The Gait Restorative Effects of Robotic-Assisted Gait Training for Individuals with Neurodegenerative Disease: A Review

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Abstract: *Background*: Neurodegenerative diseases and disorders present with a wide range of clinical and neuropathological symptoms caused by progressive neuronal dysfunction and eventual neuronal death. As individuals with neurodegenerative diseases experience gradual sensory, motor, and cognitive debilitation, the maintenance and recovery of a functional gait holds physiological, psychological, and financial importance. Developments in robotically-aided therapies are becoming more commonly used as a therapeutic tool for the improvement of gait characteristics and overall motor function for individuals with various gait impairments. To date, studies examining the effects of robotic-assisted gait training (RAGT) as treatment for neurodegenerative diseases, have only been performed in individuals with multiple sclerosis (MS), Parkinson's disease (PD), and progressive supranuclear palsy (PSP).

Purpose: The purpose of this review is to summarize and show trends to the efficacy of RAGT as a gait restorative and preservative modality for individuals with these neurodegenerative diseases including MS, PD, and PSP.

Results: The overall trends reported by these reviewed studies show that RAGT may be an effective therapy for producing significant improvements in multiple gait characteristics including balance, walking speed, endurance, leg strength, gait safety, and motor function for individuals with neurodegenerative disease.

Conclusion: The studies in this review suggest that RAGT therapies may be an effective substitute for, or addition to, present conventional therapies for individuals with neurodegenerative disease, however the long-term effects of this therapy are still not known for these individuals.

Keywords: Robotic-assisted gait training, robotics. neurodegenerative disease, Parkinson's disease, multiple sclerosis, progressive supranuclear palsy, gait.

Neurodegenerative diseases and disorders present with a wide range of neuropathological and clinical symptoms caused by progressive neuronal dysfunction and eventual neuronal death [1, 2]. As individuals with neurodegenerative diseases experience gradual sensory, motor, and cognitive debilitation, the maintenance of a functional gait holds physiological, psychological, and financial importance [3, 23, 39, 63].

One commonly used gait therapy for individuals with motor impairment and disability is body-weight supported treadmill training (BWSTT). This therapeutic intervention allows for the patient to practice a normal gait pattern while provided with needed body-weight support. In several systematic reviews, this therapy has been shown to help improve walking endurance, gait function, muscle strength, balance, and quality of life in individuals with neurological gait impairment [4-6]. Despite these improvements in walking ability, BWSTT is a relatively labor-intensive therapeutic modality, and recent research reported that a ≥ 3 to 1 ratio of therapist to patient is needed during BWSTT, which often beyond the staffing capability of rehabilitation facilities [7]. Developments in robotic therapies have helped to alleviate the demand for manual assistance by multiple therapists while also producing similar benefits in impaired gait characteristics for individuals with motor disability [8]. Robotic-assisted gait training (RAGT), in addition to providing the patient with body weight support, utilizes an automated exoskeleton that assists with limb movement and produces a synchronized gait pattern similar to normal gait stance, movement, and cadence [9,10]. Of additional benefit, during RAGT sessions, attending therapists are free to move around the patient, examining limb mechanics, gait, and posture, as well as providing the patient with motivation and verbal feedback [11]. While RAGT lessens the physical stress on the treating therapist, recent research reports that this therapy can both unnaturally limit the movement of the pelvis, trunk and upper limbs of treated patients, and produce a muscle activation pattern that differs from that of traditional BWSTT [12, 13].

Regardless of differences between therapeutic interventions, RAGT has been shown to produce gait improvements in both adults and children with a wide range of neural-paralytic injuries and non-neurodegenerative diseases including spinal cord injury [14], cerebral palsy [15], stroke [16], and traumatic

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brain injury [17]. With a limited number of studies testing the effects of robotic gait restorative therapies for individuals with neurodegenerative disease, to date, no review has been performed summarizing the whole of these results. For the purposes of this review, multiple sclerosis will be included with other neurodegenerative diseases due to the characteristic gradual neuropathological damage and concomitant neuromuscular disability. To date, studies examining the effects of RAGT as treatment for neurodegenerative diseases have only done so in individuals with multiple sclerosis (MS), Parkinson's disease (PD), and progressive supranuclear palsy (PSP). The purpose of this review is to summarize the efficacy of RAGT as a gait-restorative modality for individuals with neurodegenerative disease.

RAGT FOR MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, neurodegenerative autoimmune disease characterized by widespread inflammation, demyelination, and axonal damage of the central nervous system [18,19]. Individuals with MS experience complex and highly variable symptoms including coordination, balance, and strength disorders, as well as cognitive and sensory deficits that range in severity from extremely debilitating, to having minimal impact on an individual's daily life [20,21]. These symptoms most commonly begin between the ages of 20 and 40 years old, and vary widely among the 4 phenotypes of MS: relapse-remitting MS (approximately 80% of cases), secondary progressive MS (10-20% of cases), primary progressive MS (<10% of cases), and progressive relapsing MS (<5% of cases) [22].

