Dalfampridine Extended Release Tablets—Clinical Need and Use

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Abstract

Walking impairment is one of the most serious and frequent problems reported by multiple sclerosis (MS) patients. Treatments to restore walking ability are an unmet clinical need. Dalfampridine, a potassium channel blocker, is the first US Food and Drug Administration (FDA)-approved drug to be indicated specifically to improve walking in patients with MS. In clinical trials the drug showed improved walking speeds, demonstrating efficacy in all four types of MS. In phase III trials, dalfampridine provided significant benefits to 35–43% of treated patients. Therefore, it will be critical to manage patient expectations appropriately.

Keywords

4-Aminopyridine, dalfampridine, fampridine, multiple sclerosis, walking impairment

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Multiple sclerosis (MS) affects more than 2.1 million people worldwide and is the most common cause of non-traumatic chronic neurological disability in young and middle-aged adults.[1,2] MS is associated with a considerable economic burden from medical costs and lost productivity.

MS presents patients with many challenges, among which walking impairment is one of the most serious. Walking impairment is most prevalent in patients who have had progressive MS for many years, but subtle changes in walking and gait may be discerned even in patients with recent disease onset.[3] These may not be apparent to observers, including healthcare providers, and may not be detectable in a routine physical examination. Decreased walking ability is regarded by most MS patients as the worst consequence of MS and has the most serious impact on their ability to continue in employment and to participate in leisure and social activities.[4,5] Therefore medications that can help restore walking ability in MS are greatly needed.[6]

While drugs such as baclofen and tizanidine are routinely prescribed to reduce spasticity in MS patients,[2] dalfampridine is the first drug specifically intended to improve walking in MS by targeting the neuropathology of demyelination. Dalfampridine extended release tablets (referred to in this article as 'dalfampridine') was the formulation used in recent pivotal clinical trials in MS. Dalfampridine gained US Food and Drug Adminstration (FDA) approval for the improvement of walking in patients with MS, as demonstrated by an increase in walking speed in January, 2010, and was the first drug approved for this indication.[2,7] Dalfampridine is also known by its previous US Adopted Name (USAN) and current International Nonproprietary Name (INN), 'fampridine', as well as its chemical name '4-aminopyridine' (4-AP).

The purpose of this article is to discuss the clinical need for a treatment to improve walking ability in MS. The discussion will consider the extent to which dalfampridine fulfills this need and how the expectations of patients receiving dalfampridine can be managed.

The Need for Treatments of Walking Impairment in Multiple Sclerosis

In MS, walking impairment is a frequent and serious problem. A majority (64–85%) of MS patients report some degree of walking impairment and 70% of people with walking difficulty as a result of MS report it to be the most challenging aspect of the disease.[8,9] The effect of MS on walking ability is often evaluated using the Expanded Disability Status Scale (EDSS) and the MS functional composite, which include walking performance as a major component.

Table 1: Pivotal Studies in the Development of Dalfampridine

Phase/Study/Design	No. Patients & Centers	Treatments	End-points	Efficacy Findings	Safety Findings
Phase II MS-F202[29] randomized, placebo-controlled (OL study extension in progress)	206 patients (with PRMS, RRMS, PPMS, or SPMS) at 24 centers in US and Canada	Randomized to dalfampridine (10, 15, or 20mg twice daily) or placebo for 15 weeks	% change in walking speed as determined by T25FW	10mg twice daily was optimal dose. There were significantly more consistent responders with all dalfampridine doses than with placebo (36.7% compared with 8.5%). The effect was sustained for at least 14 weeks.	Serious adverse events occurred in 4%, 0%, 8%, and 12% for placebo, 10, 15, and 20mg dalfampridine. These included MS relapse and seizure. Other adverse events that were increased with dalfampridine were headache, UTI, nausea, balance disorder, and fatigue.
Phase III MS-F203[30] randomized, placebo-controlled (OL study extension in progress)	301 patients (with PRMS, RRMS, PPMS, or SPMS) at 33 MS centers in US and Canada	Randomized to dalfampridine (10mg twice daily) or placebo for 14 weeks	% timed walk responders in T25FW (validated by MSWS-12)	Proportion of responders: 34.8% for dalfampridine and 8.3% for placebo (p<0.0001). Improvement in walking speed for timed-walk responders was 25.2% for dalfampridine and 4.7% for placebo-treated patients. Efficacy maintained over 14 weeks.	Serious adverse events including UTI and MS exacerbation occurred in 7% of dalfampridine and 0% of placebo-treated patients. Other adverse events increased with dalfampridine were balance disorder, headache, insomnia, nausea, and back pain.
Phase III MS-204[52] randomized, placebo-controlled (OL study extension in progress)	239 patients (with PRMS, RRMS, PPMS, or SPMS) at 39 MS centers	Randomized to dalfampridine (10mg twice daily) or placebo for 9 weeks	% timed walk responders in T25FW (validated by MSWS-12) (designed to confirm primary end-point)	Dalfampridine significantly increased the T25FW response: 42.9% for dalfampridine and 9.3% for placebo (p<0.0001).	The most notable increase in AE frequency for dalfampridine versus placebo was in UTIs, insomnia, headache, asthenia, dizziness, and nausea.

