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Gait Abnormalities in Multiple Sclerosis: Pathogenesis, Evaluation, and Advances in Treatment

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Abstract Multiple sclerosis (MS) is a demyelinating disease of the central nervous system characterized by episodic decline in various neurologic functions. Gait dysfunction in MS is distinguished by decreased gait speed, walking endurance, step length, cadence and joint motion, as well as increased metabolic cost of walking and increased variability of gait. Standardized clinical, timed, and patient-based measures can identify MS patients with gait dysfunction, and observational gait analysis, instrumented walkways, or three-dimensional gait analysis can help determine which problem underlies their gait dysfunction to help direct effective treatment. Exercise may ameliorate all types of gait dysfunction. In addition, gait dysfunction due to weakness may be alleviated by orthoses or functional electrical stimulation; gait dysfunction due to spasticity may be relieved by oral, intrathecal, or intramuscular medications. Assistive devices and balance training may reduce gait dysfunction from imbalance, and dalfampridine may accelerate gait in people with MS who walk slowly.

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Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system and the most common neurologic disease of young adults. By conservative estimates, there are 400,000 people living with MS in the United States today and over 2.5 million people with MS worldwide. Almost 200 new cases of MS are diagnosed each week, and most of these are in young women. The average age of MS diagnosis is around 30 years, and MS is 2 to 4 times more common in women than in men.

MS is thought to have an autoimmune inflammatory etiology that causes demyelination as well as axonal degeneration in the brain, spinal cord, and optic nerves. MS is characterized by episodic decline in a wide range of neurologic functions including cognition, vision, muscle strength and tone, coordination, and sensation, all of which may contribute to gait dysfunction and thus reduced mobility and quality of life in people with MS.

Gait dysfunction is common in people with MS, and walking endurance, gait speed, and gait quality are components of the two most commonly used measures of MS-related disability and disease progression, the Expanded Disability Status Scale (EDSS) [1] and the Multiple Sclerosis Functional Composite (MSFC) [2]. Studies show that people with MS have a range of gait abnormalities including decreased step length [3•, 4], decreased cadence [3•, 5], reduced joint motion [4, 6, 7], and more variability of most gait parameters [7] compared with healthy controls. These abnormalities result in reduced gait speed [3, 5–8],

reduced walking endurance [9], an increased metabolic cost of walking [10], and reduced community mobility [11]. Furthermore, people with MS reduce their walking speed and increase the variability of their gait when they walk while performing a cognitive task more than healthy controls [12], suggesting that they need to devote greater cognitive reserve to walking than do people without MS.

Several factors may contribute to the gait dysfunction seen in people with MS, and gait evaluation can often determine the problem(s) underlying the gait dysfunction, and then be used to direct effective treatment. This is particularly helpful today when a number of pharmacologic and nonpharmacologic interventions are available to ameliorate gait dysfunction in MS. In this article we focus on the evaluation of gait dysfunction in people with MS and on the selection of intervention(s) based on the findings of this evaluation.

Pathogenesis of Gait Dysfunction in MS

Although a wide range of factors can contribute to gait dysfunction in people with MS, sensory changes and resulting imbalance, lower extremity weakness or spasticity, and cerebellar ataxia are thought to contribute to most of the gait abnormalities observed in MS. Directed examination and evaluation of gait can generally identify the cause (s) of gait dysfunction in a person with MS and, even when a specific cause cannot be identified, symptomatic therapy can often increase gait speed and endurance, and improve community mobility and participation.

Evaluation of Gait Dysfunction in MS

Gait dysfunction in people with MS can be evaluated using standardized clinical measures, timed measures, patient-based measures, observational gait analysis (OGA), instrumented walkways, or three-dimensional (3-D) gait analysis. The ideal method for evaluating gait dysfunction depends on the examiner's expertise, the time and equipment available, and the goals of the assessment (Table 1).

Standardized Clinical Measures

Standardized clinical measures such as the EDSS [1] and the Hauser Ambulation Index (AI) [13] are used to assess walking in MS. The EDSS is a frequently used disability score that ranges from 0 (no impairment) to 10 (death from MS). EDSS scores of 0 to 3.5 are directly related to the neurologic examination, whereas scores of 4.0 to 7.0 are largely based on the maximum distance walked and the level of assistance needed for walking. The AI is a rating scale used to assess mobility by evaluating the time and degree of assistance required to walk 25 ft [13]. The patient is asked to walk a marked 25-foot course as quickly and safely as possible and the examiner records the time and type of assistance (eg, cane, walker, crutches) needed. Although the patient's walking is timed, the time is not used directly but is used in conjunction with other factors to rate the patient's walking limitations and need for assistance on an ordinal scale with 11 gradations.

