

Guidelines and Best Practices for Appropriate Use of Dalfampridine in Managed Care Populations

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Multiple sclerosis (MS) is a complex chronic, progressive neurological disorder that leads to significant disability among young individuals, resulting in poor quality of life (QOL) for patients and high costs for managed care organizations. Currently disease-modifying treatments (DMTs) constitute the platform pharmacotherapy for MS patients. Eight DMTs are currently approved by the Food and Drug Administration (FDA) for the treatment of MS. Clinical efficacy is usually measured by the ability of these medications to decrease the number of clinical relapses or exacerbations, to minimize the development of new lesions on the brain or spinal cord of patients, and to reduce the accumulation of disability over time. Despite their efficacy, for many patients DMTs do not adequately address QOL in general and impaired walking in particular. Annual direct medical costs for MS with gait impairment average nearly \$21,000 per patient.¹ Decreased mobility is also associated with higher absenteeism rates,² thus raising indirect costs. Over 3 years, a 1-level change reflecting worse mobility on the patient self-report Performance Scale Mobility Subscale resulted in an average of 4.4 missed work-days per 6 months.² Indirect costs also include lost income from eventual unemployment, often related to impaired mobility.^{1,3}

Ampyra (dalfampridine extended release tablets, hereafter “dalfampridine”) is approved as a treatment to improve walking in patients with MS.⁴ It has been shown to increase walking speed by approximately 25% in responders (patients whose walking speed was faster for at least 3 of the 4 treatment period visits than the maximum speed of the 5 off-drug visits [4 visits before and 1 visit 2 weeks after the end of double-blind treatment]).^{5,6} Responders, independent of treatment, showed improvements in the 12-item Multiple Sclerosis Walking Scale (MSWS-12), which measures the patient perspective on ambulatory disability, and Subject Global Impression (SGI).^{5,6}

The active ingredient in dalfampridine is 4-aminopyridine (4-AP).⁴ The United States Adopted Name (USAN) for 4-AP was fampridine, but at approval the FDA required the name change to avoid potential confusion with an existing drug, and the name dalfampridine was accepted by the USAN Council.⁶ Outside

Abstract

Multiple sclerosis (MS) is a complex chronic, progressing disease that contributes to poor quality of life (QOL) for patients and high costs for managed care organizations. Currently, disease-modifying treatments (DMTs) constitute the platform pharmacotherapy for MS patients. Despite their efficacy, for many patients taking DMTs there is little evidence of their effect on QOL in general or symptom management. Impaired mobility contributes to direct and indirect costs. Annual direct medical costs for MS with gait impairment average nearly \$21,000 per patient. Decreased mobility is also associated with higher absenteeism rates, thus raising indirect costs. Dalfampridine has been shown to improve walking in patients with MS. The effects of dalfampridine can complement those of DMTs by improving walking ability as a key component of overall mobility and a primary concern among many MS patients. Improved walking could potentially help contain some of the direct and indirect costs associated with MS care.

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For author information and disclosures, see end of text.

the United States, the drug continues to be known by the International Nonproprietary Name fampridine.⁷

The effects of dalfampridine can complement those of DMTs by addressing walking, which ranks as a primary concern among many MS patients.¹ Dalfampridine is not a substitute for DMTs, but can be safely combined with them. Its use should not preclude the use of DMTs or inhibit full access to DMTs. Managed care professionals may find that dalfampridine opens new opportunities for improving patient outcomes and containing costs.

Current Pharmacotherapies and Advances in Treatment

Because no cure exists and current primary agents have high costs and limited results, MS care can be frustrating for patients, providers, and payers. The number of relapses can predict total costs to managed care organizations.⁸ DMTs, the current foundation of treatment,⁸ are essential in reducing the frequency of relapses, reducing accumulation of disability, and delaying disease progression. Nevertheless, it is estimated that only 67% of patients with MS receive appropriate DMT therapy.^{8,9}

Nonpersistence and discontinuation rates for DMT treatment have been reported as high as 43%.^{10,11} Common reasons for discontinuation include adverse events (AEs) (52% of patients), disease progression documented by a physician (40%), and patient perception of ineffectiveness (20%).¹⁰ The clinical efficacy of DMTs is measured by long-term outcomes. This leads to the perception from patients that the medications are not helpful or effective. Many also have other symptomatic and QOL needs that might be addressed by other pharmacotherapies.

