J Neural Transm
DOI 10.1007/s00702-008-0139-z

BASIC NEUROSCIENCES, GENETICS AND IMMUNOLOGY - REVIEW ARTICLE

Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review

T. Herman · N. Giladi · J. M. Hausdorff

Received: 2 September 2008 / Accepted: 6 October 2008

Abstract This report reviews recent investigations of the effects of treadmill training (TT) on the gait of patients with Parkinson's disease. A literature search identified 14 relevant studies. Three studies reported on the immediate effects of TT; over-ground walking improved (e.g., increased speed and stride length) after one treadmill session. Effects persisted even 15 min later. Eleven longer-term trials demonstrated feasibility, safety and efficacy, reporting positive benefits in gait speed, stride length and other measures such as disease severity (e.g., Unified Parkinson's Disease Rating Scale) and health-related quality of life, even several weeks after cessation of the TT. Long-term carryover effects also raise the possibility that TT may elicit positive neural plastic changes. While encouraging, the work to date is preliminary; none of the identified studies received a quality rating of Gold or level Ia. Additional high quality randomized controlled studies are needed before TT can be recommended with evidence-based support.

T. Herman · N. Giladi · J. M. Hausdorff (✉)
Laboratory for Gait and Neurodynamics, Movement Disorders Unit and Parkinson Center, Department of Neurology, Tel-Aviv Sourasky Medical Center, 6 Weizman Street, 64239 Tel Aviv, Israel
e-mail: jhausdor@bidmc.harvard.edu

J. M. Hausdorff
Department of Physical Therapy, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

J. M. Hausdorff
Division on Aging, Harvard Medical School, Boston, MA, USA

N. Giladi
Department of Neurology, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

Keywords Parkinson's disease · Gait · Treadmill · Neuroplasticity

Introduction

Treadmill training (TT) is only infrequently prescribed as a treatment option for patients with Parkinson's disease (PD). In contrast, bodyweight supported treadmill training (BWSTT) is often used to promote gait training in patients with spinal cord injuries and post-stroke (Hesse et al. 1995; Laufer et al. 2001; Behrman and Harkema 2000; Dietz et al. 1994; Dobkin et al. 2007; Dobkin 2005; van Hedel et al. 2006). The off loading of bodyweight allows for early intervention and plays a critical role in this rehabilitation process, enabling patients who have difficulties standing to begin gait training. In PD, patients typically are able to stand throughout most of the stages of the disease and they do not suffer from marked muscle weakness. The challenge in PD is to improve motor control, but not necessarily to target muscle strength. Perhaps, this explains why BWSTT has not been widely applied to PD in the past. Nonetheless, recent studies have demonstrated the potential of TT training in PD. Here we review this evidence and describe the rationale for applying TT to PD (and perhaps other disorders that share similar symptoms).

Gait disturbances are an integral part of the clinical manifestation of PD and among the most disabling symptoms of the disease. The gait of patients with PD is typically marked by reduced speed, shortened stride length, and longer double support phase (Ebersbach et al. 1999; Sofuwa et al. 2005; Morris et al. 1994). In addition, gait dynamics are characterized by exaggerated stride-to-stride variability (Blin et al. 1990; Hausdorff et al. 1998; Schaafsma et al. 2003; Baltadjieva et al. 2006). This high

stride-to-stride variability reflects a disturbance in gait rhythmicity and an inconsistency of the locomotor pattern, and is a marker for increased fall risk (Hausdorff et al. 2001; Hausdorff 2005; Nakamura et al. 1996; Schaafsma et al. 2003). The mobility problems related to gait disturbances, instability and falls, have a profound negative impact on patients' quality of life and their mental well-being (de Boer et al. 1996; Martinez-Martin 1998). Despite advances in pharmacological therapy and surgical procedures, impairment in gait and balance remain common in PD patients and the therapeutic options for treating these gait disturbances and reducing fall risk in PD are not yet ideal (Bloem et al. 2004; Grimbergen et al. 2004; Thurman et al. 2008), leaving much room for alternative interventions.

Anti-parkinsonian medications are probably the most common means of treating parkinsonian symptoms. Levodopa and dopamine agonists ameliorate many of these symptoms, including balance and gait disturbances, to some degree. Certain balance and gait deficits are likely related to the loss of central dopaminergic transmission, however, levodopa is not very effective in treating all gait abnormalities and preventing falls. In a prospective survey of fall circumstances during daily life (Bloem et al. 2001), most falls occurred when patients were in their best clinical condition ("on" state), possibly reflecting their increased mobility when symptoms are well controlled by medications and/or the incomplete effectiveness of this therapy. Quantitative studies of postural reactions to sudden perturbations have also shown that dopamine agonists provide insufficient relief of many postural instability symptoms, though some aspects partially improve in response to this anti-parkinsonian therapy (Bloem et al. 1996; Beckley et al. 1995; Frank et al. 2000). Furthermore, levodopa and dopamine agonists may sometime worsen gait and provoke falls, e.g., in the case of "on" freezing and freezing of gait in general.

Deep brain stimulation (DBS) is another therapeutic option. When targeting the internal globus pallidus or subthalamic nucleus, DBS can partially alleviate "off" related gait impairment and instability in well-selected patients with PD (Herzog et al. 2003; Krack et al. 2003; Stolze et al. 2001; Maurer et al. 2003; Balash et al. 2005). The effects are generally greatest for "off" state axial symptoms. A particular concern is that several years after an initially good response, some patients develop severe gait and balance deficits that are resistant to further therapeutic intervention (Krack et al. 2003; Ferraye et al. 2008). Moreover, these invasive techniques are expensive, carry a certain degree of risk, and are generally recommended only for a small subset of patients.

Physical therapy (PT) is often prescribed to PD patients. It may include strength training, gait training, and flexibility exercises. Despite its relatively long history, the evidence supporting the use of conventional PT for treatment of gait in PD is not very strong. Meta-analyses concluded that there is little evidence to support or refute the use of PT, in part because of methodological flaws in published studies (de Goede et al. 2001; Rubenstein et al. 2002; Deane et al. 2001a, b, 2002; Keus et al. 2006). While traditional PT may help and benefit patients with PD, efficacy is limited in part because it may not directly address the underlying deficits specific to PD and the nature of the disease. Application of external cueing in forms such as visual and rhythmic auditory cueing is an exciting area of research, but it is not yet widely used in clinical practice (Lim et al. 2005; Nieuwboer et al. 2007; Rubenstein et al. 2002; Hausdorff et al. 2007).

