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Pharmacological treatment in Parkinson's disease: effects on gait

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Abstract

Gait impairments are a hallmark of Parkinson's disease (PD), both as an early symptom and an important cause of disability later in the disease course. Although levodopa has been shown to improve gait speed and step length, the effect of dopamine replacement therapy on other aspects of gait is less well understood. In fact, falls are not reduced and some aspects of postural instability during gait are unresponsive to dopaminergic treatment. Moreover, many medications, other than dopaminergic agents, can benefit or impair gait in people with PD. We review the effects of pharmacological interventions used in PD on gait, discriminating, whenever possible, among effects on four components of everyday mobility: straight walking, gait initiation, turning, gait adaptability. Additionally, we summarize the effects on freezing of gait. There is substantial evidence for improvement of spatial characteristics of simple, straight-ahead gait with levodopa and levodopa-enhancing drugs. Recent work suggests that drugs aiming to enhance the acetylcholine system might improve gait stability measures. There is a lack of well-designed studies to evaluate effects on more complex, but highly relevant walking abilities such as turning and flexible adjustments of gait. Finally, paucity in the literature exists on detrimental effects of drugs used in PD that are known to worsen gait and postural stability in the elderly population.

Keywords

Gait; dopamine; acetylcholine; turning; falls

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Conflict of Interest

Oregon Health & Science University and Dr. Horak have a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology. This potential institutional and individual conflict has been reviewed and managed by OHSU. All other authors declare no conflict of interest.

Introduction

Gait difficulty is a highly disabling symptom of Parkinson's disease. In the earliest stages of the disease bradykinesia is reflected in smaller arm swing, slower turns and reductions in step length [1-4]. With disease progression, gait becomes more unstable , freezing of gait (FoG) episodes occur, and falls are frequently reported [5-7]. These gait deficits severely impact mobility and quality of life [8, 9]. Although the main therapies for PD, dopamine restoring agents, are helpful for bradykinesia, rigidity, and tremor, they have a mixed effect on gait and postural instability. The effects of other pharmacological therapies on control of gait are even less well studied than levodopa. Other therapies include adjunctive therapies to levodopa, as well as medications that are used to treat cognitive deficits or other co-morbidities. The aim of this review is to give an overview of the current knowledge on the effects of different pharmacological interventions on gait. We will not limit this to medications that improve gait, but also discuss medication associated with deterioration of gait or increased fall risk. Where possible, four components of gait will be discriminated: straight walking, gait initiation, turning, gait adaptability. In addition we will discuss pharmacological effects on FoG.

Gait in healthy individuals

Gait has a multitude of components, each of which requires varying degrees of cognitive, and therefore, cortical control (Figure 1). The first, and least cognitive (or most automatic) component, straight walking over a flat surface, requires only minimal attention in healthy young adults [10, 11]. The main parameters for straight walking reflect speed (gait speed, step or stride time, cadence), amplitude (step or stride length, arm swing), regularity of movement (step-to-step variability, step width variability), and control of balance (step width, trunk motion).

A second component, initiation of gait, involves more cortical control than straight walking as it generates goal-directed movements. Gait initiation consists of a postural weight shift forward and toward the stance leg in order to unload the stepping leg, which is defined as the anticipatory postural adjustment (APA). Following the APA, the foot pushes off and moves forward to execute the first step. Relevant parameters for gait initiation include the duration and amplitude of the APA, push-off forces, and first step length and latency of foot-off.

A third component of walking ability, turning, requires even more cognitive control to modify the gait pattern, execute an asymmetrical stepping pattern, and regulate dynamic balance [12]. In daily life, people make as many as 80-100 turns each hour, and patients with PD make just as many turns as control subjects [13]. The stepping pattern during turning involves asymmetric rotation of the foot in space and of the upper body over the leg on the ground. Healthy adults turn by first turning their eyes, then head, towards the new direction, followed by the trunk, pelvis and legs [14]. The number of steps taken to complete the turn, speed of turning, dynamic postural stability (i.e. relation of the body center of mass (CoM) to the edge of foot support) and coordination of head-trunk-feet motion are used to quantify turning [15].

A fourth component of everyday gait is the ability to adjust gait to negotiate environmental hazards, such as irregular surfaces and crowded spaces. This form of gait is highly dependent on cognitive control to plan, make judgments, and inhibit actions [16-18]. Adaptability of gait is tested using obstacle avoidance paradigms, in which the subjects walk while stepping over or around obstacles. Typical outcome measures of gait adaptability using obstacle avoidance are success rates, clearance of the obstacles (distance between foot and obstacle), and stability during obstacle crossing.

Gait deficits in Parkinson's disease

Straight walking

The hallmark motor symptom of PD, bradykinesia, is reflected in gait. The slow gait associated with PD is predominantly due to short steps, rather than slow cadence [19, 20]. Short steps are caused by slow, weak force development to push-off the foot [21, 22]. Short steps may also reflect imbalance as it is associated with higher double support time, i.e. both feet are on the ground for a longer proportion of the step cycle. Short steps may thus reflect an inability to control body CoM on one leg during a long step. Patients with PD are capable of modulating cadence, thereby at least partly compensating for small step length [20, 23]. In the upper body, bradykinesia is expressed by reduced arm swing amplitude and velocity, particularly in the most affected arm, and decreased range of motion of the trunk [4, 24].

