown. Another option for patients with PSP is amitriptyline, which has been reported sometimes to cause substantial mobility improvements in patients treated with this drug for concurrent depression.[97,98] The reports did not state whether or not freezing of gait was improved, and large controlled studies are needed to confirm these findings. In our experience, amitriptyline often does not improve freezing of gait in patients with PSP. Transient improvement of freezing of gait in a patient with PSP treated with droxidopa has been reported,[99] but no large clinical trials have been done. Finally, deep-brain stimulation is not usually considered an option for patients with atypical parkinsonism, who are generally not good candidates for the procedure because symptoms generally do not improve after deep-brain stimulation.[100]

Conclusions and future directions

We hope that, pending further evidence, this practical algorithm will support clinicians in their management of freezing of gait in daily clinical practice. However, the level of evidence underlying several steps in our treatment algorithm is limited, and further investigation is needed. Randomised clinical trials are needed that include freezing of gait not just as one of many outcomes, but rather as the primary outcome. These future studies should include patients with dopamine-responsive, dopamine-induced, and dopamine-resistant freezing of gait, on the basis of unequivocal therapeutic responses obtained during history taking and—if needed—on the basis of observation of freezing of gait before and after a challenge with a supramaximal levodopa dose before inclusion.[39,101] We recommend inclusion of patients whose freezing of gait has been confirmed during neurological examination by an experienced observer (the so-called definite freezers).[102] Future studies should use a combination of subjective assessment (using the validated freezing of gait questionnaire)[49] and neurological examination (which should always include an assessment of rapid turning in place).[48,103] However, even this combination of tests might miss relevant freezing of gait episodes in the patient's own home environment, highlighting the need for development of new measures that quantify the overall amount of freezing of gait across the day. An interesting development is the introduction of wearable sensors (accelerometers or goniometers)[104,105] and perhaps even ambulatory electromyography[106] that might enable objective, continuous,

Search strategy and selection criteria

We searched PubMed for relevant articles published in English from database inception to April 1, 2015. Potential papers were identified with the terms "freezing of gait", "Parkinson's", "parkinsonism", and "treatment". Selected articles were also obtained from the reference lists of papers identified by the PubMed search and from searches of the authors' own files. Relevant studies were classified by level of evidence; studies with the highest level of evidence are reported for each treatment option.

and quantitative detection of freezing of gait during daily life. Although the initial findings with use of such sensors is promising,[107] their sensitivity and specificity are imperfect. Further work is therefore needed to identify which type of sensor, which number of sensors, and which sensor positions give the best diagnostic yield for use in future clinical trials.

The inadequate evidence base for most available treatments listed in table 1 suggests a template for the research agenda for this specialty. Development and assessment of new, more effective therapeutic approaches is needed, including pharmacological approaches (particularly non-dopaminergic drugs) and non-pharmacological approaches (such as visual cues provided by smart-glasses). Further investigation of the effect of amantadine on dopamine-responsive freezing of gait and study of the effect of methylphenidate on dopamine-resistant freezing might be worthwhile. Surgical interventions for patients with Parkinson's disease are developing at a rapid pace, with beneficial, and sometimes adverse, effects on gait;[70,108] the challenge is to identify which targets and which stimulation protocols offer the greatest improvements in freezing of gait for the different subtypes of freezing. In the specialty of physiotherapy, an interesting challenge is to ascertain whether cueing can be delivered safely and effectively in an on-demand manner—ie, with external cues being delivered only at a time when they are needed most. This challenge depends on development of reliable measures of freezing of gait during free walking and, especially, of early markers that signal development of a new freezing of gait episode. Initial research in this specialty is promising,[107] but more work is needed. Finally, assessment is needed of whether occupational therapy interventions can help to alleviate freezing of gait.

Contributors

JN and AHS did the literature search. All authors were involved in drafting and revision of the manuscript and design of the flow chart.

Declaration of interests

GD reports lecture fees from UCB, Medtronic, and Desitin, and has served as a consultant for Medtronic, Sapiens, Boston Scientific, and Britannica. NG serves as a consultant for Teva-Lundbeck, IntecPharma, Neuroderm, Armon Neuromedical Ltd, and Pharma Two B. NG has received payment for lectures from Teva-Lundbeck, Novartis, and UCB. BRB has received honoraria for serving on scientific advisory boards for Danone and UCB, and has received fees for speaking at conferences from Abbvie. None of these payments is connected to the production of this paper. JN, AHS, and JGN declare no competing interests.

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