Briefly then, the three most common approaches to the treatment of parkinsonian symptoms do not fully alleviate the gait disturbances associated with PD. As we detail below, a growing body of relatively recent evidence suggests that TT may be used as a complementary, alternative option for treating these gait disturbances and enhancing health-related quality of life. Moreover, a few studies have demonstrated that TT may not only provide symptom relief; in addition, it may promote neuroplasticity. The purpose of this paper is to review the literature that supports this idea and the potential utility of TT in PD.

Methods

Search strategy

A search was conducted of the major electronic databases including MEDLINE, EMBASE, Web of Science, and Cochrane. The key words searched for were: treadmill and PD. We also looked for related studies using search terms such as gait, rehabilitation, exercise, PT, and falls. Relevant abstracts were reviewed and references cited were also followed to check for additional related studies. A study was included in the present review if it met the following criteria: 1. The target population was patients with PD; 2. The effects of TT intervention were tested (as the primary intervention); 3. The paper was available in English; and 4. The study was available as of August 1, 2008. A study was excluded if: 1. The treadmill was used as an assessment tool rather than as a therapeutic, intervention tool; 2. A case report study (i.e., three subjects or less); 3. Animal experiments were studied. Because of the relatively small numbers of studies identified, a formal meta-analysis was not applied. No previous reviews or meta-analysis on this topic were identified.

Quality ranking

The quality of the identified studies that reported on the long-term effects of TT were graded using two scales. The "Level of Evidence" was ranked using the standard scale where A Ia is evidence providing the best recommendation and highest level of evidence, while on the other end of the spectrum, D 5 represents a low recommendation and low level of evidence. In addition, the grading system recommended by the Cochrane Musculoskeletal Review Group (Tugwell et al. 2004) was applied as adapted by Bartels et al. (2007). In this scheme, the ranking ranges from Platinum (best), to Gold, Silver and Bronze. As summarized by Bartels et al. Platinum is a published systematic review that has at least two individual controlled trials each satisfying Gold criteria. Gold refers to a randomized clinical trial meeting all of the following criteria for the major outcome(s) as reported: (a) Sample sizes of at least 50 per group—if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome. (b) Blinding of patients and assessors for outcomes. (c) Handling of withdrawals; >80% follow up (imputations based on methods such as LOCF are acceptable) and (d) Concealment of treatment allocation. Silver: randomized trials that do not meet the above criteria. Silver ranking would also refer to a study of non-randomized cohorts that did and did not receive the therapy, or evidence from at least one high quality case–control study. Bronze: The bronze ranking is given to high quality case series without controls (including simple before/after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

Results

Fourteen studies were identified that met the inclusion and exclusion criteria (see Tables 1, 2). Here we briefly summarize some of the salient features of these investigations.

Immediate effects

Three studies examined the immediate effects of TT (see Table 1). Using a cross-over, four consecutive-day trial in 17 patients with early PD, Pohl et al. (2003) found that gait speed and stride length can be improved through a single intervention of TT (even without body weight support), but not through conventional gait training. Two training modes were used: Structured speed-dependent treadmill training (STT) and limited progressive treadmill training (LTT). In

Table 1 Studies that examined the immediate effects of walking on a treadmill in patients with Parkinson's disease

Number of PD patients/ reference	Intervention	Duration/frequency	Follow-up	Primary and secondary outcomes	RCT	Summary of findings
17 PD patients Pohl et al. (2003)	STT, LTT, CGT and control: four conditions, cross-over No BW support	Four consecutive days, 30 min each day	No	GS, stride length, double support	Cross-over design	A single session of TT improved GS and stride length, but the control intervention did not
30 PD 30 Healthy controls Frenkel-Toledo et al. (2005b)	Walking at three conditions: over-ground, with a walker, treadmill No BW support	Single session ~ 10 min TT	No	GS, gait variability	No	The treadmill decreased gait variability in the patients, independent of gait speed
16 PD 8 Healthy controls Bello et al. (2008)	Over-ground walking and TT three groups: 1. moderate 2. advanced 3. control No BW support	Single session 20 min TT	No	GS, step length, cadence, stride variability	No	All subjects improved over-ground GS after training; effect lasted 15 min. Step length increases more prominent in advanced patients

TT treadmill training, *GS* gait speed, *STT* structured speed-dependent treadmill training, *LTT* limited progressive treadmill training, *CGT* conventional gait training

Table 2 Studies of long-term effects of treadmill training in patients with Parkinson's disease

Number of PD patients/reference	Intervention	Duration/ frequency	Follow-up	Primary and secondary outcomes	RCT	Level of evidence	Grading of evidence	Summary of findings
10 PD patients Miyai et al. (2000)	BW support TT vs. PT	1 month 45 min/day 3 days/week	No	UPDRS, GS, stride length	No cross-over design	C IIb	Bronze	TT with different amount of BWS improved ADL, motor performance, and ambulation, more than PT
20 PD in total 11 intervention 9 control Miyai et al. (2002)	20% BW support TT vs. PT	1 month 45 min/day 3 days/week	5 months	UPDRS, GS, stride length	Yes	B IIa	Silver	TT group had greater improvement in GS than PT group at 1 month; improvement in stride length at 1 and 4 months post-training
23 PD patients Toole et al. (2005)	3 groups: (1) TT no load (2) BW −25% (3) BW +5%	6 weeks 20 min/day 3 days/week	1 month	BBS, UPDRS, strength and ROM, sensory organization test/ dynamic posturography	No	C IIb	Bronze	Improvements in SOT, balance, BBS, UPDRS (Motor Exam), and gait parameters for the three groups regardless of the body-weight loading
18 PD in total 9 intervention 9 control Protas et al. (2005)	Intervention group had TT at a greater speed then over-ground while walking in four directions (no BW support) vs. control only pre/post-testing	8 weeks 60 min/day 3 days/week	No	Falls, GS, step length, five-steps test	Yes Not attention controlled	B IIa	Silver	Training resulted in a reduction in falls and improved gait performance and dynamic balance
7 PD Pelosin et al. (2007) (Abstract)	Trained without BW support	10 sessions 30 min/day 3 days/week	1 month	UPDRS, GS, Timed up and go, 6-min walk, fatigue severity, PDQ-39, VO_2 max	No	C III	Bronze	All walking parameters and QOL improved significantly. Cardiopulmonary capacity increased. Improvement persisted after 1 month
31 PD in total 21 intervention 10 control Cakit et al. (2007)	Incremental speed-dependent TT and stretching and ROM vs. control (BW support not mentioned)	8 weeks 30 min/day	No	Treadmill walking distance and speed, BBS, DGI, FES	Yes Not clear how attention controlled	B IIa	Silver	Mobility, postural stability, and balance-confidence improved significantly after the training program
9 PD Herman et al. (2007)	Intensive-progressive training without BW support	6 weeks 30 min/day 4 days/week	1 month	UPDRS, GS, stride length, Timed up and go, gait variability, PDQ-39	No	C IIb	Bronze	UPDRS, gait speed and stride length, mobility and QOL improved. Some gains at 5 weeks follow up