AE = adverse event; MS = multiple sclerosis; MSWS-12 = 12-Item Multiple Sclerosis Walking Scale; OL = open label; PRMS = progressive–relapsing multiple sclerosis; PPMS = primary–progressive multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis; SPMS = secondary–progressive multiple sclerosis; T25FW = Timed 25-Foot Walk; UTI = urinary tract infection.

The impact of walking impairment on daily life is substantial. Walking difficulty was reported to have a negative impact on the working lives of 79% of employed MS patients.[10] A recent study found a decrease in mean and annual incomes as mobility scores increase, and an association with unemployment even at low mobility scores of zero, one and two (mild gait disability).[9]

In another recent study patients reported that walking difficulty was the effect of MS that caused them the most concern (38% in patients who had MS for more than five years and 28% in patients who had MS for more than 15 years).[4] Gait impairment has also been associated with significant reductions in other patient-reported outcomes, notably quality of life (QOL) and activities of daily living (ADL).[6] Walking difficulty has been reported to cause the largest decrease in QOL (as measured by a health utility score) compared with pain and other problems affecting cognition, emotion, dexterity, and vision.[5]

As MS progresses, patients face increasing mobility impairment in the course of their disease. Reviewing the natural history of untreated MS indicates that some degree of walking impairment is likely to occur by eight years, a walking stick or cane is often needed by 15 years, and patients are usually confined to a wheelchair by 25–30 years.[11,12]

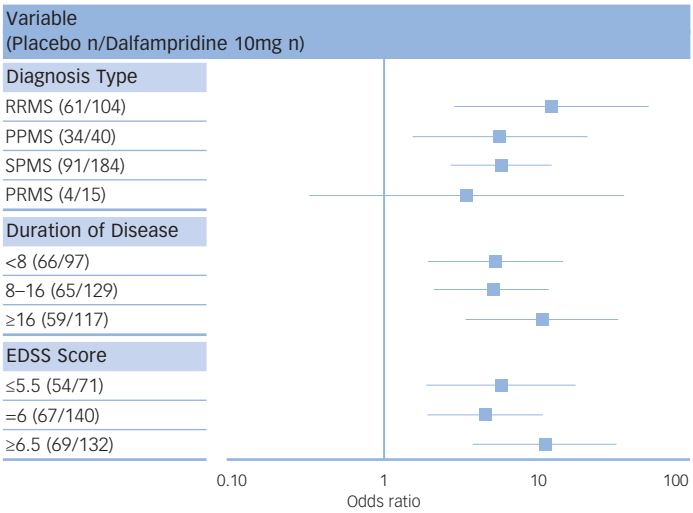
Until recently, no medication was approved to improve walking, although sometimes medications approved for the treatment of spasticity (e.g. baclofen and tizanidine) could be helpful. The only other treatments available until now have been rehabilitation, physiotherapy, exercise programs, use of a hip flexion orthosis, and electrical stimulation.[13–16] Physical treatments have been shown to play an important role in symptom management, but as of yet there has been insufficient research in this area. A randomized controlled trial is currently in progress to determine which form of physical activity optimizes outcome for MS patients.[17] Large numbers of patients with MS have differing levels of walking impairment and their abilities are likely to progressively decline. Therefore, there is a need for drug therapies in the treatment of walking impairment in MS.