Timed Measures

Timed measures such as the Timed 25-Foot Walk Test (T25FWT) [14] and the 6-minute walk test (6MWT) [15] are used to quickly assess readily quantified aspects of gait such as speed and endurance. The T25FWT is used to assess maximal walking speed and is a component of the MSFC. To perform the T25FWT, the patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 ft as quickly as possible, but safely. The test is immediately administered again by having the patient walk back the same distance. The score for the T25FWT is the average time of the two trials (Fig. 1a). The 6MWT is used to assess walking endurance. To perform the test, the patient is asked to walk as far as possible and as fast as possible for 6 min. The total distance walked is recorded and used as the score. These two timed tests are simple and readily quantified by personnel with minimal training and are quick to execute. Published normative data are available for the T25FWT [16] and the 6MWT [15], allowing these measures to assess for abnormal performance.

Patient-Based Measures

Patient-based measures can be used to assess the patient's perspective of their walking disability. The 12-item Multiple Sclerosis Walking Scale (MSWS-12) is a patient-based measure of the impact of MS on walking. Each item is scored on a scale of 1 (not limited) to 5 (extremely limited). A total score is generated and transformed to a 0 to 100 scale, with larger numbers associated with a greater self-perception of walking disability. The MSWS-12 is a valid and reliable standardized measure of self-perceived limitations in walking due to MS [17].

Because the validity, reliability, and responsiveness of these aforementioned measures vary [18, 19], and each measure has distinct advantages and disadvantages, it is important to consider the purpose of the assessment when selecting a specific clinical measure. These measures provide limited, if any, information about gait quality and the mechanisms underlying the gait dysfunction. They also have limited precision compared with instrumented gait measures (see below). Therefore, these gait measures are

Table 1 Methods of gait evaluation: advantages and disadvantages

	Advantages	Disadvantages
Standardized clinical measures	Take into account the use of assistive devices	Require a skilled examiner
	EDSS: directly related to neurologic examination; used in clinical trials	Do not identify mechanisms underlying gait dysfunction
	AI: simple and quick	EDSS and AI have limited precision and responsiveness
		No normative data
Timed measures	Simple Readily quantified	Do not identify mechanisms underlying gait dysfunction
	Require limited training	
	Published norms available	
Patient-based measures	Document the patient's perspective Require little time to complete	Do not identify mechanisms underlying gait dysfunction
Observational gait analysis	Identify mechanisms underlying gait dysfunction	Limited validity, reliability, and precision
	Require limited time and equipment	Require skilled examiner
Instrumented walkways	Simple	Require equipment
	Provide precise spatiotemporal data	Do not identify mechanisms underlying gait dysfunction
Three-dimensional gait analysis	Identify mechanisms underlying gait dysfunction Provide precise kinematic, kinetic, and spatiotemporal data	Require expensive equipment and skilled examiner

AI ambulation index; *EDSS* expanded disability status scale

most useful for identifying individuals with certain gait dysfunction and for assessing for improvements in walking capacity, but they have limited ability to direct or assess more subtle impacts of interventions aimed at reducing gait dysfunction in people with MS.

Observational Gait Analysis

OGA is the clinical tool most commonly use to assess gait quality. OGA involves observing a person walk and analyzing their gait pattern in terms of kinematic and

