

Will the Newer Oral MS Agents Be Welcomed by Managed Care Organizations?

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A new generation of multiple sclerosis (MS) therapies is currently emerging. Among them are 4 oral agents, dalfampridine, laquinimod, cladribine, and fingolimod, that have been or likely will be approved for managing patients with MS.¹⁻¹¹ Efficacy data for these new oral agents are impressive and demonstrate that they have the potential to eventually replace injectable treatment options currently used by most patients with MS. With any new treatment regimen, however, there are concerns relating to safety and cost. In addition, patients with MS have poor treatment adherence to the current available therapies¹²⁻¹⁸ and it is uncertain if the introduction of oral agents will increase patient adherence.

The purpose of this article is to discuss the possible ways that these new agents may affect patient adherence and how placement of these oral agents in managed care organization (MCO)'s formularies may also influence adherence and therefore outcomes.

Current MS Agents and Adherence

For over a decade, 3 disease-modifying drugs (DMDs) have dominated the treatment of MS: interferon beta-1a (IFNB-1a), interferon beta-1b (IFNB-1b), and glatiramer acetate (GA).¹⁹⁻²² These agents, as discussed in the earlier articles,^{23,24} have shown clinically significant efficacy in treating MS. One of the most notable limitations of the current first-line MS therapies is that they can only be delivered via injection. This is not simply a matter of inconvenience, but a factor that contributes to the poor patient adherence associated with MS treatment.

Patient adherence is a major concern for clinicians treating patients with MS. Rates of discontinuation are between 9% and 20% in the first 6 months of treatment.¹²⁻¹⁴ Although a recent review by Patti noted that patients are most likely to discontinue treatment within the first 6 months,¹² a long-term, follow-up study (ie, 4.2 years) found that discontinuation rates were as high as 46%.¹⁵ Many factors influence adherence to MS therapy; the 4 main factors appear to be: (1) lack of efficacy (perceived and real); (2) adverse drug reactions; (3) cost to the patient; and (4) injection anxiety.

Lack of Efficacy: Perceived and Real

One major therapeutic goal for patients with relapsing-remitting MS is the reduction or prevention of further relapses. The natural

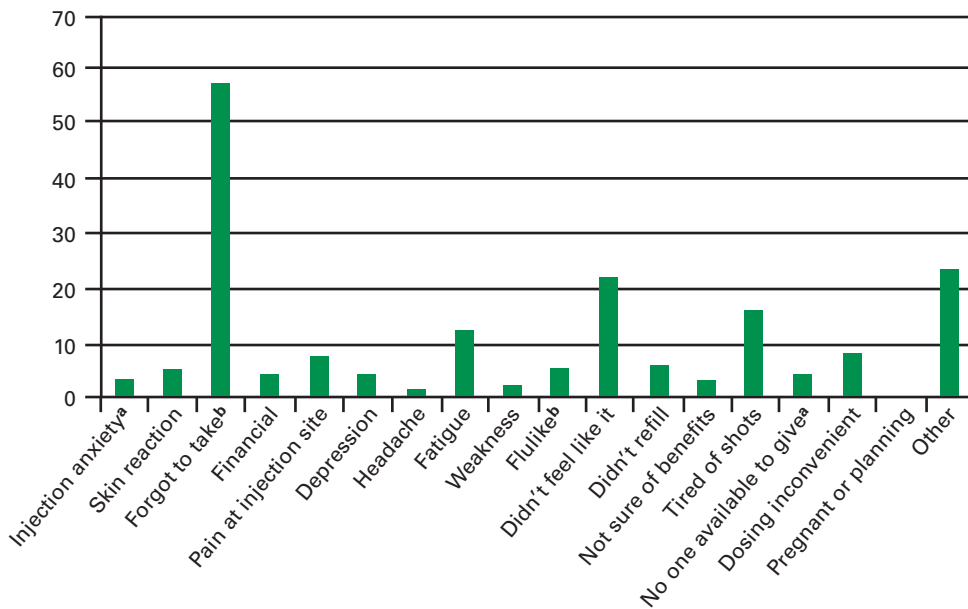
Abstract

Of the new generation of multiple sclerosis (MS) drugs, 4 oral agents—dalfampridine, laquinimod, cladribine, and fingolimod—could produce significant changes in the treatment landscape for MS. Current first-line treatments, which are administered via injection, are associated with poor treatment adherence, often due to lack of efficacy (perceived and real), adverse drug reactions, cost, and injection anxiety. Although concerns about safety and cost remain, preliminary results indicate that these oral agents are as effective as, or even more effective than, current injectable treatments. Oral MS agents are expected to cost patients less in out-of-pocket expenses, which will likely increase treatment adherence and lead to an overall reduction in medical costs. While many patients may prefer an oral MS drug, the ultimate choice of therapy will be a shared patient-physician decision based on a multitude of factors, including the efficacy of the current treatment regimen, patient compliance history, and the difference in out-of-pocket expenses.

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■ **Figure 1. Reasons for Discontinuing MS Medications¹⁸**



^a*P* < .01 among drugs.

^b*P* < .05 among drugs.

MS indicates multiple sclerosis.