Dalfampridine—A New Treatment for Walking Impairment in Multiple Sclerosis

History and Clinical Use

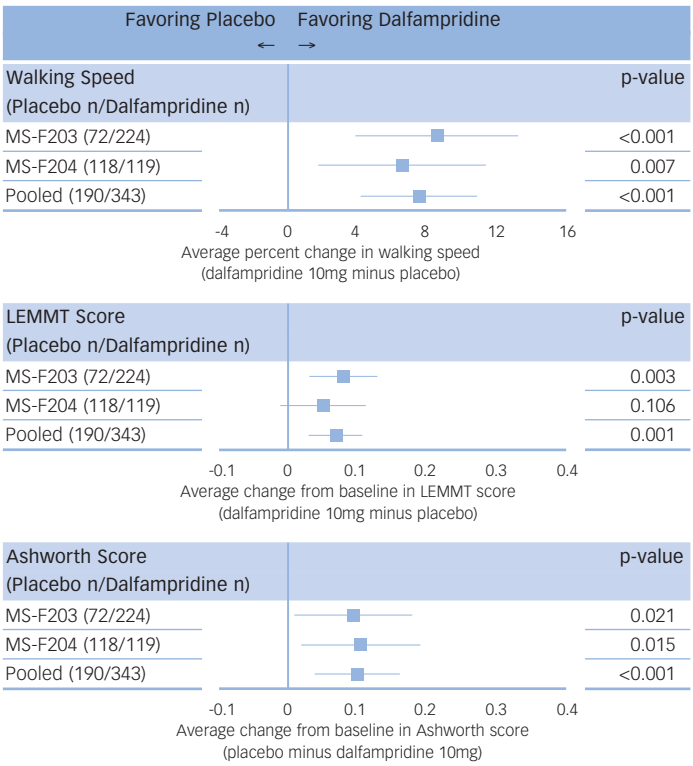
The active component of dalfampridine is 4-AP, which binds reversibly to potassium channels on neurons, blocking the ion conductance pathway. This blockade leads to the prolongation of action potentials in unmyelinated nerve fibers, increased transmitter release at synaptic endings and improved conduction in demyelinated nerve fibers.[18–20] Early 4-AP studies employed immediate release formulations and noted positive effects on visual, motor, and walking functions. However, adverse events including confusion, respiratory distress, locomotor, and balance problems, dizziness, and seizures were associated with doses higher than 20mg/day.[21,22] Furthermore, plasma levels were difficult to regulate with immediate release formulations. Pharmacokinetic studies showed that the improvement in neurological function was related to the total dose of 4-AP, whereas seizure induction was related to peak serum levels. Between 1991 and 1994, the development of sustained release

Figure 1: Timed Walk Responder Odds Ratios Comparing Dalfampridine with Placebo in Multiple Sclerosis Disease Subgroups in the MS-F203 and MS-F204 Clinical Studies



EDSS = Expanded Disability Status Scale; PPMS = primary–progressive multiple sclerosis; PRMS = progressive–relapsing multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis; SPMS = secondary–progressive multiple sclerosis.
Source: Acorda Therapeutics Inc., 2009.[32]

Figure 2: Changes in Objective Measures for Walking Speed, Muscle Strength and Muscle Tone in the MS-F203 and MS-F204 Clinical Studies Comparing Dalfampridine with Placebo



The Ashworth score is a five-point scale measuring an increase in muscle tone after a neurological event.[27] *LEMMT = Lower-extremity Manual Muscle Test;*[28,29] *MS = multiple sclerosis.*
Source: Acorda Therapeutics Inc., 2009;[32] *Brown et al. 2010.*[35]

(SR) technology for 4-AP enabled lower and more stable plasma levels with twice daily dosing, and resulted in the first clinical trials of the drug in MS that showed a significant improvement in timed ambulation.[23] The current oral formulation of dalfampridine is an extended release matrix containing 10mg of active ingredient.

The clinical development program of dalfampridine to date has included several randomized placebo-controlled clinical trials and respective ongoing extension studies. The main outcome measure of the trials has been the Timed 25-Foot Walk (T25FW), a widely used functional measurement in MS, which correlated strongly with performance on long-distance walking and endurance.[24,25] Other outcome measures included the 12-Item Multiple Sclerosis Walking Scale (MSWS-12), which assesses 12 different clinical aspects of walking;[26] the Lower Extremity Manual Muscle Test (LEMMT); the Ashworth score,[27] Clinician Global Impression (CGI), and Subject Global Impression (SGI). The design and results of these trials are summarized in *Table 1*.

The primary objective of the phase II trial (MS-F201) was to determine the tolerability of escalating doses of dalfampridine from 10 to 40mg twice daily. While the study demonstrated an increase in lower-extremity muscle strength and walking speed, two patients experienced seizures, one at 30mg twice daily, the other at 35mg twice daily. Discontinuations due to adverse events occurred at doses of 25mg and higher. Therefore, subsequent studies concentrated on evaluating doses in the range of 10-20mg.[28] A follow-up phase II trial, (MS-F202) determined the optimal dose (10mg twice daily) and concluded that the T25FW was an appropriate response criterion.[29]

