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# Therapies for mobility disability in persons with multiple sclerosis

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## Abstract

**Introduction:** Mobility disability is one of the most widespread and impactful consequences of multiple sclerosis (MS). Disease modifying drugs (DMDs) may delay the progression of disability over time; however, there is minimal evidence supporting the efficacy of DMDs for reversing mobility disability or restoring ambulatory function in persons with MS.

**Areas covered:** This review outlines symptomatic pharmacologic and non-pharmacologic therapeutic approaches that target mobility disability with the goal of restoring and improving walking function. First, the efficacy of dalfampridine, currently the only Food and Drug Administration approved symptomatic pharmacologic agent that improves walking in persons with MS is described. Next, a review of the efficacy of non-pharmacologic therapies for improving walking, including exercise training, physical therapy, and gait training is given. Lastly, guidance on future research on mobility in MS is provided by emphasizing the importance of combinatory treatment approaches that include multiple intervention modalities, as the best treatment plan likely involves a comprehensive, multidisciplinary approach.

**Expert commentary:** There has been an increased effort to develop symptom-specific treatments in MS that directly target mobility disability; however, more research is needed to determine the efficacy of these rehabilitative strategies alone and together for improving walking in persons with MS.

### Keywords

Dalfampridine; Exercise Training; Gait Training; Mobility Disability; Multiple Sclerosis; Physical Therapy; Walking

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Declaration of interest

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## 1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) with a prevalence exceeding 1 million people in the United States and 2.5 million people worldwide [1]. The initial pathology of MS is characterized by a series of inflammatory episodes [2] that precipitates demyelination and eventual transection of axons in the CNS [2, 3, 4]; this pathology is later accompanied by loss of neurons associated with lack of neurotrophic support. The accumulation of damage over time within the CNS can manifest as physical disability, particularly mobility disability in MS [5]. In the context of this review, mobility disability is defined as an impairment in ambulation that can be expressed as a reduction in walking speed, a decrease in walking endurance, and/or reduced postural stability during walking or standing.

Mobility disability is one of the most widespread and impactful consequences of MS [6, 7, 8]. Data from a survey of 436 persons with MS indicated that 45% of patients reported mobility disability within the first month following diagnosis, with upwards of 90% of patients reporting mobility disability within ten years post-diagnosis [9]. Another study indicated that walking was most frequently rated as the bodily function of greatest importance among people with MS, and was valued more highly than vision, thinking and memory, and speech [10]. Persons with MS often report feeling frustrated, powerless, and limited by mobility disability [9]. MS-related mobility disability further has broad consequences on everyday life, including emotional well-being, activities of daily living (ADL), quality of life (QOL), and autonomy [11, 12]. Collectively, this supports the need for identifying approaches that result in meaningful improvements in mobility disability for those with MS.

One approach that has been considered for reducing mobility disability in MS involves disease-modifying drugs (DMDs). Currently, DMDs represent first-line MS treatments, and have demonstrated efficacy for reducing relapse rates and severity, as well as moderating the development of new lesions in the CNS [13]. DMDs may further slow long-term disease progression and delay the onset of neurological disability [13, 14, 15]. However, there is minimal evidence supporting the efficacy of DMDs for reversing mobility disability or restoring ambulatory function in MS [13, 14, 16]. This is not surprising, as DMDs target immune cells or immune signaling proteins for arresting disease activity and reducing its impact, but do not target other consequences of MS itself nor the factors that contribute to mobility disability, such as physiological deconditioning, impaired balance, and decreased motor control [17].

The prevalence and burden of mobility disability and the incomplete efficacy of DMDs has prompted an interest in both pharmacologic (e.g., dalfampridine) and non-pharmacologic (e.g., exercise training, physical therapy) symptomatic treatments for improving mobility in MS [18, 19, 20]. Symptomatic therapies that directly target mobility disability not only slow the progression of disability, but may even improve or restore walking function [18, 19]. To that end, a thorough understanding of the efficacy and mechanistic properties of various therapeutic strategies may support the inclusion of these approaches into the comprehensive management of mobility disability among persons with MS.

The current review highlights several treatment strategies that specifically target mobility disability, with particular focus on those that may restore mobility and walking function in MS. This review presents: (a) pharmacologic symptomatic therapies that target mobility disability; (b) non-pharmacologic approaches that target mobility disability (i.e., rehabilitation); and (c) guidelines for directing future research based on the overview of the currently available therapeutic strategies. In particular, the importance of combining therapeutic approaches in future research efforts is underscored, as any one strategy alone may not be fully effective nor address all primary determinants of mobility disability in MS. This paper is not intended to be an exhaustive review of the literature or a critical appraisal of the therapies, but rather, provide an overview of mobility-targeted therapies that may be included in the comprehensive, multi-disciplinary care of persons with MS. This approach is largely based on the presence of meta-analyses and systematic reviews that are supplemented with reporting of evidence from RCTs when particularly relevant, as a review of individual studies per approach is beyond the scope of a single review paper.