Table 2 continued

Number of PD patients/reference	Intervention	Duration/ frequency	Follow-up	Primary and secondaryoutcomes	RCT	Level of evidence	Grading of evidence	Summary of findings
30 PD in total 10 per group Fisher et al. (2008)	3 groups: High intensity-treadmill (10% BW support); Low intensity-exercise; Zero intensity-education	High and low: 8 weeks 1 h/day 3 days/week; Zero: six education sessions	No	UPDRS,GS, stride length, Sit-to-stand, ground reaction force, Bio-mechanic properties, CSP	Yes	B Ib	Silver	All improve in UPDRS; In high-intensity group: improvement in GS, stride length, joint excursion, lower extremity symmetry, Lengthening CSP
5 PD Skidmore et al. (2008)	3-month progressive TT as AE (no BW support)	12 weeks 10–20 min 3 days/week	No	UPDRS, falls and near-falls, regular and fast GS, SBP drops, activity monitoring	No	C III	Bronze	UPDRS, GS and home ambulation improved. Aerobic program is feasible in PD. Best to monitor autonomic function
24 PD in total 12 intervention 12 control Kurtais et al. (2008)	2 groups of instructed ROM exercise. Intervention group also TT (BW not mentioned)	6 weeks 40 min/day 3 days/week	No	Timed lower extremities tasks, physical assessment and ergo-spirometric test	Yes	B Ib	Silver	Significant improvement in tasks, fitness and self-report of physical well-being, and ergo-spirometric parameters
20 PD in total 8 completed TT 10 controls (Abstract) Canning et al. (2008)	2 groups: Home-based TT vs. control group maintain activity level	6 weeks 30–40 min/day 3 days/week	6 weeks	6-min walk test, PDQ-39, fatigue	Yes Not attention controlled	C IIb	Bronze	Improvement in QOL and reduced fatigue. No effect on walking capacity. Home-based treadmill training is feasible and safe

TT treadmill training, *GS* gait speed, *STT* structured speed-dependent treadmill training, *LTT* limited progressive treadmill training, *CGT* conventional gait training, *PT* physical therapy, *ROM* range of motion, *BBS* Berg balance scale, *BW* body weight, *FES* falls efficacy scale, *PDQ-39* Parkinson's disease questionnaire, *QOL* quality of life, *UPDRS* Unified Parkinson's Disease Rating Scale, *CSP* cortical silent period, *SOT* sensory organization test, *DGI* dynamic gait index, *SBP* systolic blood pressure, *AE* aerobic exercise, *RCT* randomized controlled trial

STT, the treadmill speed was increased by 10% each time the patient successfully completed 10 s of walking at a set speed. In LTT, the initial self-adapted over-ground speed was used without increasing treadmill speed. Over-ground gait speed improved from 1.37 ± 0.23 to 1.56 ± 0.23 m/s ($P < 0.001$) and from 1.35 ± 0.21 to 1.52 ± 0.20 m/s ($P < 0.001$) after SST and LTT, respectively. Similarly, stride length improved from 0.72 ± 0.12 to 0.78 ± 0.14 m and from 0.71 ± 0.10 to 0.77 ± 0.09 m ($P < 0.001$), after SST and LTT, respectively. Similarly, Bello et al. (2008) found that a single session of 20 min of treadmill walking increased over-ground gait speed and step length, especially in more advanced patients. Interestingly, these positive effects persisted as much as 15 min later. Frenkel-Toledo et al. (2005b) assessed the influence of a single session of TT on stride-to-stride variability. While walking on a treadmill, gait variability was reduced, even when walking at the same over-ground speed. This suggests that the treadmill was able to generate a more consistent gait pattern with a reduced stride-to-stride variability, a marker related to fall risk (Schaafsma et al. 2003; Hausdorff et al. 1997, 2001, 2003; Baltadjieva et al. 2006).

These findings indicate that treadmill walking can promote a faster and a more stable walking pattern in patients with PD and suggest that perhaps an intervention program that includes long-term treadmill walking—without using body weight support—might enhance gait speed, restore rhythmicity, reduce gait variability and perhaps succeed at lowering fall risk. As can be seen below, long-term intervention studies support this notion.

Long-term intervention studies

Eleven studies examined the effects of intensive TT with the training durations ranging from 3.5 to 12 weeks (Miyai et al. 2000, 2002; Toole et al. 2005; Protas et al. 2005; Pelosin et al. 2007; Cakit et al. 2007; Herman et al. 2007; Fisher et al. 2008; Skidmore et al. 2008; Kurtais et al. 2008; Canning et al. 2008) (see Table 2). All studies trained at a frequency of three times per week for about 20–40 min each session, except for one study which trained four times a week (Herman et al. 2007). Six studies were defined as randomized controlled studies, but in three of these it was not clear exactly if and how attention was controlled. All studies reported some benefits immediately post-training, compared to pre-training values and/or compared to changes seen in a control group.

In the first report on TT in PD, Miyai et al. (2000) investigated the effects of 20% BWSTT on gait and parkinsonian symptoms of PD patients. Patients were supported by a harness (taking partial body weight to reduce the gravitational load on the legs). In this 4-week cross-over study, BWSTT produced greater improvement in motor performance compared to conventional PT, increasing gait speed (from 1.0 ± 0.1 to 1.2 ± 0.1 m/s), stride length (from 0.89 ± 0.09 to 1.02 ± 0.11 m) and reducing parkinsonian symptoms [motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) decreased (improved) from 18.2 ± 1.4 to 15.0 ± 1.3] (Miyai et al. 2000). While promising, a key question left open by this study is whether the improvement in gait was due to the load reduction or to the TT itself. A follow-up randomized controlled trial by the same group demonstrated a long-term effect of BWSTT on gait, after the TT was completed, beyond that of conventional PT, which lasted for about 4 months (Miyai et al. 2002). For example, the BWSTT group had significantly ($P < 0.005$) greater improvement than the PT group in gait speed immediate post-training. In the BWSTT group, gait speed was 0.92 ± 0.07 m/s and increased to 1.18 ± 0.09 m/s, while in the group that received only PT, gait speed was 0.87 ± 0.13 m/s at baseline and 0.92 ± 0.15 m/s post-training..