The pivotal MS-F203 trial (a phase III study involving 301 patients with all four types of MS), demonstrated that dalfampridine improved walking speed as measured by the prospectively-defined responder rate. A responder was defined as a patient who showed faster walking speed for at least three of four 'on-drug' visits than the fastest speed achieved among five 'off-drug' visits. The effect was maintained over 14 weeks.[30] The MS-F204 phase III trial of 239 MS patients also demonstrated an improvement in walking speed in dalfampridine-treated timed walk responders, with the results on the primary end-point and safety data consistent with MS-F202 and MS-F203. It also demonstrated that the effect was maintained over the inter-dosing period.[31]

Analyses of combined data from the MS-F202, MS-F203, and MS-F204 trials showed that the primary outcome measure was achieved with high statistical significance. Pooled analysis included 639 patients (67.4% female, mean age 51.5 years). Most had progressive disease: 51.5% had secondary-progressive MS, 29.6% had relapsing–remitting MS, 16.0% with primary-progressive MS, and 3.0% had progressive-relapsing MS. Timed walk response was markedly improved for patients receiving dalfampridine 10mg compared with placebo, regardless of disease progression, duration of disease or EDSS score as shown by odds ratios for these parameters plotted in *Figure 1*.[32–34] The average improvement in walking speed among timed walk responders was 25.3% (range 3.9–110.4%). Responders also showed significantly reduced MSWS-12 scores (indicating improvement), significantly improved CGI and SGI scores, and significant improvements over placebo in lower-extremity muscle strength and Ashworth score (see *Figure 2*).[32,35] More

dalfampridine-treated than placebo patients had increases in walking speed of ≥20, ≥30 and, ≥40%, moving from restricted (household) mobility (walking speed <1.3ft/s) to full community mobility (walking speed >2.6ft/s).[34] These community ambulation categories were originally developed for assessing stroke patients.[36] No dalfampridine responders showed a decline in this ability (see *Table 2*).[34] Efficacy was independent of MS disease type, duration of disease, and baseline EDSS score. Efficacy was also similar irrespective of concomitant immunomodulator use: interferon betas (IFNβ) (36.8%), glatiramer acetate (37.1%), or natalizumab (27.3%) compared with efficacy in 39.8% of patients not on immunomodulatory therapy.[33]

However, not all patients receiving dalfampridine showed improvements in walking ability. The mean effect was small, since 35–43% of people had a consistent response to treatment, but that group experienced meaningful change. In general, the greater the increase in walking speed, the smaller the proportion of patients achieving it. For example, 54.1% of patients showed an improvement in walking speed of ≥10% but only 31.5% showed an improvement of ≥20%.[37]

An interim analysis of two open-label extension studies (MS-F203EXT and MS-F204EXT) has recently been presented. Patients were assessed at two, 14, and 26 weeks, and every six months up to 2.5 years. The walking speed of patients who continued on dalfampridine from the double-blind trial remained above baseline whereas those not on dalfampridine fell below that level. The response tended to drop back to baseline for patients continuing on dalfampridine at 2.5 years in MS-F203EXT and at 1.2 years in MS-F204EXT.[38]

Safety Data

The safety analysis population for the combined studies included 638 patients. The profile of adverse effects was consistent over all three studies. The most common adverse effects were falls, urinary tract infections (UTI), insomnia, asthenia, dizziness, headaches, nausea, and back pain, which were mostly mild to moderate and transient in nature (see *Table 3*).[37] In the treatment group, 2.8% of patients withdrew from the study because of adverse effects compared with 2.1% in the placebo group. Falls were seen at similar levels across treatment and placebo group patients, but UTIs were slightly more frequent with dalfampridine. These findings are consistent with previous safety results shown in clinical studies using dalfampridine.[2,28,30]

The incidence of seizures was the biggest safety concern in these trials, since earlier studies indicated that dalfampridine had a narrow toxic–therapeutic ratio.[39] However, those studies did not use extended release formulations. The frequency of seizures in these trials was low and similar to the background rate of first seizure of approximately 0.35/100 patient-years. Five additional seizures were reported in patients in the open-label extension studies but the onset of seizure is unrelated to the time on the drug. No new adverse effects have been noted.[40] The incidence of MS relapse was low in the pooled treatment (5.3%) and placebo groups (3.8%). Post-treatment, the incidence of relapse was higher in the treatment group than the placebo group (1.8 versus 0.4%).[41]

Cases of unintentional overdose of compounded 4-AP in MS have been reported[42] and seizures can occur with overdose of both the immediate and extended-release formulations.[28,43] Overall, dalfampridine is well tolerated. However, it is contraindicated in patients with a history of seizures and in those with moderate or severe renal impairment. A risk evaluation and mitigation strategy (REMS) program, involving a detailed medication guide that stresses the necessity for adherence to the 10mg twice-daily dosage, is now available.[44]