## 2. Pharmacologic Therapies

DMDs may indirectly prevent the worsening of mobility disability over long periods of time by slowing the overall rate of disease progression; however, DMDs are not intended to directly restore or improve walking ability in persons with MS. Recently, pharmacologic therapy for mobility problems in MS has moved beyond these first-generation approaches, and now focuses on targeted, symptom-specific treatments that minimize MS-related mobility disability and restore function [21]. In particular, dalfampridine represents the best-characterized pharmacologic agent that has been developed to specifically target mobility disability and improve walking ability in MS. This section provides an overview of the efficacy of dalfampridine – currently the only Food and Drug Administration (FDA) approved pharmacologic therapy for improving walking in persons with MS [22].

### 2.1 Dalfampridine

Extended-release dalfampridine (D-ER), chemically known as 4-aminopyridine, is a potassium channel blocker that was approved by the FDA in 2010 for improving walking in persons with MS [22]. The extended release formula was specially designed to maintain stable plasma concentrations of the drug when given one, 10 mg tablet twice daily (approximately 12 hours apart) [23]. This dosage is generally considered safe and is well-tolerated [*24]. An increased risk of seizures has been associated with a higher dosage, though this risk is minimal when D-ER is taken at the recommended therapeutic dose [22]. Other adverse events such as falls, urinary tract infections, insomnia, and fatigue have been reported with D-ER use, but as these events were also evident in persons not receiving D-ER (i.e., receiving a placebo), it is unclear if they were a direct consequence of treatment [*24].

Over the last ten years, the efficacy of D-ER to improve walking in persons with MS has been examined in phase I [25] through phase III [23, 26] clinical trials. One recent paper presented a pooled analysis of data from a pair of pivotal, double-blind, placebo-controlled, phase III clinical trials [23, 26] that examined the efficacy of D-ER for improving walking speed [*24]. The pooled analysis included 540 persons with MS (D-ER n = 349, mean

Expanded Disability Status Scale [EDSS] score of 5.8 ± 1.0; placebo n = 191, mean EDSS score of 5.6 ± 1.2). The efficacy of D-ER for improving walking speed was characterized by responder status – the proportion of participants who were classified as responders in the treatment group was compared to the proportion of participants who were classified as responders in the placebo group. A responder was defined as someone who had faster walking speeds on the Timed 25-Foot Walk (T25FW) at the majority of "on drug" visits compared with the fastest walking speed during "off drug" visits. Results from the pooled analysis demonstrated that the proportion of responders in the D-ER treatment group (37.6%) was significantly greater than the proportion of responders in the placebo group (8.9%, $p < 0.0001$). Compared with baseline, the average walking speed improved 25% among individuals who were D-ER responders, whereas improvements of 7% and 6.5% were reported for D-ER non-responders and the placebo group (including responders and non-responders), respectively. Among D-ER responders, the change in walking speed did not differ by level of disability (based on EDSS scores), as improvements in walking speed of 25.6%, 22.4%, and 27.1% were reported for those with EDSS scores of ≤ 5.5, 6.0, and ≥ 6.5, respectively. Importantly, these results suggest that even those with more severe mobility disability may demonstrate an improvement in walking speed with D-ER treatment. Collectively, results of the two phase III trials indicate that D-ER may significantly improve walking speed, but only in those people who are responders.

The results summarized in the pooled analysis of the phase III trials were confirmed by one systematic review that investigated the efficacy of D-ER on gait outcomes in persons with MS [27]. The systematic review defined efficacy as the overall effect of D-ER on walking speed compared with the overall effect of placebo on walking speed (i.e., independent of responder/non-responder status). Five studies were included in the analysis that yielded a clinically meaningful [28] mean difference of 3.75 seconds in improvement on the T25FW between the groups in favor of D-ER (D-ER mean improvement = 7.48 seconds, Placebo mean improvement = 3.73 seconds). The overall proportion of responders versus non-responders was not calculated in this review, but further examination of the individual studies indicated a comparable trend with the phase III trials. Approximately one-third of the individuals in D-ER treatment groups could be classified as responders, compared with less than 10% of individuals in the placebo groups [25, 29]. Whereas most of the D-ER studies included walking speed based on the T25FW as a primary endpoint, the efficacy of D-ER to improve walking endurance (measured by the Six-Minute Walk test [6MWT]) was examined in two of the five studies. The studies reported that the recommended dose of 10mg D-ER twice daily yielded a significant beneficial, but not clinically meaningful [30], effect on walking endurance (improvements from baseline were reported as a raw increase of 39.2 m for one study [29] and a 4% increase in distance for the other study [31]).

