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Clinical assessment, management and rehabilitation of walking impairment in MS: An Expert Review

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Abstract

Introduction: One of the most common and life-altering consequences of Multiple Sclerosis (MS) is walking impairment. The distance, speed and Gait pattern functions are components of the International Classification of Functioning, Disability and Health (ICF) and are also predictors of dependency in terms of daily living activities in patients with MS (pwMS).

Areas covered: This article provides an overview of walking impairment in pwMS, with focus on the assessment of gait and the rehabilitation approaches.

Expert opinion: The authors recommend that pwMS undergo gait assessment integrating the ICF perspective using validated clinical outcome measures that cover spatiotemporal gait parameters. Moreover, assessment of walking speed with short walking capacity tests such as the Timed-25-Foot-Walk (T25FW) or the 10-meter-walk-test (10MWT) and tests for walking distance with middle distance tests such as the 2-Minute-Walk-Test (2MWT) and the 6-Minute-Walk-Test (6MWT). This review further highlights strategies that may restore walking function including pharmacological symptomatic treatment and non-pharmacological rehabilitation approaches such as exercise and task specific training providing an appraisal of mobility targeted therapies to be considered when planning multidisciplinary comprehensive-care of pwMS. Finally, new and novel strategies such as motor imagery and rhythmic auditory stimulation have been developed to improve walking speed and distance in pwMS.

Keywords: Ambulation, ICF, multiple sclerosis, rehabilitation, walking assessment

Article highlights

- Walking dysfunction is present in the majority of pwMS and contributes to disability and daily living restrictions.
- Walking can be categorized according to ICF, where the gait pattern is categorized at the “ICF body function level”, whereas walking capacity and perceived walking ability are categorized at “ICF activity level”.
- The abnormal MS gait pattern can most often be characterized as either paretic or spastic, cerebellar, sensory ataxia or mixed, which have consequences for the subsequent symptomatic treatment and rehabilitation strategies.

- Research and clinical practice are encouraged to apply validated walking outcomes with well-established MS specific values of clinical meaningful changes.
- Symptomatic treatment focuses on impairments and can effectively improve walking speed and gait pattern in pwMS, and should therefore be included in multi-disciplinary treatment programs.
- Exercise and task-specific training have well-established beneficial effects on walking speed and distance in pwMS.

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory, neurodegenerative disease that causes demyelination as well as axonal degeneration in the central nervous system (CNS). It is the leading cause of progressive functional impairment in young adults, affecting approximately 2.5 million people worldwide (1, 2). One of the most common and life-altering consequences of MS is walking dysfunction, caused by a variety of impairments including ataxia, muscular weakness and spasticity. Other factors that contribute to gait dysfunction and thus reduced mobility are cognition, fatigability and urinary symptoms.

Three of four persons with MS (pwMS) report reduced mobility due to impaired walking function at some point during their lifetime (3, 4). Walking impairment is perceived as the most limiting symptom, affecting the quality of life of patients (4-6). Indeed, walking performance is included when determining the level of disability in pwMS. For example, the Timed 25-Foot Walk (T25FW) is part of the Multiple Sclerosis Functional Walking Composite (MSFC), while walking performance is of major importance in the 4-7 range of the Expanded Disability Status Scale (EDSS) (7). Walking is affected in up 89% in patients with EDSS score between 4.5 and 5 and 22% in patients with EDSS between 1 and 3.5 (8).

The International classification of functioning, disability and Health (ICF) developed by the World Health Organization (WHO), conceptualizes the

functioning of patients at the levels of body function and structure, activity and participation, taking into account environmental and personal factors (see figure 1). The ICF is a tool that allows the classification and the labelling of the different components of walking that are evaluated.

ICF defines walking as “moving along the surface on foot, step by step, so that one foot is always on the ground, such as when rolling, sauntering, walking forwards, backwards or side-ways”. The distance, speed and Gait pattern (b770) are predictors of dependency in terms of activities of daily living (8) (9). The ICF proposes that, at the ICF activity, walking can be measured over short distances (d4500) and walking over long distances. We additionally proposed the evaluation of “middle” distances for the 2- and 6-minutes walking test (8). At ICF body function and structures level, gait can be measured with the analyses of temporal and spatial parameters such as cadence and step length, being part of the Gait pattern situated within neuromusculoskeletal and movement-related functions (b770). In this review, we focus on the evaluation of ICF body function and activity level related to walking dysfunction and related impairments, without including physical activity.

Moreover, this article mainly aims to provide an overview of walking impairment in pwMS, focusing on the assessment of gait within the ICF framework. Progress has been made in comprehensive care including management and rehabilitation of symptoms (7). Therefore, we also highlight strategies that may restore walking function including pharmacologic symptomatic treatment and rehabilitation interventions. We therefore provide an appraisal of mobility targeted therapies that may be included in the multidisciplinary and comprehensive care of pwMS.