Studies have shown that approximately 80-90% of individuals with MS experience a loss of mobility and require an assistive device for ambulation [23,24]. Motor impairments specific to the gait cycle commonly include decreased hip extension during stance phase, exaggerated hip flexion during swing phase, decreased step length and walking speed, and overall deficiencies in walking dynamics [25, 26]. These gait deficits are both highly variable among individuals, and tend to increase in severity as the disease progresses over time [27]. Additionally, patients with MS rate gait function as the single most important function affected by the disease, as the loss of independent mobility has a significantly negative impact on their social participation, quality of life, and employment [23, 28,29]. Thus the impact of effective gait therapies has the potential to have multiple benefits in lives of individuals with MS.

Due to RAGT being a relatively new gait therapy for individuals with motor disability, many studies have compared its effects with those of equal intensity protocols of therapies such as BWSTT, treadmill walking, sensory integration balance training (SIBT), and conventional physiotherapy. In a study performed by *Gandolfi et al.* testing the effects of RAGT on walking ability and balance, 22 MS patients with Expanded Disability Status Score (EDSS) of 1.5-6.5 were divided into an RAGT group, and a SIBT group, each completing 6 weeks of twice weekly sessions of their allotted therapy [30]. Both therapies were progressive in nature and individualized to the abilities of the patients. Individuals in the RAGT group completed two 15-minute walks each session that increased in walking speed (1.3-1.6 km/h) and decreased in body-weight support (20-10%) from the first walk to the second. The SIBT sessions were designed to improve multisensory input integration completion of multiple highly repetitive balance tasks. Post-test results showed significant within-group improvements in balance and step length for both the RAGT and SIBT groups. However, between-group comparisons showed no significant differences in gait speed or balance immediately after the 6-week protocol or at a 1-month follow-up as measured by the GAITRite system and Berg balance scale (BBS), respectively. Additionally, no between-group differences were found in the Sensory Organization Balance Test (SOT), Fatigue Severity Scale, Activities-specific Balance Confidence (ABC) scale, step length, cadence, or Multiple Sclerosis Quality of Life-54 assessment. Significant improvement was found in step length for the RAGT group compared to pre-test values, as well as a small improvement in gait speed. Though significant improvements were shown in a greater number of different balance tests for the SIBT group compared to the RAGT group, all measured variables for both groups returned to baseline values by the 6-month follow-up. This study suggests that RAGT is similar in efficacy to SIBT in improving balance, and may have additional benefits to the gait cycle.

In a similarly designed study, *Straudi et al.* compared the therapeutic effects of RAGT and conventional physiotherapy using the same 6-week, twice weekly exercise protocol for each therapy [31]. In this study, 16 individuals with EDSS 4.5-6.5 MS were divided into either an RAGT group (experimental), or conventional physiotherapy group (control). All RAGT sessions consisted of approximately 30 minutes of total walking time, while conventional physiotherapy concentrated on lower limb and trunk flexibility, and strengthening. Both protocols were progressive and tailored to the abilities of the subjects. Pre-test baseline functional and clinical parameters were similar between groups with the exception of step length. Post-test results for the RAGT group showed significantly greater improvements in walking endurance as measured by 6-minute walk time (6MWT), step length, cadence, and gait speed compared to the control group. Additionally, all improvements, with the exception of cadence, persisted at a 3-month follow-up. No significant improvements where seen for either group in mobility (Timed Up and Go Test), or pelvis and hip kinematics during post-test or 3-month follow-up. These results showed that RAGT may be more effective than conventional physiotherapy at increasing gait competency for individuals with MS.

Further study comparing RAGT to conventional therapies was performed by *Beer et al.* In this study 19 inpatient participants with EDSS 6.0-7.5 MS, completed 3 weeks of 5 times per week, 30-minute sessions of either RAGT (n=14) or conventional walking training (n=15) [32]. Compared to pre-test values, the RAGT group showed significant improvement in walking speed (20 meter walking test), walking endurance (6MWT), and knee-extensor strength, while the group that completed the conventional walking training only showed significant improvement in walking speed. Additionally, both groups showed a significant improvement in activity of daily living (ADL) assessment using the Extended Barthel Index. Comparison of the two groups showed a moderate to large effect size difference favoring the RAGT group in walking distance, speed, and knee-extensor strength, although this difference did not reach statistical significance. Despite these improvements in activities of daily living and gait, all outcome measures returned to baseline values by the 6-month follow-up.