In addition to bradykinesia of gait, PD gait is characterized by postural instability. Postural instability during gait can be observed in larger step-to-step variability compared to healthy subjects [1, 25]. For example, the duration, length, and width of steps vary more over multiple steps in people with PD than their healthy peers. This variability is believed to be related to increased fall risk in PD [26, 27], although this could not be confirmed in a large prospective study in PD [28].

Gait initiation

Subjects with PD show hypometric APAs when initiating a step. They produce less force, resulting in a smaller weight shift forward and toward the stance leg than would be required for taking a step [21, 29]. This reduction in push-off force causes a delay in step execution [21, 30]. Moreover, the length of the first step is shorter than in healthy elderly subjects [29, 31-33]. In contrast to healthy people, people with PD do not scale the APA size in proportion to their stance width [33]. Unlike the spatial control of APAs, the relative timing (coordination of the movement pattern) is unaffected by PD [30].

Turning

The sequential eyes-head-trunk-feet movement observed during turning in healthy adults is lost in PD patients; they turn “en bloc”, with a more simultaneous onset of eyes, head, trunk and leg movement [34-37]. Speed of turning in people with PD is related to axial tone in the neck, but not trunk or hips [38]. In addition, turning in people with PD is characterized by slow, jerky turning and additional steps are needed to complete the turn [39-41]. When people with PD are asked to turn quickly, they become unstable as they spend more time than control subjects with their body CoM outside their base of foot support [15].

Gait adaptability

Problems stepping over an obstacle while walking are apparent in people with PD who have moderate (H&Y 2-3) disease severity [42-44]. People with PD have a higher number of obstacle hits compared to healthy subjects [44, 45]. During obstacle crossing, people with PD are less stable than healthy subjects, reflected in more mediolateral movement of the CoM [46]. In addition, breakdown in motor planning can result in riskier situations. For example, the time needed to step over the obstacle is longer, resulting in more time spent standing on one leg [44, 47]. Also, the typical foot placement relative to the obstacle is smaller in PD patients than in healthy subjects, increasing the risk of collision [42, 44, 45].

Freezing of gait

A majority of people with PD eventually develop freezing of gait (FoG) – the subjective feeling that the feet are 'glued to the ground' – during the course of the disease [48]. Even without a freezing event, patients prone to FoG show differences in gait parameters compared to PD patients who do not freeze. People with PD and FoG walk more slowly with shorter stride lengths than non-freezers [49, 50], which could be due to more advanced disease stage in FoG [7]. Nevertheless, FoG has been associated with greater spatial stride-to-stride variability [50, 51], more time spent in double support phase [49, 52], and increased asymmetry between the right and left legs [52]. During turning, subjects with PD who have FoG require more time to turn and have a smaller step width than those without FoG [53].

All abovementioned aspects of gait impairments typically call for more attentional control of walking [54]. A loss of automaticity of gait can be reflected in more deterioration of gait while performing a secondary task (dual task cost). In people with PD, increased dual task costs in comparison to age-matched control subjects are most prominent in gait stability measures, and in people with more severe gait impairments, such as FoG [1, 55, 56].

Effects of dopaminergic treatment

Pharmacological treatment aiming to increase the dopamine neurotransmitter is most effective for bradykinesia, rigidity and tremor. Although less effective for postural instability and falls, gait can partly be improved by levodopa, dopamine agonists, or inhibitors of dopamine metabolism. In this section, we discuss which specific gait components and parameters are sensitive to dopaminergic interventions. We limit this section to studies using motion analysis systems or wearable sensors, i.e. objective measures to assess gait.

Note that almost all of the studies reviewed in this section have evaluated only short-term differences between 'on' and 'off' levodopa states. Typically, subjects were tested at baseline, after >12 hrs of withdrawal of all dopaminergic medication, and tested again on the same day about an hour after taking their medication. Only two studies compared the effect of dopaminergic treatment over placebo [23, 57], and only two out of nine studies counterbalanced 'on-off' and 'off-on' order (Table 1) [57, 58]. All studies are based on effects of monotherapy or combination therapy of levodopa and/or DA agonists, amantadine, MAO-I, or COMT inhibitors, dependent on individual use.

Straight walking (Table 1)

Similar to improvements in other measures of bradykinesia, gait parameters that are related to movement amplitude and speed benefit from dopaminergic treatment. For example, increases in the amplitude of the movements of the legs, trunk and arms result in larger step length, trunk motions, arm swing [24], and faster stride velocity [59-62]. In contrast to spatial gait metrics, temporal metrics are not improved as much by levodopa. Cadence improves to a lesser extent [59], or not at all [61]. There is no evidence for decrease in double support time, which might be expected if levodopa reduced imbalance. However, and contrary to the evidence above, one study suggests that variability of step time, stride length, and gait speed can improve with dopaminergic treatment [61]. Some evidence also suggests that asymmetry of arm swing movements benefit from dopaminergic therapy [24].