2. Characteristics of gait patterns

Gait pattern is defined by the ICF as functions of movement patterns associated with walking, running or other whole-body movements including impairments such as spastic gait, hemiplegic gait and asymmetric gait.

The gait patterns in MS can be divided into four subgroups (pyramidal or spastic paresis pattern, sensory or unstable gait pattern, cerebellar gait pattern and mixed gait pattern) and are typified by decreased knee and ankle flexion, reduced dynamic stability and increased variability of movements (7, 10). Even in pwMS with low disability (EDSS <3.5) gait analysis shows slower walking speed with decreased cadence, shorter and wider steps, an increased variability in time between steps and with longer time spent in double support when compared to controls (7, 11).

From all gait parameters, reduced knee range of motion (ROM) is one of the main kinematic features of MS gait having an accuracy of 83% when differentiating gait in pwMS from controls (4). Furthermore, this kinematic feature is more pronounced in patients with a pyramidal pattern, which were also the patients that demonstrated the most marked deterioration of walking performance in the clinical walking test over one year in the Filli et al study (4).

The most common pattern in MS is asymmetric spastic paraparesis, but all pyramidal patterns can be observed. The ankle-foot paresis is the most common form, with reduced dorsiflexion and or weak push-off; and fatigability which is defined as increased weakness over time (11). The kinematic studies showed a pronounced reduction of knee flexion ROM (particularly during swing phase), resulting in increased left-right asymmetry, and also decreased excursions in the

ankle joints (4). The reduced knee ROM is associated with the slower walking speed present in MS and other pathologies.

Cerebellar gait is characterized by ataxia, poor postural control, dysmetria, dysdiachokinesia and increased variability in stride length as well as wide base of support and stooped trunk position (11). The kinematic studies showed an increased spatial variability of leg and trunk movements accompanied by increased toe height during mid swing phase that may serve as a compensatory strategy to prevent tripping or falling.

The sensory ataxia gait is clinically characterized by postural instability, heel strikes, with a higher walking cadence (number of steps per minute) (11). The kinematic is characterized by increased dynamic instability as evident by a broad - based gait and excessive trunk movements, both in the mediolateral and anteroposterior direction. These patients have increased ROM in their ankle joints, which may be a strategy for the balance control or may reflect deficient ankle stabilization in gait (4).

3. Assessing walking dysfunction

To closely monitor disease progression and changes related to symptomatic treatment and rehabilitation regular assessment of gait is recommended (12). Such testing includes evaluations of the Gait pattern, kinematics, walking speed and walking distance as further outlined below (see figure 2).

3.1 Spatiotemporal parameters:

Spatiotemporal parameters offer an evaluation of gait pattern with specific equipment for gait analysis with instrumented walkway such as the GaitRite system (13) (14), as well as using wearable inertial sensors (15). The assessment of

spatiotemporal gait parameters generates fast and reliable results regarding asymmetries and changes in gait patterns that may not be detected through a clinical walking test (16). A systematic review and meta-analysis of gait impairment in pwMS reported significant differences between the gait of pwMS and healthy controls (HC) (17). The walking impairments depend on the level of disability, but across 9 studies an average deficit of 22% was reported when compared to HC for walking with fast speed considering spatiotemporal gait parameters (17). A moderate effect of MS could be observed in stride time and step length, with pwMS displaying longer stride time and reduced step length. Duration of double support was significantly increased, as well as the step width in pwMS, which also represents balance control during walking. A shorter time spent in the swing phase as a percentage of the gait cycle and reduced cadence was also detected in MS. In addition, during maximal walking speed condition, the effect of MS on cadence was increased. The same was reported for other gait parameters, in which there is a greater differential effect as the walking speed increases. The study suggests that regardless of the low state of disability of patients (EDSS range: 1.5 to 4.5) reported in the studies, MS has a considerable effect on most of the spatiotemporal parameters, suggesting a gait deficiency in pwMS. To assist interpretation of the reliability and the minimum detectable changes in spatiotemporal gait parameters have been investigated by Decavel et al (18). For the T25FW in the fastest speed, the minimum detectable changes for pwMS were the following [for each gait parameter]: 35 % [velocity], 23 % [cadence], 17 % [stride length], 31 % [stride time], 7% [stance time], 28 % [double support], 38% [base of support].