Table 2: Combined Changes in Walking Ability in Dalfampridine Responders, Dalfampridine Non-responders, and Patients Receiving Placebo in the MS-F202, MS-F203, and MS-F204 Studies

Change in Walking Ability	Dalfampridine-treated		Placebo-treated
	Responders	Non-responders	
Limited → full community mobility (improvement)	+22.4%	+9.7%	+10.5%
Household → limited community mobility (improvement)	+10.2%	+1.2%	+1.7%
Full community → limited community (worsening)	0%	–1.6%	–2.1%
Limited community → household	0%	–1.6%	–1.7%
Net shift in mobility	+32.6%	+7.7%	+8.4%

Source: Edwards et al., 2010.[34]

Table 3: Combined Numbers (and Percentage) of Treatment-emergent Adverse Events Reported by ≥5% of Patients Receiving Either Dalfampridine or Placebo in the MS-F202, MS-F203, and MS-F204 Studies

Treatment-emergent Adverse Events (TEAEs)	Incidence Number of Patients (%)	
	Dalfampridine 10mg (n=400)	Placebo (n=238)
Total patients reporting any TEAE	339 (84.8)	175 (73.5)
TEAEs leading to discontinuation	11 (2.8)	5 (2.1)
Fall	64 (16.0)	39 (16.4)
UTIs	58 (14.5)	22 (9.2)
Insomnia	37 (9.3)	9 (3.8)
Asthenia	33 (8.3)	10 (4.2)
Dizziness	31 (7.8)	10 (4.2)
Headache	30 (7.5)	10 (4.2)
Nausea	28 (7.0)	6 (2.5)
Fatigue	26 (6.5)	11 (4.6)
Balance disorder	23 (5.8)	3 (1.3)
Upper respiratory tract infection	23 (5.8)	17 (7.1)
MS relapse	21 (5.3)	9 (3.8)
Back pain	22 (5.5)	5 (2.1)

MS = multiple sclerosis; UTI = urinary tract infection. Source: Schapiro et al. 2010.[37]

Managing Expectations of Dalfampridine in Multiple Sclerosis Patients

Any medication that offers improvements in walking in MS will be of great interest to patients and may raise hopes of restoring lost mobility. However, patient expectations of dalfampridine could be too high and it is critical that patients have a realistic view. Dalfampridine provides

Figure 3: Combined Improvement in Walking Speed Produced by Dalfampridine or Placebo in Three Pivotal Clinical Trials (MS-F202, MS-F203 and MS-F204)

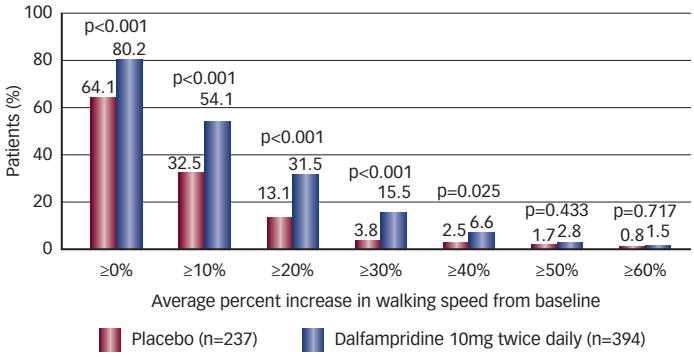
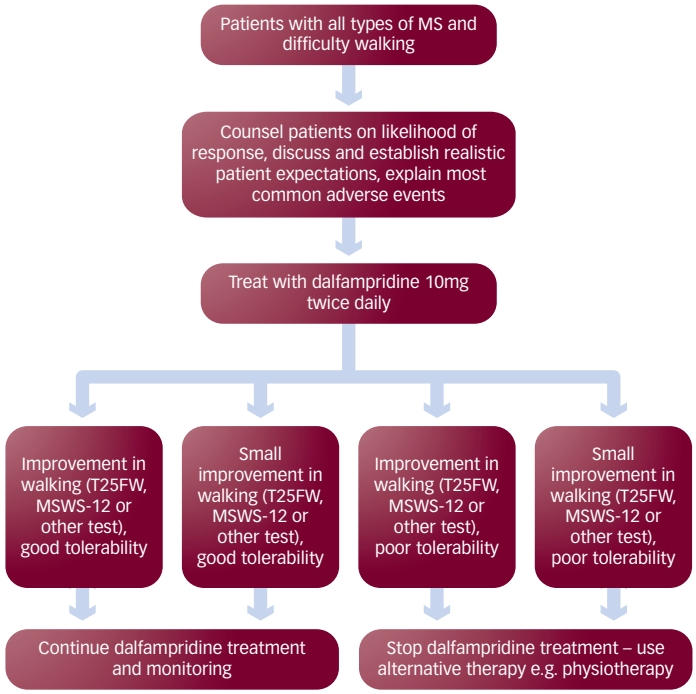