Gait initiation (Table 2)

Levodopa can improve the hypometria of the preparatory stepping phases. Force generation for push off increases, resulting in higher amplitudes of the postural preparation phase (APA [21, 33, 59]) and larger first steps [33]. In contrast, neither the duration of the APA, nor the size of the first step was improved by levodopa in the study of Curtze et al. [59].

Turning (Table 2)

Whereas turning in place does not seem to benefit from dopaminergic treatment [38, 63], making a turn to change walking direction does. Turning speed and number of steps to complete the turn improved with levodopa [38, 59], but to a lesser extent than parameters of straight walking [59]. Interestingly, some evidence suggested that only patients with dyskinesia improved turning speed on dopaminergic medication [59].

Gait adaptability (Table 2)

Two studies evaluated the effect of dopaminergic treatment on gait adaptability. The ability to step over an obstacle during walking improved when using dopaminergic medication [45]. Success rates at avoiding obstacles changed in the ON state, with shorter and faster steps to cross the obstacle, suggestive of less cautious behavior [45, 64].

Freezing of gait

In most patients with PD and FoG, FoG episodes are more frequent, and last longer, when they are off dopaminergic medication compared to the on state [51, 65, 66]. In sharp contrast, a small group of people with PD have FoG that is induced by levodopa [67]. The ELLDOPA trial showed that FOG severity could be reduced or delayed when on dopaminergic treatment [68]. However, there is very limited evidence that administration of levodopa and other dopaminergic agents can ameliorate stride length and stride time variability in FoG to levels approaching non-freezers ([52, 65, 69]).

Other antiparkinsonian drugs

In this section, we will summarize the effects of antiparkinsonian drugs other than levodopa on gait, mostly as adjuncts to levodopa treatment. In contrast to studies focusing on

levodopa, studies evaluating drugs other than levodopa are primarily clinical trials in which gait was most commonly assessed using subjective measures.

Dopamine Agonists

Dopamine D2 agonists are commonly used in PD, either as monotherapy in early PD, or to reduce levodopa dose needed in more advanced disease stages [70]. The specific effect of dopamine agonists as monotherapy has been evaluated in an open-label uncontrolled study with previously-untreated subjects with PD. In this study, six month use of the transdermal patch rotigotine improved all aspects of gait compared to baseline, including straight walking, gait initiation and turning [71].

The additional value of DA agonists as an adjunct to levodopa has been evaluated in three studies. Two studies found beneficial, immediate effects on gait speed of the DA agonist apomorphine (sublingual) and pramipexole compared to levodopa alone [72, 73]. In a large-scale, placebo-controlled study, the long-term effect of pergolide, in combination with levodopa, yielded better effects on the gait item of the UPDRS-III than placebo or levodopa alone [74]. Together, these studies suggest that dopamine agonists augment the effects of levodopa in advanced PD.

Catechol-O-Methyl Transferase (COMT) inhibitors

The effects of COMT inhibitors (entacapone, tolcapone) are similar to DA agonists, extending the effects of levodopa therapy. COMT inhibitors inhibit the methylation of levodopa, thereby increasing the concentration of levodopa that enters the brain. As such, COMT inhibitors, in conjunction with levodopa, are recommended to decrease the amount of OFF time. Only two small studies looked at the effects of COMT inhibitors on gait parameters, providing support for tolcapone as an effective add-on to levodopa to prolong beneficial effects on gait speed [75, 76].

Monoamine oxidase type B inhibitors (MAOB-I)

MAOB inhibitors (selegiline and rasagiline) have been evaluated in people recently diagnosed with PD, in two large-scale studies, with the aim to modify disease progression: DATATOP [77] and ADAGIO [78]. Although gait was not an outcome in the original study, results from a follow-up study suggested that PD patients on MAOB-I were less likely to develop FoG [79, 80] and had less increase of PIGD scores over a period of 36 weeks [81]. These findings were in line with earlier work showing marginally faster gait speed in PD subjects on MAOB-I compared to placebo [82]. However, a more recent, retrospective study could not replicate a beneficial long-term effect of MAOB-I on FoG or fall risk [83]. In addition, clinical lore suggests that addition of a MAOB-I to a patient developing FoG does not reduce the symptom. Future work to evaluate the effects of MAOB-I could benefit from the use of more objective and sensitive measures of gait.

Amantadine

Amantadine, an older antiviral agent, is a glutamate antagonist recommended for the treatment of dyskinesia in PD [70]. Recently, amantadine has been tested for its potential ameliorative effect on FoG in PD. Although there was initially some promise for short-term

benefits for FoG from an uncontrolled trial [84], two double-blind studies failed to see improvement of FoG in people with PD after several days of amantadine use when compared with placebo [85, 86]. However, a double-blind, placebo-controlled study reported some improvements on secondary outcome measures of FoG, such as whether or not subjects reported FoG on a questionnaire [85]. In addition, amantadine has been tested for PD patients with axial impairments after STN-DBS surgery [87]. This uncontrolled study reported improvement on the gait item of the UPDRS-III. To conclude, more long-term and well-controlled studies are needed to confirm a potential effect of amantadine on objective gait measures.