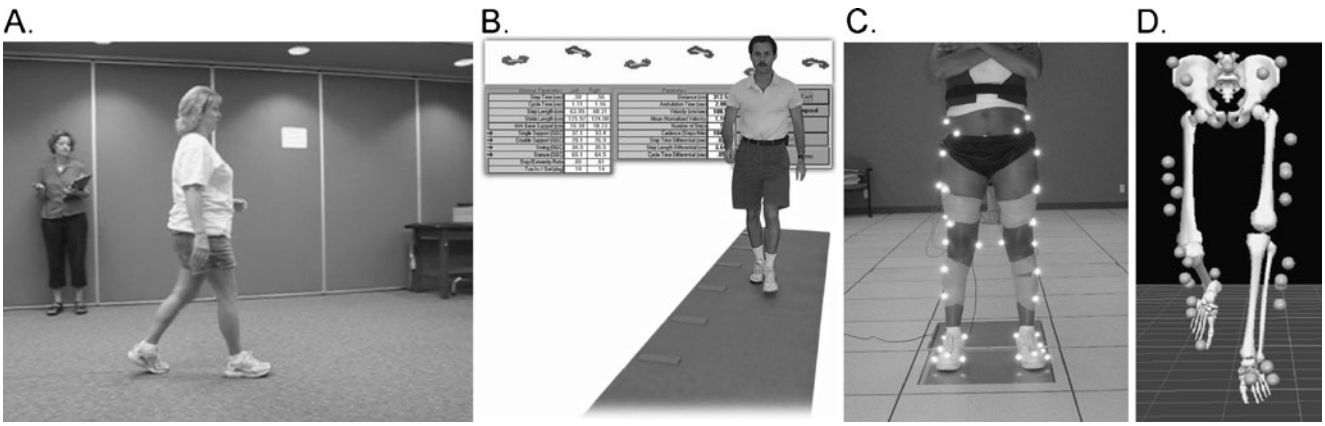

Fig. 1 **a** An individual performing the Timed 25-Foot Walk Test (T25FWT) while the clinician conducts observational gait analysis. (*Courtesy of* Joanne M. Wagner, Saint Louis University, St. Louis, MO.) **b** An individual walking across an instrumented walkway. (*Courtesy of* GAITRite® Walkway System; CIR Systems Inc., Havertown, PA.) The footfall contacts captured during the walk and the spatiotemporal parameters calculated from the footfall contacts are shown in the background. **c** An individual standing with the reflective markers used for a three-dimensional (3-D) gait analysis adhered to the skin. (*Courtesy of* Joanne M. Wagner, Saint Louis University, St. Louis, MO.) **d** An example of a 3-D model calculated from the reflective markers. (*Courtesy of* Joanne M. Wagner, Saint Louis University, St. Louis, MO.)

spatiotemporal parameters. OGA can be conducted during a clinic visit, during standardized clinical testing of gait such as the T25FWT (Fig. 1a), or under walking conditions that best match the patient's complaints, such as walking along a narrow path to challenge the balance of a patient complaining of imbalance during community ambulation. Because particular impairments such as weakness or spasticity in certain muscles, dyscoordination, or sensory loss generally cause particular identifiable changes to the gait pattern, OGA can be used to determine the mechanisms underlying gait dysfunction and thus help with selection of treatment strategies to reduce walking dysfunction in people with MS. Although OGA can be quick and requires little space and no specific equipment, this method of gait analysis requires a high level of skill and has been criticized for its limited accuracy and reliability [20]. However, OGA accuracy and reliability are improved when the observers are highly experienced [21], and when a standardized assessment rubric is used [22].

Instrumented Walkways

An instrumented walkway is a portable strip of carpet with sensors embedded in a grid-like pattern to electronically capture footfall contact when a person walks on it. Instrumented walkways can precisely quantify the spatiotemporal parameters of gait (Fig. 1b). An instrumented walkway can be used to collect detailed measures during standardized clinical testing such as the T25FWT or during OGA. Instrumented walkways are portable, affordable, and require minimal training to use and provide a valid and reliable assessment of clinically relevant gait parameters, including gait speed, step length, single support time, swing time, and base of support [23]. These gait parameters may be used to identify the functional system(s) contributing to a person's gait dysfunction. For example, certain spatiotemporal gait variables can differentiate patients with MS with pyramidal dysfunction from patients with MS with cerebellar dysfunction [3•]. The precision provided by an instrumented walkway can be valuable for directing treatment and for assessing the impact of interventions for gait dysfunction in MS.

3-D Gait Analysis

3-D gait analysis is the gold standard for the assessment of gait. 3-D gait analysis is performed by placing reflective markers on a person and recording their movement with infrared cameras while they walk (Fig. 1c). Computer software then reconstructs the markers to produce a 3-D image of the person moving (Fig. 1d). This method provides detailed quantitative measures of kinematic, kinetic, and spatiotemporal parameters of gait and can thus provide information about the mechanisms underlying the gait dysfunction as well as precise spatiotemporal data. This type of gait analysis can be used to identify subtle gait impairments [4] and abnormal postural control strategies [8] not captured by other methods of gait analysis. Because performing 3-D gait analysis requires specialized expensive equipment, is time consuming, and requires highly trained and experienced personnel, this method of gait analysis can be a valuable research tool but it has a limited role in clinical practice.