These results are in direct contrast to those found by *Vaney et al.*, which also compared the effects of RAGT and conventional physiotherapy for individuals with MS [33]. However, subjects in this study possessed a lower baseline EDSS scored of 3-6.5 and completed a less intensive protocol of 6-10, half-hour sessions of either RAGT (n=26) or conventional walking training (n=23), for 3 weeks. Post-test results showed that while both groups improved in gait speed and quality of life, greater improvements were found in the conventional physiotherapy group.

Further study by *Straudi et al.* compared the effects of twice-weekly sessions of either RAGT or conventional walking therapy for individuals with moderate to severe MS and EDSS scores of 6-7 [34]. Although sessions in both groups were held less frequently than those in studies by *Beer et al.* and *Vaney et al.,* participants in each group of this study completed a total of 6 weeks of gait therapy. Post-study results showed a statistically significant improvement in both balance and walking endurance for the RAGT only, while minimal effects were seen in fatigue levels of either group. However, at the time of this review, this study is ahead of print, and will not be included in Table **1**.

Additional study comparing the efficacy of RAGT to conventional therapy was performed by *Schwartz et al.* in which 22 MS patients with EDSS scores of 5-7 completed 4 weeks of 2-3 times per week of RAGT (n=15) or conventional walking training (n=17) sessions lasting approximately 30-45 minutes each [35]. Immediate post-study results show that individuals that completed conventional walking training improved significantly in both walking endurance and gait speed as measured by 6MWT and 10-meter walk test (10MWT), respectively. However these improvements returned to baseline values by the 6-month follow-up. Only subjects in the RAGT group showed significant improvement in gait efficiency, as measured by the Timed Up and Go test (TUG), and these results remained at significant levels at the 6-month follow-up. Significant improvements were found in balance function as measured by the Berg Balance Test (BBT) for both groups immediately following treatment, though these values were reduced to insignificant levels by the 6-month follow up. Comparison of between-group mean change values for gait characteristics and balance function showed no significant difference between the therapeutic approaches, suggesting that neither therapy held any significant therapeutic outcome advantage.

Similar results supporting a lack of therapeutic advantage for RAGT compared to more conventional therapies were found by *Lo et al.* [36]. This study utilized a cross-over design during which a total of 13 MS patients with an average EDSS score of 4.9 completed twice weekly 30-40 minute RAGT or non-robotic-assisted BWSTT for 3 weeks. While post-test study results showed that both groups showed statistically significant improvements in walking speed and walking endurance, no statistical difference was found in outcomes between groups.

Table 1: RAGT and Patients with Multiple Sclerosis

Study	Exercise Protocol	Subjects	Results (Stat. Sign. In Bold)
Gandolfi *et al.* [30]	RAGT: 2x/wk, 6 weeks (15 minute walks x2/session)	n=12, MS, (mean EDSS=3.96)	**Inc. Balance** [1,2](BBS, SOT) **Inc. Step Length**[1,2] Gait Speed
	SIBT: 2x/wk, 6 weeks (50 min/session)	n=10, MS, (mean EDSS=4.35)	**Inc. Balance** [1] (BBS, SOT) **Inc. Step Length**[1,2]
Straudi *et al*. [31]	RAGT: 2x/wk, 6 weeks. (Exp. Group)	n=8, MS, (mean EDSS=5.8)	**Inc.gait speed** [3] (6MWT) **Inc. Step Length**[3] **Inc. RAGT Walking Endurance**[3] Mobility (TUG) Pelvis and Hip Kinematics
	Conv. Physio.: 2x/wk, 6 weeks. (Control)	n=8, MS, (mean EDSS=5.7)	No statistically significant gains in any variable
Beer *et al.* [32]	RAGT: 5x/wk, 3wks, 30 min.	n=14, MS (mean EDSS 6.5)	**Inc. Walking speed** [1,2](20 meter walking test) **Inc. Walking distance** (6MWT) **Inc. Knee-extensor strength** **Inc. ADL**[1,2]
	Conv. Physio.: 5x/wk, 3wks, 30 min.	n=15, MS (mean EDSS 6.5)	**Inc. Walking Speed** [1,2] **Inc. ADL** [1,2]
Vaney C *et al.* [33]	RAGT: Ave. 9 session over 3 weeks.	n=26, MS, (mean EDSS 5.9)	Inc. Walking Speed [4]
	Conv. Physio.: Ave. 8 sessions over 3 weeks.	n=23, MS, (mean EDSS 5.7)	Inc. Walking Speed [4]
Schwartz *et al*. [35]	RAGT: 2-3/wk, 4wks	n=15, MS, (mean EDSS 6.2)	**Inc. Gait Efficiency** [2,5] (TUG) **Inc. Balance** [2,6]
	Conv. Physio.: 2-3/wk, 4wks	n=17, MS, (mean EDSS 6.0)	**Inc. Gait speed** [1,2] (6MWT) **Inc. Endurance** [1,2] (10MWT) **Inc. Balance** [2,6]
Lo *et al*. [36]	RAGT: 2-3x/wk (6 sessions)	n=13, MS, (mean EDSS 4.9) (Crossover study design)	<u>Both Interventions:</u> **Inc. Walking Speed**[2] **Inc. Walking Endurance**[2]
	Non-robotic BWSTT: 2-3x/wk (6 sessions)		
Ruiz *et al*. [37]	Combined RAGT and non-robotic BWSTT (20 minutes each per session) 2x/wk, 8wks	n=7, MS, (median EDSS 5.0)	**Inc. Walking Endurance** (6MWT) **Inc. Balance** (FRT)