Of current DMTs, the 4 interferon-beta agents (IFNB) have potential for reduced treatment effect over time because of neutralizing antibodies.^{12,13,14} The evidence for IFNB and glatiramer acetate (GA) includes many clinical trials that did not include dropouts in the analysis or measure the effect of treatment on QOL.¹⁰ Of more recent additions to the DMTs, natalizumab was temporarily withdrawn from the market because of progressive multifocal leukoencephalopathy and is now available only under highly restricted conditions at special centers.^{15,16} Mitoxantrone has a black box warning about cardiotoxicity and treatment-related leukemia.¹⁷ The recent approval of an oral DMT, fingolimod,¹² was an important advance over DMTs that require injection. However, it too has serious safety concerns, including risk of infections, bradycardia, and atrioventricular block.^{18,19} While researchers work to develop safer and more effective agents, managed care

organizations still must find cost-effective ways to optimize patient outcomes with currently available treatments.

With the advent of DMTs, the ability to delay progression was a major scientific advance over previous treatments. However, it is equally important to approach the disease from the perspective of the patient experiencing symptoms and deterioration of QOL. Therefore, symptom-specific treatments with new FDA indications should also be viewed as important advances. New FDA approvals in 2010 included onabotulinumtoxin A (Botox) for upper-limb spasticity,²⁰ dextromethorphan hydrobromide with quinidine sulfate (Nuedexta) for pseudobulbar affect,²¹ and dalfampridine (Ampyra) for walking.⁴ Of the 3, dalfampridine, the first FDA-approved treatment to improve walking, should have wide application, because approximately 90% of patients with MS have mobility impairments¹ and most consider mobility their biggest disease-related challenge.^{1,22}

Using dalfampridine concomitantly with DMTs is safe and effective; 63% of patients in the dalfampridine phase 3 clinical trials were taking DMTs and no differences in efficacy were noted.⁴ In open-label extensions of the trials, also with positive results, many patients were continuing with DMTs.²³ Dalfampridine can also be used with medications for other MS symptoms and comorbidities.

Dalfampridine has different actions from DMTs and is intended for symptom management only, not delay of disease progression. Therefore, dalfampridine can be considered complementary to DMTs. Use of one should not preclude or restrict access to the other.

Expert Recommendations and Treatment Guidelines for MS

With disease management programs, education, and other initiatives that apply nationally accepted guidelines, managed care organizations and health plans have produced improvements in chronic diseases.⁸ Although no single set of guidelines is generally recognized for overall MS management,⁸ expert recommendations evaluate some current treatment options.

In Clinical Practice Guidelines released in 2002, the American Academy of Neurology (AAN) recommended IFNB and GA for patients with relapsing-remitting MS (RRMS).²⁴ The guidelines also recommended glucocorticoids for treatment of acute relapse.²⁴ An AAN evidence-based review of mitoxantrone (2003) did not recommend against its use in MS, but concluded that its potential toxicity “considerably limits its use.”²⁵ A 2010 analysis of more recent evidence concluded that mitoxantrone-related

Table 1. Consortium of Multiple Sclerosis Centers Principles for Positive MS Outcomes³¹

Persons affected by MS should have:
• Timely and accurate diagnosis
• Knowledge necessary for disease management
• Effective disease management skills and strategies
• An integrated care plan that promotes empowerment
• Functional abilities and safety measures maximized
• Relationship with an interdisciplinary team established and sustained
• Optimal symptom management
• Optimal health-related quality of life
• Care management that stimulates research possibilities related to evidence-based practice
MS indicates multiple sclerosis.

risk of systolic dysfunction and leukemia is higher than at the time of the previous report.¹⁷ After a similar review of natalizumab (2008), the AAN recommended that the agent be reserved for relapsing-remitting patients who have failed other therapies or who have a particularly aggressive disease course.²⁶ The AAN has not published practice guidelines regarding fingolimod (the newest FDA-approved DMT) or regarding treatment of individual symptoms of MS.