Figure 4: Strategy for Treating Walking Impairment in Multiple Sclerosis Patients with Dalfampridine



In the case of a patient receiving dalfampridine who has very limited or no perceived improvement in walking ability but has good tolerability, one strategy may be to discontinue the drug and observe whether the patient subsequently becomes aware that the drug was more effective than they realized. MS = multiple sclerosis; MSWS-12 = 12-Item Multiple Sclerosis Walking Scale; T25FW = Timed 25-Foot Walk.

significant benefits to some patients but not all. A substantial proportion of patients may show little or no improvement in walking and a minority may suffer adverse effects that they can find difficult to tolerate. It is very important that prescribers are aware of these limitations and explain them to patients before they begin treatment.

Unrealistic expectations of disease modifying therapies (DMTs) have been previously shown to result in poor treatment adherence, and a perceived lack of efficacy accounts for 30 to 52% of discontinuations of DMTs.[45,46] Among patients receiving IFNβ therapy in one study, 57% of patients had unrealistic expectations regarding reduction in attack rate and 34% regarding improvement in functional status before the initiation of therapy. Education reduced these figures, but following this education, expectations remained high and were significantly related to the discontinuation of therapy within six months.[47] In addition, depression and flu-like symptoms were also found to be associated with the discontinuation of therapy.

Previous studies have shown that managing patient expectations and maintaining good communications between healthcare providers and patients can improve adherence to DMT and, consequently, improve outcomes.[48,49] Self-efficacy, self-esteem, and hope have been reported as predictors of adherence to DMT.[50] Therefore it is important to maintain an open and trusting relationship between patients and healthcare providers. Understanding of and empathy for the patient's fears, expectations, and health beliefs are crucial. Healthcare providers should give patients the necessary information for them to make informed decisions regarding the available treatment options and should monitor and counsel them throughout treatment. In the case of dalfampridine, patients could be prescribed this drug for a number of years; therefore it will be critical to ensure that only those patients who respond to treatment and tolerate it well receive longer-term dalfampridine therapy.

Conclusion and Future Developments

Dalfampridine has been shown in clinical trials to improve walking ability in MS and therefore has the potential to increase the function and QOL of many patients with MS. It remains to be determined how to identify those most likely to respond to treatment. Since recent clinical trials demonstrate that approximately one-third of patients with all disease types and disability ranges show benefit from dalfampridine treatment, patient education programs should include this information. These programs should help to limit unrealistic expectations of treatment effects and guide patients to understand the chances of treatment efficacy and the risk of adverse events. Such strategies are also likely to help limit dalfampridine treatment to those patients who may potentially respond to the medication. Patients receiving dalfampridine should be encouraged to maintain frequent communication with their healthcare provider. Guidelines should be established to describe the best practice when using dalfampridine to treat walking impairment in MS and to recommend the best treatment practice for both responders and non-responders to dalfampridine. A potential strategy for guidance for the use of dalfampridine, integrating patient counseling stages, and measurement of walking ability is outlined in *Figure 4*.

The increased incidence of seizures has been of concern in the clinical development of dalfampridine. However, given the low frequency of seizures observed so far in clinical trials, it is impossible to draw firm conclusions on the exposure-response relationship. At the intended dose of 10mg twice daily, the data suggest that the risk is low. This emphasizes the critical need to educate practitioners and patients on the critical importance of using only the recommended dose of dalfampridine. A growing body of evidence suggests that the combination of pharmacological management and rehabilitation may result in better outcomes than one therapeutic intervention alone.[51] Dalfampridine should be part of a wellness program including a DMT, exercise, time and stress management, diet, sleep, and regular visits to the healthcare provider.[2] ■