3.2 Kinematics:

To assess additional factors that lead to changes in gait pattern and deficits in ambulation in pwMS, three-dimensional gait analysis (3D), using video cameras in a laboratory environment has been increasingly used in MS research (19). In addition, in MS kinematics was performed by means of a portable motion analysis system, which consists of small body-worn sensors housing a 3-dimensional gyroscope and tri-axial accelerometer (13). The quantitative measures acquired by a gait analysis system can be used as indicators of the disease progression and to tailor and evaluate the effects of interventions in MS (19) (13). In the Severini et al. study (20), kinematic parameters relating to hip extension, knee flexion and knee adduction observed during the swing phase were changed in pwMS, which have been associated with lower walking speed and MS disability. In addition, a high variability was found in the kinematics of the ankle joint and peak dorsiflexion during stance. A marked plantar flexion during the swing phase was also found, highlighting the importance of investigating the ankle joint kinematic pattern in MS during walking. This could indicate weakness or lack of voluntary control, but further studies are required to corroborated this hypothesis. Furthermore, greater pelvic tilt was negatively associated with walking speed, and a marked pelvis rotation during the swing phase suggested that pwMS compensate by changes in the hip, knee and ankle kinematics to promote the advancement of the lower limb (20). In another study (21), a lower mechanical work was produced at the ankle joint of the more impaired leg compared to the less impaired leg in pwMS suggests a compensatory gait strategy involving reduction in knee flexion and the decrement of knee range of motion during the swing phase which resulted in an increment of lower limb asymmetry and decreased excursion of the ankle joint, leading to the

gait deterioration over a period of 1 year (4). Although the above-mentioned kinematic parameters have been shown as the most prominent findings related to ambulation deficits in MS, kinematic values to define clinical meaningful changes are still to be defined for pwMS.

3.3 Walking short distance:

In MS clinical practice, the assessment of walking speed has frequently been done by short walking capacity tests such as the timed 25-foot walk (T25FW) and the 10-meter walk test (10MWT) (22). The T25FW is a component of the MSFC and represents the most well-characterised direct measure of specific walking disability (12), and has been selected as a primary outcome for trials concerning rehabilitation interventions, exercise training and pharmacological treatments. Short walking tests represent an ideal assessment of walking speed, being easy to administer to a wide range of patients, reliable and valid (23). From a static start, patients must walk a 25-foot/7.62-metres course as fast as possible, which may resemble relevant daily life situations (24, 25).

As a marker of gait function and its relation with functional and health indicators, the T25FW performance can be used to define ecologically valid benchmarks (26, 27). Patients who complete the T25FW in between 6 and 7.99 seconds are more likely to be unemployed, walking using a cane, require assistance with instrumental activities at daily living and had reduced community ambulation as measured by accelerometer (26). PwMS who complete the T25FW in 8 or more seconds are associated with unemployment, government health care assistance, divorce, walking with walkers and in 70% people are unable to perform instrumental activities at daily living.

Walking speed reserve, which is the increase from a preferred walking speed to maximal walking speed, reflects the capacity (what the person can do in an idealised environment) to increase speed in response to different environmental demands. Low walking speed reserve represents the incapacity of increasing walking speed, suggesting that the individual typically walks at, or close to, their maximal speed (28). Gijbels et al. (24) investigated the characteristics of short walking tests and the impact of pace instructions on walking performance in mild and moderate MS. It was found that the difference between usual and fastest speed decreases as the degree of ambulatory dysfunction increases. This finding was also evidenced by Kalron et al. (28), revealing a significant association between disability status and the walking speed reserve.

Regarding the T25FW performance in MS, a meta-analysis based on 50 studies quantified differences between pwMS and HC, as well as the influence of the disease severity and the MS types (29). People with mild EDSS (EDSS≲3) performed considerably worse on the T25FW when compared to HC, with a mean difference of 2.4 (± 2.7) seconds the deficit in walking speed was 55%. Considering the disease severity based on the reviewed studies, pwMS with moderate and/or severe disability walked 51% slower than those with mild MS disability, spending an average of 5.5 (± 8.1) seconds more to complete the T25FW. Substantial worse T25FW performance was also found in the progressive MS course compared to the relapsing-remitting MS. The mean difference in time between the MS course was 13±18 seconds. To understand the overall impact of symptomatic treatment or rehabilitation on walking speed, it is important to highlight the clinically meaningful performance regarding walking speed in MS. Clinical meaningful change

represents the amount of change or difference in walking speed that is not likely due to variations in trials or measurements errors and reflects the relevant impact in real-life activities. Studies regarding the T25FW in MS had identified the value of 20% as the minimal difference or change necessary to reflect real change above measurement error (23, 26).

