The effects of levodopa on gait in Parkinson's disease

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ABSTRACT

This literature review aimed to explore the effects of levodopa on gait in Parkinson's disease. Understanding the degree of and fluctuations in spatiotemporal, kinematic and kinetic gait variables over the course of the levodopa cycle aids clinicians in determining the effectiveness of treatment. A literature search was carried out between August 2015 and October 2015. Databases were searched and abstracts were read for suitability. Appropriate articles were read in full and their reference lists were checked for further relevant titles. The evidence suggests during the 'off' phase of the levodopa cycle, the Parkinson's disease gait is considerably slower, shuffling and flexed compared to that of healthy age match controls. During the 'on' phase, spatiotemporal, kinematic and kinetic gait parameters appear to improve compared to the 'off' phase, although the improvements are still less than that of healthy matched controls. The effects of levodopa on Parkinson's disease gait are dependent on the stage of the medication cycle. Further research is needed to evaluate the effects of levodopa on gait in functionally relevant settings.

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Key words: Parkinson's disease, Levodopa, Gait, Physiotherapy

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting 1 in every 100 people over the age of 65 worldwide (Svehlik et al., 2009). Therefore it could be estimated that more than 6000 New Zealanders currently have PD (Statistics New Zealand, 2013). However the prevalence of PD in New Zealand is largely unknown due to the lack of data. This is surprising considering the increasing proportion of older adults in New Zealand and the fact that within three years of diagnosis, 85% of people with PD will develop gait problems leading to an increased risk of falls and decreased quality of life (Kelly, Eusterbrock, & Shumway-Cook, 2012) putting an increasing strain on medical and physiotherapy services.

Gait may be initiated by voluntary (visuomotor), emotional (fight or flight reactions) and autonomic systems controlled by the brain, spinal cord and peripheral muscles (Takakusaki, Tomita, & Yano, 2008). Gait deficiencies can be caused by changes in any of the above systems. The control of movement in relation to the basal ganglia is complex. The basal ganglia is made up of several nuclei at the base of the forebrain (Graybiel, 2000). The nuclei work together with the thalamus and motor cortex to allow us to make and control movement and prevent unwanted movement (Graybiel, 2000).

PD is caused by a loss of dopamine containing neurons in the substantia nigra, one of the nuclei of the basal ganglia (Soufa et al., 2005). The cause for the loss of dopamine is unclear. Data suggests ageing, genetics, viruses, free radicals and or environmental factors may have a role to play (Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011). A loss of dopamine neurons causes a reduction in the amount of dopamine travelling in the nigrostriatal pathway from the substania nigra to the striatum (Smith et al., 1998). This means the substantia nigra cannot prevent an excessive reduction in movement (Smith et al., 1998). A 60-70% loss of dopamine concentration (Rodriguez-Oroz et al., 2009) in the striatum results in the characteristic motor signs of PD namely hypokinesia, bradykinesia, rigidity and tremor (Kimmeskamp & Hennig, 2001).

The characteristic Parkinsonian gait pattern has several hypokinetic features including reduced stride length, velocity and step height resulting in short shuffling steps, associated with a flexed posture and poor arm swing (Peppe, Chiavalon, Pasqualetti, Crovato, & Caltagirone, 2007). Bradykinesia is also evident in Parkinsonian gait (Rodriguez-Oroz et al., 2009; Soufa et al., 2005).

With age, gait can become slower with a reduced stride length and flat footed heel strike. This together with a reduced arm swing and stooped posture gives the presentation of a Parkinsonian gait pattern (Friedman, 2012). This may be due to a small natural loss of dopamine with age (Ostrosky, Van Swearingen, Burdett, & Gee, 1994), but may also be due to neuromuscular and vestibular changes that occur during the ageing process (Friedman, 2012).

There are, however, some characteristic differences between an ageing gait and a Parkinsonian gait, which may only be observed through clinical gait analysis and analysis of spatiotemporal, kinematic and kinetic data. Gait analysis is a functionally relevant objective outcome measure and it can provide a better understanding of gait patterns and identify impairments which may help to facilitate a clinician's rehabilitation programme (MacKay-Lyons, 1998). Observational gait analysis may be the initial stage in constructing a patient's gait pattern. Other methods include 2D and 3D motion analysis and pressure sensitive insoles.

Despite advances in surgical treatments, including bilateral subthalamic nucleus deep brain stimulation and stem cell therapy (Fox et al., 2011); and pharmacological therapies, including Rivastigmine (Henderson et al., 2016) and

Methlyphenidate (Espay, Dwivedi & Payne, 2011) for PD suffers with gait disorders, there is no cure and treatments are aimed at managing the symptoms.

PD causes a progressive deterioration in motor performance, function, independence and cognition. Increasingly doctors are referring people with PD for physiotherapy assessment to evaluate the motor response to PD medication. The most common and effective pharmacological management of PD is the administration of levodopa, a precursor to dopamine (Contin & Martinelli, 2010). By monitoring a person's motor performance in response to levodopa, physiotherapists can measure the level of disability and modify their treatments, thus maximising function. In the clinical setting, motor performance can be measured by functional tasks including walking. Therefore knowledge of the effects of levodopa on gait is important for physiotherapists.

The aim of this review was to investigate the effects of levodopa on gait in PD, which could aid the assessment process and treatment planning for physiotherapists.