Other classes of medication

In this section, we will describe effects of drugs other than dopaminergic agents that are less commonly used to treat parkinsonian symptoms, or might be used for co-morbidities. Table 3 summarizes these studies.

Glutamatergic agents

Apart from amantadine, memantine is a glutamate agent acting as N-methyl-D-aspartic-acid-related (NMDA) receptor antagonists that has shown promising gait benefits in demented subjects [88]. There is one (phase I) study in PD evaluating the use memantine as adjunct-therapy to levodopa in patients with severe gait and balance impairments [89]. This pilot study did not report improvements in gait speed or stride length in the group on memantine compared to placebo. However, axial signs as assessed in the UPDRS-III did show some improvement.

Cholinergic medication

Recent research has highlighted the role of cholinergic activity in gait and balance impairments in Parkinson's disease [90-93]. Loss of cholinergic activity of the PPN-thalamus tract in PD has been related to fall risk [91, 94], and reduced cholinergic activity in the cortex associates with slower gait speed in people with PD [90]. This could suggest that loss of cholinergic activity in the cortex reduces gait speed through attentional loss, in line with consistently reported associations between attention and gait parameters [1, 28, 95, 96].

Cholinergic treatment with cholinesterase inhibitors (ChE-I; for example rivastigmine, donepezil) is commonly used for cognitive enhancement in patients with Alzheimer's disease (AD), and has also shown efficacy in patients with Parkinson's disease dementia [97]. Preliminary findings suggested that ChE-I can reduce falls in people with PD at high risk for falling [98] and improve gait in AD [99-101], potentially through improving attention. A recent, large double-blind, placebo-controlled trial (RESPOND trial [102]) evaluating gait variability and, secondarily, fall risk provided additional support for the beneficial effects of rivastigmine on gait for PD patients at risk for falls. Another phase II study is currently underway to establish the effect of donepezil on gait, postural stability and fall risk in PD, and evaluate its effect on attentional demands of gait [103].

Norephinephrine agents

In the early 1980s, a number of studies in Japan were conducted to evaluate the effect of L-threo-3,4-dihydroxyphenylserine (L-DOPS), a precursor of norepinephrine, on FoG in PD. Two open-label, uncontrolled studies reported conflicting results on FoG through L-DOPS administration [104, 105]. More recently, the a study on the effect of L-DOPS in combination with a COMT inhibitor found that self-reported FoG was alleviated in the group taking L-DOPS and entacapone, whereas this effect was absent the groups on L-DOPS or entacapone alone [106].

Another norepinephrine agent, droxidopa, has been reported to improve neurogenic orthostatic hypotension in PD [107]. Recent evidence suggests that normalizing orthostatic hypotension in PD subjects reduces the risk for falls [108]. No studies have evaluated the effects of norephinephrine agents on objective measures of gait.

Methylphenidate

The effect of methylphenidate is commonly used in attention-deficit disorders to enhance attention functions, acting primarily as a dopamine reuptake inhibitor [109]. In combination with levodopa, methylphenidate improved immediate levodopa effects on gait speed [110, 111] and temporal variability of gait [110] in people with PD. More recently, methylphenidate has been used in more advanced PD patients with treatment-resistant FoG after STN-DBS. A multi-center RCT reported improvements in FoG in these advanced patients [89], in line with previous non-RCT studies [110, 112]. However, using more specific measurements of gait in a small sample (n=12) in the same study did not provide evidence for improvement [113]. In subjects with PD with moderate gait impairments (no DBS), no beneficial effects of methylphenidate could be demonstrated, although the authors reported some slight improvements on methylphenidate in a gait composite score when off, but not when on dopaminergic treatment [114]. In summary, there is inconclusive evidence for a benefit of methylphenidate to improve gait function in PD.

Drugs for co-morbidities

Different classes of drugs are known to increase fall risk in elderly [115-117] and hospitalized people [118-121]. These drugs include anti-depressive, anti-psychotic, sedative/hypnotic, and opiod analgesic agents. There is, however, a lack of research investigating the effects of these classes of drugs on fall risk in people with Parkinson's disease. Also, it is not well understood what aspects of gait and balance these drugs worsen.

Drugs with high sedative properties, including antipsychotics, tricyclic anti-depressants, benzodiazepines and hypnotics, have found to result in lower gait speed in elderly [122]. It is likely that psychomotor slowing is a main driver of this effect. With regard to antidepressants, evidence suggests that effects on gait depend on the specific type of prescribed medication. For example, there is interesting work on the impact of anti-depressants on obstacle avoidance performance in elderly, showing that tricyclic antidepressants (here amitriptyline), but not paroxetine, deteriorates gait adaptability [123, 124].

Another class of drugs that may cause gait impairments and increase fall risk are anti-hypertensives. Particularly diuretics and angiotensin system modifiers seem to increase fall risk in elderly populations [115, 118]. There is some pilot work in PD suggesting that correcting hypotension in patients with PD (SBP > 80 during standing for all subjects) leads to improved gait, reflected in higher gait velocity [125].

