Gait disorders and balance disturbances in Parkinson's disease: clinical update and pathophysiology

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Purpose of review

Gait disorders and balance impairments are one of the most incapacitating symptoms of Parkinson's disease. Here, we discuss the latest findings regarding epidemiology, assessment, pathophysiology and treatment of gait and balance impairments in Parkinson's disease.

Recent findings

Recent studies have confirmed the high rate and high risk of falls of patients with Parkinson's disease. Therefore, it is crucial to detect patients who are at risk of falling and how to prevent falls. Several studies have shown that multiple balance tests improve the prediction of falls in Parkinson's disease. Difficulty turning may be caused by axial rigidity, affected interlimb coordination and asymmetries. Turning difficulties are easily assessed by timed performance and the number of steps during a turn. Impaired sensorimotor integration, inability of switching between sensory modalities and lack of compensatory stepping may all contribute to the high incidence of falls in patients with Parkinson's disease. Similarly, various studies highlighted that pharmacotherapy, neurosurgery and physiotherapy may adversely affect balance and gait in Parkinson's disease.

Summary

Insights into the pathophysiology of Parkinson's disease continue to grow. At the same time, it is becoming clear that some patients may in fact deteriorate with treatment. Future research should focus on the development and evaluation of multifactorial fall prevention strategies.

Keywords

balance, deep brain stimulation, falls, freezing, Parkinson

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Introduction

Parkinson's disease is an incapacitating disease that negatively affects the quality of life for many reasons, not the least of which is the presence of axial disability (gait disorders, balance impairment, falls and fall-related injuries) [1••,2]. Here, we review recent clinical and fundamental studies dealing with gait, balance and falls in Parkinson's disease, covering approximately the period of January 2006 until February 2008. First, we provide an overview of the epidemiology and clinical significance, followed by recommendations on clinical assessment techniques. We subsequently discuss new pathophysiological insights, aiming specifically at turning strategies, the relevance of asymmetries in axial motor control and impaired sensorimotor integration. We also highlight developments in the field of neuroimaging. Treatment issues are covered next, focusing on drug treatment, deep brain stimulation [in particular pedunculopontine nucleus (PPN) stimulation] and physiotherapy. We conclude by providing recommendations for future research.

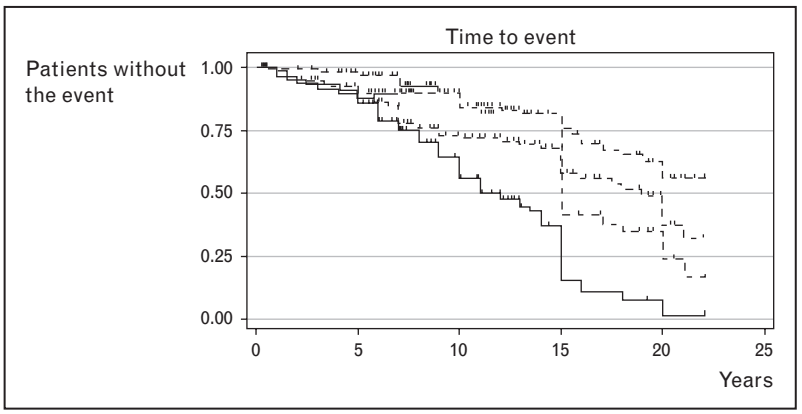
Epidemiology

Recent studies have confirmed the high rate of falls in Parkinson's disease. Additionally, risk factors and predictors for falls were identified.

Prevalence and clinical impact

Prior studies on falls in Parkinson's disease included relatively small patient groups. A recent meta-analysis addressed this by pooling the results of six independent prospective studies of falling in Parkinson's disease [1••]. The pooled sample size included 473 patients. The 3-month fall rate was 46% (95% confidence interval: 38–54%). Interestingly, even among patients without prior falls, this fall rate was substantial (21%, 12–35%).

Figure 1 Kaplan–Meier plot of time to falls, dysphagia, symptomatic postural hypotension, and first fracture



Adapted from [2]. —— First fall; - - - - - Hypotension; - - - Dysphagia; ····· First fracture.