METHOD

A literature search was conducted between August - October 2015, using the electronic data bases Ovid, Scopus, PEDro, Medline, the Cochrane Library, CINAHL and the Allied and Complementary Medicine Database (AMED). The search terms were levodopa, Parkinson's disease, gait, gait analysis and rehabilitation.

Search limits included articles that were written in English and published in a peer reviewed journal. The search was confined to articles published since 1990. These constraints were chosen for practicality purposes and to provide the reader with up to date information. Only studies using adult participants were included. Conference abstracts and qualitative studies, studies using deep brain stimulation with levodopa and studies using other PD medication with levodopa were excluded.

The search resulted in 299 articles. All abstracts with any of the search terms in the title were read. Relevant studies were read in full to see if they met the inclusion / exclusion criteria. The reference lists from retrieved relevant studies were searched for further articles. This process continued until no new articles were found. See Figure 1 for the flow diagram showing the study selection process.

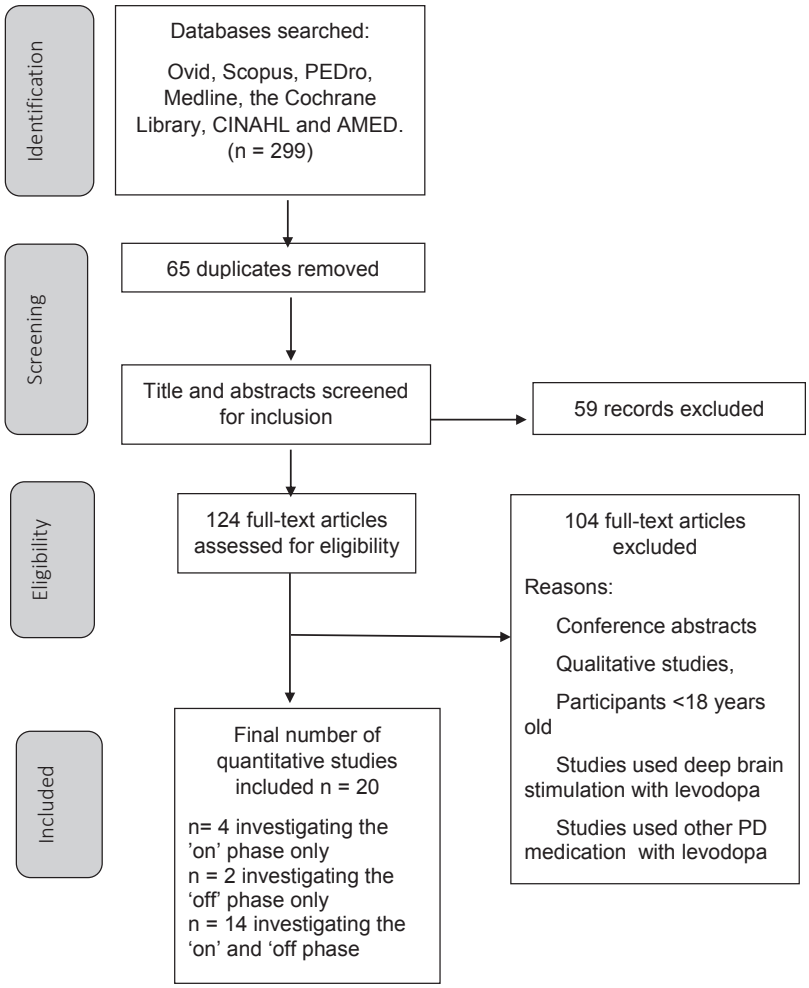

Figure 1: Flow chart of the literature search and selection process.

Table 1: PD gait in the 'off' phase of the levodopa medication cycle: a summary of findings

Authors (Year)	Length of time since levodopa	Main results
Blin et al. (1991)	12 hours off levodopa	Decreased velocity and stride length
Bowes et al. (1990)	12 hours off levodopa	Decreased stride length and velocity; double support duration within normal range.
Bryant et al. (2011)	12 hours off levodopa	Decreased velocity, stride length and increased double support time compared to the 'on' phase.
Calinadro et al. (2011)	12 hours off levodopa	RMS decreased in 30% of patients and decreased tendoachilles function compared to 'on' and controls
Chien et al. (2006)	12 hours off levodopa.	Significant difference between 'off' values and controls in terms of velocity, stride length, single leg stance, double leg stance – all worse in 'off' values. No difference in cadence.
Cioni et al. (1997)	3-18 hours off levodopa	When 'off' decreased **EMG**: Tibialis anterior activation in early stance and swing phase and decreased heel strike; increased proximal muscle activation in stance phase, increased hip, knee and ankle flexion in stance on EMG. **Spatiotemporal:** decreased velocity and stride length; increased gat cycle length and stance phase (compared to controls and 'on').
Galli et al. (2008)	12 hours off levodopa.	**Spatiotemporal:** shorter step length decreased speed and increased stance phase. Kinematics: decreased total ROM in all joints of lower limb.
Kurz et al. (2010)	8 hours off levodopa.	**Kinematics:** Structural variations at the ankle joint between 'on' and 'off' phases. No significant differences at hip and knee between 'on' and 'off' phase.
Lubik et al. (2006)	12 hours off levodopa.	Compared to 'on' phase: • UPDRS sub score decreased by 40%. • Velocity, cadence, step length and symmetry reduced. • Increased single leg support, double leg support, and stance and step time.
MacKay-Lyons et al. (1998)	Measured at 10% intervals throughout levodopa cycle	Unpredictable variation in spatiotemporal parameters throughout medication cycle.
Moore et al. (2008)	12 hours off levodopa	Reduced stride length, speed compared to 'on' phase.
Morris et al. (1999)	12 hours off levodopa	**Spatiotemporal:** Decreased velocity and step length. **Kinematics:** Flexed posture, decreased hip, knee and ankle range of motion during gait **Kinetics:** Altered force generation throughout the lower limbs during the gait cycle.
Pourmoghaddam et al. (2015)	8 hours off levodopa	Overall activity of lower limb muscles increased in 'off' phase. Decreased gait speed in 'off' phase.
Schaafsma et al. (2003)	12 hours off levodopa	Stride variability not related to tremor, rigidity of bradykinesia in 'off' phase. Stride time and variability were worse in the 'off' phase than 'on' phase
Svehlik et al. (2009)	12 hours off levodopa	Compared to controls, PD patients in 'off' phase; **Spatiotemporal:** Walked slower with decreased stride length and cadence and increased double support times. **Kinematics:** Decreased ROM at hip, knee, and ankle joints. Hip extension and ankle plantarflexion significantly decreased. **Kinetics:** Decreased ankle push off power and lift off hip power.
Vokaer et al. (2003)	12 hours off levodopa	Compared to 'on' phase decreased gait velocity and stride length.