3.4 Walking middle distance:

The evaluation of functional ambulation in MS clinical practice also includes longer distance walking tests to assess walking endurance. The most common functional capacity tests for walking long distance with evaluation of physical endurance are the 2-minute walk test (2MWT) and the 6-minute walk test (6MWT) (30) (22). Both tests were newly categorized as 'middle' distance, by Valet et al (31), as clearly different from the T25FW (ICF short distance) and walking 1 kilometer (ICF long distance). The 6MWT is a valid and reliable walking test and have been suggested as more convenient than the 500-meter walk test to the ambulation scoring of the EDSS (30, 32), while at the same time providing a score to all patients as opposed to the 500-meter test which a substantial fraction of the patients will not be able to complete. Although the 6MWT has extensively been used as a primary ambulation outcome in rehabilitation trials (22), the feasibility of the 6MWT in neurological clinical practice has also been debated given that it is time consuming, while the strong association between the 2MWT and the 6MWT suggests that these two walking tests capture the same aspects of ambulation in well-functioning pwMS (33). The ecological validity of the 2MWT and the 6MWT also showed that both walking tests similarly explained variances in real-life walking speed (25). Furthermore, it has been shown that both tests, 2MWT and

6MWT, exhibit equivalent predictability for the number of steps taken in daily life. In addition, a similar high correlation coefficient (r = - 0.76) was reported for the 2MWT and the 6MWT with the EDSS score (34). The replacement of the 6MWT by the 2MWT would enhance feasibility of testing, by bringing a briefer test that is easier to introduce in clinical practice (24, 35). However, in more disabled pwMS particularly, one may also miss information by the application of the 2MWT. Moreover, walking related fatigability defined as slowing of walking speed over time requires a longer test targeting walking endurance, such as the 6MWT (36). The decline in distance from the first to the sixth minute of the 6 MWT is the most reliable measure of walking fatigability. Leone et al. previously proposed a cut-off value of 15% decline in walking distance over time (DWI) (37), which may be adapted to 10% based on the study by Van Geel et al. study (38). Walking related fatigability is prevalent in up to half of persons with moderate to severe disability (EDSS>4), and intuitively of ecological relevance in daily life (37).

Regarding deficits in walking endurance, it has been shown that pwMS walk 61 ± 25 % and 58.5 ± 26 % slower during the 2MWT and the 6MWT compared to the predicted speed for HC, respectively (34). Concerning the walking distance in long walking tests, a meta-analysis study (39) including the 6MWT identified that the mean distance walked by all MS participants included in the studies was approximately 450±100 meters, presenting a mean difference of about 170 ±19 meters compared to HC people. When considering the disease severity, pwMS with mild disability walked about 520 ±90 meters, while those with moderate or severe disability walked about 330 ± 110 meters, revealing a mean difference of about 185 ± 9 meters between groups (40). Studies investigating day to day

variability of long walk tests in MS have suggested a minimal detectable change in walking distance (23) (41) (42). Feys et al (43), investigated within-day variability in 102 pwMS and found this was approximately 19 and 54 meters, in the 2MWT and 6MWT, respectively. Other studies also provide minimal detectable changes for the 6MWT of about 70 to 100 meters (3,16,17), however the sample sizes are considerably smaller.

3.5 Perceived walking ability:

The 12-item Multiple Sclerosis Walking Scale (MSWS-12) is a self-reported measure with 12 items which asks patients to rate the impact of MS on their walking and walking-related activities over 2 weeks, including questions about running, climbing stairs, effort, speed, need of support and balance. The MSWS-12 scale has an excellent test retest reliability (ICC 0,94), internal consistency and concurrent validity (44). It has a cut-off of 75, has a sensibility of 52% and specificity of 82% in predicting fallers (11, 44). The clinically meaningful improvement is 8 to 10 (45).

4. Interventions to improve walking

Various pharmacological and non-pharmacological interventions have been developed for gait dysfunction.

4.1 Pharmacological treatment:

Several symptomatic treatments may affect gait, by specialized drugs as fampridine or those prescribed to target symptoms such as spasticity and thereby gait dysfunction like baclofen, botulinum toxin and cannabinoids.

Fampridine, or 4-aminopyridine, acts through several mechanisms of action in MS. Blockage of the exposed voltage-activated potassium (Kv) channels among demyelinated axons is considered the main mechanism (46). Immune modulation and stimulation of the release of acetylcholine at the neuromuscular junction by direct activation of Ca^{2+} channels may be another pharmacodynamic pathway of fampridine in MS (47, 48). Fampridine was approved by the US Food and Drug Administration in 2010 for improving walking ability in patients with MS (49). The medication is generally safe and with few adverse events being recorded in clinical trials. Those include urinary tract infections and seizures (31). A prolonged-release form is preferred over direct release because of easier administration and a more constant serum level, leading to theoretically more stable effects and a lower risk of adverse effects (50).

Generally speaking, fampridine improves mobility in pwMS (51). A positive effect on walking speed in short distances, functional mobility and perceived walking capacity has been consistently demonstrated. However, a meta-analysis showed that the effect on walking capacity on middle distances (*i.e.,* as assessed by 2MWT or 6MWT) is not significant (31). The effects of PR-fampridine on balance, coordination and risk of fall are unclear, to date, although substantial improvements have been found on the six-spot step test which encompass coordination (51).