[1]Returned to baseline by 6-month follow-up.
[2]No significant differences between groups.
[3]Significantly greater improvements than conventional physiotherapy group.
[4]Greater improvements were found in the conventional physiotherapy group.
[5]Remained at significant levels at the 6-months follow-up.
[6]Reduced to insignificant levels by the 6-months follow up.

Additional study on the effects of RAGT on gait and balance was performed by *Ruiz et al.* during which 7 individuals with relapse remitting and primary progressive MS (EDSS score 3.5-6) were divided into 2 groups [37]. One group immediately began twice weekly combined RAGT/non-robotic BWSTT sessions of up to 40 minutes each for 2 months. A second group completed the same exercise protocol after the first group was completed, as to provide initial control group comparison. This rehabilitation protocol however differed from others as each session consisted of 20 minutes of RAGT, immediately followed by 20 minutes of non-robotic BWSTT. Each rehabilitation protocol was progressive in nature and individualized to the abilities of each subject. Post-study results showed significant improvements in both walking endurance (6MWT), and balance, measured by the functional reach test (FRT) for both groups compared to their independent pre-test values. Additionally, subjects in the first intervention group showed significantly greater endurance and balance than those serving as a control in the delayed intervention group. However, between-group comparisons may be misleading, as differences were present between groups in baseline values for EDSS and motor function test scores. Regardless of possible between-group comparison inaccuracies, pre-post test comparisons showed that combining RAGT with conventional BWSTT may significantly improve both gait endurance and balance.

RAGT AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a common neurodegenerative disease characterized by both dopaminergic and nondopaminergic deficiencies that cause motor symptoms such as resting tremor, bradykinesia, impaired postural reflexes, unexpected voluntary movement, and rigidity, as well as non-motor symptoms such as pain, tingling, and deficiencies in memory function [38-40]. Most common in older middle-aged and elderly individuals, the concomitance of these symptoms result in a highly abnormal gait pattern characterized by increased double-limb support phase time, reduced gait speed, increased postural sway, decreased stride length, and freezing of gait (FOG) [41-43]. The severity of these motor symptoms is commonly measured by the Unified Parkinson's Disease Rating Scale section 3 (UPDRS-III) and the Hoehn and Yahr Scale (HYS) [44, 45]. Exercise and physiotherapy have long been studied as non-pharmacological treatments for the physical symptoms of PD. However despite ample research in multiple intervention modalities, to date there is no clear evidence proposing a superior therapeutic approach [46, 47]. Several studies have been performed examining the efficacy of RAGT in improving gait characteristics [46-52]. However, while many of these studies report improvements in balance, walking speed, FOG, cadence, and walking endurance, [48-53] contrasting studies report that RAGT is comparable to or less effective than conventional physiotherapy and other non-robotic treatments [54,55].

Preliminary study by *Lo et al.* examined the effects of a 5-week, twice weekly RAGT protocol for 4 patients with PD [48]. Subjects in this study had a mean age of 63.3 years, a mean disease duration (DD) of 6.2 years, and a mean UPDRS-III score of 20.8. All RAGT session were progressive in nature and tailored to the abilities of the subjects. Post-study results showed a 20.7% decrease in average FOG episodes as well as a 13.8% improvement in the Freezing of Gait-Questionnaire (FOG-Q), and a 41.7% improvement in severity of FOG. Additionally, results showed 24.1% and 23.8% increases in walking speed and stride length, respectively. These findings are similar to those found in a case by *Ustinova et al.* examining the use of RAGT with a 67 year old woman with PD [49]. This subject, possessing HYS stage III PD, with a UPDRS-III score of 40, and DD of 8 years, completed 2 weeks of 3x/week RAGT for 20-45 minutes each session. Post-interventions results showed an almost 2-fold increase in gait velocity, and 62% faster gait initiation. Additionally, results showed a 56% decrease in turning time, as well as increases in cadence and stride length of 66% and 27%, respectively. However, little to no effect was seen in step width or gait symmetry. Although these gait improvements accompanied a 7-point decrease in UPDRS-III score immediately after training, all gait parameters except for stride length, gait cadence, and turning time, returned to near pre-treatment values by the 15-week follow-up.