Interventions for Gait Dysfunction in MS

Various pharmacologic and nonpharmacologic interventions can ameliorate gait dysfunction in people with MS. Ideally, these interventions address the specific impairments underlying the gait dysfunction, and are selected based on the findings from gait analysis and the clinical neurologic examination. The following section briefly describes specific interventions for weakness, spasticity, imbalance, and reduced gait velocity that contribute to gait dysfunction in MS (Table 2).

Weakness

Lower extremity weakness resulting from corticospinal tract pathology or general deconditioning likely contributes to slow walking speed, reduced walking endurance, and increased energy expenditure during walking [5]. When weakness is identified as a significant contributor to gait dysfunction, exercise-based therapies, hip and ankle orthoses, and functional electrical stimulation (FES) may improve walking.

Table 2 Impairment-specific interventions for gait dysfunction in multiple sclerosis

Impairment	Intervention
Weakness	Exercise
	Orthoses
	Functional electrical stimulation
Spasticity	Oral medications
	Intrathecal baclofen
	Intramuscular botulinum toxin
	Stretching, active and passive range of motion
Imbalance	Exercise
	Assistive devices
	Balance training
Reduced gait velocity	Exercise
	Dalfampridine

Exercise-Based Therapies

Exercise-based therapies include resistance training, aerobic training, and body weight-supported treadmill training (BWSTT). All of these have been shown to improve walking in select groups of people with MS. Resistance training has been shown to increase lower extremity strength of persons with MS with mild to moderate clinical disability [24] and for some individuals, improve gait kinematics [25], walking speed, and walking endurance [24]. Although there is limited evidence that aerobic training improves lower extremity strength in people with MS [26], this type of training has been shown to increase aerobic capacity, reduce energy expenditure during walking, and improve walking speed and endurance in some individuals with MS [27]. For individuals who cannot walk independently on a treadmill, BWSTT may provide aerobic training together with task-specific functional training. There is emerging evidence that BWSTT helps people with MS with severe clinical disability (EDSS > 6.0) accelerate their walking speed and improve their walking endurance [26].

Orthoses and FES

Gait abnormalities that are primarily the result of isolated weakness of the hip flexor or ankle dorsiflexor muscles may be treated with the appropriate orthosis. A hip flexion assist orthosis is a simple device that uses dynamic tension bands running from the waist to the foot to assist with toe clearance during walking in a person with unilateral hip flexor weakness. This type of device is inexpensive, easily used, and well tolerated by people with MS, and has been shown to increase walking speed and walking endurance, most likely by improving the gait pattern and reducing energy expenditure when walking [28].

An ankle foot orthosis (AFO) or FES device may improve the gait of a person with MS and foot drop. Foot drop hinders foot clearance during the swing phase of gait, decreasing gait safety and efficiency, limiting mobility, increasing the risk for falls, and increasing energy expenditure during walking. An AFO is a simple device, usually made of plastic, which wraps under the foot and behind the calf to passively assist ankle dorsiflexion. Although often effective, the passive dorsiflexion assistance provided by an AFO can limit ankle range of motion and many patients find AFOs uncomfortable, bulky, or unsightly and therefore do not use them. FES is a technologically advanced alternative to an AFO [29]. There are currently two FES devices on the market for foot drop: the Walkaide (Innovative Neurotronics, Austin, TX) and the Bioness L300 (Bioness Inc., Valencia, CA). Both of these cost around $5000 and this is generally not covered by insurance. An FES device for foot drop uses a battery-driven generator to deliver electrical current via transcutaneous electrodes to the common peroneal nerve to produce contraction of the tibialis anterior and peroneal muscles during the swing phase of gait. The stimulation is triggered by angular acceleration of the leg or by the heel coming off the ground. FES for foot drop reduces energy consumption [30], and improves walking speed, distance, and efficiency [31] in people with MS. Although FES improves gait in some people with MS its benefits are limited to those in whom foot drop is the primary cause of gait dysfunction.

Spasticity

Gait dysfunction that is primarily a result of lower extremity spasticity may be effectively treated with medications and/or physical interventions. Medications to address spasticity are best selected according to their efficacy, tolerability, and route of administration and thus localization of effect.