The existing evidence supports the efficacy of D-ER for improving mobility (based on walking speed), but the beneficial effects only occur in a subset of persons with MS (i.e., responders). Responder status was not related to demographic characteristics, disease duration, level of disability, baseline walking speed, type of MS, or use of DMDs [32]. This indicates that the differences in responsiveness may be related to the underlying mechanism of action of D-ER [23]. D-ER is designed to increase nerve conduction through a blockade of voltage-dependent potassium channels in demyelinated nerve fibers [23, 33]. The

inhibition of potassium channels along demyelinated axons causes an improvement in action potential propagation along the nerve that can increase neurotransmitter release at the synapse and neuromuscular junction [34]. However, not all individuals seemingly have axons that are sensitive to the effects of D-ER, and individuals with typical central motor conduction times, indicating a lack of neuropathology in those nerves, were less likely to respond to D-ER treatment [35]. This combined with other evidence that demonstrated an effect of D-ER on nerve conduction in responders [**36] may indicate that only individuals with pathology in relevant axons (e.g. corticospinal tract) may respond to the treatment.

## 3. Non-Pharmacologic Therapies

This section contains an overview of non-pharmacologic, rehabilitative approaches for improving MS-related mobility disability. Such a focus is necessary, in part, as dalfampridine therapy yields a heterogeneous response across people with MS [37], and there is a strong interest in non-pharmacological approaches among people living with MS [38]. It should be further noted that not all symptoms that contribute to walking disability, such as muscle weakness, spasticity, cardiorespiratory deconditioning, and fatigue, are amenable to drug treatment [37, 39]. Non-pharmacologic rehabilitative approaches, including exercise training, physical therapy, and gait training, promote change in mobility disability through both central and peripheral mechanisms [40, 41]. For example, a central mechanism might include adaptation of CNS structures and connectivity [42], whereas peripheral mechanisms might include physiological improvements in aerobic capacity, muscle strength, and postural control [43, 44]. The following subsections describe several currently-available, non-pharmacologic rehabilitative approaches for improving mobility in persons with MS.

### 3.1 Exercise Training

Exercise training has been characterized as the most efficacious non-pharmacologic rehabilitative approach for mobility disability in MS [37]. Exercise training is a behavioral treatment strategy defined by planned, structured, and repeated bouts of physical activity over a prolonged period of time to improve fitness, symptoms, and/or function [45]. It is generally considered safe with minimal reported side effects or serious adverse events [37, 46]. Exercise training includes routine physical activity sessions that are comprised of aerobic exercise (e.g., walking, cycling, or jogging), resistance exercise (e.g., weight training with free weights or machines), or combinatory approaches with both aerobic and resistance exercise that may further incorporate balance or stretching activities as part of the training regimen [47]. The sessions can be described based on intensity (the amount of effort or work during exercise), duration (the length of time of an individual exercise session), and frequency (how often the exercise sessions occur).

There is evidence supporting the beneficial effects of exercise training on walking function as markers of mobility disability in persons with MS [40, 47, 48, *49]. One meta-analysis of 22 studies (randomized control trials [RCTs] and non-RCTs) investigated the effects of exercise training on markers of mobility disability in persons with MS and reported a small, yet clinically meaningful, aggregate effect size of 0.19 (95% Confidence Interval [CI] =

0.09, 0.28) standard deviations [40]; this effect size supported the efficacy of exercise training for having beneficial effects on markers of mobility disability in MS. The meta-analysis further focused on the exercise type (aerobic, resistance, combined aerobic + resistance), disability severity (indicated by EDSS scores), disease course (MS type and duration), and parameters of the exercise program (duration of each exercise session, number of sessions per week, length of program) as moderators of the overall effect size. The moderator analysis indicated minimal heterogeneity in the overall effect of exercise training on mobility disability outcomes in persons with MS as only three of the possible 13 categorical moderators were associated with the average effect size. The exercise setting, program duration, and type of MS were the only moderators of the average effect size, wherein supervised exercise interventions that were shorter than 3 months in duration, and samples that involved both persons with relapsing-remitting and progressive MS, respectively, were associated with larger beneficial effects on mobility. The exercise setting may be particularly relevant, as it indicates that compliance (maintaining exercise consistently) and guidance (properly completing the exercise) are important factors in the efficacy of exercise training, and that improvements in mobility disability may be better achieved in a supervised exercise program compared with a home-based unsupervised setting. Indeed, one study reported greater adherence for supervised exercise training than a home-based, unsupervised training program (supervised: 93%, unsupervised: 60%) in persons with MS [50]. The supervised exercise training intervention yielded a significant improvement in mobility (based on Timed Up-and-Go [TUG], Dynamic Gait Index [DGI]) compared to the unsupervised exercise training intervention; however, this difference cannot be entirely attributed to adherence as the exercise interventions involved different exercise protocols.