Other studies examining the efficacy of RAGT in individuals with PD compared the application of similar protocols of both RAGT and commonly used physiotherapy techniques. One such study performed by *Picelli et al.* evenly divided 36 individuals with a mean HYS stage of 2.7, a mean UPDRS-III score of 17.4, a mean DD of 7 years, and mean age of 68.4 years into 2 groups [50]. One group completed 3, 10-minute long RAGT sessions, held 3x/week, for 4 weeks. A second group completed 4 weeks of thrice weekly conventional physiotherapy sessions focused on gait training and active joint mobilization at the same session frequency. Results from this study showed that individuals who completed the RAGT protocol experienced statistically significant improvements in gait speed, stride length, cadence, single-and double-support duration, walking endurance, Parkinson's Fatigue Scale (PFS), and UPDRS compared to pre-test within-group means, and persisted at significant levels during a 1-month follow-up. However no statistically significant improvements were found in any variable for individuals who completed the conventional physiotherapy protocol. Additionally, a statistically significant positive difference between interventions favoring the RAGT was found in gait speed, walking endurance, stride length, and single-and double-support duration. It should be noted however, that although this study reported a statistically significant improvement in gait speed and endurance of 0.12m/s (10MWT) and 45.8 meters (6MWT) respectively, previous research suggests that minimum changes of 0.25m/s and 83 meters can be considered clinically significant [56].

Another study by *Picelli et al.* comparing RAGT to conventional physiotherapy utilized the same 4-week, 3 times weekly therapy protocol in 31 individuals with a mean age of 68.3, a mean HYS stage of 3.45, a mean UPDRS-III score of 46.8, and a mean DD of 7.5 years [51]. Individuals in the RAGT group (n=16) completed two, 15-minute walks per session, while individuals in the conventional therapy group (n=15) completed 10 non-balance specific mobilization, coordination, and stretching exercises performed in supine, standing, and sitting positions. Post-study results showed that the RAGT group scored significantly greater than the conventional physiotherapy group on all examined balance and gait tests including BBS, TUG, 10MWT, Activities-Specific Balance Confidence scale (ABC), Nutt's rating (NUTT), and UPDRS-III immediately after the 4-week treatment period, as well as at the 1-month post-treatment follow-up.

While previous studies have examined the efficacy of RAGT compared to conventional physiotherapy, further study by *Picelli et al.* compared the efficacy of RAGT, non-robotic treadmill training, and conventional physiotherapy [52]. In this study, 60 subjects with mild to moderate PD, a mean age of 68.3 years, a mean DD of 6.8, a mean of HYS of 3, and a mean UPDRS-III of 18 were divided evenly (n=20 each) and completed 4 consecutive weeks of thrice weekly sessions in one of the allotted interventions. Treadmill training sessions were performed without body-weight support and consisted of three, 10-minute walks at 1, 2, and 3 km/h speeds with 5 minutes rest between each walk. Physical therapy sessions consisted of 3 consecutive 10-minute slow reversal, antagonistic reversal, and rhythmic initiation exercises aimed at improving pelvic motion and control, and based on the proprioceptive neuromuscular facilitation approach [57]. The RAGT treatment consisted of three, 10-minute walks completed at the same walking speed as the treadmill group, however subjects were provided with 20%, 10%, and 0% body-weight support during each respective walk of a session. Results showed that the group that completed RAGT displayed significantly greater improvements in gait speed, walking endurance, stride length, balance, PFS, and UPDRS than the group that completed the conventional physiotherapy. Additionally, there was a significantly greater improvement in balance in the RAGT group compared to both the treadmill and conventional therapy groups. Both the RAGT and treadmill training groups showed significantly greater improvement in gait speed, walking endurance, and stride length compared to conventional physiotherapy. However, no significant difference was found between the RAGT and treadmill training groups for any variables other than balance.

A similar study comparing the efficacy of RAGT to that of an equal intensity non-body weight supported treadmill training protocol was performed by *Sale et al.* [53]. In this study, 20 individuals with a mean age of 69.4 years, a mean DD of 8.6 years, HYS range 2.5-3.5, and a mean UPDRS-III score of 54.9 PD, completed 4 consecutive weeks of 5x/week sessions of the allotted intervention. In contrast to the previous study, participants in this study completing the treadmill training protocol also received video biofeedback from a "visual biofeedback screen" included to provide the subject with additional stimulus and customization to the goals of the patient/therapist. While the reported results from this study were relatively limited compared to other similar studies, post-test values showed significant improvements in gait speed, step length, and stride length in the RAGT group while no significant improvements were found in the treadmill training group. This is in sharp contrast to the findings of the above study by *Picelli et al*. [52]. However, similar to this study, there was no statistical difference between the scores of the interventions groups.