Several other studies have found positive effects of TT in PD and indicate that the degree of weight bearing may not be critical for achieving benefits in PD (Toole et al. 2005; Cakit et al. 2007). Cakit et al. used a TT protocol of 8 weeks and reported promising effects on multiple aspects of gait and balance, including a reduction in fear of falling (Cakit et al. 2007), even though body weight was not supported. Toole et al. (Toole et al. 2005) studied the effects of 6 weeks of treadmill walking in 23 subjects with PD. The subjects were divided into three intervention groups and each group used different amounts of body weight support including one group that trained without any body weight support. Muscle strength did not change, but significant improvements in balance and gait were seen in all three groups, regardless of the degree of weight bearing.

Carry over effects from Long-term Studies

Five studies examined carry over effects after the cessation of the TT. Three studies re-tested subjects about 4 weeks after the intervention was completed (Toole et al. 2005; Herman et al. 2007; Pelosin et al. 2007), one study conducted a follow up after 6 weeks (Canning et al. 2008), and one study examined the long-term, carry over effect 5 months after termination of the training (Miyai et al. 2002). These studies all suggest that many of the effects persisted even after the patients no longer used a treadmill. For example, in the study by Miyai et al. pre-training stride length was 0.85 ± 0.08 m, and immediate post-BWSTT stride length increased to 1.00 ± 0.10 m. Significant gains in stride length were still observed 1 month (1.02 ± 0.09 m) and 2 months (0.99 ± 0.09 m) after training.

Quality of life and outcomes beyond gait and balance

A number of studies have demonstrated effects that extend beyond motor function, balance and gait. For example, Herman et al. found that the PD-Q39, a measure of quality of life, was enhanced even 4 weeks after cessation of the intervention (Herman et al. 2007). Herman et al. (Herman et al. 2007), Toole et al. (Toole et al. 2005), Skidmore et al. (Skidmore et al. 2008) and Fisher et al. (Fisher et al. 2008) all reported significant immediate effects of TT on the UPDRS, the most widely used measure of symptom severity in PD (lower scores are better). Compared to pre-training values, improvements in the UPDRS were seen weeks after completion of the training. In one study, UPDRS motor scores were 29.0 $\pm$ 9.3 pre-training and 19.7 $\pm$ 6.4 about 5 weeks after the intervention was completed ($P = 0.027$) (Herman et al. 2007). TT also apparently enhances walking confidence and reduces fear of falling (Cakit et al. 2007).

Safety and feasibility

Treadmill training may elevate heart rate (HR) and blood pressure and expose subjects to cardiovascular stress. Several studies explicitly state that subjects were excluded if they exhibited postural hypotension, uncontrolled high blood pressure or cardiovascular disorders (Toole et al. 2005; Cakit et al. 2007; Skidmore et al. 2008; Fisher et al. 2008; Herman et al. 2007). For example, all subjects in the study by Cakit et al. were screened with a stress test using the Modified Bruce Protocol to determine cardiovascular tolerance. In addition, a few studies also monitored HR and blood pressure during sessions on the TT (Toole et al. 2005; Skidmore et al. 2008; Fisher et al. 2008). In most studies, the explicit goal was not to elevate HR, instead the focus was on gait. In the few trials that measured HR on the treadmill, target HR was generally relatively low (e.g., less than 60% of theoretical HR capacity; (Toole et al. 2005)) indicating that the TT was not applied as an aerobic exercise. Other studies do not specify the steps taken to reduce cardiovascular risk.

A total of 260 patients with PD were enrolled in these 14 studies that examined the effects of TT on walking. Of those, 63 patients took part in a single session trial. One hundred and thirty-five patients completed screening and baseline testing for participation in an extended TT program and began training. Of these, 125 patients completed the intervention, i.e., 93% of the patients who began a TT program completed it successfully. Reported reasons for drop-outs included loss to follow-up and health problems not related to TT. This relatively good compliance may in part be explained by a comment by Toole et al. (2005) who noted that "there was 99% adherence to the program. Participants attended even when they did not feel their best."

Adverse events were generally not observed. In the study conducted by Skidmore et al. (2008) in eight patients, two patients were referred to a cardiologist for asymptomatic ST segment depression and one for symptomatic blood pressure drop as part of the screening process. Based on the findings in their intervention study, which included a high intensity treadmill protocol, Fisher et al. (2008) suggested that subjects with PD can be challenged and tolerate a *very high-intensity* TT. Furthermore, even a home-based treadmill walking procedure appeared to be well-tolerated by patients with PD with only minimal levels of muscle soreness and/or stiffness, and no report of adverse events (Canning et al. 2008). Cakit et al. (2007) noted that from among the 21 PD patients in the TT group, two showed ventricular extrasystole as a cardiac symptom during a training session, but they were not dropped from the study and completed it without additional side effects. Pohl et al. (2003) also specifically commented on the absence of cardiac symptoms (e.g., angina pectoris, significant arrhythmias) and other side effects (e.g., dizziness, muscle or joint trouble) in response to treadmill walking.

The safety of TT in patients with PD is supported by studies that examined the cardiovascular response to exercise in PD. In a study of the effects of treadmill exercise, HR, systolic blood pressure, and the Rate of Perceived Exertion were measured during a Modified Bruce Protocol in patients with PD and healthy controls (Werner et al. 2006). During sub-maximal exercise, no significant differences were found between the PD group and the control group for HR, blood pressure, or rate of perceived exertion. At peak exercise, one half of the subjects with PD exhibited blunted cardiovascular responses, despite reaching a comparable intensity of exercise during a Modified Bruce Protocol. This finding of a reduced cardiovascular response is consistent with other reports (Barbic et al. 2007; Oka et al. 2006; Persico et al. 1998) and supports the relatively low cardiovascular risks from TT in patients with PD.