Another meta-analysis reviewed 13 RCTs and examined the effect of exercise training as a therapy for mobility disability in MS [48]. All participants in the included studies were considered ambulatory (with or without a walking aid, EDSS ≤ 6.5), and possible exercise interventions included aerobic exercise, resistance exercise, aquatics, and yoga. Results of the meta-analysis suggested that exercise training was efficacious for improving walking speed, indicated by a clinically-meaningful 16.5% (1.76 second) improvement in the 10-m walk test (10mWT), and walking endurance, indicated by a clinically-meaningful 19% (12.51 m) improvement in the 2-minute walk test (2MWT). There were improvements on the T25FW (0.59 second improvement) and the 6MWT (36.46 m improvement) as a result of exercise training; however, these improvements in mobility were not characterized as clinically meaningful.

Based on the results of the aforementioned meta-analyses, exercise training represents a promising non-pharmacologic approach for improving mobility in MS, but the reviewed studies generally did not exclusively pre-screen individuals for the presence of mobility disability. This may raise a number of issues when interpreting the outcomes of previous research on exercise and mobility disability in MS. One issue is the uncertainty of the efficacy of exercise training for improving mobility disability among individuals with more severe walking impairment. Another issue involves the magnitude of the overall efficacy of exercise training for improving mobility disability – the focus on persons without objective or clinical walking problems likely results in floor effects of walking improvement that is

associated with an underestimate of the actual efficacy of exercise training in more severely disabled persons. To that end, examining the efficacy of exercise training among individuals with MS who have onset of mobility disability is crucial, as these individuals have the greatest need for such an intervention.

There is emerging evidence that supports the efficacy of exercise training for improving markers of mobility in persons with MS who have moderate to severe mobility disability. One recent multi-site RCT examined the efficacy of a 6-month, multimodal exercise training (progressive aerobic, resistance, and balance training) intervention compared with an active control group on mobility outcomes in persons with MS who had substantial mobility disability (EDSS score between 4.0 and 6.0) [**51]. The minimum EDSS score of 4.0 indicated that all participants had at least some mobility impairment. Of note, this study was published after the publication of the aforementioned meta-analyses. The exercise training stimulus was selected based on previous research describing aerobic fitness, muscular strength, and postural control as primary determinants of mobility disability in MS [52], suggesting that a comprehensive exercise stimulus might be required for improving mobility disability. The exercise training intervention resulted in small to moderate improvements in walking endurance (6MWT) and peak power-output compared with the stretching, minimal resistance, attention and social contact control group. Importantly, the study demonstrated the efficacy of a multimodal exercise training intervention for improving mobility disability in persons with MS who need it the most. Such exciting, but preliminary evidence warrants further examination of multimodal exercise training as a possible treatment for MS-related mobility disability in larger samples of persons with MS with severe mobility disability.

We located one systematic review on the effect of exercise training in persons with MS who have clinical evidence of mobility disability (EDSS ≥ 5.0). The review included five studies that examined traditional exercise training (aerobic or resistance exercise) [*49]. Results from three aerobic exercise training studies indicated no significant improvements on any outcomes, including those pertaining to physical fitness and physical function (mobility, balance). Results from resistance training studies were somewhat more favorable, indicating significant improvements in muscular strength, muscular endurance, balance, fatigue, and QOL; however, no direct improvements were reported for mobility disability (walking speed or endurance). Despite the limited evidence supporting exercise training in persons with MS who have severe mobility disability, these studies substantiate the safety and feasibility of such exercise training interventions. This promotes the continued investigation of exercise training to improve walking in this specific MS cohort, and highlights that what is known about the efficacy of exercise training in persons with MS with little or no mobility impairment may not directly translate to those with substantial mobility disability. Further investigation is warranted to identify the specific parameters of exercise training that would be effective in persons with MS with severe mobility disability.

Despite proliferating evidence describing exercise-related benefits on mobility in MS at a behavioral level, considerably less is known regarding possible mechanisms of such effects. The mechanism(s) of exercise effects on mobility disability in MS are speculative and have been hypothesized to involve peripheral and/or central adaptations. Exercise training is thought to improve walking by reversing, to some extent, physiological deconditioning that

is associated with MS [53]. Indeed, exercise-training studies often demonstrate an association between improvements in physical fitness (aerobic capacity, muscle strength, postural control) and mobility. For example, an exercise training study that examined three different aerobic exercise interventions (arm ergometry, rowing, and bicycle ergometry) reported a small to moderate correlation between improvements in peak oxygen consumption (i.e., aerobic capacity) and walking endurance (6MWT) [54]. Similar results have been observed for studies involving resistance exercise training. One study of high-volume progressive resistance training in persons with MS reported an improvement in walking function (T25FW, 2MWT) that was associated with increased knee extensor and flexor strength ($p < 0.01$) [55].