These results underscore that patients with Parkinson's disease have a high risk of falling, even when they have not fallen previously. This high fall rate was also observed in the Sydney multicenter study [2], in which 136 newly diagnosed patients with Parkinson's disease were followed for 20 years . Of the 36 survivors, 87% had experienced falls and 35% had sustained (multiple) fractures (Fig. 1). These falls occurred despite maximal treatment with levodopa, confirming earlier impressions that axial disability in late stage Parkinson's disease is largely dopa-resistant (likely due to extranigral and nondopaminergic brain lesions). The high risk of fractures was also demonstrated in a large case–control study [3], which showed that patients with parkinsonism (not just Parkinson's disease) had a more than two-fold increased risk of sustaining any fall-related fracture. Interestingly, levodopa was paradoxically associated with an increased overall risk of fractures, especially hip fractures. One possible explanation is that levodopa dose was merely a marker of disease severity, or that levodopa caused adverse effects that predisposed patients to falls, for example, violent dyskinesias or drug-induced orthostatic hypotension [3]. Another option is that patients on levodopa are simply more mobile and, therefore, more prone to fall. Indeed, fall rates tend to taper with disease progression, likely because patients become increasingly immobilized [1••] and thereby 'protect' themselves from further falls.

The negative impact of gait disorders on quality of life is widely appreciated, for example, because of the resultant immobility (causing loss of independence) and the risk of falling. 'Episodic' gait disorders – which are only intermittently present – are particularly incapacitating because patients cannot easily adjust their behavior to these paroxysmal walking problems [4•]. A textbook example is freezing of gait (FOG), in which patients with Parkinson's disease experience debilitating episodes during which they are unable to start walking or – while walking – suddenly fail to continue moving forward. Because of this sudden and unpredictable nature, FOG is an important cause of falls and injuries. Perhaps not surprisingly, a recent study [5] showed that FOG was independently associated with a decreased quality of life.

Risk factors and predictors

To predict patients (and in particular prior nonfallers) who are most likely to fall next remains difficult; these persons, however, would be ideal candidates for an intensive fall prevention program. In the aforementioned meta-analysis [1••], the best predictor of falling was two or more falls in the previous year (which is unsatisfactory as predictor because patients have already begun falling), and even this had a relatively modest predictive ability (sensitivity only 68%; specificity acceptable at 81%). Interestingly, among prior nonfallers, fear of falling had a moderate sensitivity in predicting falls, so maybe people sense their own instability before doctors can detect this physically. Fear of falling can be evaluated using the Activities-specific Balance Confidence (ABC) scale, which has been validated for use in Parkinson's disease and, more recently, also in abbreviated form (using only six of the original 16 questions) [6,7]. Fear of falling was also associated with prior falls in another study [8], although the strongest determinants of falls were impaired ambulation, impaired lower-limb motor planning and, interestingly, orthostasis. The relevance of orthostasis was also suggested by a retrospective case note review [9], exploring the relation between clinical features and falls and fractures in pathologically diagnosed patients. Among confirmed patients with Parkinson's disease, autonomic instability was one of the few factors that independently predicted the time to the first fall. Falls due to syncope are thought to be uncommon in Parkinson's disease [10], but these two studies suggest that clinicians may perhaps miss relevant orthostatic

Table 1 Overview of new assessment techniques to measure axial disability (gait, balance, posture and falls) in Parkinson's disease