Discussion

As shown in Table 2, there tends to have been a positive evolution of the investigations that have been performed to examine the potential utility of TT in patients with PD. Although progress was not always linear and much work still needs to be done, maturation of the research can be seen with respect to the number of subjects studied, the questions posed, and general study design. TT is relatively established as a rehabilitation paradigm for stroke patients and for patients with spinal cord injuries (Hesse et al. 1995; Laufer et al. 2001; Behrman and Harkema 2000; Dietz et al. 1994; Dobkin et al. 2007; Dobkin 2005; van Hedel

Table 3 Possible mechanisms underlying the efficacy of treadmill training in Parkinson's disease

Mechanisms	Supporting studies	Studies suggesting that this is not involved
Aerobic exercise	Skidmore et al. (2008)	All except for the Skidmore study
Strength training		Toole et al. (2005)
Pace retraining	Skidmore et al. (2008)	
	Frenkel-Toledo et al. (2005a, b)	
	Herman et al. (2007)	
Body-weight support	Fisher et al. (2008)	Herman et al. (2007)
		Bello et al. (2008)
	Miyai et al. (2000)	Toole et al. (2005)
	Miyai et al. (2002)	Pelosin et al. (2007)
Motor learning	Fisher et al. (2008)	
	Protas et al. (2005)	
Corticomotor exitability	Fisher et al. (2008)	

Many of these mechanisms are not mutually exclusive

et al. 2006). A growing body of intriguing preliminary work suggests that gait in PD, although a neurodegenerative disease, is also amenable to change via TT. Dopamine deficits and neuronal loss in PD cause a reduced stride length and gait dysrhythmicity while TT apparently may enhance gait speed, augment rhythmicity and boost walking steadiness. Moreover, these improvements in gait apparently have widespread benefits for multiple domains of QOL.

Putative mechanisms of treadmill training

As summarized in Table 3, a number of mechanisms may explain the observed benefits of TT in PD. Of course, these are not mutually exclusive. Treadmill walking may activate neuronal circuits that mediate central pattern generators (Van de Crommert et al. 1998), i.e., the paced, rhythmic motor commands that activate limb muscles repetitively. Enhanced motor learning after deficient motor activity may also play a role. Some have suggested that such learning is either reinforced at the synaptic connections in the spinal cord level or the trigger for re-organization of neural networks (Muir and Steeves 1997; Bello et al. 2008). Walking on a moving walkway (i.e., a treadmill) inherently provides external cueing that is mediated through proprioceptive and vestibular receptors; this in turn generates repetitive sensory input to the central nervous system (Mathiowetz and Haugen 1994). Interestingly, treadmill walking also activated the cerebellar vermis in a SPECT study of PD patients (Hanakawa et al. 1999).

Unlike over-ground walking where ongoing fluctuations in gait speed are unconstrained, on the treadmill, in order to successfully maintain walking, gait speed must follow the speed of the treadmill. With the treadmill, there is no getting around it. The patient must match his/her pace to the treadmill constantly. As a consequence, gait speed becomes more uniform and regular. This uniformity is expressed as a more rhythmic generation of gait cycles (Frenkel-Toledo et al. 2005b). Therefore, a treadmill may be viewed as an external pacemaker (Frenkel-Toledo et al. 2005a, b). One possible mechanism of gait motor command placement is that rhythmic stimulation is introduced to the motor system via the somatosensory pathways. Treadmill walking rhythmically stimulates pressure load receptors of the feet, muscle spindles, and Golgi tendon organs (Toole et al. 2005). Additional sensory inputs which become more rhythmic include the afferent vestibular input from the otolith organs (because of pitch head movements) and the input from neck muscle proprioceptors (because of head relative to trunk movements) which are rhythmically activated during treadmill walking (Hirasaki et al. 1999). These rhythmic inputs are transferred to neuronal circuits modulating gait throughout different CNS levels and facilitate the pacing of gait. Through these processes, neuronal plasticity and reinforcement may occur and augmented pace-making may be preserved in the neuronal circuits performing gait, even for long periods of time, depending in part on the intensity of the training.

Enhanced corticomotor excitability at the completion of the TT was also observed in patients with PD (Fisher et al. 2008) and this intriguing finding is consistent with studies on animal models of PD that demonstrated neuroplasticity after TT (Fisher et al. 2004; Petzinger et al. 2007; Yoon et al. 2007). Such changes and the observed carry over effects weeks after the TT intervention is completed are consistent with the possibility that TT may elicit neuroplastic improvements in motor function in patients with PD and that TT provides more than just simple symptom relief.

The basal ganglia assist in the regulation and control of over-learned rhythmic movements like gait. Given the basal ganglia impairment in PD, it was previously thought that training is not capable of producing long-term effects. While the theory behind the empirical data is not fully understood, recent evidence from other motor tasks

suggests that this is not the case (Graybiel 2005). Rather, patients with PD can learn "automatic" motor tasks, perhaps using other pathways to compensate (Kelly et al. 2004; Wu and Hallett 2005). Although not always at the same level as that of healthy controls, a number of studies have shown that implicit learning—the type of motor learning that may explain the observed benefits of TT—is still possible in PD (Forkstam and Petersson 2005; Guadagnoli et al. 2002; Kelly et al. 2004; Perretta et al. 2005; Smith et al. 2001; Wu and Hallett 2005). For example, van Hedel and colleagues evaluated the acquisition and performance of a high precision locomotor task in patients with PD, compared to healthy subjects (van Hedel et al. 2006). Initially, PD patients performed poorer and improved foot clearance more slowly. However, after task repetition, the groups performed similarly, indicating that adequate training can improve locomotor behavior in PD patients (van Hedel et al. 2006).

The rationale behind intensive and progressive forms of TT, despite the presence of neurodegeneration, is supported by studies using high intensity voice treatment. There are several features that underlie the voice and gait disorders common to PD: reduction in amplitude, a problem with the sensory perception of effort, and deficient internal cueing causes difficulty in generation of appropriate effort. To some extent, parallel deficiencies can be found in gait (e.g., shortened stride length as an expression of small amplitude; impaired rhythmicity as a deficient internal cueing). Ramig and colleagues have shown that PD patients can be trained to work around these deficits in speech, and that the training effects can last at least two years after cessation of an initial intensive training period (Liotti and Ramig 2003; Ramig et al. 2001a, b, 2004). In addition, imaging studies have shown that this treatment produces changes in recruitment patterns and regional cerebral blood flow, consistent with neuroplastic improvements (Liotti et al. 2003). The parallels between voice and gait suggest that re-training of gait may also be achievable. The patient learns to adapt to progressively increasing demands—a process that may enhance the automatization of motor control. Motor learning may explain the carry over effect of TT: the treadmill trains a steady gait speed and paces gait on a subconscious level while pacing cannot be ignored.

A priori, aerobic exercise is another possible mechanism whereby TT may produce benefits. If cardiovascular function is markedly impaired, gait and mobility will be affected. Conversely, improvement in aerobic capacity can lead to enhanced mobility. While some of the animal studies that found positive effects of TT were performed at a high intensity, most of the studies on TT in patients with PD were performed at exertion levels far below those typically recommended for aerobic exercise. Thus, while TT could potentially be applied for aerobic exercise, the results to date support the idea that the observed effects on gait and mobility are not achieved as a result of aerobic exercise.