A Disease Management Consensus Statement of the National Clinical Advisory Board of the National Multiple Sclerosis Society (NMSS) was released in 2007.⁹ The statement recommends initiating DMTs as soon as possible after diagnosis of MS.⁹ In 2008, the board also recommended corticosteroids for treatment of relapses.²⁷ According to the Disease Management Consensus Statement, “All of these FDA-approved agents should be included in formularies and covered by third party payers so that physicians and patients can determine the most appropriate agent on an individual basis; failure to do so is unethical and discriminatory.”²⁹ The quote, which refers to DMTs, would appear to support FDA approval as a foundation of confidence in a medication. FDA approval has since been granted to the 3 symptomatic treatments mentioned above.

The Consortium of Multiple Sclerosis Centers (CMSC) published guidelines specific to treatment of 3 MS symptoms. The guidelines for management of fatigue (1998), urinary dysfunction (1999), and spasticity (2005) discuss and recommend numerous pharmacologic agents for these symptoms.^{28,29,30} All 3 practice guidelines were issued before the most recent FDA approvals of symptom-specific treatments. In 2005, CMSC also released general

Recommendations for Care of Those Affected by MS. The recommendations stress goals to “maximize physical and psychological functioning” and state that persons with MS should have support for QOL issues (Table 1).³¹ Without mentioning specific drug classes or agents, the CMSC recommends DMTs, therapy for acute relapses, and current symptomatic treatments for patients at all levels of functional limitation.³¹

To summarize, existing treatment guidelines predate the FDA approval of dalfampridine, but support active disease management, careful consideration of medication safety, treatment individualized to patient needs, treatment for specific symptoms, and management to improve QOL.

Use of Dalfampridine in the Managed Care Setting

Dalfampridine is a potassium channel blocker with an FDA indication to improve walking in patients with MS. This was demonstrated by an increase in walking speed in clinical trials.⁴ A total of 35% to 43% of patients treated with dalfampridine were “timed walk responders,” defined as having a faster walking speed for at least 3 of 4 double-blind treatment period visits than the maximum speed for 5 off-drug visits, compared with 8% to 9% of patients in the placebo group.^{5,6} Leg strength assessed by Lower Extremity Manual Muscle Test (LEMMT) improved in the clinical trials; patient satisfaction, as assessed by the 12-item MS Walking Scale (MSWS-12) and the Subject Global Impression (SGI), improved in responders, independent of treatment assignment.^{5,6}

Managed care professionals should consider safety issues in treatment decisions and include them in patient education. In particular, clinicians and pharmacists should instruct patients not to exceed the maximum dose of 10 mg twice daily, because the risk of seizure increases at higher doses; the medication is contraindicated in patients with a history of seizure.⁴

To maintain appropriate risk:benefit ratio, dalfampridine is contraindicated in patients with moderate or severe renal impairment.⁴ Patients with renal impairment would require a dose lower than 10 mg twice daily, and strengths lower than 10 mg are not available.⁴ With 10 mg twice daily, seizure risk in mild renal impairment is unknown, but it is possible that plasma levels are elevated enough to approach those seen with a high dose, thereby increasing seizure risk.⁴

Because the active ingredient is 4-AP, dalfampridine should not be taken with compounded formulations of 4-AP, which could increase the potential for dose-related AEs.⁴ AEs associated with dalfampridine that occurred in at least 5% of patients in controlled clinical trials included urinary tract infection (UTI), insomnia, dizziness, headache,

Table 2. Adverse Reactions With an Incidence $\geq 2\%$ of Patients Treated With Dalfampridine 10 mg Twice Daily and More Frequently Than in Placebo-Treated Patients in Controlled Clinical Trials⁴