Technique	Type	Main outcome	Remarks/critique	Reference
ABC-6 (shortened version of ABC-16, a questionnaire focused on fear of falling)	Clinical	A shortened version of the ABC-16, featuring only six of the original 16 questions, is a valid tool to assess fear of falling	Minor variants may exist between different countries	[6,7]
Combination of multiple clinically based balance tests[a]	Clinical	Improved prediction of falls in PD, compared to individual tests	Ideal combination remains unknown	[12,13,14]
'Push and release' test (variant to the commonly used pull test)	Clinical	Less interrater variability and better prediction of self-reported prior falls	Relation to prospectively documented falls unknown; some patients experience the test as threatening	[15]
Tinetti mobility test	Clinical	Interrater and intrarater reliability good to excellent; moderate relation to faller status	Generic scale which fails to accommodate PD-specific features, such as asymmetrically reduced arm swing or turning 'en bloc'; relation to historical falls only moderate, and relation to prospectively documented falls unknown	[16]
Quantitative kinematic gait analysis	Quantitative	At the group level, significant differences between patients and controls, and within patients before versus after rehabilitation	Utility at individual patient level not determined; feasibility for use in clinical practice remains unclear	[17]
Global mobility task: qualitative and quantitative assessment of ability to roll over on the floor and stand up in five steps	Quantitative	Good consistency and interrater reproducibility, closely related to clinical scales and ablity to change after rehabilitation	Requires independent confirmation	[18]
Phase coordination index (PCI)	Quantitative	PCI measures interlimb coordination during gait	Feasibility for use in clinical practice remains to be determined	[19•]
Ambulatory gait assessment, using goniometers on the shank	Quantitative	Reliable detection of stride length and motor fluctuation due to levodopa therapy in the home situation	Other symptoms of PD, such as tremor and bradykinesia cannot be detected with the stride monitor	[20]
Ambulatory freezing assessment using goniometers on the shank	Quantitative	89% sensitivity for the detection of freezing, with 10% false negatives, after individual calibration in a laboratory setting	Individual calibration is needed. Discussion remains about the frequency of freezing. Feasibility for the home environment needs to be determined	[21•]
GAITRite system	Quantitative	The GAITRite system is an effective and efficient method to evaluate parkinsonian bradykinesia. Also, it is possible to use the system as a substitute for the traditional timed tests	Requires a GAITRite system to quantitatively assess gait	[22]

ABC, Activities-specific Balance Confidence; GMT, global mobility task; PCI, phase coordination index; PD, Parkinson's disease; TMT, Tinetti mobility test.
[a] Dibble *et al.*, (2006) and Dibble *et al.*, (2008): Functional reach test, Berg balance scale, dynamic gait index, timed up and go and the cognitive timed up and go tests. Jacobs *et al.*, (2006): One-leg stance test, functional reach test, and the UPDRS motor exam. Fear of falling was assessed by the ABC scale and participants reported how many times they fell during the previous year.

hypotension in some patients, either because it is simply not measured or because clinical ascertainment is not infallible [11]. Another potentially interesting predictor of falls is asking about prior near-falls as these may precede overt falls [1••], but more work is needed to develop clear definitions and a reliable way of ascertaining near-falls.

Clinical and quantitative assessment of axial disability

Several researchers have developed methods to assess gait, FOG, postural instability and balance confidence (Table 1) [6,7,12–18,19•,20,21•,22]. Note that three studies focused on predicting falls in Parkinson's disease [12–14].

Pathophysiology

New insights were gained in the area of turning, axial asymmetry, sensorimotor integration impairments and neuroimaging.

Turning

Patients with Parkinson's disease often have difficulty turning around, not only while lying recumbent in bed, but also while standing upright. These turning problems have great clinical relevance because of the relation with FOG and hip fractures. It would be helpful to have simple tools to detect turning difficulties, to estimate the risk of falling and to record the outcome of therapeutic interventions. Several recent studies [23–26] have shown that simply a timed performance and counting the number of steps during a 180 degree axial turn may suffice, as patients with Parkinson's disease require more steps and also turn slower than controls.

Quantitative measures may assist clinicians in evaluating these turning difficulties, and this would be particularly helpful for home-based assessments. Ambulatory monitors are used increasingly to better understand mobility deficits

in Parkinson's disease [19•,21•,27]. For example, it was shown that turn duration is longer in patients with Parkinson's disease compared with controls, and peak yaw and peak roll angular velocity of the trunk were reduced in Parkinson's disease [28]. Future studies need to determine whether such ambulatory monitoring techniques might be used for clinical examination in single patients, or as objective outcome measure of axial turning or FOG in a domestic setting, for example, in intervention studies.

Turning problems may result from inability to adequately maintain an interlimb coordination [19•,29,30]. This is extra difficult during turning when – by necessity – the two legs have to move more 'in phase' rather than 'out of phase' as is usual during over ground straight walking. Another important factor is axial 'stiffness' and loss of intersegmental flexibility. One study [31•] measured trunk resistance to passive axial rotations and found an increased axial rigidity in Parkinson's disease. Importantly, levodopa gave no improvement, again suggesting that axial disability is largely dopa-resistant, unlike the 'appendicular' movements (hand control), which appear to be controlled by separate dopaminergic neural systems. Two other studies [24,30] showed a loss of intersegmental axial coordination in Parkinson's disease, which corresponds to the well known clinical phenomenon of 'en bloc' turning in this disease.