Potential clinical implications

The present review indicates that walking on a treadmill apparently improves gait, mobility, and quality of life of patients with PD. TT may promote a more stable walking pattern in patients with PD and an intervention program that includes intensive long-term treadmill walking appears to be able to re-store stride length and rhyhmicity, key deficits to the gait of PD patients (Bloem et al. 2004; Morris et al. 1994; Schaafsma et al. 2003), even while off the treadmill. In the presence of PD, many see the goal as maintenance care, but do not see the feasibility or opportunity for rehabilitation. This review contributes to a growing body of evidence that demonstrates that rehabilitation-like program may be efficacious even in the presence of such a devastating neurodegenerative disease like PD.

Some of the studies (Miyai et al. 2000, 2002) suggest that TT is more effective than conventional approaches to improving gait characteristics associated with PD. While questions remain, if TT is considered, for select appropriate patients, we suggest combining conventional PT with intensive TT using a protocol of at least three sessions per week, 20–30 min each. For safety reasons, it is recommended to exclude patients with uncontrolled cardiac conditions or unstable medications, and patients that are unable to walk (with or without assistance) for moderate distances. Although TT is typically sub-maximal and not an aerobic form of exercise, standard recommendations about safety and screening for cardiac risk should be followed before a patient begins a new exercise program. In addition, consistent with the reports to date, it is advised that all training sessions take place in the "on" state. It is probably important that the physical therapist ensures a "normal" gait pattern while walking on the treadmill. However, if any gait deviations occur or if there are signs of pain or fatigue complaints, treadmill speed should be adjusted accordingly. It is advised that patients start the training while holding onto the parallel bars and gradually move to walking while holding on with one hand and eventually to walking without holding on at all.

In PD, there appears to be no need to unload the patient, unless specific issues arise. One has to take into account that due to the relatively high cost of a body-weight support treadmill, the need for a relatively large facility and increased time commitment, a TT program based on a medical treadmill (with a safety harness) may not be practical for everyone or for everyday use in the clinic. However, a harness used just to prevent falls may be less

expensive and more widely available, compared to a special partial weight bearing system. Furthermore, important safety issues should be considered when thinking about prescribing TT in the home-setting for patients with PD.

Limitations and future work

The findings of TT to date are very promising. Still, a critical look at the existing literature raises many questions. Most investigations included relatively small sample sizes that limit the ability to generalize the findings. This limitation is especially poignant when examining long-term, carry over effects. Overall, very few patients were monitored more than 1-month post-training. A number of the TT reports had no control group, did not control for attention and the placebo effect (an especially potent effect in PD), or did not include any active comparison. None of the identified studies reached a grade of Gold and the level of evidence was below A Ia. It is also helpful to keep in mind that the current literature may reflect a publication bias since studies that reported positive effects are more likely to be published. Moreover, before TT can be combined with other forms of therapy (e.g., muscle strengthening), likely the optimal form of therapy, there is a need for larger scale randomized controlled studies that demonstrate the advantages of TT compared to carefully designed control groups that receive similar amounts of attention. Questions about ideal delivery forms, dosage, frequency, intensity and the intervention prescription and their effects on compliance and outcome measures also should be addressed in follow-up studies. For example, at the moment, little is known about the effects of TT on falls. Larger scale trials will also enable us to examine if there are patients with specific PD characteristics that are more likely to respond to TT and the role of disease severity on TT efficacy. In addition, in the future, it may be helpful to more directly address the question of whether TT provides symptomatic relief only or whether it has the potential to modify disease progression. If additional work supports the latter, more remote possibility, treatment with TT early in the disease progress may become the ideal.

Conclusions

Despite these limitations and the many unresolved questions, the existing studies support the idea that TT in PD is safe, feasible, and likely to be efficacious and suggest that TT could play an important role for improving gait and mobility in PD, as it does in other patient groups. TT may be used as an adjunct treatment to complement PT, to improve physical performance, enhance gait stability and possibly reduce fall risk in PD patients, potentially improving quality of life. Hopefully the results of the present review will set the stage for larger scale, randomized controlled studies that definitively establish efficacy and long-term, carry over effects and directly measure the effects of TT on outcomes such as quality of life and fall risk, a major cause of morbidity and functional dependence in PD.

Acknowledgments This work was supported in part by NIH grants AG-14100, by the National Parkinson Foundation and by the European Union Sixth Framework Program, FET contract no. 018474-2, Dynamic Analysis of Physiological Networks (DAPHNet) and STREP 045622 (SENSing and ACTION to support mobility in Ambient Assisted Living, SENSACTION-AAL).

References

Balash Y, Peretz C, Leibovich G, Herman T, Hausdorff JM, Giladi N (2005) Falls in outpatients with Parkinson's disease: frequency, impact and identifying factors. J Neurol 252:1310–1315

Baltadjieva R, Giladi N, Gruendlinger L, Peretz C, Hausdorff JM (2006) Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. Eur J Neurosci 24:1815–1820

Barbic F, Perego F, Canesi M, Gianni M, Biagiotti S, Costantino G, Pezzoli G, Porta A, Malliani A, Furlan R (2007) Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. Hypertension 49:120–126

Bartels EM, Lund H, Hagen KB (2007) Aquatic exercise for the treatment of knee and hip osteoarthritis (review). Cochrane Libr Database Syst Rev 4:CD005523

Beckley DJ, Panzer VP, Remler MP, Ilog LB, Bloem BR (1995) Clinical correlates of motor performance during paced postural tasks in Parkinson's disease. J Neurol Sci 132:133–138

Behrman AL, Harkema SJ (2000) Locomotor training after human spinal cord injury: a series of case studies. Phys Ther 80:688–700

Bello O, Sanchez JA, Fernandez-Del-Olmo M (2008) Treadmill walking in Parkinson's disease patients: adaptation and generalization effect. Mov Disord 23(9):1243–1249

Blin O, Ferrandez AM, Serratrice G (1990) Quantitative analysis of gait in Parkinson patients: increased variability of stride length. J Neurol Sci 98:91–97

Bloem BR, Beckley DJ, van Dijk JG, Zwinderman AH, Remler MP, Roos RA (1996) Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. Mov Disord 11:509–521

Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH (2001) Prospective assessment of falls in Parkinson's disease. J Neurol 248:950–958

Bloem BR, Hausdorff JM, Visser JE, Giladi N (2004) Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord 19:871–884

Cakit BD, Saracoglu M, Genc H, Erdem HR, Inan L (2007) The effects of incremental speed-dependent treadmill training on postural instability and fear of falling in Parkinson's disease. Clin Rehabil 21:698–705