Note: PD, Parkinson's disease

The appropriate studies were then re-examined using the valid (Moher, Liberati, Tezlaff & Altman, 2009) and reliable (Maher, Sherrington, Herbert, Moseley & Elkins, 2003) PEDro Scale to assess the quality of research methodology. The PEDro Scale was chosen as it is regularly used in assessing physiotherapy based randomised controlled trials (Maher et al., 2003), the highest level of evidence. A summary of the PEDro scores is outlined in Appendix 1.

RESULTS

The literature search found 20 papers in total investigating the effects of levodopa on gait in PD. Fourteen studies investigated the effects of levodopa during the 'on' phase (where the signs and symptoms are reduced) and 'off' phase of the medication cycle; four studies looked at the 'on' phase only compared to age matched controls and two studies looked at the 'off' phase compared to age matched controls. The characteristics of each study are outlined in Appendix 2.

PD gait during the 'off' phase' of the levodopa medication cycle

The evidence suggests that during the 'off' phase of the levodopa cycle, the PD gait is considerably slower, with a short shuffling stride length and in a greater lower limb flexor pattern compared to that of age matched healthy controls (Chien et al., 2006: Svehlik et al., 2009). Sixteen papers reviewed gait parameters during the 'off' phase (see Table 1).

Spatiotemporal parameters:

There were nine studies that evaluated the spatiotemporal parameters of PD gait during the 'off' phase (see Table 1).

Velocity

All included studies found participants with PD had a reduced gait velocity during the 'off' phase ranging from 0.45 metres per second (m/s) - 1.05m/s (Blin et al., 1991; Bryant et al., 2011; Chien et al., 2006; Cioni et al., 1997; Moore et al., 2007; Svehlik et al., 2009; Voaker et al., 2003) compared to the 1.19 - 1.65 m/s found in the healthy age-matched controls (Chien et al., 2006; Galna, Lord, Burn & Rochester, 2015; Ostrosky et al., 1994; Sofuwa et al., 2005; Svehlik et al., 2009) (see Appendix 3).

Stride length

Stride length was also shown to be shorter in participants with PD, ranging from 0.49 metres (m) –1.18m (Cioni et al., 1997; Moore et al., 2007), compared to 1.3m - 1.45m found in healthy age matched controls (Chien et al., 2006; Svehlik et al., 2009) (see Appendix 3).

Double leg support

The percentage of the gait cycle spent in the double limb support in healthy older adults is 18 - 25% (Chien et al., 2006; Svehlik et al., 2009). During the 'off' phase the percentage rises to 28 - 35% (Chien et al., 2006; Moore et al., 2007; Svehlik et al., 2009) (See Appendix 3).

Single leg support

Interestingly there is very little difference in the percentage of time spent in single leg support between the 'off' phase for participants with PD (35%) and aged matched healthy controls (40%) (Chien et al., 2006; Svehlik et al., 2009).

Cadence

Cadence values for participants with PD are comparable to healthy subjects (Chien et al., 2006 & Svehlik et al., 2009). Bryant et al. (2011) and Ostrosky et al. (1994) found age matched healthy controls had a walking rate of 110 - 140 steps/minute compared to 111 - 138 steps per minute for participants with PD in the 'off' phase (Chien et al., 2006 & Svehlik et al., 2009).