Orthostatic myoclonus

A new factor that may contribute to postural instability was identified in 11 patients with Parkinson's disease with unexplained unsteadiness. Polygraphic recordings, including surface electromyography (EMG), showed an orthostatic tremor of varying frequency (ranging from 4 to 18 Hz) in eight patients and, interestingly, a hitherto undiscovered orthostatic myoclonus in the remaining three patients [32]. The findings also had treatment implications: patients with fast tremor improved on clonazepam, whereas patients with slow tremor or myoclonus improved on levodopa, and sometimes benefited further when clonazepam was added.

Asymmetries in gait and posture

By definition, Parkinson's disease is an asymmetrical disease. A unique study on 35 'de-novo' patients with Parkinson's disease who were not yet treated with any antiparkinsonian medication [30] showed that asymmetries in gait (detected with simple pressure-sensitive insoles) are also an inherent symptom of early stage Parkinson's disease, and not merely a side effect of medication or a late disease complication. Interestingly, this asymmetry was present even though stride-to-stride variability (previously thought to be one of the most sensitive measures of gait changes in Parkinson's disease) was normal in these early patients. Moreover, subtle asymmetries in balance control can be detected in Parkinson's disease by carefully analyzing the independent contribution of both legs to stance control, even before these changes are detected with the naked clinical eye [33].

Cognitive influences on gait and balance

An important new insight is the recognition that walking and standing are not purely automatic tasks, regulated by subcortical control mechanisms and requiring little if any conscious attention. Instead, gait is now increasingly seen as a complex 'higher-order' form of motor behavior, with prominent and varied influences of mental processes [34••]. For example, this becomes evident under complex circumstances, when patients with Parkinson's disease are unable to deal with multiple tasks simultaneously, either because the central processing abilities have become too limited, or because patients fail to properly prioritize their balance control over other, less important secondary tasks, placing patients at a higher risk of falling [35].

Sensorimotor integration

Most investigators would regard postural instability as being caused by disturbed motor programing of postural corrections within the basal ganglia ('efferent' deficit). However, this view has been challenged by observations that some motor deficits in Parkinson's disease are at least partially due to central proprioceptive disturbances ('afferent' deficit). Thus far, proprioceptive disturbances have mostly been demonstrated for arm movements, including for example, defective kinesthesia, defective joint position sense or disturbed tactile spatial acuity. Recent work suggests that afferent (mainly proprioceptive) disturbances could also play a role in the pathophysiology of postural deficits in Parkinson's disease. For example, one study [36•] perturbed standing patients with Parkinson's disease using very slow horizontal sinusoidal oscillations of a supporting platform, delivered at an amplitude and frequency that was kept below the semicircular canal perception threshold (i.e. patients were dependent on proprioceptive feedback to maintain balance). Patients swayed abnormally under these circumstances, but were able to partially correct this using visual feedback. Interestingly, this switch from kinesthetic-dependent to vision-dependent balance control is slower in patients with Parkinson's disease compared with controls, suggesting a difficulty in changing between different sensory modalities – an ability that is much needed in everyday life with its constantly changing environment [37,38•]. Another group showed that the response to tendon vibration – a way to deceive the muscle spindles and create a false sensation of muscle stretch – is exaggerated in patients with advanced Parkinson's disease and does not habituate well, resulting in changed patterns of body sway [39,40]. Such somatosensory deficits may produce an abnormally constructed body scheme and explain, for example, the stooped posture of patients with Parkinson's disease, of which they are often subjectively unaware [41]. This concept was confirmed by an

interesting study [42•] in which patients with Parkinson's disease were asked to perform a Functional Reach task (extending the arm forward as far as possible, with both feet fixed at the floor). Patients with Parkinson's disease tended to overestimate their limits of stability, and this may be related to their falling tendency in everyday life.