Drugs with anticholinergic properties are commonly used in PD for hyperactive bladder, treatment of tremor and depression. Apart from detrimental effects on cognition, these agents are associated with lower gait speed in elderly [126] and with increased fall risk in psychiatric inpatients [127]. As yet, no studies in PD subjects have been carried out.

Although not a prescribed medication, the care provider should always be aware of alcohol as an acute and chronic cause for gait disturbances and falls [128, 129].

Summary and future perspectives

In summary, bradykinetic and hypometric spatial characteristics of gait and turning improve with dopaminergic medication. However, it is unclear whether more complex walking skills, such as gait initiation and gait adjustments, improve with dopaminergic treatment. Dopaminergic treatment effects on stability measures of gait, such as spatial or temporal variability, are thus far inconclusive. Dopamine agonists, MAOB and COMT inhibitors as adjunctive therapy to levodopa are most likely to improve or prolong the effects of levodopa, hence improving bradykinesia and hypometria in gait. Although there is some evidence for a beneficial effect of amantadine on freezing of gait, most work yields inconclusive results.

Gait stability and balance have long been considered to be insensitive to levodopa treatment, encouraging research to look into other neurotransmitter possibilities. Recent work shows promising results for cholinesterase inhibitors to improve gait variability and potentially reduce fall risk, in patients who are at high risk for falls [98, 102]. Whether these benefits stem from increased cholinergic activity in the cortex, related to attention processes, or in the PPN – thalamic tracts is an unanswered, important question. Improving gait through attention or cognitive control processes is a relatively new approach, opening up new treatment avenues using cognition-enhancing drugs. Besides cholinergic treatment, memantine has been considered for this purpose. Although there is some efficacy evidence of memantine to improve gait variability in demented people without PD [88], a pilot study in PD failed to observe such effects [89].

There is a paucity of literature on other, common drugs that can impair gait in people with PD, such as drugs with sedative, anticholinergic or antihypertensive effects, known to increase fall risk in the general or hospitalized populations [117, 121]. Although no studies specifically address PD, it can be assumed that the same effect, if not aggravated, will be present in people with PD. Because fall risk is a rough outcome measure, and fall risk is known to be multifactorial [130, 131], research is also needed to evaluate the effects of these drugs on objective gait characteristics in the PD population.

The simple parameter, gait speed, is the most commonly used outcome parameter in the reviewed studies. However, increasing gait speed does not always mean an improvement of

gait quality, particularly in people with balance difficulty. The results of this review support the idea that gait consists of independent factors amongst which pace and stability that have at least partly different underlying neural mechanisms [132, 133]. Differentiation of gait components during clinical assessment can provide a better understanding of the walking difficulties that patients encounter in everyday life, and in the future might lead to more personalized treatment plans.

The literature reviewed here can be broadly categorized into two designs: 1) small-scale, short-term studies using objective, movement techniques with suboptimal designs, and 2) large-scale, placebo-controlled trials to evaluate effectiveness for drug use in clinical practice, using clinical, subjective measures of gait. It is apparent that combining the best of both types of studies could yield better insights into pharmacological effects on gait. With the introduction of wearable sensors, it has become much easier to apply objective gait tests in large clinical trials, and produce more detailed monitoring of gait. A second methodological improvement would be to consider walking tests that better reflect the challenges of daily life than the commonly used, straight, non-obstructed walk through the clinic hallway. As put forward in the Introduction, patients with PD have considerable difficulty with the initiation, turning and adaptability components of walking. These components have largely been neglected in research studies. Recent studies have introduced cognitively demanding secondary tasks while walking to assess attentional demands of walking [102, 134, 135]. Another option would be to assess obstacle avoidance skills. Lastly, laboratory-based studies to better understand the pharmacological effects on gait, in a mechanistic fashion, could be improved by introducing placebo-controlled designs and account for order biases by randomizing the order of ‘on’-‘off’ assessments.

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- Dopaminergic drugs improve spatial characteristics of straight-ahead gait.
- There is a lack of studies addressing other walking abilities, such as turning.
- Pro-cholinergic drugs might improve gait stability measures.
- There is a lack of studies evaluating drugs known to increase fall risk in elderly.