By comparison, exercise training might impact mobility in persons with MS based on centrally-driven (i.e., CNS) mechanisms. Cross-sectional studies have identified an association between cardiorespiratory fitness and the volume of several deep grey matter brain structures, including the basal ganglia [56]; it should be noted that both cardiorespiratory fitness and basal ganglia volume have been associated with walking outcomes in MS [57]. There is complementary evidence of a positive relationship between the amount of moderate to vigorous physical activity (MVPA) and the volumes of grey matter, white matter, and several key brain structures (hippocampus, thalamus, caudate, putamen, and pallidum) in persons with MS [58]. Physical activity may help preserve neuronal integrity, possibly through an increase in neurotrophic factors such as brain-derived neurotrophic factor [59, 60]. Work in animal models has also indicated a relationship between exercise training and neuronal plasticity mediated through the preservation of synapses [61]. Collectively, this indicates that exercise training may mediate changes in walking function via centrally-driven mechanisms.

### 3.2 Physical Therapy

Physical therapy is one of the most common approaches for managing mobility disability in persons with MS. Physical therapy encompasses a wide range of interventions including balance exercises, neuromuscular facilitation, stretching and mobilization techniques, and often involves resistance and aerobic exercise training components [19, 62]. Physical therapy is further well-tolerated and safe with minimal negative or adverse events in persons with MS [63].

One meta-analysis examined the efficacy of physical therapy on walking outcomes in persons with MS [64]. The meta-analysis included 21 RCTs that involved 555 persons with MS (EDSS ≤ 6.5) and reported a small, but significant, improvement in walking outcomes when physical therapy was compared with usual care (ES = 0.25, 95% CI = 0.09, 0.41). The physical therapy treatments included aerobic exercise, balance and neurofacilitation, combined training, massage, resistance training, whole body vibration, and yoga. A moderator analysis compared the efficacy of the individual subgroups of treatment and revealed no significant between-group differences on mobility. There was also no difference in effect size based on walking outcome, which indicated that physical therapy had a positive effect on several different aspects of mobility disability (walking speed, walking endurance, and dynamic functional walking). Although the overall magnitude of efficacy of

physical therapy interventions on walking outcomes reported in this meta-analysis was small, it does provide some evidence that physical therapy can improve walking in persons with MS

One of the primary goals of physical therapy is to improve balance. Although balance is not a direct measure of MS-related mobility disability per se, sufficient balance is required to maintain the center of mass within the limits of stability while generating coordinated movement (i.e. while walking) [*65]. Additionally, postural instability during standing or walking may contribute to impaired mobility and the increased risk of falling and this might undermine mobility in MS [66, 67]. To that end, one meta-analysis included seven RCTs that specifically examined the efficacy of physical therapy to improve balance in persons with MS (EDSS ≤ 6.5) [*65]. An overall mean effect size was not calculated, but rather, effect sizes were calculated by intervention subgroup (i.e., by physical therapy modality including specific balance exercises, exercise training, whole body vibration, group therapy, and neurotherapeutic approaches) and by outcome measure. Among the intervention subgroups, a significant effect of physical therapy on balance was reported when it included specific balance exercises compared with a no-treatment control group (total effect size [mean of effect sizes for Berg Balance Scale, Dynamic Gait Index, Activities-specific Balance Confidence Scale, Dizziness Handicap Inventory] = 0.34, 95% CI = 0.01, 0.67), and when outpatient and at-home exercises based on an individualized problem-solving approach were compared with no treatment (total effect size [one-leg stance] = 0.63, 95% CI = 0.36, 0.91). There was no effect on balance when exercise training (resistance and aerobic training) was compared to a no-treatment control. The overall effect of group therapy on balance was not significant, but there was a significant effect on center of pressure sway velocity as an objective balance outcome measure (effect size = 1.15, 95% CI = −0.12, 2.41). Overall, the results from studies examining the effects of physical therapy on balance are promising, yet heterogeneous.

The specific mechanisms of action whereby physical therapy can improve mobility in MS seemingly vary by physical therapy approach, but many physical therapy interventions are predicated on the principles of neuroplasticity and cortical reorganization [19, 68]. Therapy acts as a stimulus that facilitates neural adaptation in the CNS to improve function and movement [19, 69]. For example, in a task-oriented approach, individuals practice multiple repetitions of a functional task. This intensive multisensory (vision, vestibular, proprioceptive) input (from the repeated practice) facilitates reorganization in the CNS, and ultimately improves task performance [70]. Within the context of physical therapy, the task-dependent plasticity in the sensorimotor network may mediate the performance of the motor task by improving motor control (e.g., increased synergistic muscle activity, improved alignment of limb segments), and ultimately mobility [68]. In addition, physical therapy may act peripherally to reduce spasticity and improve strength, both of which aid in the reduction of mobility disability [19].