Comparable results were found by *Carda et al.* testing differences in efficacy between RAGT and conventional treadmill training for people with PD [54]. Subjects of this study had a mean age of 67.4 years, a mean DD of 3.7 years, a mean HYS stage of 2.2, and a mean UPDRS-III of 10.5. The 28 participants were evenly divided into either the RAGT group or the treadmill group, both of which completed 4 consecutive weeks of 3x/week sessions. Sessions for each group consisted of 2 separate 15-minute walks that increased in walking speed as the session progressed. For the RAGT group, body-weight support was also decreased from 50% to 30% for the second walk. Post-treatment results showed significant improvements in all gait performance tests including 10MWT, 6MWT, and the TUG, with no significant difference between the results of each treatment. Also, improvements were found in

Table 2: RAGT and Patients with Parkinson's Disease

Study	Exercise Protocol	Subjects (*) denotes combined group mean	Results (Stat. Sig. results in bold)
Lo *et al*. [48]	RAGT: 3x/wk, 5wks	n=4, PD, mean: UPDRS-III=20.8, DD= 6.2y, age=63.3y	**Dec. FOG** **Inc. Gait Speed** **Inc. Stride Length**
Ustinova *et al*. [49]	RAGT: 3x/wk, 2wks	n= 1, PD, mean: UPDRS-III=40, HYS=3, DD=8y, age=67y	**Inc. Gait Speed** **Inc. Step Initiation Speed** **Inc. Step Cadence**[1] **Inc. Stride Length**[1] **Dec. Turning Time**[1] UPDRS-III
Picelli *et al*. [50]	RAGT: 3x/wk, 4wks	n=18, PD, mean: UPDRS-III=17.33, HYS=2.7, DD=6.6y, age=68.1y	**Gait Speed** [2,3] **Stride Length** [2,3] **Cadence** [2] **Single-/Double-Support Duration** [2,3] **Walking Endurance** [2,3] **Parkinson's Fatigue Scale** [2] **UPDRS** [2]
	Conv. PT: 3x/wk, 4wks	n=18, PD, mean: UPDRS-III=17.5, HYS=2.7, DD=7.4, age=68.7	No statistically significant improvements in any variable.
Picelli *et al*. [51]	RAGT: 3x/wk, 4wks	n=16, PD, mean: UPDRS-III=46.3, *HYS=3.45, *DD=7.5y, *age=68.3	**Balance (BBS, TUG, ABC, NUTT)** [2,3] **Gait Speed** [2,3] **UPDRS-III** [2,3]
	Conv. PT: 3x/wk, 4wks	n=15, PD, mean: UPDRS-III=47.2, *HYS=3.45, *DD=7.5y, *age=68.3	No statistically significant improvements in any variable
Picelli *et al*. [52]	RAGT: 3x/wk, 4wks	n=20, PD, mean: UPDRS-III=18, *HYS=3, DD=6.5y, age=68.5y	**Gait Speed** [3] **Walking Endurance** [3] **Stride Length** [3] **Balance** [3,4] **Parkinson's Fatigue Scale** [3] **UPDRS** [3]
	Treadmill: 3x/wk, 4wks	n=20, PD, mean: UPDRS-III=17.8, *HYS=3, DD=7y, age=68.8y	**Gait Speed** [3] **Walking Endurance** [3] **Stride Length** [3]
	Conv. PT: 3x/wk, 4wks	n=20, PD, mean: UPDRS-III=18.3, *HYS=3, DD=6.8y, age=67.6y	No significant improvements in any variable.
Sale *et al*. [53]	RAGT: 5x/wk, 4wks	n=10, PD, mean: UPDRS-III=53.6, HYS=2.5-3.5, DD=8.4y, age=70.3y	**Gait Speed**[5] **Step Length**[5] **Stride Length**[5]
	Treadmill: 5x/wk, 4wks	n= 10, PD, mean: UPDRS-III=56.2, HYS=2.5-3.5, DD=8.7y, age=68.4y	No statistically significant improvements in any variable
Carda *et al*. [54]	RAGT: 3x/wk, 4wks	n=14, PD, mean: UPDRS-III=10.3, HYS=2.2, DD=3.7y, age=67.9y	<u>Both Groups:</u> **Gait Speed** [5] **Walking Endurance** [5,6] **Balance** [5] (TUG) UPDRS-III [5] FS-12 Questionnaire [5]
	Treadmill: 3x/wk, 4wks	n=14, PD, mean: UPDRS-III=10.7, HYS=2.2, DD=3.7y, age=66.9y	
Picelli *et al*. [55]	RAGT: 3x/wk, 4wks	n=33, mean: UPDRS-III=38.0, HYS=3, DD=7.5y, age=68.2y	<u>Both Groups:</u> **Balance** [5,6] (BBS, ABC, and TUG) **UPDRS-III** [5,6]
	Balance Training: 3x/wk, 4wks	n=33, mean: UPDRS-III=40.0, HYS=3, DD=8.3y, age=69.7y	