1. National Multiple Sclerosis Society, What we know about MS: Who gets MS, 2011. Available at: www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx (accessed January 13, 2011).
2. Kachuck NJ, Sustained release oral fampridine in the treatment of multiple sclerosis, *Expert Opin Pharmacother*, 2009;10:2025–35.
3. Martin CL, Phillips BA, Kilpatrick TJ, et al., Gait and balance impairment in early multiple sclerosis in the absence of clinical disability, *Mult Scler*, 2006;12:620–8.
4. Heesen C, Bohm J, Reich C, et al., Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable, *Mult Scler*, 2008;14:988–91.
5. Jones CA, Pohar SL, Warren S, et al., The burden of multiple sclerosis: a community health survey, *Health Qual Life Outcomes*, 2008;6:1–7.
6. Sutliff MH, Contribution of impaired mobility to patient burden in multiple sclerosis, *Curr Med Res Opin*, 2010;26:109–19.
7. Bever CT, Judge SI, Sustained-release fampridine for multiple sclerosis, *Expert Opin Investig Drugs*, 2009;18:1013–24.
8. Harris Interactive for the National MS Society and Acorda Therapeutics. Key findings from two new multiple sclerosis surveys. Available at: www.nationalmssociety.org/download.aspx?id=1018 (accessed January 19, 2011).
9. Salter AR, Cutter GR, Tyry T, et al., Impact of loss of mobility on instrumental activities of daily living and socioeconomic status in patients with MS, *Curr Med Res Opin*, 2010;26:493–500.
10. Cheo C, Larocca NG, Gait impairment in multiple sclerosis: the patient's perspective, 23rd Annual Meeting of the Consortium of Multiple Sclerosis Centers, Atlanta, Georgia, 2009; poster 25.
11. Compston A, *McAlpine's Multiple Sclerosis*, London: Churchill Livingstone, 2005.
12. Confavreux C, Vukusic S, Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment, *Clin Neurol Neurosurg*, 2006;108:327–32.
13. Barrett CL, Mann GE, Taylor PN, et al., A randomized trial to investigate the effects of functional electrical stimulation and therapeutic exercise on walking performance for people with multiple sclerosis, *Mult Scler*, 2009;15:493–504.
14. Cakt BD, Nacir B, Genc H, et al., Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study, *Am J Phys Med Rehabil*, 2010;89:446–57.
15. Goldman MD, Cohen JA, Fox RJ, et al., Multiple sclerosis: treating symptoms, and other general medical issues, *Cleve Clin J Med*, 2006;73:177–86.
16. Sutliff MH, Naft JM, Stough DK, et al., Efficacy and safety of a hip flexion assist orthosis in ambulatory multiple sclerosis patients, *Arch Phys Med Rehabil*, 2008;89:1611–7.
17. Coote S, Garrett M, Hogan N, et al., Getting the balance right: a randomised controlled trial of physiotherapy and Exercise Interventions for ambulatory people with multiple sclerosis, *BMC Neurol*, 2009;9:34.
18. Blight AR, Effect of 4-aminopyridine on axonal conduction-block in chronic spinal cord injury, *Brain Res Bull*, 1989;22:47–52.
19. Sherratt RM, Bostock H, Sears TA, Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres, *Nature*, 1980;283:570–2.
20. Shi R, Kelly TM, Blight AR, Conduction block in acute and chronic spinal cord injury: different dose-response characteristics for reversal by 4-aminopyridine, *Exp Neurol*, 1997;148:495–501.
21. Stefoski D, Davis FA, Faut M, et al., 4-Aminopyridine improves clinical signs in multiple sclerosis, *Ann Neurol*, 1987;21:71–7.
22. van Diemen HA, Polman CH, van Dongen TM, et al., The effect of 4-aminopyridine on clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study, *Ann Neurol*, 1992;32:123–30.
23. Schwid SR, Petrie MD, McDermott MP, et al., Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis, *Neurology*, 1997;48:817–21.
24. Albrecht H, Wotzel C, Erasmus LP, et al., Day-to-day variability of maximum walking distance in MS patients can mislead to relevant changes in the Expanded Disability Status Scale (EDSS): average walking speed is a more constant parameter, *Mult Scler*, 2001;7:105–9.
25. Kaufman M, Moyer D, Norton J, The significant change for the Timed 25-foot Walk in the multiple sclerosis functional composite, *Mult Scler*, 2000;6:286–90.
26. Hobart JC, Riazi A, Lamping DL, et al., Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12), *Neurology*, 2003;60:31–6.
27. Ashworth B, Preliminary Trial of Carisoprodol in Multiple Sclerosis, *Practitioner*, 1964;192:540–2.
28. Goodman AD, Cohen JA, Cross A, et al., Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study, *Mult Scler*, 2007;13:357–68.
29. Goodman AD, Brown TR, Cohen JA, et al., Dose comparison trial of sustained-release fampridine in multiple sclerosis, *Neurology*, 2008;71:1134–41.