Oral Medications for Spasticity

Baclofen, tizanidine, and benzodiazepines can all be effective oral medications to control mild to moderate spasticity [32, 33]. Baclofen is a derivative of γ-aminobutyric acid (GABA) and is a GABA B receptor agonist that acts at spinal and supraspinal sites. Tizanidine is a centrally acting α2-adrenergic agonist. Benzodiazepines act by activating GABA A receptors. GABA agonists are thought to relieve spasticity by inhibiting monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals. Supraspinal actions may also occur and contribute to their clinical efficacy. The α2-adrenergic agonist tizanidine likely exerts its effect on spasticity by increasing presynaptic motoneuron inhibition.

Use of orally administered antispasticity medications is limited primarily by sedation. Oral baclofen also sometimes causes dizziness, weakness, and fatigue. Oral baclofen is generally effective and tolerated at doses of 5 to 20 mg three to four times per day and its use is not limited by tolerance. Tizanidine, although often well tolerated, in addition to sedation, causes dry mouth in some patients and may also cause hypotension. The risk of adverse effects with tizanidine is increased when tizanidine is taken in conjunction with fluvoxamine or ciprofloxacin, both of which impair tizanidine excretion, likely due to CYP1A2 inhibition. Tizanidine is metabolized in the liver and should therefore be avoided in patients with liver dysfunction. Tizanidine dosing may range from 2 to 36 mg/day, with no single dose exceeding 12 mg. The dose should start low and be increased very slowly to minimize adverse effects.

Although benzodiazepines are not US Food and Drug Administration (FDA) approved for the treatment of spasticity, oral benzodiazepines can be very effective for controlling spasticity and are therefore often used off-label for this purpose [32]. The use of benzodiazepines for the treatment of spasticity can be significantly limited by tolerance and sedation. Several oral benzodiazepines available, with different potencies, onset, and duration of action. Dosing of an oral benzodiazepine for treatment of spasticity depends on the specific drug selected.

Because of their wide distribution, orally administered antispasticity medications have the advantage of reducing spasticity in muscles throughout the body. However, their wide distribution also has the disadvantage of producing systemic side effects, which can be limiting, particularly at higher doses. Orally administered antispasticity medications are often effective for improving gait that is impaired by generalized mild to moderate lower extremity spasticity but their use is limited by sedation at the higher doses needed to control severe spasticity, and this approach may not be effective when the person relies on spasticity for support during ambulation [34].

Intrathecal and Intramuscular Medications for Spasticity

When spasticity is more severe and the dose of an oral medication needed to be effective is not tolerated but control of spasticity is expected to improve function and quality of life, implantation of an intrathecal baclofen pump that delivers the medication directly into the cerebrospinal fluid may be recommended because it limits the sedation associated with oral administration [35]. However, the use of a baclofen pump is limited by the need for and expense of surgery and the potential for device-related complications. In addition, intrathecal baclofen affects all the muscles of the lower extremities and may cause weakness in muscles in which strength is needed for ambulation, which may explain why, in a recent small study, despite reducing spasticity, intrathecal baclofen was not found to be associated with increased gait speed in ambulatory patients with MS [36].

When spasticity is isolated to one or a few muscle groups, specific local intramuscular injection of botulinum toxin into affected lower extremity muscles may more effectively improve gait than an oral or intrathecal medication [32, 37, 38]. There are currently four botulinum toxin products available in the United States: Botox and Botox Cosmetic (Allergan Inc., Irvine, CA; botulinum toxin type A), Myobloc (Solstice Neurosciences, LLC, Louisville, KY; botulinum toxin type B), and Dysport (Ipsen Biopharm, Rockford, IL; abobotulinumtoxinA). Although providers use all of these, except Botox Cosmetic, for treatment of spasticity, only Botox is FDA approved for the treatment of spasticity and this approval, which occurred on March 9, 2010, is only for treatment of spasticity of the flexor muscles of the elbow, wrist, and fingers. Thus, the use of botulinum toxin for the treatment of lower extremity spasticity and improvement of gait is off-label.

Botulinum toxin binds presynaptically to high-affinity recognition sites on the cholinergic nerve terminals at the neuromuscular junction decreasing the release of acetylcholine. The neuromuscular denervation produced by botulinum toxin is temporary, lasting about 3 months, after which recovery and return of spasticity occur through proximal axonal sprouting and muscle re-innervation at a new neuromuscular junction. Although all four of the botulinum toxin preparations available for therapeutic use in the United States today have a similar effect and duration of action, dosing varies between products. Botulinum toxin has the advantage of local delivery and reversibility but its use is limited by cost and the need for skilled administration. Intramuscular phenol or alcohol injection can also be used for denervation of spastic muscles. Although both are effective and inexpensive, their use is limited by the permanent dysesthesias that can occur if either is injected near sensory-rich nerve branches.