Compensatory stepping

When equilibrium is truly jeopardized, there are two crucial balance correcting strategies to prevent patients from falling: stretching out the arms and taking compensatory steps. Various studies [43,44•] addressed the nature of compensatory stepping and showed that patients with Parkinson's disease have difficulties initiating a compensatory step. A newly emerging concept is that failure to initiate compensatory stepping could be due to impairment of anticipatory postural adjustments (a lateral weight shift is normally required to allow for a contralateral limb swing) [44•]. The fascinating inference is that a walking problem (gait akinesia) is in fact caused by a primary balance deficit, that is, the inability to shift weight. A related and equally interesting finding showed that patients with Parkinson's disease, when provided with an assistive (externally imposed) anticipatory postural adjustment, could step faster [45]. One report showed that visual inputs may also ameliorate compensatory stepping: patients with Parkinson's disease took longer steps when a visual target was provided, but performance deteriorated when participants were unable to see their legs [43]. These results underscore the importance of visual feedback to compensate for motor disabilities in Parkinson's disease (see section on physiotherapy).

Neuroimaging

Structural and functional neuroimaging are used increasingly to better understand the pathophysiology associated with gait and balance impairment in Parkinson's disease. An example of a structural imaging study – using magnetic resonance imaging (MRI) – showed that, in contrast to tremor, axial deficits were related to increases in ventricular volume in Parkinson's disease, but this association was accounted for by age [46].

Several groups have examined cerebral perfusion at rest to investigate the cerebral-based gait impairment in Parkinson's disease. This approach has the considerable advantage of perfectly matched 'performance' across different patient groups (assuming that pathological alterations in brain activity are present not only during task performance but also during rest). One study [47] used *N*-isopropyl-*p*[^{123}I] iodoamphetamine single photon emission computed tomography (SPECT) to compare cerebral blood flow between patients with either the 'tremor-dominant' subtype or the 'postural instability and gait difficulty (PIGD)' subtype of Parkinson's disease. The results showed hypoperfusion in the anterior cingulate cortex and primary visual cortex, but only in the PIGD group. The frontal reduction in perfusion is particularly interesting in light of the aforementioned relation with frontal executive deficits [34••]. A further study used PET [48], allowing for better spatial resolution than previous studies. Specifically, the relation between FOG and using 2-deoxy-2[^{18}F]fluoro-D-glucose-PET (FDG-PET) – to measure striatal glucose uptake – and 18[F]-6-fluoro-levodopa (FDOPA)-PET – to measure striatal decarboxylase activity – was measured in patients with Parkinson's disease with and without FOG. In patients with FOG, lower putaminal FDOPA uptake with increased FDG uptake was observed, whereas caudate uptake of both FDG and FDOPA was reduced. In addition, patients with FOG had a decreased FDG uptake in the parietal cortices. However, a general problem in interpreting such studies is the matching between subgroups. Ideally, the only difference between groups would be their gait problems, and this is difficult to achieve because gait is closely related to other relevant variables such as disease severity and disease duration. This is illustrated by the above-cited papers, in which subgroups were not matched for disease severity or disease duration [46,47].

Motor imagery of gait is a new approach to partially circumvent the problems associated with functional imaging of gait, assuming that imagined walking shares at least some of the cerebral processes with gait, but without the need to engage in actual gait. Several groups have developed paradigms for this [49,50]. In such studies, it is crucial to verify performance and ascertain that patients are actually specifically engaged in motor imagery of gait, for example, by testing whether imagined movement times increase as a function of distance that patients are requested to travel. This approach has been used successfully in healthy individuals [49,51] and is now ready for application in Parkinson's disease.

Treatment

New insights were gained in the field of pharmacotherapy, deep brain stimulation and physiotherapy. A brief discussion of recruitment issues and guidelines for randomized controlled trials (RCTs) is given.