### 3.3 Gait Training

There is evidence describing altered gait kinematics in persons with MS that contribute toward mobility disability [71]. To that end, gait training has been proposed as a

rehabilitative approach for reducing mobility disability in this population. Gait training therapies are designed to improve walking by enhancing gait kinematics through the repetition of the movements performed during walking, and generally includes body-weight supported treadmill training (BWSTT) and robot-assisted treadmill training (RATT). BWSTT enables an individual with substantial mobility disability to walk on a treadmill while being partially supported by a harness that is attached overhead to a pulley system [72]. Typically, treatment is assisted by therapists who manually guide the lower-limbs through the gait cycle as individuals walk on the treadmill [73]. However, these manually guided movements are difficult to consistently reproduce from session-to-session, which may undermine the efficacy and effectiveness of the therapy. Recently, RATT was developed to facilitate BWSTT. Rather than manually guiding gait, RATT delivers consistently reproducible, robot-guided movements [74]. Both therapy strategies are generally well-tolerated and safe, although minor discomfort or pain has been reported from wearing the harness [75]. The optimal intensity, duration, and frequency of treatment has yet to be identified; however, several studies with varying treatment protocols report results that support the efficacy of BWSTT and RATT for improving walking [74, 75, 76].

We located a systematic review that included eight studies (RCT and non-RCT) on the efficacy of BWSTT with or without robot-assistance in persons with MS with severe mobility disability (EDSS scores ranged from 3.0 to 8.0 across studies, but all studies included participants with EDSS scores of at least 6.5) [*49]. The duration of the training interventions ranged from 3 to 20 weeks, the length of each session was between 30 to 60 minutes, and the intensity of the exercise varied by both treadmill speed and the amount of support from the harness. Overall, the results of the systematic review indicated conflicting evidence for the efficacy of BWSTT in persons with MS. This is based on several studies that reported significant improvements in knee extensor strength, walking endurance (6MWT), and walking speed (T25FW, 10MWT, or treadmill training gait speed), compared with other trials that reported non-significant improvements in the same outcomes. However, the high level of safety provided by the harness for all levels of disability, and the potential of BWSTT to improve functional walking outcomes, suggest that BWSTT (with or without robot-assistance) is a feasible treatment approach for improving walking in persons with MS.

One meta-analysis reviewed seven RCTs that involved a total 205 persons with MS (EDSS ≤ 7.5) and compared the benefits of RATT and conventional walking therapy (CWT) [73]; CWT was defined as walking exercises completed over ground as opposed to on a treadmill. Overall, the improvements in walking speed (10MWT or treadmill training gait speed) did not significantly differ between the two intervention modalities. In contrast, the improvements in walking endurance (6MWT) were significantly different based on intervention type. The pooled mean difference between the intervention types was 14.25 m (95% CI = 3.19, 25.32) indicating a greater walking endurance benefit in response to RATT compared to CWT. Although walking endurance did significantly differ between RATT and CWT, the amount of change is less than the reported minimally important change value (22m) for walking improvement from the patient perspective [77], which precluded any definitive conclusions about the benefit of RATT over CWT.

A noteworthy benefit of BWSTT and RATT is its potential efficacy in individuals with MS across all levels of disability. One study in persons with severe MS mobility disability (EDSS scores 6 to 7.5) reported a greater improvement in walking speed (20 m walking velocity, RATT = 0.11 m/s, CWT = 0.07 m/s) and walking endurance (6MWT, RATT = 22 m, CWT = 16 m) in response to RATT compared to CWT, although these differences were not significant between the interventions [75]. One other study that also examined the efficacy of RATT for reducing mobility disability in persons with MS with severe disability (EDSS scores 6 to 7.5) reported a significant improvement in walking endurance (2MWT) following RATT [*78]. By comparison, CWT did not yield a significant improvement in walking endurance. Given the limited evidence supporting other non-pharmacologic therapies for reducing mobility disability in persons with MS with severe mobility disability, the reported potential benefits of BWSTT and RATT in this specific MS cohort are promising.

The mechanism(s) of action for gait training on mobility outcomes is unknown. The training stimuli for gait rehabilitation approaches are seemingly not intense enough to elicit fitness adaptations such as increased muscular strength or improved aerobic capacity. Instead, activity-dependent neuroplasticity involving spinal pattern generators or motor pathways in the brain is probably the primary mechanism that supports change in mobility in response to BWSTT and RATT [79]. As a task-specific (i.e. walking-specific) therapy approach, the repeated practice of walking reinforces the neural circuits that contribute to the control of gait and balance [74]. Generally, sensorimotor integration occurs in the CNS in response to the repeated stimuli, which increases motor control and improves gait. However, the therapist or robot-assisted gait may actually undermine the principles of activity-dependent neuroplasticity that they were designed to support. If too much guidance is given, the situation may become too passive so that the neural drive that stimulates change in the CNS is not sufficient [73, 74]. The restriction of gait kinematics may limit the opportunity for self-corrected gait, which may hinder the recovery process and limit potential adaptations [*49]. These issues highlight the need to establish appropriate, and standardized treatment protocols for BWSTT and RATT. More than the frequency and duration, the intensity (amount of support from the harness) and the amount of movement assistance provided by the therapist or robot may be the crucial parameters that determine change.