Physical Interventions for Spasticity

Physical interventions, such as passive or active exercise and stretching regimens, can be used alone or in combination with antispasticity medications to reduce spasticity. These physical interventions are presumed to maintain or increase the length of spastic muscles and reduce contractures by increasing soft tissue extensibility through viscous deformation and structural adaptation of muscles and other soft tissues and/or by changing the excitability of motoneurons innervating the spastic muscles [39]. Although these interventions are commonly recommended for people with MS and spasticity, the limited evidence available has only shown small effects of active range-of-motion exercise on spasticity in this population [40, 41], and a recent study indicated that, in isolation, stretching exercises do not produce clinically important changes in spasticity in people with neurologic conditions [42]. However, when combined with antispasticity medications, passive and active exercises and stretching enhance the impact on spasticity provided by the medication alone [43].

Imbalance

Gait dysfunction due to imbalance may be managed by reducing the specific impairments contributing to imbalance (eg, reducing spasticity with oral baclofen), prescribing assistive devices, and improving standing balance via balance-specific exercise training. The ideal management

strategy depends on the presence of other identifiable impairments and the degree of balance dysfunction. Pharmacologic and exercise-based strategies aimed at reducing sensorimotor impairment have been shown to improve balance, and subsequently, reduce gait dysfunction in people with MS [44•]. However, gait ataxia and somatosensory loss are not easily managed with medications or exercise-based therapies. Gait dysfunctions resulting from ataxia and somatosensory loss are often best managed by instructing the patient in the use of an assistive device, such as a straight cane or walker. Assistive devices can improve gait by increasing an individual's base of support, thus proving greater postural stability, and for those individuals with impaired lower extremity somatosensation, by providing augmented sensory input through the upper extremities and thus bypassing the thoracic and lumbar cord. Balance-specific exercise training has also been shown to improve balance in persons with MS [45], and there is emerging evidence that balance training (including novel exercise-based therapies such as balance-based torso weighting [46], virtual reality-based balance training [47], and visuoproprioceptive training [48]) improves walking in adults with MS.

Reduced Gait Velocity

In addition to specific interventions directed to address specific impairments contributing to gait dysfunction in MS, recently a drug, dalfampridine, was found effective and was FDA approved to improve walking in people with MS. Dalfampridine is an extended-release formulation of 4-aminopyridine (4-AP), a potassium channel blocker that improves conduction in demyelinated nerves. Dalfampridine is taken orally in 10-mg tablets every 12 h. Specifically, in subjects with MS and slowed walking (25-foot timed walk >8 s), in two trials, dalfampridine was associated with approximately 25% increase in walking speed in drug responders, who were about one third of the subjects in each of these trials [49, 50•]. At this time, no a priori indicators of dalfampridine responders have been identified. One can conjecture that the drug is most likely to be effective in people whose gait is slowed by spinal cord demyelination and whose examination shows slowed gait with weakness, imbalance, or spasticity, but this has not been tested. Prior to the FDA approval of dalfampridine in 2010, 4-AP was occasionally prescribed via compounding pharmacists to people with MS but use of this preparation was limited by seizures associated with fluctuating serum drug levels. The current extended-release formulation of 4-AP, dalfampridine, is contraindicated in people with a history of seizures and it should not be used in those with impaired renal function due to the risk of elevated serum levels. In clinical trials, dalfampridine was associated with a greater than 5% incidence of urinary tract infections, insomnia, dizziness, headaches, and nausea. In addition, use of this drug may be limited by its cost of over $1000 per 30-day supply.

Conclusions

Gait abnormalities are common in people with MS and these abnormalities affect activity, participation, and quality of life. A brief but careful assessment of a person's walking can often detect the cause(s) of the gait impairment and help direct the most effective treatment. Common findings include weakness, spasticity, imbalance, and slowing. Evidence supports that specific treatment of these deficits (Table 2) can lead to specific improvements in the underlying impairments and also improved gait quality, speed, and efficiency, likely contributing to increased activity, community participation, and quality of life for people with MS.

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