Pharmacotherapy

Gait and balance problems in Parkinson's disease tend to be perceived as being 'untreatable', but there are various therapeutic options [52]. For example, one report showed that, although the proportion of 'mid-line' motor disability increases with time, these deficits do not become unresponsive to levodopa [53]. Vital information also came from the seminal ELLDOPA study (a placebo-controlled trial comparing various doses of levodopa) [54], which showed that FOG was most common in the placebo group and

low-dose levodopa group, compared with groups taking higher levodopa dosages. However, levodopa may also adversely affect gait or balance control. For example, one study [55] showed that timing of gait to an external stimulus was worse in medicated patients compared with patients who had withdrawn from medication, perhaps due to drug-induced dyskinesias. Patients with Parkinson's disease using neuroleptics have an increased risk of sustaining any fall-related fracture [3], but causality is difficult to prove (patients requiring neuroleptics may simply have more advanced disease). A new approach is methylphenidate (traditionally used to combat attention-deficit-hyperactivity disorder). Methylphenidate can decrease fall risks in community dwelling older adults, conceivably by increasing availability of striatal dopamine or by improving attention [56]. Three further trials have now shown that methylphenidate also improves gait and FOG in Parkinson's disease [57–59].

Stereotactic neurosurgery

Bilateral subthalamic nucleus (STN) stimulation is an effective treatment for Parkinson's disease, especially for appendicular symptoms that responded well to levodopa preoperatively. However, the effects of STN stimulation on axial motor signs remain debatable. It is impossible to draw overriding conclusions because of the differences in surgical techniques, candidates selected for surgery and outcome measures used. A few tendencies are worth reporting. First, it has been suggested that medication and deep brain surgery may affect axial mobility deficits by acting on different neural systems. Indeed, some studies [60–62] reported improvement in postural deficits, beyond the effects afforded by medication alone. Specifically, at least some of the effect of STN stimulation may act via 'downward' projections onto the PPN [62].

Second, there are increasing concerns that deep brain stimulation may worsen axial mobility, sometimes as an immediate adverse effect of surgery, but also as a long-term complication. For example, one report showed that after a 3-year follow-up of 36 patients with Parkinson's disease, STN stimulation had improved the United Parkinson's Disease Rating Scale (UPDRS) motor score by 54.2% and gait scores by 45.3%, but dopa-unresponsive axial signs had worsened in some patients [62]. Another study [63] investigated gait changes after STN stimulation and found that gait had improved in half the patients, but had worsened in the others. This inconsistent response was also found in a dynamic posturography study [64] that assessed postural control in patients with Parkinson's disease exposed to a random mix of multidirectional tilts of a supporting forceplate. Participants were tested with their STN stimulators switched on and off, 60–90 min after a suprathreshold dose of levodopa. Overall balance – defined as displacement of the center of mass following the postural perturbation – improved in nine patients but deteriorated in the remaining four patients. A particular worry is the development of new gait and balance deficits several years after surgery, even in the face of persistent beneficial effects on appendicular motor control. This was demonstrated in a study that used a standardized questionnaire to ask patients about both their global outcome and gait, at 6 months postoperatively and at the time of examination (about 2.7 years postoperatively) (van Nuenen BF, Esselink RA, Munneke M, *et al*. Secondary gait deterioration after bilateral subthalamic nucleus stimulation in Parkinson's disease. Mov Disord 2008, in preparation). A striking 42% of patients experienced a worsening of gait in the medication OFF phase, and this appeared to be fairly selective because global outcome scales continued to be improved. A major drawback of this study was the lack of control group; hence some postoperative gait problems could have been ascribed to natural disease progression.

An important target for future research is the development of reliable determinants for success or failure of deep brain surgery. It has been speculated that variability in electrode placement can explain the inconsistent effects on axial mobility across patients. Specifically, it could be that misplaced electrodes project unintentionally to the PPN [65] which, when stimulated at high frequencies, worsens gait and balance [66••,67]. This hypothesis was addressed in an interesting study of 13 patients with Parkinson's disease with severe postoperative gait disorders [68••] whose typical stimulator settings (130 Hz) were changed to a much lower frequency of 60 Hz, while keeping the total energy delivered constant. All outcome measures (including UPDRS, a timed walking task and FOG) clearly improved during the 60 Hz condition compared with the 130 Hz condition. The explanation put forward was that, because the PPN is just 5 mm away from the STN, high-frequency STN stimulation could negatively affect the PPN (and the opposite for low-frequency STN stimulation of course). On the basis of these findings, the authors proposed a two-staged STN frequency optimization: 130 Hz during the initial years of STN stimulation; and 60 Hz (at a higher voltage) after gait disorders have become manifest.