[1]Results persisted at 15-week follow-up.
[2]Results persisted at 1-month follow-up.
[3]Significantly greater results than conventional physiotherapy group.
[4]Significantly greater results than treadmill group.
[5]No significant differences in results between groups.
[6]Results persisted at 3 and 6-month follow-up.

Table 3: RAGT and Patients with Progressive Supranuclear Palsy

Study	Exercise Protocol	Subjects	Results
Sale *et al*. [68]	RAGT:5x/wk, 4wks	n=5, PSP, mean: age=67.8, DD= 3.6 yrs PSPRS=32.0	Inc. Gait Speed [1] Imp. Cadence[1] Imp Step Length[1] Dec. Step Width[1]

[1]Statistically insignificant.

UPDRS-III and the FS-12 Questionnaire for both groups, however within- and between- group differences were insignificant. Interestingly, resulting improvements for both groups on the 6MWT remained at significant levels for the 3- and 6-month follow-up.

While most studies compare the efficacy of RAGT with that of conventional physiotherapy or treadmill training, only one has compared it to a balance-specific training protocol. This most recent study by *Picelli et al.* evenly divided 66 PD patients with a mean age of 69 years, a mean DD of 7.9 years, a mean HYS stage of 3, and a mean UPDRS-III score of 39, into either an RAGT group or a balance training group [55]. The RAGT sessions consisted of 3, 10-minute walks of progressively increasing speeds (1.0- 2.0 km/h) and decreasing body-weight support (20-0%) over the course of each session. The balance training sessions consisted of 3, 10 minute bouts of body stabilization, postural control, and body-weight transfer exercises. Both groups completed 4 consecutive weeks of 3x/weekly sessions. Post-study results showed statistically significant improvements for both groups in balance via BBS, ABC, and TUG, as well as motor function via UPDRS-III both immediately after treatment and at 1-month follow-up, compared to pre-treatment values. However, no there were no significant difference in these improvements between groups.

RAGT AND PROGESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) is a relatively rare neurodegenerative disease that causes slow but continuous atrophy of multiple brain structures including the frontal lobes, pontine nuclei, thalamus, palliidum, midbrain, subthalamic nucleus and periaqueductal gray matter [58, 59]. Though the atrophic effects are typically structure-specific, the clinical and neuropathological presentations of PSP are highly variable [60]. Gait-specific motor symptoms typically present after middle-age, and include a shuffling gait, balance impairments and FOG [61-63]. Disease progression is commonly measured using either UPDRS, or the recently developed Progressive Supranuclear Palsy Rating Scale (PSPRS) [64]. Historically, non-pharmacological treatments for the motor symptoms of PSP have centered on reducing the frequency of falls, maintaining a functional gait, and improving patient independence through various balance and locomotor training physical therapy techniques [65-68]. However, due to the progressive nature of PSP, functional gains are often short-lived.

To date, only one study has shown the effects of an RAGT protocol as treatment for individuals with PSP. This study performed by *Sale et al.* examined an intensive 5x/wk, 4-week RAGT protocol in 5 PSP patients with a mean age of 67.8, a mean DD of 3.6 years, and a mean PSPRS of 32.0 [68]. The RAGT protocol was progressive in nature, as provided body-weight support decreased and treadmill speed increased over the course of treatment, dependent on the abilities of the subjects. Post-study results showed an average increase in gait speed of 15%, a 23% improvement in walking cadence, a decrease in step width of 9%, and an 11-35% improvement in step length. However, analysis of these improvements showed they did not reach statistically significant levels. Due to the paucity of research performed on the effects of RAGT for individuals with PSP, as well as the small sample size and lack of a control group of the presented study, no defensible conclusions can be drawn to treatment efficacy.

DISCUSSION

This review presents research performed on the therapeutic effects of RAGT therapies for adults with neurodegenerative diseases, specifically, MS, PD, and PSP. Individuals with neurodegenerative diseases demonstrate complex and highly variable symptoms including coordination, balance, and strength dysfunction, that ultimately affect motor function, gait, functional independence, and quality of life [3,23,68]. While there are considerable differences in the disease processes and symptom patterns of these reviewed neurodegenerative diseases, each can be characterized by the gradual debilitation of sensory, motor, and cognitive abilities.