## 4. Conclusion

Mobility disability is one of the most burdensome consequences of MS. As such, treatment approaches that reduce mobility disability and improve walking are in high demand. Both pharmacologic and non-pharmacologic therapies yield promising results; however, the evidence collectively does not support any single approach as solely efficacious enough to be the primary therapeutic approach. For example, D-ER only improves walking speed in a subset of individuals who respond to the drug. Similarly, non-pharmacologic approaches, such as exercise training, physical therapy, and gait training, are too heterogeneous, both in their delivery (e.g., wide-range of training protocols) and in the efficacy of the response they elicit. This is, in part, associated with an incomplete understanding of the underlying mechanisms of action of these approaches. Future work that better defines the mechanisms of action of each approach could facilitate the development of individualized treatment

strategies that include a combinatory therapy approach that incorporates multiple intervention modalities.

## 5. Expert Commentary

Both the pharmacologic and non-pharmacologic therapies discussed in the current review demonstrate efficacy for improving walking in persons with MS such that all are capable of producing a positive effect. The results are often classified as clinically meaningful, but the meta-analyses and systematic reviews highlighted in this paper have reported relatively small effect sizes – this may be attributable to the notion that no single approach is likely to be powerful enough for restoring and improving walking function in MS. There is further a seemingly large amount of inter-individual variability both in the effectiveness of these treatment approaches and the magnitude of the change elicited. This variability may be related to the heterogeneity within the MS patient population (e.g., degree of CNS damage, disease type, disability severity), indicating that treatments may need to be individual-specific in addition to symptom-specific. This line of symptom-specific research, particularly as it pertains to mobility disability, is still developing, and more evidence is needed before definitive conclusions can be made. To date, research has demonstrated that these therapeutic approaches have the potential to be effective, which is an important first step, but the focus needs to shift towards optimizing these approaches to maximize both the number of people these therapies can help, and the benefits on mobility disability. In the next section, the next logical steps in this line of research are highlighted. Answering these questions will facilitate the advancement of mobility-specific treatment approaches in persons with MS.

## 6. Five-year View

The present review of current therapeutic approaches that target mobility disability in persons with MS has identified many areas that should be a focus of future research efforts. One emerging area involves the systematic examination of possible mechanisms of action that support each rehabilitation strategy. As there is a growing body of evidence supporting various therapeutic approaches for improving mobility based on behavioral outcomes, there lacks a comprehensive, mechanistic understanding of why each approach may or may not be efficacious at the biological/neural level. Evaluating such mechanisms is necessary to continue the development of targeted, efficacious treatment approaches. Particularly, the hypothesized complex mechanisms that facilitate walking improvement in response to the non-pharmacologic therapies discussed in this review warrant further investigation. Exercise training, physical therapy, and gait training likely improve walking function through two distinct, yet complementary, mechanisms (i.e., peripherally- and centrally-mediated processes). Peripherally, rehabilitative therapies can produce physiological changes such as increased muscular strength, aerobic capacity, and postural control [43, 44], leading to improvements in mobility. Concurrently, rehabilitation may induce general and selective neural adaptations in the CNS, including changes in brain structure, function, and connectivity, which may, in turn, lead to improved mobility [42]. A comprehensive model that incorporates possible peripheral *and* central mechanisms of rehabilitation that facilitate walking improvement in persons with MS would provide a useful framework for examining

how such peripheral and central processes function both independently and interactively, potentially resulting in mobility benefits. Such a framework and model could further provide guidance for adapting various rehabilitation strategies for improving specific outcomes across MS clinical courses and the mobility disability spectrum. In addition, elucidating underlying mechanisms of each therapy approach individually could provide critical information on potential additive effects of combined interventions for comprehensively rehabilitating mobility disability in MS.