Adverse Reaction	Placebo (n = 238)	Dalfampridine (n = 400)
Urinary tract infection	8%	12%
Insomnia	4%	9%
Dizziness	4%	7%
Headache	4%	7%
Nausea	3%	7%
Asthenia	4%	7%
Back pain	2%	5%
Balance disorder	1%	5%
MS relapse	3%	4%
Paresthesia	3%	4%
Nasopharyngitis	2%	4%
Constipation	2%	3%
Dyspepsia	1%	2%
Pharyngolaryngeal pain	1%	2%

nausea, asthenia, back pain, and balance disorder (Table 2).⁴ UTIs occurred in 12% of patients given dalfampridine and 8% given placebo.⁴ Because UTIs are not uncommon in patients with MS, regardless of their medication regimens, patient education should include the importance of early recognition and treatment of UTIs.⁸

In accordance with FDA approval, dalfampridine has a Risk Evaluation and Mitigation Strategy (REMS).³² The REMS is intended to inform healthcare professionals about the risk of seizures and the change of the established name from fampridine to dalfampridine in the United States, and to inform patients about the risks and best way to safely use dalfampridine.³² The REMS includes a patient Medication Guide and a communication plan for professionals, with letters to all pharmacists, key pharmacy organizations, and potential prescribers explaining the risks and the name change.³²

Dalfampridine is chemically 4-AP, which has been compounded by pharmacies.²² There is some concern about compounded 4-AP due to inconsistent quality, the potential for lowering the seizure threshold, and the narrow safety window regarding seizures.^{22,33} At the pharmacies that make it, the quality and purity of wholesale ingredients, training of personnel, methods, and equipment are largely unregulated and may vary, thus raising questions about potentially inconsistent results and increased seizure risk.²² A study of 4-AP capsules compounded at 3 pharma-

cies in 3 states found variable dissolution profiles and storage stability; all samples failed US Pharmacopeia Level 1 product release testing.³³ In addition, if compounded 4-AP is prescribed and the results in individual patients are unsatisfactory or inconsistent, the patients and clinicians have no way of knowing whether it is the fault of the medication or the way it was produced. Therefore, prescribing compounded 4-AP to patients with walking difficulty is not recommended.

In contrast, dalfampridine has undergone the lengthy and careful process of FDA approval and continues to have manufacturing regulation and postmarketing monitoring of outcomes. The pre-approval clinical trials of dalfampridine established proper dosing and satisfied safety concerns. The extended-release formulation maintains consistent blood levels to prevent spikes that could increase seizure risk. Managed care organizations can reassure prescribers and patients about the safety of dalfampridine and educate them about its use in MS.

Disease Management of MS

Disease management processes, which may include specialty pharmacies, frequent patient contact, targeted interventions, periodic clinical assessments, data collection, and data analysis, can potentially improve outcomes while reducing direct and indirect costs.⁸ Disease management programs have been beneficial in MS care. A claims database and patient self-assessment study evaluated the success of a 7-month MS disease management program including regular telephone consultations and patient educational efforts.¹¹ Patients who completed disease management had significantly greater persistence on injectable DMT therapy compared with retail pharmacy patients ($P < .001$) and specialty pharmacy patients ($P = .002$).¹¹ The proportion of patients in disease management who reported a relapse decreased by 33.6% from month 0 to month 6.¹¹ Based on previous findings of \$13,026 in direct medical costs per relapse, the investigators estimated the medical cost savings of their disease management program, if it had enrolled 283 patients, to be \$173,246, or \$612 per patient.¹¹ At 6 months, 97% of patients in the program reported that it was somewhat or very helpful in enabling them to better manage their health.¹¹ However, work productivity by Work Productivity and Activity Impairment questionnaire and QOL by SF-12 had not changed significantly at 6 months.¹¹

Dalfampridine can become an integral part of outcome-driven, comprehensive integrated MS care that includes patient education, self-management training, pharmaco-