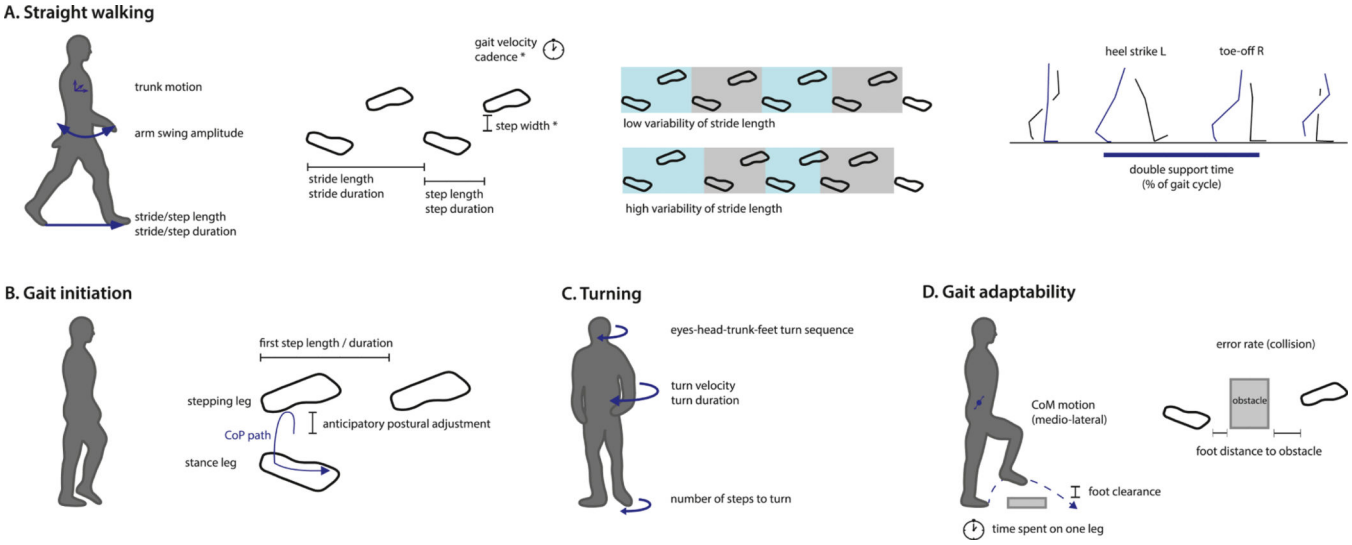

Figure 1.

Different components of walking in everyday life and related objective outcome measures.

A. Straight walking can be characterized by spatial and temporal variables of the stride (left-left heel strike) and step (left-right heel strike), motion of the arm and trunk, and gait speed and cadence (steps per minute). Stability of gait can be indicated by step-to-step or stride-to-stride (depicted here) variability of stride length. Low variability indicates that the stride length or stride time is relatively constant, whereas high variability indicates large changes of stride length or stride time between strides. Double support time is defined as the percentage of the gait cycle during which both feet are in contact with the ground; i.e. between heel strike of one foot and toe-off of the other foot.

B. Gait initiation can be characterized by the anticipatory postural adjustment (APA) that precedes the onset of the first step. The CoP first moves posteriorly and toward the stepping foot in order to accelerate the CoM forward and toward the stance foot. Execution of the first step is described in terms of step length and step duration.

C. Turning during walking consists of a sequence of rotations of eyes-head-trunk-feet. The turning velocity and duration are most commonly quantified using the trunk motion. Finally number of steps needed to complete the turn is a common outcome measure.

D. Gait adaptability, here limited to obstacle avoidance, can be quantified as the ability to prevent collision with the obstacle, the clearance of the crossing foot, foot placement, time spent on one leg and total duration of obstacle crossing. Stability during obstacle crossing can be measured by quantifying CoM movement.

* Variables that are not affected in PD as compared to their healthy peers.

Abbreviations: CoP: center of pressure; CoM: center of mass.