Others examined the merits of direct PPN stimulation. Smaller previous studies had shown the technical feasibility of this approach, but interesting new insights came from a study of six patients with Parkinson's disease [66••] whose gait and balance responded unsatisfactorily to drug treatment, and therefore underwent bilateral implantation of electrodes in both the STN and PPN. The most interesting results were seen during the medication ON phase, when an extra treatment push (i.e. over and above optimal drug therapy) is mostly needed. During this ON state, PPN stimulation alone had a positive effect on the UPDRS items for gait and balance,

whereas STN stimulation did not. PPN stimulation improved axial symptoms directly postoperatively and this persisted for 6 months. However, an extended follow-up is needed to evaluate the long-term effects. An important critique was that the electrodes might have been misplaced, that is, not in the PPN, but rather in the nucleus peripeduncularis [69]. Therefore, the obtained results should be interpreted with care, and further research is needed to investigate the effects in more detail (e.g. using objective measures such as posturography), to study the effects of electrode (mis)placements and to evaluate long-term effects.

Physiotherapy

Many patients with Parkinson's disease receive physiotherapy to alleviate symptoms of the disease. Here, we review the most recent findings of studies investigating treatments such as cueing and different forms of exercise.

Cueing

It is widely appreciated from clinical experience and experimental, mainly lab-based studies that patients with Parkinson's disease can improve their gait using external cues. In a seminal study for the field of physiotherapy, this knowledge was taken to the test in a large, multicenter and single-blind crossover study (RESCUE trial) [70••] that examined the effect of a 3-week training program, featuring three rhythmic cueing modalities: visual, auditory or tactile. Immediately after the training period, small but significant improvements were found for clinical gait and balance scores, for FOG severity (among freezers), for gait speed and step length, and for timed balance tests [including the confidence to carry out functional activities, as measured with the falls efficacy scale (FES)].

Knowing whether beneficial effects persist after training has ended is crucially important if one wants to implement cueing as treatment into clinical practice. In a lab-based study [71], improvements in gait after rhythmic auditory stimulation persisted at 2 and 15 min after actual cueing, suggesting some degree of retention. However, in the RESCUE trial [70••], the observed improvements were no longer present in the noncued situation 6 weeks after training. Note that assessments were carried out in the absence of cues, whereas in daily life patients with Parkinson's disease will specifically use cues under those circumstances in which they need them. Therefore, the results found in the RESCUE trial might be an underestimation of the real effect when using cues.

Another relevant issue is a possible carry over of specific training effects to other, nontrained tasks. Encouraging findings were reported in a study [72] in which participants completed a 4-week training program in which they practiced gait and rhythmic tapping. The tasks used as outcome measure did not match the practiced tasks, but nevertheless showed significant improvements following this nonspecific training. In contrast, the much larger RESCUE trial [70••] found no carry over of gait cueing to other modalities, such as functional outcome measures or quality of life.

A further issue – again with great clinical relevance – is the emerging insight that cueing can also have adverse effects. For example, one study [73] showed that rhythmic auditory stimulation can differentially affect freezers and nonfreezers. Specifically, the results showed that rhythmic auditory stimulation (set at 110% of preferred walking speed) afforded increases in step length for nonfreezers, but produced the opposite effect for freezers. Another study [74] showed that visual cueing may also adversely affect gait, depending on disease severity. Falls may paradoxically increase when patients receive cueing treatment, simply because mobility improves, and also because the cueing may distract patients from paying attention to environmental hazards. Fortunately, cueing was not associated with more falls in the RESCUE trial [70••], although the study was not properly powered to address this issue. The take home message is that cueing should not be prescribed as a 'one size fits all' treatment, but should be carefully tailored to specific factors such as disease severity and individual symptomatology.

A final practical concern is whether cueing – even when effective in the lab under carefully controlled 'single task' conditions – will also benefit patients in daily life with its complex situations, typically requiring patients to deal with multiple tasks simultaneously. This was addressed in two studies that showed that auditory cues helped to improve walking speed during a dual task situation (e.g. walking with filled cups on a tray), whereas somatosensory cues (vibration on the wrist) had no effect, and visual cues (a light emitting diode attached to the patient's own spectacles, or a pair of clear glasses) had a negative effect. Furthermore, the studies, somewhat surprisingly, showed that rhythmic auditory cues had no effect in a single task situation (normal walking) [75,76]. Perhaps participants were challenged more during the dual task, with heightened levels of arousal, or patients relied more on external information during the complex tasks [75]. External cues could theoretically reduce attentional loads by reducing the need to prepare and plan a movement, but this hypothesis requires further testing.