30. Goodman AD, Brown TR, Krupp LB, et al., Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial, *Lancet*, 2009;373:732–8.
31. Goodman AD, Schwid SR, Brown TR, Sustained-release fampridine consistently improves walking speed and leg strength in multiple sclerosis: a phase 3 trial, World Congress on Treatment and Research in Multiple Sclerosis (WCTRIMS), Montreal, Canada, 2008;abstract P909.
32. Acorda Therapeutics Inc., NDA 22–250 FDA. Peripheral and Central Nervous System Drugs Advisory Committee. Fampridine-SR for improved walking ability in patients with multiple sclerosis, 2009. Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM191030.pdf (accessed January 14, 2011).
33. Brown T, Schapiro R, Edwards K, Response to treatment with dalfampridine extended release tablets in patients with multiple sclerosis is independent of baseline patient characteristics and concomitant immunomodulator therapy, 62nd American Academy of Neurology Annual Meeting, Toronto, Ontario, Canada, 2010;P06.136.
34. Edwards K, Brown T, Schapiro R, Dalfampridine extended release tablets improve walking speed across a wide range of baseline deficits: pooled data from three placebo-controlled studies in patients with multiple sclerosis, 62nd American Academy of Neurology Annual Meeting, Toronto, Ontario, Canada, 2010;P06.223.
35. Brown T, Schapiro R, Goodman AD, Response to treatment with prolonged-release fampridine tablets in patients with multiple sclerosis is independent of demographic, clinical, and patient-reported characteristics, 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Gothenburg, Sweden, 2010;P921.
36. Perry J, Garrett M, Gronley JK, et al., Classification of walking handicap in the stroke population, *Stroke*, 1995;26:982–9.
37. Schapiro R, Goodman AD, Brown T, et al., dalfampridine improves walking in ms patients: pooled data from 3 clinical trials, presented at the 24th Annual Meeting of the Consortium of Multiple Sclerosis Centers San Antonio, Texas, 2010.
38. Goodman AD, Brown TR, Edwards KR, et al. interim analysis of open-label extension studies of sustained release fampridine in patients with multiple sclerosis, 62nd American Academy of Neurology Annual Meeting, Toronto, Ontario, Canada, 2010; S01.008.
39. Polman CH, Bertelsmann FW, de Waal R, et al., 4-Aminopyridine is superior to 3,4-diaminopyridine in the treatment of patients with multiple sclerosis, *Arch Neurol*, 1994;51:1136–9.
40. Goodman AD, Brown T, Edwards K, et al., analysis of open-label extension studies of prolonged-release fampridine tablets (fampridine) in multiple sclerosis, 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Gothenburg, Sweden, 2010;P518.
41. FDA, NDA 22–250: Fampridine AC Backgrounder, 2009; 41–2. Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM185663.pdf (accessed January 14, 2011).
42. Burton JM, Bell CM, Walker SE, et al., 4-aminopyridine toxicity with unintentional overdose in four patients with multiple sclerosis, *Neurology*, 2008;71:1833–4.
43. Solari A, Uitdehaag B, Giuliani G, et al., Aminopyridines for symptomatic treatment in multiple sclerosis, *Cochrane Database Syst Rev*, 2002;CD001330.
44. Acorda Therapeutics Inc., NDA 22–250 Ampyra (Dalfampridine) extended release tablets, 2010. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2010/022250s000REMS.pdf (accessed January 14, 2011).
45. Tremlett HL, Oger J, Interrupted therapy: stopping and switching of the beta-interferons prescribed for MS, *Neurology*, 2003;61:551–4.
46. Walther EU, Dietrich E, Hohlfeld R, Therapy of multiple sclerosis with interferon-beta-1b. Educating the patient and managing side-effects, *Nervenarzt*, 1996;67:452–6.
47. Mohr DC, Goodkin DE, Likosky W, et al., Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment, *Mult Scler*, 1996;2:222–6.
48. Brandes DW, Callender T, Lathi E, et al., A review of disease-modifying therapies for MS: maximizing adherence and minimizing adverse events, *Curr Med Res Opin*, 2009;25:77–92.
49. Osterberg L, Blaschke T, Adherence to medication, *N Engl J Med*, 2005;353:487–97.
50. Fraser C, Hadjimichael O, Vollmer T, Predictors of adherence to Copaxone therapy in individuals with relapsing-remitting multiple sclerosis, *J Neurosci Nurs*, 2001;33:231–9.
51. Bennett SE, Effective rehabilitation methods in patients with multiple sclerosis, *US Neurology*, 2010;5(2):67–71.
52. Goodman AD, Brown TR, Edwards KR, et al., A phase 3 trial of extended release oral dalfampridine in multiple sclerosis, *Ann Neurol*, 2010;68:494–502.