Canning CG, Allen NE, Fung VSC, Morris JGL, Dean CM (2008) Home-based treadmill walking for individuals with Parkinson's disease: a pilot randomized controlled trial. Mov Disord 23:S210

de Boer AG, Wijker W, Speelman JD, de Haes JC (1996) Quality of life in patients with Parkinson's disease: development of a questionnaire. J Neurol Neurosurg Psychiatry 61:70–74

de Goede CJ, Keus SH, Kwakkel G, Wagenaar RC (2001) The effects of physical therapy in Parkinson's disease: a research synthesis. Arch Phys Med Rehabil 82:509–515

Deane KH, Ellis-Hill C, Jones D, Whurr R, Ben Shlomo Y, Playford ED, Clarke CE (2002) Systematic review of paramedical therapies for Parkinson's disease. Mov Disord 17:984–991

Deane KH, Jones D, Ellis-Hill C, Clarke CE, Playford ED, Ben Shlomo Y (2001a) A comparison of physiotherapy techniques for patients with Parkinson's disease. Cochrane Database Syst Rev 1:CD002815

Deane KH, Jones D, Playford ED, Ben Shlomo Y, Clarke CE (2001b) Physiotherapy for patients with Parkinson's disease: a comparison of techniques. Cochrane Database Syst Rev 3:CD002817

Dietz V, Colombo G, Jensen L (1994) Locomotor activity in spinal man. Lancet 344:1260–1263

Dobkin B, Barbeau H, Deforge D, Ditunno J, Elashoff R, Apple D, Basso M, Behrman A, Harkema S, Saulino M, Scott M (2007) The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized Spinal Cord Injury Locomotor Trial. Neurorehabil Neural Repair 21:25–35

Dobkin BH (2005) Clinical practice. Rehabilitation after stroke. N Engl J Med 352:1677–1684

Ebersbach G, Sojer M, Valldeoriola F, Wissel J, Muller J, Tolosa E, Poewe W (1999) Comparative analysis of gait in Parkinson's disease, cerebellar ataxia and subcortical arteriosclerotic encephalopathy. Brain 122(7):1349–1355

Ferraye MU, Debu B, Pollak P (2008) Deep brain stimulation effect on freezing of gait. Mov Disord 23(Suppl 2):S489–S494

Fisher BE, Petzinger GM, Nixon K, Hogg E, Bremmer S, Meshul CK, Jakowec MW (2004) Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-lesioned mouse basal ganglia. J Neurosci Res 77:378–390

Fisher BE, Wu AD, Salem GJ, Song J, Lin CH, Yip J, Cen S, Gordon J, Jakowec M, Petzinger G (2008) The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. Arch Phys Med Rehabil 89(7):1221–1229

Forkstam C, Petersson KM (2005) Towards an explicit account of implicit learning. Curr Opin Neurol 18:435–441

Frank JS, Horak FB, Nutt J (2000) Centrally initiated postural adjustments in parkinsonian patients on and off levodopa. J Neurophysiol 84:2440–2448

Frenkel-Toledo S, Giladi N, Peretz C, Herman T, Gruendlinger L, Hausdorff JM (2005a) Effect of gait speed on gait rhythmicity in Parkinson's disease: variability of stride time and swing time respond differently. J NeuroEng Rehabil 2. doi:10.1186/1743-0003-2-23

Frenkel-Toledo S, Giladi N, Peretz C, Herman T, Gruendlinger L, Hausdorff JM (2005b) Treadmill walking as an external pacemaker to improve gait rhythm and stability in Parkinson's disease. Mov Disord 20:1109–1114

Graybiel AM (2005) The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol 15:638–644

Grimbergen YA, Munneke M, Bloem BR (2004) Falls in Parkinson's disease. Curr Opin Neurol 17:405–415

Guadagnoli MA, Leis B, Van Gemmert AW, Stelmach GE (2002) The relationship between knowledge of results and motor learning in Parkinsonian patients. Parkinsonism Relat Disord 9:89–95

Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, Shibasaki H (1999) Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. Brain 122(7):1271–1282

Hausdorff JM (2005) Gait variability: methods, modeling and meaning. J NeuroEng Rehabil 2. doi:10.1186/1743-0003-2-19

Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL (1998) Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. Mov Disord 13:428–437

Hausdorff JM, Edelberg HK, Mitchell SL, Goldberger AL, Wei JY (1997) Increased gait unsteadiness in community-dwelling elderly fallers. Arch Phys Med Rehabil 78:278–283

Hausdorff JM, Lowenthal J, Herman T, Gruendlinger L, Peretz C, Giladi N (2007) Rhythmic auditory stimulation modulates gait variability in Parkinson's disease. Eur J Neurosci 26:2369–2375

Hausdorff JM, Rios D, Edelberg HK (2001) Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil 82:1050–1056

Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N (2003) Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res 149:187–194

Herman T, Giladi N, Gruendlinger L, Hausdorff JM (2007) Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. Arch Phys Med Rehabil 88:1154–1158

Herzog J, Volkmann J, Krack P, Kopper F, Potter M, Lorenz D, Steinbach M, Klebe S, Hamel W, Schrader B, Weinert D, Muller D, Mehdorn HM, Deuschl G (2003) Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 18:1332–1337

Hesse S, Bertelt C, Jahnke MT, Schaffrin A, Baake P, Malezic M, Mauritz KH (1995) Treadmill training with partial body weight support compared with physiotherapy in nonambulatory hemiparetic patients. Stroke 26:976–981

Hirasaki E, Moore ST, Raphan T, Cohen B (1999) Effects of walking velocity on vertical head and body movements during locomotion. Exp Brain Res 127:117–130

Kelly SW, Jahanshahi M, Dirnberger G (2004) Learning of ambiguous versus hybrid sequences by patients with Parkinson's disease. Neuropsychologia 42:1350–1357

Keus SH, Bloem BR, Hendriks EJ, Bredero-Cohen AB, Munneke M (2006) Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. Mov Disord 22:451–460

Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349:1925–1934

Kurtais Y, Kutlay S, Tur BS, Gok H, Akbostanci C (2008) Does treadmill training improve lower-extremity tasks in Parkinson disease? A randomized controlled trial. Clin J Sport Med 18:289–291

Laufer Y, Dickstein R, Chefez Y, Marcovitz E (2001) The effect of treadmill training on the ambulation of stroke survivors in the early stages of rehabilitation: a randomized study. J Rehabil Res Dev 38:69–78

Lim I, Van WE, de Goede C, Deutekom M, Nieuwboer A, Willems A, Jones D, Rochester L, Kwakkel G (2005) Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. Clin Rehabil 19:695–713

Liotti M, Ramig L (2003) Improvement of voicing in patients with Parkinson's disease by speech therapy. Neurology 61:1316–1317