Kinematic and kinetic variables:

Morris et al. (1999) found a significant reduction in movement excursion during the 'off' phase, in the hip, knee and ankle, showing decreased range of motion (ROM) during walking compared to healthy age matched controls. The findings of Morris et al. (1999) are in agreement with later studies by Galli, Cimolin, de Pandis, Onorati and Albertini (2008), Morris et al. (2001) and Svehlik et al. (2009). Svehlik et al. (2009), Morris et al. (2001) and Cinoni et al. (1997) also found a non-significant increase in hip and knee flexion during single leg stance phase compared to controls (34° flexion throughout stance, compared to 32° at the hip and 8° flexion during stance compared to 3° flexion at the knee). Likewise Svehlik et al. (2009) and Morris et al. (2001) found the difference between groups was most pronounced at the ankle joint in the sagittal plane. Participants with PD remained in 10° dorsiflexion at late stance compared to 8° in age matched controls. Data demonstrated increased dorsiflexion in stance and reduced plantar flexion at toe-off resulting in decreased ankle ROM at push off in the PD group.

Svehlik et al. (2009) found reduced maximum hip extensor moment and power generation in first double support in participants with PD during the 'off' phase of the levodopa cycle, compared to healthy age matched controls. Maximum hip flexor and power generation in the PD group was also reduced compared to controls in the second double support and pre-swing phase.

At the ankle Svehlik et al. (2009) and Morris et al. (1999) found the moment loading response, maximal extensor moment, power generation and absorption during stance and push off were decreased in participants with PD compared to controls.

PD gait during the 'on' phase' of the levodopa medication cycle

There were 18 papers that reviewed gait parameters during the 'on' phase.

Spatiotemporal parameters:

Velocity, stride length, single leg support time and swing time

Six studies found an increase in gait velocity; stride length, single leg support time and swing time, and a decrease in the percentage of the gait cycle in stance during the 'on' phase of the medication cycle compared to the 'off' phase (see Appendix 3). Although there was an overall improvement in the spatiotemporal parameters, they were still less than that of healthy aged matched controls (see Appendix 3).

Double leg support

Bryant et al. (2011) found a decreased percentage of the gait cycle in double leg support after levodopa (34% in the 'off' phase, 30% in the 'on' phase). These findings are comparable

to Chien et al. (2006) and Lubik et al. (2006), who both found an 8% reduction in double stance support after levodopa (see Appendix 3) and 0.08s reduction after levodopa respectively (see Appendix 1).

Cadence

The normal cadence for healthy age matched controls is on average 110 - 140 steps/minute (Bryant et al., 2011 & Ostrosky et al., 1994). Bryant et al. (2011), Chien et al. (2006), Cioni et al. (1997) and Vokaer et al. (2003), found cadence for their participants with PD before levodopa ranged from 111 steps/ minute (Bryant et al., 2011) to 138 steps/minute (Vokaer et al., 2003). These values were comparable to that of healthy age matched controls. After levodopa, cadence ranged from 111 steps/ minute (Cioni et al., 1997) to 142 steps/ minute (Vokaer et al., 2003).

Kinematic and kinetic variables:

Galli et al. (2008), Cioni et al. (1997) and Morris et al. (1999) found significant increases in hip, knee and ankle ROM in the sagittal plane for participants with PD, compared to the 'off' phase, with values close to controls after taking their morning dose of levodopa. Kurz and Hou (2010) however found no significant difference in the mean ROM at the hip and knee during the 'on' and 'off' states, indicating levodopa did not change functional ROM at these joints. However, resistance to hip and knee joint changes in response to levodopa in this study may be due to the treadmill acting as an external cueing device.

Despite the use of levodopa, kinematic differences are most pronounced at the ankle joint. Soufa et al. (2005) found ankle ROM during push-off was significantly reduced in the 'on' phase in participants with PD compared to control participants (19.8%).

In an electromyographic (EMG) study by Cioni et al. (1997) data showed significant improvement in tibialis anterior activation during the 'on' phase compared to participants with PD in the 'off' phase, although the values were still a lot lower than for age matched control participants. These findings are comparable to later studies by Calinandro et al. (2011) and Mitoma et al. (2000). However despite levodopa, the same studies reported an increase in hip and knee flexion in stance compared to control participants. Conversely Pourmoghaddam, Dettmer, O'Connor, Paloski and Layne (2015), found a decrease in EMG activity of all lower limb muscles with significant reduction in tibialis anterior.

Using pressure sensitive insoles Kimmeskamp and Hennig (2001) and Nieuwboer et al. (1999) found that participants with PD in the 'on' phase have reduced heel strike and increasing forefoot loading especially on the medial aspect of the foot, compared to age matched control participants. These authors also found the amount of forefoot loading was related to disease severity. Pressure sensitive insoles however have been found to have decreased measurement reliability when participants exhibit a shuffling gait pattern, therefore this could have affected the results (Mansfield and Lyons 2003).

Using force plates, Diehl, Schneider, Konietzko & Hennerici (1992), found during the 'on' phase of the levodopa cycle, participants with moderate to severe PD (Hoehn and Yahr stage 3-4 (Hoehn & Yahr, 2011)) had a shuffling gait pattern and a ground reaction force (GRF) curve consisting of one narrow peak (not two) (Zijlstra, Rutgers & Van Weerden, 1998). Similarly, Kimmeskamp and Hennig (2001) and Morris et al. (1999) showed under scaling in the vertical and frontal GRF and decreased ankle joint loading response.

Morris et al. (1999) and Sofuwa et al. (2005) found decreased EMG activity of gastrocnemius in participants with PD during the 'on 'phase of the levodopa cycle compared to healthy age matched control participants.