Therapeutic robotic systems have been shown to provide patients with body weight support, as well as a synchronized stepping pattern similar to that of normal gait stance, rhythm, and motion [9,10]. Although the use of robotics has been shown to aid in the gait rehabilitation of individuals with neuromotor impairment, some studies have reported that these robotically aided movements may not be as beneficial or conducive to elicitation of a natural gait cycle as previously predicted [12,13]. However, RAGT therapies may provide specific benefits to the therapeutic process due to their relatively low labor-intensivity for therapists, and their ability to provide a consistent, repetitive step motion for the patient [8].

While the amount of documented research on the effects of RAGT in individuals with neurodegenerative disease is relatively limited, there are noticeable trends and commonalities in the studies perform in individuals with MS and PD. This paper is also limited to the review of RAGT therapies in only three neurodegenerative diseases, as to date, these are the only neurodegenerative diseases in which RAGT therapies have been studied.

In the studies examining the effects of RAGT therapies on individuals with MS (Table **1**), a few outcome trends can be identified. One common trend is that all these studies, with the exception of one [33], showed statistically significant improvement in a minimum of two gait characteristics [30-32, 35-37]. Though RAGT was shown to be an effective therapy for improving gait characteristics in all reviewed studies, there are large differences in the session frequencies and therapy durations of these tested protocols. Thus no reliable conclusions can be drawn about the efficacy of specific therapeutic protocols. Furthermore, with the possible exception of one study [33], the improvements found in all gait characteristics as a result of RAGT therapies were as substantial, or more substantial than those found in the other tested therapies in the control groups. This trend may provide testament to the efficacy of RAGT therapies compared to more conventionally used therapies. However the majority of the studies that conducted follow-up assessments showed that the improvements made by the subjects in both the RAGT and control groups were short lived, and returned to pre-test values within 6 months [30,32,35].

Further outcome trends can be identified in the studies examining the effects of RAGT therapies on individuals with PD (Table **2**). These studies show that RAGT was an effective therapy for producing statistically significant improvements in gait characteristics in all tested protocols. However similar to the studies examining RAGT in individuals with MS, these studies contain large differences in the session frequencies and therapy durations. While 7 of the 8 total reviewed studies tested RAGT protocols held at three times per week, these studies vary in treatment duration from 2 weeks to 5 weeks. Moreover, the improvements found in all gait characteristic as a result of RAGT therapies were consistently better than those resulting from conventional physiotherapy protocols [50-52] and comparable to or better than those found in non-body weight-supported treadmill training protocols [52-54]. Interestingly, statistically significant improvements in the gait speed of individuals with PD were reported in every reviewed study but one as a result of RAGT [48-54]. Additionally, 5 of these studies reported significant improvements in stride length, [48-50, 52,53] 3 studies reported significant improvements in walking endurance, [50,52, 53] 4 studies reported significant improvements in UPDRS, [50-52, 55] and 4 studies reported significant improvements in balance [51,52,54,55]. Improvements in balance as a result of RAGT were also comparable to those found in balance-specific treatments [55]. Furthermore, a majority of the performed RAGT protocols resulted in improvements that persisted at significant levels at 1- 6 month follow-ups.

The study examining the efficacy of RAGT in individuals with PSP differed from the consistent significant improvement found in studies performed with individuals with MS and PD. This study failed to produce statistically significant improvements in any tested variable [68]. Furthermore, with only 5 study subjects and the lack of a control group, no reliable conclusions can be drawn from these results.

Considerable improvements continue to be made in the fields of both robotically-aided gait rehabilitation and gait-restoration for individuals with neurodegenerative disease. Research in pairing the shown benefits of RAGT and treadmill walking with a virtual reality platform has been proposed [69-71] and is a possibly promising therapeutic technique considering its proven benefits for individuals with neurodegenerative disease [72-73]. The application of a virtual reality in the therapeutic process allows for the manipulation of many characteristics in both the perceived gait and environment of the patient. Thus this may possibly provide a more comprehensive therapeutic modality for individuals with impaired physical and perceived gait characteristics.

CONCLUSION

The variability between both study protocols and study outcomes, as well as the limited amount of published research on the efficacy of RAGT for individuals with neurodegenerative disease make it difficult to state specific claims to the efficacy of the therapy. However the overall trends reported by these reviewed studies show that RAGT may be an effective therapy for producing significant improvements in multiple gait characteristics for individuals with neurodegenerative disease. While the majority of the included research studies in this review supported positive results in both MS and PD, little is known about the effects of RAGT on PSP. The studies in this review suggest that RAGT therapies may be an effective substitute for, or addition to, present conventional therapies for individuals with neurodegenerative disease, however the long-term effects of this therapy are still not known for these individuals.

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