Exercise

There is increasing attention for the possible beneficial effects of physical exercise in Parkinson's disease [77••]. Overall, physical functioning, balance, gait speed, strength and health-related quality of life improve for people with Parkinson's disease after a physical exercise intervention. Exercise therapy may also lead to a

reduction in FOG [78]. Management guidelines of the American Academy for Neurology concluded that exercise may be helpful in improving motor function in people with Parkinson's disease [79]. However, there is insufficient evidence to support (or refute) that physical exercise is beneficial for reducing falls or depression [77••]. The lack of clear effect on falls was also shown in an RCT, which showed that a combination of exercise and movement strategies (i.e. prevention of falls and movement initiation) only tended to decrease the incidence of falls compared with controls receiving usual care [80••]. However, it was encouraging that recurrent near-falls were decreased in the intervention group, and either with longer follow-up, a more intensive intervention or prolonged treatment this may eventually translate into fewer actual falls and injuries, possibly even among prior nonfallers.

Treadmill training may be one way to safely exercise patients with Parkinson's disease; for example, because supervision is present or because a safety harness can prevent actual falls. Several studies [81,82] have shown that treadmill training can improve gait in Parkinson's disease. In addition, the Berg Balance Test, the Dynamic Gait Index (a measure of gait adaptability) and FES scores (a measure of balance confidence) improved after 6 weeks of intensive treadmill training [81]. An alternative – and perhaps more enjoyable – way of exercise training is dancing. One single-blind, small sample RCT showed that tango dancing (20 sessions) benefits patients with Parkinson's disease, with improvements in UPDRS, Berg Balance scale and a tendency for less FOG [83].

A novel approach in delivering exercise is using motor imagery, engaged previously to promote recovery of stroke patients [84]. An innovative study [85•] compared a control group that was treated with physical exercise alone with an experimental group that was treated with a combination of actual physical exercise and imagery of the very same exercises. The combined treatment group showed the greatest improvement, but much work is needed to fully underpin the merits of motor imagery for rehabilitation in Parkinson's disease.

Recruitment problems

A coincidental finding in two physiotherapy trials was the problems encountered in finding and recruiting eligible patients. In one UK-based study [86], only 13% out of all patients listed in the clinical registers of Parkinson's disease specialists could be included in a falls prevention trial, eligibility being the main problem. Similarly, a pilot study based in the Netherlands was also troubled by recruitment problems, but now mainly because most patients in the Netherlands already receive physiotherapy, so many declined the risk of being randomly allocated to a 'no physiotherapy' control group [87]. These studies provide important lessons for future trials of physiotherapy in Parkinson's disease.

Guidelines

In 2007, evidence-based guidelines of physiotherapy for Parkinson's disease were published, including definitions of the core treatment goals for physiotherapy (transfers, posture, reaching and grasping, balance, gait, and physical capacity), as well as menus of treatment strategies tailored to each of these domains [88•]. Specific recommendations included: cueing strategies to improve gait; cognitive movement strategies to improve transfers; exercises to improve balance; and training of joint mobility and muscle power to improve physical capacity.

Conclusion

The field of axial mobility deficits in Parkinson's disease continues to advance at a rapid pace, with significant progress both at the fundamental level (improved insights into the complex, multifactorial causes of falls, gait and balance impairment) and at the clinical level (with large scale trials now beginning to see the light). Having said that, further work remains necessary to design optimal treatment strategies and to adequately prevent falls in Parkinson's disease. Key targets for new research include development of reliable and sensitive outcome measures that are sufficiently feasible for widespread application, in trials as well as everyday clinical practice; and the development of improved treatment strategies, including both pharmacotherapy (aimed at more than just dopaminergic motor circuitries), stereotactic surgery (optimizing STN stimulation and defining new targets such as the PPN) and physiotherapy. A particular challenge will be to combine these insights into a comprehensive multifactorial approach aimed to prevent falls, not only among those who have already presented with falls, but also among prior nonfallers.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 513).

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