DISCUSSION

Levodopa allows dopamine to cross the blood brain barrier (Anderson & Nutt, 2011) and increase dopamine levels in the basal ganglia, restoring normal movement. The effectiveness of levodopa decreases after several years because the substantia nigra slowly loses its ability to make the enzyme that converts levodopa into dopamine (Anderson & Nutt, 2011). After this time, the effects of levodopa tend to wear off before the next dose is taken and patients experience fluctuations in their Parkinson's signs and symptoms with definite 'on' (where the signs and symptoms are reduced) and 'off' phases (Contin & Martinelli, 2010). The fluctuation of signs and symptoms can have a detrimental effect on the person's quality of life and function and can increase the risk of falls (Morris, Huxham, McGinley, Dodd & Iansek, 2001).

Analysing gait during the 'on' phase provides feedback to clinicians on the effects the medication has on movement patterns and function. This information allows doctors to make informed decisions around medication changes as the disease progresses and helps physiotherapists provide appropriate walking aids and treatment plans.

It is also important for clinicians to have knowledge of gait parameters at the end dose or 'off' phase of the medication cycle and of normal values for healthy age matched controls. It allows clinicians to see the effect PD pathology has on gait, aiding the provision of relevant treatment plans. All included studies reviewed had stopped levodopa 8-12 hours (see Table 1) before measurements were taken. Research however has shown that it can take up to three to four weeks for the complete effects of levodopa to leave the body after it is withdrawn (Anderson & Nutt, 2011). Therefore, during the 'off' phase, the 'short term response' to the drug will have worn off but the 'long term effect' of the drug may still have been in the person's system and having a small effect on gait. However, it may be considered unethical to stop medication for three to four weeks to see the true effects of PD on gait.

The evidence suggests changes in spatiotemporal, kinematic and kinetic lower limb variables ultimately affect gait velocity. All studies looking at spatiotemporal parameters included gait velocity. Gait velocity is a commonly used outcome measure in the clinical setting as it requires very little and non-sophisticated equipment and it is a valid and practical measure of mobility and can reflect a patient's level of function (Prince, Corrveau, Herbert, & Winter, 1997).

When initial contact occurs at one foot, the toes of the other foot are still in contact with the ground. This is an

unstable position. During the 'off' phase, people with PD will compensate for decreased balance and postural instability by reducing their heel strike and increasing forefoot loading especially on the medial aspect of the foot, compared to age matched control participants. A decreased heel strike (and push off) may account for the single peak in the GRF curve. Calinandro et al. (2011), Cioni et al (1997) and Mitoma, Hayashi, Yanagisawa & Tsukagoshi (2000), found levodopa improved tibialis anterior activity in the late swing, early stance phase of gait, allowing adequate foot placement and preventing stumbling.

Kinematic data from Kimmeskamp and Hennig (2001) and Nieuwboer et al. (1999) showed an increase in hip and knee flexion in mid-stance compared to controls. This may be due to the knee generating less power during single stance and decreased power absorption in late stance, resulting in less extension and passive stabilisation of the knee via the hamstrings (Svehlik et al., 2009). Although people with PD may still be more flexed than normal, they are straighter in mid-stance after levodopa (Galli et al., 2008).This suggests that levodopa may 'energise' distal leg muscles restoring functional 'key' parts of gait (Cioni et al., 1997). Whereas non dopaminergic neural structures may control activity in the proximal leg muscles and is not responsive to levodopa (Morris et al., 2001). Pourmoghaddam et al. (2015) suggested levodopa decreases symptoms by decreasing overall coactivity of lower limb muscles allowing for an optimal movement pattern. Their study was however carried out on a treadmill where participants held onto the safety bars to aid balance at a constant speed. Walking on a treadmill has been shown to stimulate peripheral proprioceptive afferents in the upper limb and lower limbs increasing EMG activity (Murray, Spurr, Sepic & Gardner, 1985), which could have affected the results. The treadmill may also have acted as an external cueing device which has been shown to have a positive effect on PD gait (Pourmoghaddam et al., 2015).

Double leg stance time reduced during the 'on' phase but was still more throughout the whole medication cycle compared to healthy age matched controls (Ostrosky et al., 1999). This may be to compensate for a fear of falling, postural instability and decreased balance which are common characteristics at the end stage of the disease. Similarly an increase in double support time may be due to muscle weakness, dystonia or soft tissue tightness, making it difficult to maintain control of the lower limb muscle during single leg stance (Svehlik et al., 2009).

The little difference in the percentage of time spent in single leg support between the 'on' and 'off' phase for participants with PD and aged matched healthy controls may be because during the natural ageing process step height reduces and double support time increases to compensate for instability (Murray, Sepic, Gardner & Downs, 1978).

EMG activity of gastrocnemius improved during the 'on' phase compared to the 'off' phase, however the activity was still less than of healthy age matched controls. This would account for the reduced ankle push off power generation and reduced hip flexion (pull off) power seen in participants with PD compared to controls. Ankle push off is an important body propulsion mechanism (Prince et al., 1997) and hip power generation is required to move the leg into swing phase. In PD, decreased ankle (push off) and hip flexion (pull off) power, may limit trunk progression and hip power generation in stance**,** thus reducing gait velocity, stride length and step height, despite the positive effects of levodopa. Decreased hip and knee extension in single leg stance and reduced plantar flexion of the ankle at toe off may also account for the decreased stride length seen in PD throughput the medication cycle which has also been proven be a cause of reduced velocity (Morris et al., 1999). Judge, Davis & Ounpuu (1996), found greater ankle strength led to increased gait velocity and stride length and is believed to be the strongest predictor of step length in older adults. Further research is needed to see if the results are applicable to the PD population.