A responder versus non-responder approach is frequently used, both in research and clinical practice. This distinction assumes that some patients will benefit from the drug above a clinically significant threshold while others will not. As walking is the most studied outcome in fampridine research and it is only

labelled clinical indication, responders are mainly defined based on walking-based outcomes. The 25FWT is the most commonly used test to determine the responder status. A patient performing better in the T25FW after an open trial period of fampridine is generally considered a responder. This approach was adopted in several seminal works on the topic (52-57). Other studies relied on 6MWT(58) or MSWS-12 (59) to determine the responder status. Interestingly, a 6MWT below 211m has been shown to be a good predictor of therapeutic responsiveness to PR-fampridine (60).

Gait dysfunction that is primarily a result of lower limb spasticity may be treated with medication like Baclofen, which is a derivative of γ aminobutyric acid (GABA) and it is a GABA B receptor and glycine receptor agonist that acts at spinal and supraspinal sites. The side effects of oral baclofen are dizziness, weakness, fatigue and seizures. It is generally effective and tolerated. When spasticity is severe or the oral treatment dose is not tolerated, but control of spasticity could improve function and quality of life, intrathecal baclofen pump may be recommended. Intrathecal baclofen is administered by a programmable, subcutaneously implanted drug delivery system with a reservoir and catheter, delivering low doses of baclofen (<1% of the oral dose) (61), directly to the spinal cord. Intrathecal baclofen therapy should be considered when spasticity is inadequately managed by others treatments or side effects of such are unacceptable.

Clinical trials with oral and intrathecal baclofen for treating MS spasticity related gait impairment are of low quality and the results are equivocal, because they focus on spasticity rather than walking, and only a small number of patients

are ambulatory (61). In the study of Saqid et al. the total number ambulatory patients (only 36) retained ambulatory function and 25% of the patients showed improvement in ambulatory function at two years or more of follow-up (62). In the most recent and largest study intrathecal baclofen improved spasticity outcome but had no statistically effect on the T25FW test over time in patients, but 72.3% of the patients remained ambulatory at 6 months (63, 64). As such, medical spasticity treatment with baclofen may preserve rather than improve walking over time.

The oromucosal spray is composed of delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). The THC acts on cannabinoid receptor CB1 and CB2 as a partial agonist and it modulates the excitatory effects of glutamate and the inhibitory effects of GABA; and the CBD is a CB2 receptor antagonist. The THC:CBD oromucosal spray has shown improvement in the 10MW test (65-68), and a smaller pilot study with 20 pwMS reported spatial-temporal and kinematic gait parameters improvement (63, 69).

When spasticity is isolated to one or few muscle groups, specific intramuscular injection of botulinum toxin may more effectively improve gait than oral or intrathecal medication (70). Botulinum toxin binds presynaptically to high-affinity recognition sites on the cholinergic nerve terminal at the neuromuscular junction decreasing the release of acetylcholine producing a temporal neuromuscular denervation for an average of 3 months. Intramuscular phenol or alcohol injections can also be used for denervation of spastic muscles; however, their use is limited by permanent dysesthesias that can occur if either are injected near sensory nerve (70).

4.2 Exercise interventions:

A review study from Pearson et al. (6), summarized the effects of different interventions on walking, suggesting that pooled data from aerobic, resistance training, cycling, home-based exercise, yoga and combined training (aerobic and resistance training) showed significant results on walking capacity. Decrement of about 2 seconds was found on the time to complete the 10MWT, however, a non-significant result was found for the T25FW. In addition, when analysing the modalities separately, the most effective exercise modality to improve walking speed was the combined training. The most effective exercise for the 6MWT was resistance training, improving the walked distance by about 55 meters. Combined training showed the greatest improvement in 2MWT results, with an average improvement of about 25 meters. Resistance training (i.e., strength training) promotes significant improvement in walking speed, ranging from 9% to 12% for the T25FW and 7.5% to 24.5% for the 10MWT. Improvements in walking endurance could also be found, ranging from 14 to 22 meters on the 2MWT and from about 27 to 81 meters on the 6MWT (71). On the other hand, meta-analysis evaluating the effects of Pilates (72) and Yoga (73) on mobility did not show any evidence of improvement when compared to other interventions such as physical therapy sessions.

In terms of the impact of exercise on spatiotemporal and kinematics gait parameters, 6 months of an adapted exercise program including aerobic training (cycling) and resistance training provided an increment of 23.4% in walking speed was shown along with a significant increment in cadence and stride length, and decrement in stance phase (% gait cycle) and double support (% gait cycle). In addition, a trend of improvement in dynamic range of motion of the hip, knee and

ankle were shown (74). Another study including resistance training also found that pwMS significantly decreased double support and stance phase, and increased the swing phase in percentage of the gait cycle. Furthermore, the less-affected leg presented increased stride and step length and plantar flexion, with decrement in toe clearance.