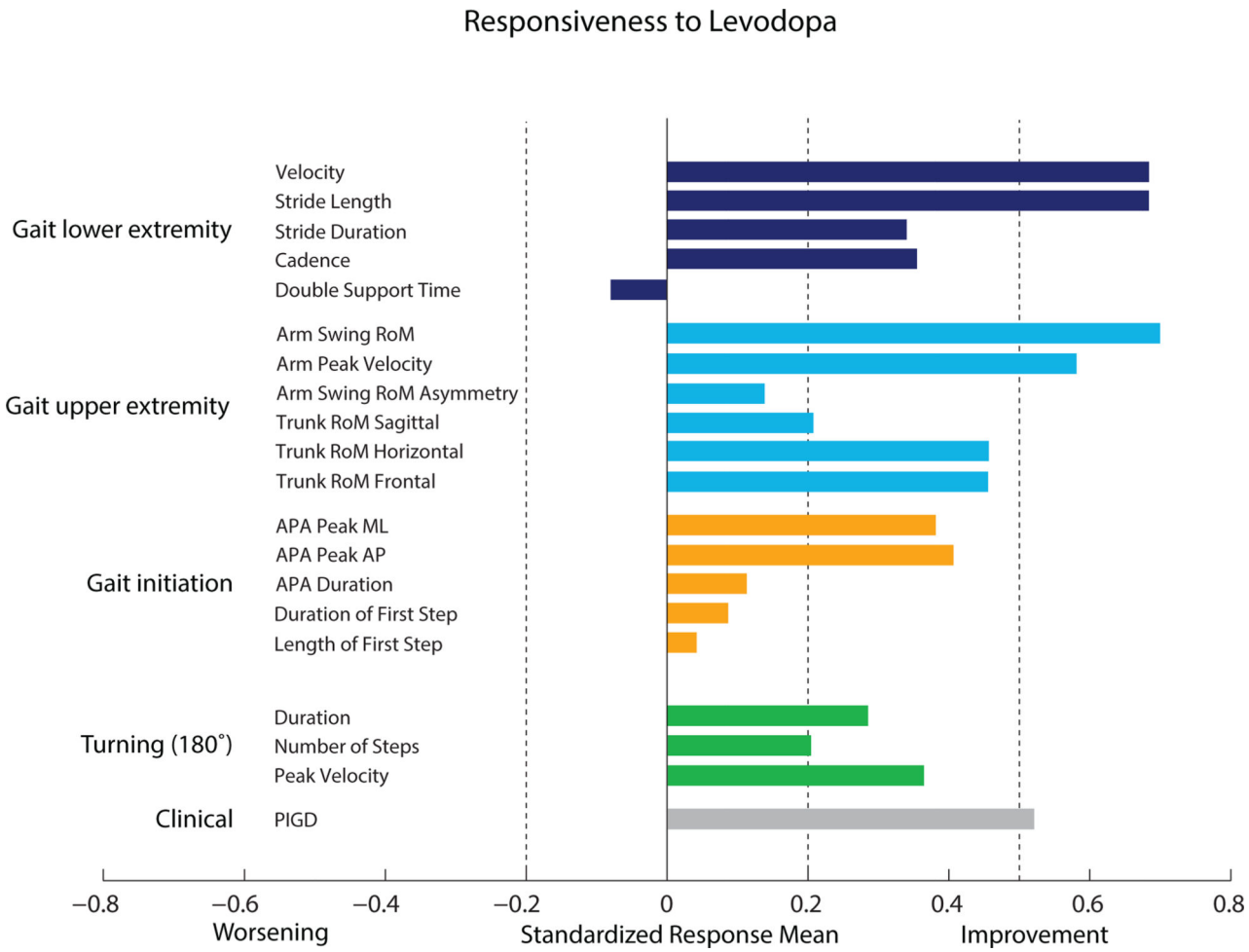

Figure 2.

A summary of the relative effects of taking levodopa on a wide variety of gait parameters during straight walking, gait initiation, and turning in a study of 100 people with PD. This study is an example of how upper and lower body bradykinetic aspects of gait improve with levodopa, whereas measures related to stability of gait (such as double support time) did not. The standardized response mean reflects the size of the improvement with levodopa and is calculated as the mean score change divided by the standard deviation of the score change. Adapted from C. Curtze, J.G. Nutt, P. Carlson-Kuhta, M. Mancini, F.B. Horak, Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease, Mov Disord (2015). Copyright 2015 by the John Wiley & Sons, Inc. Adapted with permission.

Table 1

Overview of studies evaluating effects of dopaminergic treatment (On vs. Off) using quantitative measures during straight walking.

Authors	Design	N	Gait velocity	Stride/step length	Stride/step duration	Cadence	Spatial variability	Temporal variability	Double support time	Arm swing	Trunk movement
Curtze et al. 2015	Off then On	104									
Rochester et al. 2011	Order counterbalanced	50									
Bryant et al. 2011a	Off then On	33									
Bryant et al. 2011b	Off then On	21									
Bowes et al. 1990	Placebo controlled	14									
Blin et al. 1991	Off then On	20									
Fregni et al. 2006	Order counterbalanced	14									
Weller et al. 1993	Placebo controlled	9									
Sterling et al. 2015	Off then On	16									

Note: Green highlighted cells indicate a significant improvement of gait in ON state compared to OFF state. Yellow highlighted cells indicate that no significant difference was reported between ON and OFF state. Empty cells indicate that the variable was not tested in the study.

Table 2

Overview of studies evaluating effects of dopaminergic treatment (On vs. Off) using quantitative measures for gait initiation, turning and gait adaptability

Authors	Design	N	Gait initiation		Turning during walking (180°)	Gait adaptability
			APA	Step execution		
Curtze et al. 2015	Off then On	104				
Rocchi et al. 2006	Off then On	21				
Burleigh-Jacobs et al. 1997	Order counterbalanced	6*	**			
Jacobs et al. 2009	Off then On	10*	**			
Franzen & Horak 2009	Off then On	15				
Doan et al. 2013	Off then On	10				
Pieruccini et al. 2013	Off then On	12				

Note: Green highlighted cells indicate an improvement of gait on ON state compared to OFF state. Yellow highlighted cells indicate that no difference was reported between ON and OFF state. Empty cells indicate that the variable was not tested in the study.

*All PD subjects had FoG.