The data suggests all but one of the spatiotemporal parameters of gait appear to be 'dopa sensitive' (Blin et al., 1991). Gait velocity, stride length and foot clearance improve; and stance time reduces during the 'on' phase of the medication cycle. Bryant et al. (2011), Chien et al. (2006), Cioni et al. (1997) and Vokaer et al. (2003), found levodopa did not improve cadence (see Appendix 3). It is still unclear why this temporal characteristic is 'dopa resistant' (Blin et al., 1991). The data suggests cadence cannot be improved by levodopa as it has already reached its normal ceiling value during the 'off' phase. Similarly, there is a growing body of evidence to suggest the velocity and stride length are controlled by the basal ganglia whereas cadence is not (Vokaer et al., 2003). Therefore levodopa could not affect cadence. It is unknown how cadence is regulated (Vokaer et al., 2003).

Despite levodopa improving most spatiotemporal, kinematic and kinetic variables people with PD still have a slower, more shuffling gait throughout the medication cycle, compared to healthy age matched controls.

Limitations

Whilst laboratory gait analysis allows researchers to set up a standardised protocol easily to ensure the reliability of results, the data collected may not be relevant to the community setting. All studies used a straight walk way over a short distance (3m (Bryant et al., 2011) to 20m (Schaafsma et al., 2005) (see Appendix 2), in an uncluttered environment. This has been found to temporarily enhance participants with PDs' performance (Yekutiel, 1993). The unnatural environment also may not highlight any balance or gait problems encountered in everyday life such as crossing uneven or different surfaces, narrow doorways, cluttered environments, crowds, and turning, which have been shown to affect gait and induce freezing in the later stages of PD (Moore et al., 2007). However Graham, Ostir, Fisher and Ottenbacher (2008), found walking over short distances of 10 - 12m a valid measure of velocity. Similarly, people with PD have trouble initiating and terminating gait. Therefore each study eliminated the first and last steps of each trial to allow for a constant speed to be recorded. Graham et al. (2008) also found five to six strides enough to obtain valid spatiotemporal-kinematic data. Therefore the reduced distance available for data collection would not affect the validity of the results.

All studies except Pourmoghaddam et al. (2015) and Kurz et al. (2010), allowed participants to walk at their self-selected walking speed, which would vary considerably between

individuals (see Appendix 2). Pourmoghaddam et al. (2015) and Kurz et al. (2010) used a treadmill for data collection. Whilst a treadmill allows for a constant speed, it has been shown to decrease stride length (Pourmoghaddam et al. 2015). Similarly both studies allowed upper limb support which may affect gait. All the other studies collected data whilst the participant was walking independently unaided (see Appendix 2). This is surprising considering the majority of the studies used participants in the moderate to severe stages of PD (Hoehn and Yahr staging 3-4), where balance problems are evident (see Appendix 2) and most people with PD would be using a walking aid for community ambulation.

The studies did not consider the influence of the upper limbs, trunk and pelvis on gait. This is surprising, considering a reduced arm swing, axial rigidity and flexed posture are characteristic signs of a Parkinsonian gait (Constantinescu, Leonard, Deeley & Kurlan, 2007), and are part of and therefore affect the lower limb kinetic chain and gait.

Most of the studies reviewed carried out data collection at one point in time. Only MacKay-Lyons (1998), investigated PD gait 11 times at 10% intervals over the medication cycle, whilst Galna et al. (2015) investigated PD gait at regular intervals over an 18 month period. Participants' gait pattern may vary from step to step, walk to walk, hour to hour, day to day – especially in individuals with PD, as seen in the review.

Clinical Implications

Overall levodopa has been shown to improve the spatiotemporal parameters of gait and some kinematic and kinetic factors in the early moderate and severe stages of PD. Clinicians need to be aware that the effectiveness of levodopa wears off after time and the 'on' phase gets progressively shorter as the disease progresses. Therefore timing of therapy with maximum levodopa dose effect is important. Clinical assessment should be conducted at a similar time within the medication cycle to allow for comparability of data. However rehabilitation should also be considered in the 'off' phase so patients and carers can adopt strategies to cope with the variation in gait.

The review highlights variations in gait spatiotemporal, kinematic and kinetic variables throughout the levodopa cycle, via gait analysis. By identifying the gait impairments and seeing how levodopa affects them, physiotherapists are able to provide appropriate strength training, exercise advice, balance and gait re-education, including the provision of walking aids. This will help to reduce the risk of falls and improve a patient's confidence and frequency of mobility, ultimately improving the person's function and quality of life.