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therapies, and rehabilitation. Managed care has approved a variety of mobility-assistance devices; a medication that improves mobility may add value to the use of an assistive device. With the addition of dalfampridine, patients in disease management programs like the one described above may derive additional help for improved walking that is not provided by DMTs or self-management. Improvements with dalfampridine are rapid, measurable, and reversible after treatment discontinuation, enabling objective evaluation of efficacy for individual patients.⁵

In clinical trials, responders showed greater improvements than nonresponders, independent of treatment, in MSWS-12 (a rating scale that captures patients' perspectives on their ambulatory disability) as well as SGI (a rating scale that captures patients' perceptions of the effects of the study medication on their physical well-being).^{5,6} With apparent improvements in walking, individual patients may gain improved abilities in activities of daily living and work productivity, which might inspire greater motivation and adherence to medications. Improving walking may also make some walking-related rehabilitation easier, which might inspire greater adherence to physical and occupational therapy.

Unlike medications that are sometimes used off-label in MS, dalfampridine is approved specifically for improvement of walking in patients with MS. Clinicians and pharmacists can discuss dalfampridine with patients in the confidence that it has an FDA indication and clinical trial evidence to support its efficacy. It should be included in formularies along with other FDA-approved medications. The beneficial effects of dalfampridine are not dependent on the use of DMTs or any other medication; therefore, full access should be at the discretion of prescribers based on individual patient needs and clinical factors.

Candidates and duration of treatment: Because dalfampridine improves and helps maintain walking, it may have the greatest impact on outcomes in patients who begin treatment at an early stage of MS. Patients and providers should not be required to wait to try dalfampridine until some threshold has been reached (eg, unemployment, requiring assistive device for walking). As with the NMSS recommendation to begin DMTs immediately after diagnosis, ethical treatment and fair consideration of patient needs and satisfaction would mean initiating dalfampridine as soon after diagnosis as it is recommended by the clinician and agreed upon by the patient.

However, more advanced disease does not mean it is too late for dalfampridine treatment. The clinical trials demonstrated that dalfampridine can be used safely and with

measurable benefits in patients with all forms of MS regardless of the time from diagnosis.^{5,6} All subjects in the clinical trials could walk at baseline; however, the NMSS has stated, "There is currently insufficient experience using this drug... to predict at what level of disability or mobility problems the drug would *not* help" (emphasis added).²²

According to the prescribing information, safety and effectiveness have not been established in patients under the age of 18, and the clinical trials included insufficient numbers of patients aged 65 and over to determine whether they responded differently than younger patients.⁴

In the double-blind clinical trials of dalfampridine, a reversal of effect was noted at follow-up visits after treatment ended.^{5,6} After reinitiation of dalfampridine in open-label extension studies, walking speed improvements returned.²³ The percentage improvement over double-blind baseline speed decreased over time, which may be partially due to disease progression in the 69% of enrolled patients with a progressive form of MS.²³ Despite the attenuated effect relative to baseline, the speed of responders remained improved relative to nonresponders for up to approximately 3.5 years,²³ suggesting that dalfampridine may be beneficial as a long-term treatment to improve walking.

Costs and education: The actions of dalfampridine to improve walking suggest the potential to delay or save indirect costs of reduced productivity, disability, and unemployment as well as costs of assistive devices, home modification, and caregivers. In some patients the need for intensive physical and occupational therapy services may be reduced or delayed.

For treatment candidates for whom cost is a concern, Acorda Therapeutics has established support services and patient assistance programs to work with payers and improve access to dalfampridine.²²

For optimal disease management, managed care organizations can educate providers about the benefits and appropriate use of dalfampridine. Because ideal MS care is a team effort, this education should be provided to primary care and specialist physicians, nurses, occupational and physical therapists, and other involved professionals.

Conclusions

Dalfampridine has been shown to be effective in improving walking in patients with MS. Therefore, dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improving walking helps optimize function and may help MS patients maintain hope and motivation, thereby increasing compliance. This can aid the success of individual patient treatment plans as well as large disease-management programs. Improved walking could

potentially help contain some of the direct and indirect costs associated with MS. Taken together, this information suggests that access to dalfampridine and appropriate utilization of dalfampridine have the potential to improve outcomes for patients with MS.

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