Given the complex, heterogeneous pathology and disease course of MS, it is unlikely that any singular treatment approach will be sufficient to effectively improve walking in most individuals. Rather, combinatory treatment approaches that include multiple intervention modalities are likely to maximize the possible benefits gained from a single intervention. For example, as pharmacologic and non-pharmacologic therapies seemingly involve different mechanisms of action, combining these intervention types may have additive, synergistic effects on mobility. The beneficial effects of one approach, for example D-ER, may further facilitate engagement in another approach, such as exercise training, which could yield even larger adaptations and benefits on mobility. Although this line of research is still in its infancy, there is some preliminary evidence from several published abstracts that might support the efficacy of combinatory approaches for improving walking in MS. For instance, one recent case study (59 year old female with relapsing-remitting MS) reported a 15% improvement of walking speed (T25FW) when D-ER was combined with physical therapy, compared to a 7% improvement of walking speed when receiving D-ER alone [80]. By extension, another abstract described a larger study (N = 21) that compared the effects of D-ER + physical therapy to D-ER + a home-based exercise program that consisted of lower-extremity stretching on walking outcomes [81]. A significant improvement in walking endurance (2MWT) was seen after D-ER + physical therapy, whereas an improvement in walking endurance was not seen after D-ER + home-based stretching exercises (essentially a D-ER control group). A similar trend was evident for walking speed (T25FW), although results were not statistically significant. Together, these preliminary results are promising, and support the further examination of combinatory therapy approaches for comprehensively improving walking in persons with MS.

When considering combinatory therapeutic approaches for mobility disability, it is important to recognize that walking involves functional motor ability and cognitive input [82]. Indeed, there is evidence indicating an association between cognitive function and the T25FW in persons with MS [5]. This suggests that perhaps rehabilitative approaches that include a cognitive training component might result in further improvements in mobility outcomes among persons with MS; one such approach involves dual-task training [83, 84]. Dual-task training typically consists of performing cognitive tasks while simultaneously walking over a prescribed period of time. Indeed, there is evidence that supports the efficacy of dual-task training for improving functional aspects of gait among older cognitively impaired adults [85] and individuals with Parkinson’s disease and Alzheimer’s disease [83]. By comparison, the literature on dual-task training effects on mobility in persons with MS is in its infancy. Whereas several studies have examined the dual-task cost of walking in individuals with MS [86, 87, 88], there has only been one small feasibility study examining the effects of dual-task training over time on mobility outcomes in this population [89]. Nevertheless,

simultaneous cognitive-motor walking therapy represents a promising approach for reducing cognitive-motor interference during walking which may result in secondary improvements in walking performance in MS. In addition to dual-task training, it should be noted that combined exercise training and cognitive rehabilitation has been proposed as another framework involving a cognitive component for reducing mobility disability in persons with MS [84].

Future research should focus on defining training protocols that yield the greatest effect on walking ability (i.e., optimized training interventions). By systematically examining different intensities, frequencies, durations, and types of training via pilot research, optimal training protocols can be developed that maximize benefits while minimizing negative consequences such as fatigue. Importantly, training modalities should be adaptable to a variety of individuals with different clinical needs. A focus on individualized treatment approaches further is necessary considering the response heterogeneity associated with most therapeutic approaches [27, 48, *65, 73, 90, 91]. Understanding an individual's (or subset of clinically-similar individuals) responsiveness to certain symptomatic therapeutic strategies may provide valuable insight into the underlying mechanisms of that specific treatment, and enable targeted, tailored training protocols designed to optimally improve walking in a specific clinical cohort.

To achieve these research goals, high-quality studies are sorely needed that focus on different MS subtypes and levels of disability. Indeed, persons with severe mobility disability and progressive MS have been consistently underrepresented in study samples across a variety of intervention modalities [92]. In addition, precise descriptions of interventions would enhance reproducibility, and aid the comprehensive, systematic investigation of the effectiveness of a specific therapy approach. Lastly, studies should aim to use meaningful outcome measures with minimally clinically important change scores to accurately assess the efficacy of different rehabilitation strategies.

## 7. Key Issues

- Mobility disability is one of the most widespread and impactful consequences of MS.
- Less than half of the individuals who receive dalfampridine for mobility disability in MS are classified as "responders" – those who experience a significant improvement in walking speed.
- Exercise training can positively influence walking speed and endurance, yet little is known about the efficacy of this approach in clinically diverse MS-cohorts.
- Physical therapy encompasses a wide-range of rehabilitation techniques that demonstrate a small, yet significant improvement in walking outcomes, which are likely supported by increased balance and motor control.
- There is conflicting evidence regarding the effects of body-weight supported treadmill training with or without robot-assistance and conventional over ground or treadmill walking therapy on mobility in MS; however, the increased safety

provided by the support of the harness highlights the feasibility of this approach in persons with more severe disability.

- A comprehensive, systematic examination of the possible mechanisms of action that support each therapy approach is necessary to continue the development of targeted, efficacious treatments that could potentially be adapted across various MS clinical courses and levels of disability.
- A singular treatment approach may not sufficiently improve walking in most individuals; however, combinatory treatment approaches that include multiple intervention modalities may maximize the possible benefits gained from a particular intervention.
- Future research should focus on defining training protocols that yield the greatest effect on walking ability (i.e., optimized training interventions) by systematically examining different intensities, frequencies, durations, and types of training.

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