Considering the above-mentioned results from the reviews as well as from clinical trials, it is suggested that exercise interventions positively impact walking performance, and consequently contribute to the management of ambulation. It is unclear to which extent exercise intensity matters when it is aimed to improve walking specifically (75). Dalgas et al (76) reported the summarized effects of exercise in MS proposing an exercise-induced postponement theory, where regular moderate-to-high intensity exercise could postpone the onset of clinical MS diagnosis and the occurrence and worsening of prominent symptoms. In addition, it was suggested that exercise should be prescribed from early stage to pwMS.

4.3 Task-oriented training (over ground, treadmill):

It is hypothesized that task specific training improves mobility through changes in neural circuits within the central nervous system enhancing gait kinematics through the repetition of movements performed during walking (77). The cortex responds to the demands of task-specific training by reorganizing the injured and uninjured parts of the brain. These neuroplastic changes stimulate neural output changing overall functional performance.

Task specific training includes overground walking, walking treadmill, body-weight supported treadmill training (BWSTT) and robot assisted gait training (RAGT) (78).

A meta-analysis by Robinson et al. (79) including only 40 participants from two studies, demonstrates that treadmill training may be effective in improving mobility in pwMS who were able to walk (mild to moderate MS), by improving spatiotemporal measures of gait enhancing comfortable walking velocity and improving walking endurance. Training in studies were completed for 30 minutes, three times per week across an eight-week period. Treadmill training at a moderate to high intensity has been found to reduce energy expenditure and effort when walking and to improve cardiovascular function (80).

Body weight supported treadmill training (BWSTT) enables a patient with significant mobility impairment to walk on a treadmill while being partially supported by a harness, typically the patient is assisted by a therapist who guide the lower-limbs through the gait cycle. Recently Robot assisted gait training (RAGT) was developed to deliver consistently reproducible, high repetitive robot guided movements (77). Clinical robotic gait machines can be divided into grounded-end effectors and exoskeleton.

The grounded-end effectors have an electromechanical driven footplate that guide the feet and reproduce gait trajectories with a varying degree of support provided (81). The exoskeleton is a system with robotic driven gait orthosis, where the knee and hip drives movements can be adjusted from 100% to 0% for either or both legs, and can be in a system with body weight support and walk on a treadmill, such as in the Lokomat (Hocoma, Zurich; CH). The wearable exoskeletons assist individuals with lower limb paresis for ambulation and can be used as a gait training device and provides the opportunity to walk over ground in both indoor and outdoor environments. Most wearables exoskeleton devices such

as Ekso and ReWalk, utilize the user`s trunk movements to control externally powered gait (82).

The quality of movements during RAGT in terms of kinematics (83) and muscle activity (84) is not identical with the physiological gait, furthermore, RAGT is less energy-consuming and cardiorespiratory stressful than overground gait training (81, 85, 86). Several studies revealed positive effects of RAGT for pwMS in gait speed (87, 88), walking endurance (89, 90) and kinematic (81, 91). The different studies show a positive but short-lasting effect, however, without a clear superiority of RAGT on traditional overground gait training (78, 81, 92). Afzal et al. have shown in a small group study that wearable exoskeleton may increase self-selected gait speed and reduce metabolic expenditure during short distance walks in patients with high EDSS (82).

4.4 Novel strategies:

In the last years novel strategies such as motor imagery and rhythmic auditory stimulation have been developed to improve walking speed and distance in people with neurologic disorders. Motor imaginary is the mental execution of movements without any actual movement performance (93). Two different perspectives can be adopted during motor imagery; the internal or first-person perspective (kinaesthetic mode) where a person experiences his or her own body moving. The external or third-person (visual mode) perspective, the person imagining watches himself or herself (93, 94).

For motor imagery of walking, individuals need to be ambulatory since there is a relationship between mental and physical execution of a movement (95). It has

been indicated that in people with motor impairment, the kinesthetic mode is more effective than the visual mode because of a more efficient motor learning due to sensory information (96).

Music-based interventions have been reported to positively impact cognitive and motor functions in the neurological population (97). In this context, rhythm-based intervention is introduced, which consists of walking in the presence of an auditory stimuli (music and metronome). In pwMS, a few studies have investigated the effect of rhythm-based interventions on gait kinematics, and found that the intervention yielded positive results on gait kinematic (98, 99). Also, an intervention of 4 weeks comparing the effect of cued (using music and metronomes) and non-cued motor imagery in pwMS and walking impairment, revealed, in the cued motor-imagery conditions, improvements on walking, fatigue and quality of life (100). Furthermore, studies have been conducted in order to understand both the processes underlying walking to auditory-stimuli, such as entrainment and synchronization, as well as understanding the ingredients of applying such stimuli during walking for functional task-oriented training (101).