**Step initiation in response to external perturbation (compensatory stepping)

Table 3

Description of studies evaluating medication effects (other than levodopa) on gait and/or falls in PD

	Authors	Drug	Subjects	Study design	Time (mean)	Objective (O) / Subjective (S) Assessment	Effect on gait	Effect on falls
Dopamine Agonists	Serrao et al., 2015	Rotigotine	PD untreated (n=24)	Uncontrolled study	6 months	O	Improves all gait aspects	
	Brodsky et al., 2010	Pramipexole	PD with dyskinesia/ fluctuations (n=13)	Double-blind, placebo-controlled, cross-over study.	immediate	O	Increases walking speed	
	Ondo et al., 1999	Apomorphine (sublingual)	PD with dyskinesia and fluctuations (n=10)	Double-blind, placebo-controlled study	Immediate	O	Increases walking speed	
	Olanow et al., 1994	Pergolide	PD with dyskinesia/wearing off (N=367)	Double-blind, placebo-controlled study.	6 months	S	Improves gait (UPDRS)	
COMT Inhibitors	Ondo et al., 2000	Tolcapone with apomorphine (sublingual)	PD with fluctuations (n=5)	Double-blind, placebo-controlled, cross-over study.	Immediate	O	No effect on gait speed	
	Napolitano et al., 1999	Tolcapone with levodopa	PD (n=7)	Uncontrolled study	Immediate and 6 weeks	O	Improvement on gait speed	
Monoamine oxidase type B inhibitor (MAOB-I)	Jankovic et al., 2014	Rasagiline	PD untreated (n=392)	Double-blind, placebo-controlled, delayed start study.	36-72 weeks	S	Less increase in PIGD over time	
	Dashtipour et al., 2015	MAOB-I (grouped)	PD (n=302)	Retrospective study cross-sectional study	12 months (minimal)	S	No effect on FOG	No effect
	Shoulson et al., 1998	Selegiline	PD de novo (n=368)	Double-blind, placebo-controlled study	14 months	S	Less FOG	
	Giladi et al., 2001							
	Hubble et al., 1993	Selegiline	PD with motor fluctuations (n=16)	Double-blind, cross-over trial	3 weeks	O	Higher gait speed	
Amantadine	Lee et al., 2013	Amantadine	PD with FoG (n=40)	Double-blind placebo controlled study	5 days	S	No effect on primary FOG outcome	
	Chan et al., 2013	Amantadine	PD patients with STN-DBS and incomplete axial benefit (n=46)	Uncontrolled study	10 months	S	Improves gait item UPDRS-III	
	Kim et al., 2012	Amantadine	PD with FoG (n=8)	Double-blind placebo controlled study.	2 days	S + O	No improved gait speed over placebo	
	Malkani et al., 2012	Amantadine	PD with FoG (n=11)	10/11 short-term benefits, 4 report reduced benefits later. Self-reports, no controlled conditions.	20 months	S	Improves FOG	
Glutamatergic agents	Moreau et al., 2013	Memantine (adjunct)	PD with severe gait disability (n=25)	Double-blind, placebo-controlled.	90 days	S + O	No improvement	

	Authors	Drug	Subjects	Study design	Time (mean)	Objective (O) / Subjective (S) Assessment	Effect on gait	Effect on falls
Cholinergic agents	Henderson et al., 2016	Rivastigmine	PD moderate severity (n=114)	Double-blind, placebo-controlled trial	32 weeks	O	Improved gait (speed and variability)	Improved
	Chung et al., 2010	Donepezil	PD with recurrent falls (n=23)	Double-blind study, placebo-controlled, crossover trial	6 weeks	S		Improved
	Litvinenko et al., 2008	Galantamine	PD with dementia (n=41)	Open-label, randomized controlled trial.	24 weeks	S	Improved	Improved
Norepinephrinergic agents	Hauser et al., 2015	Droxidopa	PD with neurogenic orthostatic hypotension (n=147 over 2 groups)	Placebo-controlled, double-blind randomized trial.	15 days	S		Inconclusive
	Fukada et al., 2013	Droxidopa with entacapone	PD with FoG (n=18 over 3 groups)	Uncontrolled, open-label.	4 weeks	S	Combination lessens FoG severity	
	Tohgi et al., 1993	Droxidopa	PD with FoG (n=11)	Uncontrolled, open-label.	Not reported	S	No overall effect	
	Narabayashi et al. 1981	Droxidopa	PD with FoG (n=9)	Uncontrolled, open-label.	Not reported	S	Improves FoG	
Methylphenidate	Delval et al., 2015	Methylphenidate	PD with STN stim (n=12)	Double-blind, placebo-controlled trial	3 months	O	No effects on gait hypokinesia, in ST and DT	
	Moreau et al., 2012	Methylphenidate	PD with STN stim (n=65)	Double-blind placebo-controlled trial.	90 days	O	Off dopa: improved speed, FOG less ON dopa: gait NS, FOG less	
	Espay et al., 2011	Methylphenidate	PD (n=17)	Double-blind placebo controlled trial. Composite score of gait, initiation, turning	12 weeks	O	OFF: slight gait improvement ON: no improvements	
	Devos et al., 2007	Methylphenidate	PD advanced, with STN stimulator (n=17)	Uncontrolled.	3 months	S + O	Stand-walk-sit improved. Less FoG	
	Nutt et al., 2007	Methylphenidate	PD (n=17)	Double-blind, placebo-controlled trial	Immediate (2 hrs)	O	Improves TUG speed in combination with l-dopa	
	Auriel et al., 2006	Methylphenidate	PD (n=21)	Single dose, open-label	Immediate	O	Improves TUG and gait (speed and variability)	

Grey highlighted cells indicate that the variable (gait or falls) was not tested in the study.