Physiotherapists quantify the improvements in their treatment through a variety of outcome measures. Observational gait analysis is a valid tool for evaluating changes in PD gait and for quantifying the improvement made through rehabilitation and or medication (Peppe et al., 2007) and is easy to use in the clinical setting. Clinicians should have a good understanding of normal gait pattern before carrying out gait analysis on participants with PD. Physiotherapists may improve their observational gait analysis skills by watching and/or videoing 'normal' and a variety of pathological gaits and discussing them at peer review. Gait velocity has been shown to have a clinically significant response to levodopa (a change of more than 0.14m/s (Perera, Mody, Woodman & Studenski, 2006). Gait velocity, the Tinetti Mobility Test and the Unified Parkinson's Disease Rating Scale (UPDRS) are quick, easy, valid and reliable outcome measures to use in the PD population (Siderowf et al., 2002, & Kostyk, Kegelmeyer, Kloos & Thomas, 2007). These tests assess a variety of functional tasks including gait, balance, sit to stand and turning; and the UPDRS also assesses activities of daily living, falls and complications of therapy including fluctuations in symptoms, all of which are affected by medication status.

Future Research

An important role physiotherapists have in the clinical setting is the assessment for and provision of suitable walking aids. Future research should investigate the effect walking aids have on spatiotemporal, kinematic and kinetic variables, and their efficacy and or safety in PD gait. Similarly, researchers could investigate the effects physiotherapists' cueing strategies have on gait during the levodopa cycle. The upper limb, trunk and pelvis have an important role to play during the gait cycle but were not investigated in previous research on PD gait and levodopa. Likewise, the effects of levodopa on community ambulation should be studied as turning, stepping back and enclosed spaces which are necessary for community ambulation, have been shown to affect PD gait (Morris et al., 2001) and were not considered in the current research. Most of the studies collected data in the sagittal plane (see Appendix 2). Future research should consider data collection in the sagittal, transverse and coronal planes which would give a more complete picture of PD gait.

CONCLUSION

The effects of levodopa on PD gait are variable, depending on the stage of the medication cycle and severity of PD. Despite the improvements in some spatiotemporal, kinematic and kinetic characteristics of gait in response to levodopa, the research has shown some gait parameters are levodopa resistant and the typical Parkinson's gait pattern is still slower, more flexed and shuffling than that of healthy age matched controls throughout the medication cycle. Clinical gait analysis is an important tool to evaluate the effects of levodopa and to guide rehabilitation programmes. Further research is needed to evaluate the effects of levodopa on gait in functionally relevant settings.

KEY POINTS

1. The effects of levodopa on Parkinson's disease gait are dependent on the stage of the medication cycle.
2. During the 'on' phase of the levodopa cycle, some spatiotemporal, kinematic and kinetic gait parameters appear to improve compared to the 'off' phase.
3. Timing therapy within the medication cycle is important at maximum dose effect, but also rehabilitation should be considered in the 'off' phase.
4. Future research should explore the effects of levodopa on gait in functionally relevant environments and situations.

DISCLOSURES

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Appendix 1

A summary of the PEDro scores of the studies used in the review.

Study	PEDro score (out of 11)
Blin et al. (1991)	6
Bowes et al. (1990)	7
Bryant et al. (2011)	7
Caliandro et al. (2011)	6
Chien et al. (2006)	6
Cioni et al. (1997)	6
Galli et al. (2008)	6
Galna et al. (2015)	6
Lubik et al. (2005)	5
Kimmeska-mp & Hennig (2001)	4
Kurz & Hou (2010)	6
MacKay-Lyons (1998)	6
Mitoma et al. (2000)	6
Moore et al. (2008)	6
Morris et al. (1999)	5
Pourmoghaddam et al. (2015)	6
Schaafsma et al. (2003)	6
Sofuwa et al. (2005)	5
Svehilk et al. (2009)	4
Vokaer et al. (2003)	6

Appendix 2

Characteristics of each of the studies investigating the effects of levodopa on gait

Study	n	Distance Walked (m)	Number of Trials	H&Y stage	UPDRS III scores	Own speed or treadmill	Walking Aid Yes/No	Type of Gait Analysis Equipment	Plane of data	'Off' phase time since levodopa	'On' phase time since levodopa	Type of data collected
Blin et al. (1991)	20 PD	10m	2	1-4	NA	Own speed	No	2D	Sagittal	12hr	1hr	ST Kinematic
Bowes et al. (1990)	14 PD	6m	1 for each time over 4 days	2-5	NA	Own speed	No	Gait assessing trolley	ND	12hr	2,4,6hr	ST
Bryant et al. (2011)	21 PD	3m	2	'on' 2-3	'off' 32.91 'on' 20.62	Own comfortable speed	No	GAITRite	ND	12hr	45min-1hr	ST
Caliandro et al. (2011)	30 PD	10m	2	NA	'off' median 19.5, 'on' median 4.5	Own speed	No	UPDRS, EMG	ND	12hr	2hr	Kinetics
Chien et al. (2006)	13 PD 13 C	4.6m	2x in 5min for each time	3	'off' 37.7, 'on' 21.1	Own speed – fastest possible	No	GAITRite	ND	12hr	1,2,4hr	ST Kinematic
Cioni et al. (1997)	10 C 15 PD	8m	10	2-4	NA	Own speed	No	Custom made foot switch, EMG	Sagittal	12hr	ND	ST, Kinematic Kinetic
Galli et al. (2008)	14 C 9 PD	ND	4	NA	NA	Own speed	No	3D	Sagittal	12hr	50min	ST Kinematic Kinetic
Galna et al. (2015)	184 C 121PD	7m	Over 18 months	1-3	25.5 to 32.8	Own speed	No	GAITRite	Sagittal	NA	1hr	ST
Lubik et al. (2005)	12 PD	12m	1x over 20s	NA	Raw data ND	Own speed	No	3D	ND	12hr	1hr	ST
Kimmeska-mp & Hennig (2001)	24 C 24 PD	11m	ND	NA	NA	Own speed	No	Pressure sensitive insoles	ND	NA	1hr	ST Kinematic Kinetics
Kurz & Hou (2010)	10 PD	3 mins	ND	2-3	'on' 28.6	Treadmill-own comfortable speed	Treadmill	3D Vicon	ND	8hr	45min	Kinematic

