Multiple Sclerosis

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.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.5 Therefore medications that can help restore walking ability in MS are greatly needed.

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 Administration (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 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.1,2 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.
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. 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). In another recent study patients reported that walking difficulty was related to progressively decline. Therefore, there is a need for drug therapies in patients. 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

Exercise programs, use of a hip flexion orthosis, and electrical stimulation 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. A randomized controlled trial is currently in progress to determine which form of physical activity optimizes outcome for MS patients. A randomized controlled trial is currently in progress to determine which form of physical activity optimizes outcome for MS patients.

**Dalfampridine Extended Release Tablets—Clinical Need and Use**

**Table 1: Pivotal Studies in the Development of Dalfampridine**

<table>
<thead>
<tr>
<th>Phase/Study/Design</th>
<th>No. Patients &amp; Centers</th>
<th>Treatments</th>
<th>End-points</th>
<th>Efficacy Findings</th>
<th>Safety Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II MS-F2022 randomized, placebo-controlled (OL study extension in progress)</td>
<td>206 patients (with PRMS, RRMS, PPMS, or SPMS) at 24 centers in US and Canada</td>
<td>Randomized to dalfampridine (10, 15, or 20mg twice daily) or placebo for 15 weeks</td>
<td>% change in walking speed as determined by T25FW</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Phase III MS-F203 randomized, placebo-controlled (OL study extension in progress)</td>
<td>301 patients (with PRMS, RRMS, PPMS, or SPMS) at 33 MS centers in US and Canada</td>
<td>Randomized to dalfampridine (10mg twice daily) or placebo for 14 weeks</td>
<td>% timed walk responders in T25FW (validated by MSWS-12)</td>
<td>Proportion of responders: 34.8% for dalfampridine and 8.3% for placebo (p&lt;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</td>
<td>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.</td>
</tr>
<tr>
<td>Phase III MS-204 randomized, placebo-controlled (OL study extension in progress)</td>
<td>239 patients (with PRMS, RRMS, PPMS, or SPMS) at 39 MS centers</td>
<td>Randomized to dalfampridine (10mg twice daily) or placebo for 9 weeks</td>
<td>% timed walk responders in T25FW (validated by MSWS-12) (designed to confirm primary end-point)</td>
<td>Dalfampridine significantly increased the T25FW response: 42.9% for dalfampridine and 9.3% for placebo (p&lt;0.0001).</td>
<td>The most notable increase in AE frequency for dalfampridine versus placebo was in UTIs, insomnia, headache, asthma, dizziness, and nausea.</td>
</tr>
</tbody>
</table>

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

**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**

<table>
<thead>
<tr>
<th>Variable (Placebo n/Dalfampridine 10mg n)</th>
<th>Diagnosis Type</th>
<th>Duration of Disease</th>
<th>EDSS Score</th>
<th>Ashworth Score</th>
<th>LEMMT Score</th>
<th>Walking Speed</th>
<th>Pooled (190/343)</th>
<th>MS-F204 (118/119)</th>
<th>MS-F203 (72/224)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RRMS (61/104)</td>
<td>&lt;8 (66/97)</td>
<td>≤5.5 (54/71)</td>
<td>−0.1</td>
<td>−0.1</td>
<td>−0.1</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PPMS (34/40)</td>
<td>8–16 (65/129)</td>
<td>=5 (68/140)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>SPMS (91/184)</td>
<td>≥16 (59/117)</td>
<td>≥5.5 (69/132)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>PRMS (4/15)</td>
<td>≥16 (59/117)</td>
<td>≥5.5 (69/132)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**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 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. Other outcome measures included the 12-item Multiple Sclerosis Walking Scale (MSWS-12), which assesses 12 different clinical aspects of walking; the Lower Extremity Manual Muscle Test (LEMMT); the Ashworth score; 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. 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.

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. 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).
dalfampridine-treated than placebo patients had increases in walking speed of ≥20, ≥30, and ≥40%, moving from restricted (household) mobility (walking speed <1.3 ft/s) to full community mobility (walking speed ≥2.6 ft/s).28 These community ambulation categories were originally developed for assessing stroke patients.28 No dalfampridine responders showed a decline in this ability (see Table 2).28 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.32

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%.32

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.35

### 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).33 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 placebo group. Falls were seen at similar levels across treatment and placebo group patients, but UTIs were slightly more frequent with placebo group.

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.39 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%).39

### 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...
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. 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.