Liotti M, Ramig LO, Vogel D, New P, Cook CI, Ingham RJ, Ingham JC, Fox PT (2003) Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. Neurology 60:432–440

Martinez-Martin P (1998) An introduction to the concept of "quality of life in Parkinson's disease". J Neurol 245(1):S2–S6

Mathiowetz V, Haugen JB (1994) Motor behavior research: implications for therapeutic approaches to central nervous system dysfunction. Am J Occup Ther 48:733–745

Maurer C, Mergner T, Xie J, Faist M, Pollak P, Lucking CH (2003) Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. Brain 126:1146–1163

Miyai I, Fujimoto Y, Ueda Y, Yamamoto H, Nozaki S, Saito T, Kang J (2000) Treadmill training with body weight support: its effect on Parkinson's disease. Arch Phys Med Rehabil 81:849–852

Miyai I, Fujimoto Y, Yamamoto H, Ueda Y, Saito T, Nozaki S, Kang J (2002) Long-term effect of body weight-supported treadmill training in Parkinson's disease: a randomized controlled trial. Arch Phys Med Rehabil 83:1370–1373

Morris ME, Iansek R, Matyas TA, Summers JJ (1994) The pathogenesis of gait hypokinesia in Parkinson's disease. Brain 117(Pt 5):1169–1181

Muir GD, Steeves JD (1997) Sensorimotor stimulation to improve locomotor recovery after spinal cord injury. Trends Neurosci 20:72–77

Nakamura T, Meguro K, Sasaki H (1996) Relationship between falls and stride length variability in senile dementia of the Alzheimer type. Gerontology 42:108–113

Nieuwboer A, Kwakkel G, Rochester L, Jones D, Van WE, Willems AM, Chavret F, Hetherington V, Baker K, Lim I (2007) Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. J Neurol Neurosurg Psychiatry 78:134–140

Oka H, Mochio S, Onouchi K, Morita M, Yoshioka M, Inoue K (2006) Cardiovascular dysautonomia in de novo Parkinson's disease. J Neurol Sci 241:59–65

Pelosin E, Faelli E, Lofrano F, Marinelli L, Bove M, Ruggeri P, Abbruzzese G (2007) Treadmill training improves functional ability and cardiopulmonary capacity in stable Parkinson's disease. Mov Disord 22:S175

Perretta JG, Pari G, Beninger RJ (2005) Effects of Parkinson disease on two putative nondeclarative learning tasks: probabilistic classification and gambling. Cogn Behav Neurol 18:185–192

Persico AM, Reich S, Henningfield JE, Kuhar MJ, Uhl GR (1998) Parkinsonian patients report blunted subjective effects of methylphenidate. Exp Clin Psychopharmacol 6:54–63

Petzinger GM, Walsh JP, Akopian G, Hogg E, Abernathy A, Arevalo P, Turnquist P, Vuckovic M, Fisher BE, Togasaki DM, Jakowec MW (2007) Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci 27:5291–5300

Pohl M, Rockstroh G, Ruckriem S, Mrass G, Mehrholz J (2003) Immediate effects of speed-dependent treadmill training on gait parameters in early Parkinson's disease. Arch Phys Med Rehabil 84:1760–1766

Protas EJ, Mitchell K, Williams A, Qureshy H, Caroline K, Lai EC (2005) Gait and step training to reduce falls in Parkinson's disease. NeuroRehabilitation 20:183–190

Ramig LO, Fox C, Sapir S (2004) Parkinson's disease: speech and voice disorders and their treatment with the Lee Silverman Voice Treatment. Semin Speech Lang 25:169–180

Ramig LO, Sapir S, Countryman S, Pawlas AA, O'Brien C, Hoehn M, Thompson LL (2001a) Intensive voice treatment (LSVT) for patients with Parkinson's disease: a 2 year follow up. J Neurol Neurosurg Psychiatry 71:493–498

Ramig LO, Sapir S, Fox C, Countryman S (2001b) Changes in vocal loudness following intensive voice treatment (LSVT) in individuals with Parkinson's disease: a comparison with untreated patients and normal age-matched controls. Mov Disord 16:79–83

Rubenstein TC, Giladi N, Hausdorff JM (2002) The power of cueing to circumvent dopamine deficits: a review of physical therapy treatment of gait disturbances in Parkinson's disease. Mov Disord 17:1148–1160

Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM (2003) Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. J Neurol Sci 212:47–53

Skidmore FM, Patterson SL, Shulman LM, Sorkin JD, Macko RF (2008) Pilot safety and feasibility study of treadmill aerobic exercise in Parkinson disease with gait impairment. J Rehabil Res Dev 45:117–124

Smith J, Siegert RJ, McDowall J, Abernethy D (2001) Preserved implicit learning on both the serial reaction time task and artificial grammar in patients with Parkinson's disease. Brain Cogn 45:378–391

Sofuwa O, Nieuwboer A, Desloovere K, Willems AM, Chavret F, Jonkers I (2005) Quantitative gait analysis in Parkinson's disease: comparison with a healthy control group. Arch Phys Med Rehabil 86:1007–1013

Stolze H, Klebe S, Poepping M, Lorenz D, Herzog J, Hamel W, Schrader B, Raethjen J, Wenzelburger R, Mehdorn HM, Deuschl G, Krack P (2001) Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait. Neurology 57:144–146

Thurman DJ, Stevens JA, Rao JK (2008) Practice parameter: assessing patients in a neurology practice for risk of falls (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 70:473–479

Toole T, Maitland CG, Warren E, Hubmann MF, Panton L (2005) The effects of loading and unloading treadmill walking on balance, gait, fall risk, and daily function in Parkinsonism. NeuroRehabilitation 20:307–322

Tugwell P, Shea B, Boers M (2004) Evidence based rheumatology. BMJ Books, Boston, USA

Van de Crommert HW, Mulder T, Duysens J (1998) Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training. Gait Posture 7:251–263

van Hedel HJ, Waldvogel D, Dietz V (2006) Learning a high-precision locomotor task in patients with Parkinson's disease. Mov Disord 21:406–411

Werner WG, Francisco-Donoghue J, Lamberg EM (2006) Cardiovascular response to treadmill testing in Parkinson disease. J Neurol Phys Ther 30:68–73

Wu T, Hallett M (2005) A functional MRI study of automatic movements in patients with Parkinson's disease. Brain 128:2250–2259

Yoon MC, Shin MS, Kim TS, Kim BK, Ko IG, Sung YH, Kim SE, Lee HH, Kim YP, Kim CJ (2007) Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats. Neurosci Lett 423:12–17