MacKay-Lyons (1998)	5 PD	12m	11 times at 10% intervals of levodopa cycle=4-6hr	3-4	NA	Own speed	No	3D	ND	12hr	11 times at 10% intervals of levodopa cycle=4-6hr	ST, Kinematic
Mitoma et al. (2000)	17 C 16 PD	6m	3	1-4	NA	Own speed	No	EMG and force plates, 3D	Sagittal	NA	1hr	EMG
Moore et al. (2008)	13 PD	10m	Walked every 13min over 90min	3-4	ND	Own speed	No	2D	ND	12 hrs	Walked every 13min over 90min	ST
Morris et al. (1999)	1 PD	10m	3	NA	'off' 51, 'on' 44	Own speed	No	3D, Vicon, force plates, foot switches	ND	12hr	1hr	ST Kinematic Kinetics
Pourmoghaddam et al. (2015)	9 PD	2 mins	1	'off' 2-3	'on' 28.6	Motorised Treadmill – own speed	Treadmill	EMG, 3D Vicon	ND	8hr	45min	EMG Kinematic
Schaafsma et al. (2003)	32 PD	20m	4	'off' 2.9 'on' 2.7	'off' 21.4 'on'10.7	Own speed	No	Force sensitive insoles	Sagittal	12hr	Subjective	ST
Sofuwa et al. (2005)	9 C 15 PD	8m	3	2-3	161 (group average score)	Own speed	No	3D Vicon	Sagittal	NA	1-2hr	ST, Kinematic Kinetic
Svehilk et al. (2009)	20 C 20 PD	12m	5	2-3	'off' phase 15-57.	Own speed	No	3D Vicon	Sagittal	12hr	NA	ST, Kinematic Kinetic
Vokaer et al. (2003)	23 PD	14m	2	'off' 3 'on' 2	'off' 39 'on' 9.5	Fast as possible	No	Observation analysis	ND	12hr	50min	ST

Notes: H&Y Stage, Hoehn & Yahr staging; C, controls; ND, not documented; NA, not assessed; ST, Spatiotemporal; hr, hour; min, minutes

Appendix 3

Raw data for the spatiotemporal parameters recorded in the studies investigating the effects of levodopa on gait

Study	Velocity (m/s)			Cadence (steps/min)			Stride length (m)			Stride time (m/s)			Double support time (% of gait cycle)			Single support time (% of gait cycle)			Stance (%)			Swing (%)		
	C	Off	On	C	Off	On	C	Off	On	C	Off	On	C	Off	On	C	Off	On	C	Off	On	C	Off	On
Ostrosky et al (1994) Healthy older adults only	1.21 - 1.33			136 -146			1.19			1.09 -1.17			25			NA			NA			NA		
Blin et al. (1991)	NA	0.45	0.57				NA	0.57	0.69	NA	1.28	1.2	NA	32					NA	80	75			26
Bryant et al. (2011)	NA	0.841	1.01	NA	111	114	NA	0.91	1.08				NA	34	30									
Chien et al. (2006)	1.65	1.05	1.36	136	132	131	1.45	0.97	1.24				18	29	21	40	35	39	NA	74	71	40	45	39
Cioni et al. (1997)	NA	0.52	0.59	NA	77-116	87-111	NA	0.54	0.98															
Galna et al. (2015)	1.26	NA	1.12				0.67	NA	0.62	1.6	NA	1.9							20	NA	23	15	NA	17
Lubik et al. (2005)	NA	0.43	0.79							NA	1.56	1.24	NA	26	18	NA	40	42						
Kimmeskamp & Hennig (2001)	1.1	0.97	NA	NA	92	100	NA	0.56	0.94															
Kurz & Hou (2010)	NA	NA	0.62	110	104	NA																		
MacKay-Lyons (1998)	NA	NA	0.70										20	NA	22	41	NA	35						
Mitoma et al. (2000)	0.63	NA	0.66				NA	NA	0.89															
Moore et al. (2008)	NA	0.56	0.87				0.80	NA																
Morris et al. (1999)	NA	0.56	0.63	NA	115	119	NA	0.44	0.83															
Pourmoghaddam et al. (2015)	NA	NA	0.62				NA	0.97	1.06															
Schaafsma et al. (2003)										NA	0.98	1.2												
Sofuwa et al. (2005)	1.19	NA	0.94	115	NA	108	1.24	NA	1.03				23	NA	25	38	NA	37						
Svehlik et al. (2009)	1.27	1.01	NA	115	147	NA	1.31	1.02	NA				24	28	NA	36	35	NA	61	64	NA			
Vokaer et al. (2003)	NA	0.83	1.14	NA	61	79	NA	1.38	1.42															

Notes: NA, not assessed; C, healthy aged matched control group; Off, 'off' phase of medication cycle; On, 'on' phase of medication cycle.