The daily life performance is associated with the simultaneous execution of motor and cognitive tasks. This can result in worsened performance on one or both tasks indicating cognitive-motor interference (CMI). The CMI is often quantified by the dual task cost which is the percentage of change in dual task performance relative to single task performance (102). Different approaches have been proposed on how training might improve dual task performance

Given the complexity of daily living activities and walking, rather a combinatory treatment approach is advocated. One model focuses on

automatization of an individual task, thereby reducing attentional requirements. For the other side, the task-integration model proposed the two-task integration for improvement and in this context, the task needs to be practiced simultaneously in a dual task training. This dual task training integrating cognitive tasks in the physical therapy program, was shown to lead to improvements of walking during dual task conditions (102).

4.5 Orthotic devices and assistive technology:

In more disabled patients, a compensatory approach is needed. On the ICF environmental factors level, assistive technology is described as a means to improve functioning. Orthotic devices and functional electrical stimulation (FES) are two classes of assistive devices with the potential to mitigate specific deficits in the lower extremity that lead to a decrease in walking ability.

Orthoses are a broad range of devices applied outside the body to support, correct or accommodate specific structures. An AFO consists of a foot plate and a shin section, which is adapted to produce the optimal fit and function for the individual patient. Ankle-foot orthoses (AFO) are commonly described to minimize gait deficits caused by weakness or balance impairment, addressing problems such as decreased foot clearance in the swing phase of gait, reduced heel strike at initial contact and poor stability in the stance phase. AFO are effective for compensating weakness, restoring energy and ankle/knee control. The literature on the effects of AFO in walking ability of pwMS is characterized by small samples. The research showed improved walking speeds, decreased energy consumption, static balance (103, 104). The hip flexion assist orthosis (HFAO) is design to supplement the hip and knee flexors in the affected limb and additionally,

dorsiflexion assistance is provided from the distal attachment. HFAO is safe and effective in pwMS with unilateral (or unilaterally predominant) hip flexor weakness, improving the gait speed during T25FW and walking distance in pwMS (105).

The functional electrical stimulation (FES) is a clinical application of a small electrical current to trigger a muscle contraction that is then incorporated into a functional activity. It has an effect as orthotic and a therapeutic effect. The orthotic effect is defined as the difference in walking ability at any given time between with FES and without FES conditions. The improvement, caused by FES use over time in function measured without the device is defined as the therapeutic effect (103). Patients should be able to achieve neutral dorsiflexion (passively or assisted), skin tolerance to the electrodes, cognitive capacity or support to manage technology and have realistic expectations (103). The FES in pwMS with drop foot increased walking speed (T25FW), produced a reduction in energy expenditure and resulted in a significant improvement in patient-reported outcomes (MSWS-12)(106, 107, 11).

The literature in MS on the comparative use of FES versus AFO devices in the management of dropped foot is scarce. The available information in stroke and MS suggest a comparable effect of both methods on walking speed but with a slight increase in stability with AFO and better physical activity and obstacle avoidance with FES (107).

4.6 Assistive devices:

Single-point canes enlarge the patient base support and are recommended to assist with even weight distribution during ambulation, helping patients with unstable gait and moderate balance control (11). Quad canes provide more

stability, however decrease overall gait velocity and do not improve asymmetrical gait pattern (11, 108). Forearm crutches gives a good base support, decreasing weight bearing on a single lower extremity in patients with mild to moderate balance deficit, however the patient needs to have a good upper limb control. Finally, walkers provide the largest base of stability for increased stability during ambulation, and are recommended for patients with moderate gait and balance deficits (11).

5. Conclusion

Walking impairment is frequently in pwMS and impacts the functional status, private and professional life and the quality of life. Gait disorders need to be identified and managed early in the course of MS, using a multimodal approach that needs to be adjusted over time based on the results of periodic assessments. Validated clinical outcome assessments that are frequently applied in pwMS include T25FW, 2MWT, 6MWT, and MSWS-12.

Finally, a growing body of evidence demonstrates the benefits of various pharmacological and non-pharmacological rehabilitation interventions on walking performance

6. Expert opinion

Some degree of walking dysfunction is present in the majority of pwMS and contributes to disability and daily living restrictions. Walking can be categorized according to ICF where gait pattern classifies at body function level, while walking capacity and perceived ability are classified at activity level. The gait pattern can most often be characterized as paretic or spastic, cerebellar, sensory ataxia or

mixed, which have consequences for the subsequent symptomatic treatment and the applied rehabilitation strategy.

Accordingly, there are different walking evaluation methods that have been validated in pwMS. Clinical practice choices would, beside clinical observations of normal or compensatory walking, benefit from insights of the gait pattern by means of spatiotemporal (for example, step length versus cadence and step width) or kinematic (for example, knee flexion angle and push-off momentum) parameters measured by stationary or body worn sensors. It would enhance personalization and specification of symptomatic treatment and would help refine the rehabilitation strategy. We recommend that routine clinical practice include the assessment of short walking distance, preferably by means of the T25FW. We further recommend application of the 2MWT if rehabilitation has been undertaken to further expand the understanding of the clinical impact of rehabilitation as the 2MWT has shown robust psychometric properties including better responsiveness than the T25FW. Furthermore, the 6MWT is advocated in case of suspicion of walking-related fatigability. In addition to objective walking outcomes, the self-reported MSWS-12 is applicable across the disability spectrum, and further seems to be a very sensitive outcome in the patients with mild MS. For all tests, values of clinical meaningful changes are available and should be integrated when interpreting the results in both clinical practice and research.

Symptomatic treatment focuses on impairments and is effective at improving walking speed and distance while at the same time also having the potential to normalise the gait pattern in pwMS. Subsequently, relevant interventions targeting walking should be included in multi-disciplinary treatment programs. The most well-

established interventions to increase walking speed and distance in pwMS, that are underpinned by evidence, are exercise and task-specific training. Positive effects on walking following exercise and task-specific training are also seen in more disabled MS patients and in progressive. For the latter, compensatory aids are needed and interventions such as FES, body weight supported walking or robot-assisted training may be considered although the effects hereof need to be further elucidated. Moreover, the existing (positive) evidence supporting the use of these interventions needs to be cautiously interpreted, as studies were often performed in selected patient groups without major comorbidities, high levels of fatigue or cognitive deficits.

In the latter perspective, novel interventional strategies such as rhythmic facilitation or integrated cognitive-motor training have emerged and proven potentially useful in clinical practice.

Next steps are to expand our understanding of whether effects are temporary or may lead to neuroplastic changes that are more sustainable. A further perspective for the future includes the potential synergistic effect of combining pharmacological interventions (e.g. Fampridine) with different interventions targeting walking in pwMS. Interestingly, preliminary evidence suggests superiority of such combined interventions, but further studies elucidating the interaction between medication and physical interventions targeting walking are warranted.

Finally, not addressed in this review, is the importance of persons practicing exercise and walking during daily life, while being on their own. Moreover, further development of methodologies to enhance implementation of a physical healthy

lifestyle should also address the importance of social support and (remote) supervision.

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Figure 1. The biopsychosocial perspective of the International Classification of Functioning, Disability and Health (ICF): An overview of the categories from each component (Body functions and structure; Activities and participation; Environmental factors) included in the current work.

T25FWT: 25 timed foot walking test, 10 MWT: 10 meters walking test, MSWS-12: 12-Item multiple sclerosis walking scale, 2MWT: 2 minutes walking test, 6MWT: 6minutes walking test, DWI: distance walking index, MFIS: Modified Fatigue Impact scale.

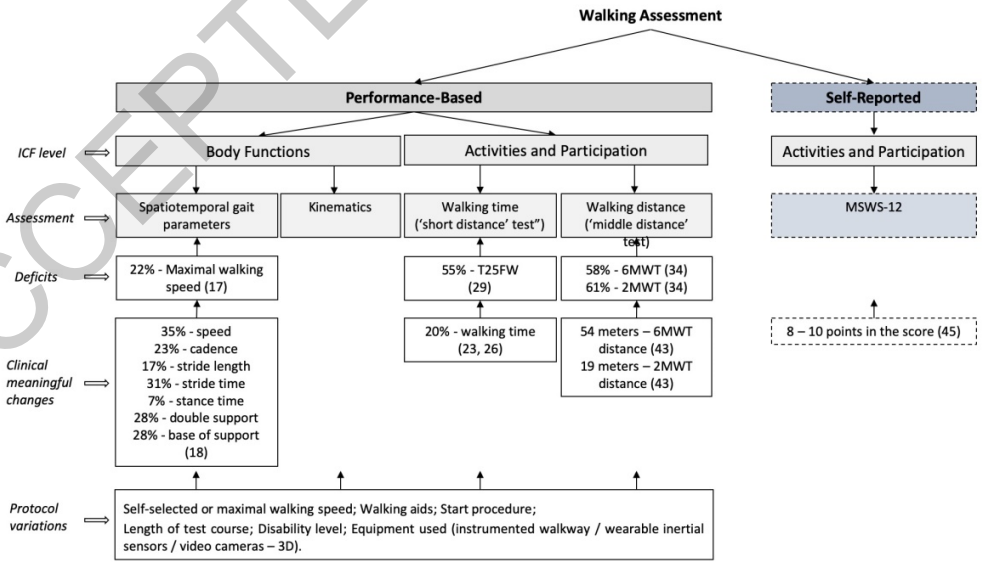

Figure 2. Assessing walking in MS: The assessment of walking recommended, with clinical meaningful change and protocol variants.

25FWT: 25 timed foot walking test, 10 MWT: 10 meters walking test, MSWS-12: 12-Item multiple sclerosis walking scale, 2MWT: 2 minutes walking test, 6MWT: 6minutes walking test, DWI: distance walking index, MFIS: Modified Fatigue Impact scale