The distribution (by percent) of the reasons described for missing injections by those patients who were nonadherent are presented. Forgetting to take injections represented the most common explanation for missing any doses of the medication, irrespective of which disease-modifying therapy was being utilized. By percentages, about one third of the reasons offered for missing shots were in some way related to injection therapy itself (ie, pain, side effects). Reprinted with permission from Tradaway K, et al. *J Neurol.* 2009;256(4):568-576.

history of MS leads to a reduction in relapses, as does effective therapy. In addition, many clinical trials with newly diagnosed patients have shown infrequent relapses at baseline. All of these factors often make it hard for patients to know if the therapy is working or not. This can lead to a perception that the medicine is not effective. Adding to that, these agents may not be entirely effective for some patients, and switching may be necessary. The lack of efficacy, whether it is real or not, is a substantial problem in MS therapy adherence. A study by Portaccio et al followed 225 patients with relapsing-remitting MS treated with IFNB and observed that 46% suspended therapy.¹⁵ Most of these patients (28%) suspended therapy because of a perceived lack of efficacy. The majority of these patients switched to another MS agent (62 of the 65 patients). The perceived critical importance of injections may be one reason why patients have an unrealistic expectation of efficacy with the current injectable MS agents.

Mohr et al also noted that many patients have unrealistic expectations of efficacy and that this can lead to poor adherence.¹⁴ In their interview study involving 99 patients with MS starting on IFNB-1b therapy, they observed that 57% of the patients had unrealistically optimistic expectations regarding reduction in attack rate. Education on the

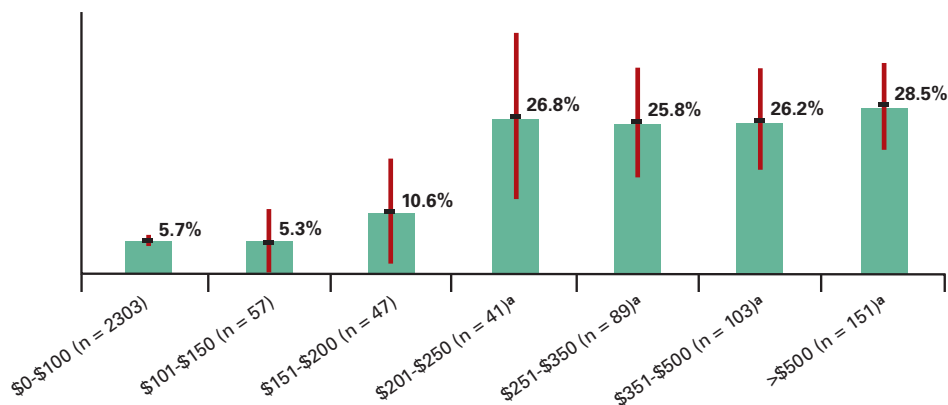
expected outcomes of therapy lowered that percentage to 33%. Among patients who discontinued therapy, 64% had overly optimistic expectations. In contrast, only 28% of the patients who were compliant with therapy expressed overly optimistic expectations.

Adverse Drug Reactions

MS agents are fairly well tolerated, but some adverse events are common and can lead to discontinuation. In the study by Portaccio et al, 15% of patients stopped therapy due to adverse events. Common adverse events included flulike syndrome, injection-site reactions, liver function abnormalities, and depression.¹⁵ Interestingly, patients suspending therapy due to adverse events tended to be those with higher relapse rates in the year prior to therapy. So, it is possible that some of these patients assigned a lower benefit-to-risk ratio to the drugs.

Patients who discontinue treatment due to adverse events generally do so in the first year of treatment. A retrospective chart analysis by O'Rourke and Hutchinson determined that flulike symptoms, depression, fatigue, and injection-site reactions were the most common adverse events leading to discontinuation in patients treated with IFNB.¹⁶ In patients given GA, common adverse events that led to discontinu-

■ **Figure 2A.** Poor Compliance Associated With Higher Out-of-Pocket Expenses (MS Medication)²⁶



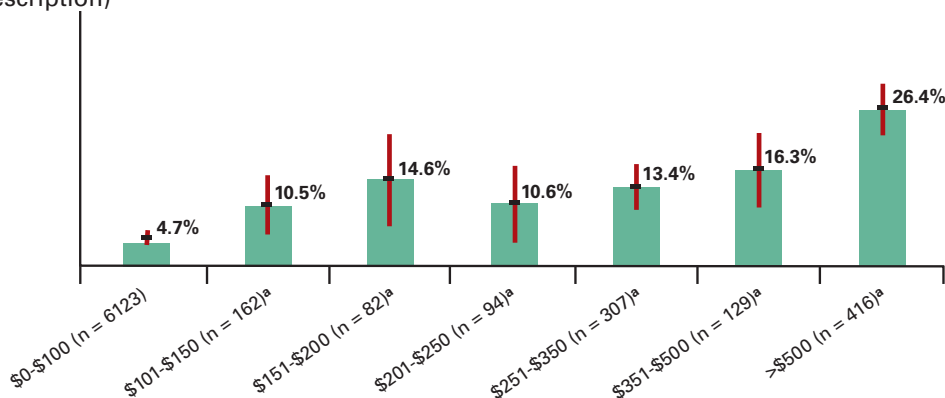
^a*P* < .001 compared with \$0-\$100 group.

Bars represent 95% confidence intervals.

MS indicates multiple sclerosis.

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■ **Figure 2B.** Poor Compliance Associated With Higher Out-of-Pocket Expenses (Anti-Tumor Necrosis Factor Blocker Prescription)²⁶



^a*P* < .001 compared with \$0-\$100 group.

Bars represent 95% confidence intervals.

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ation included injection-site reactions, dyspnea, urticaria, vasodilatation, and/or hypersensitivity.²¹

Injection Anxiety

Since all current MS agents are administered by injection, some patients may not adhere to treatment due to their fear of needles. A recent study by Turner et al noted that injection anxiety was a strong predictor of nonadherence.¹⁷ Fortunately, few patients have injection anxiety severe enough to prompt poor adherence. Treadaway et al suggested that injection anxiety was not a major contributor to nonadherence.¹⁸ Instead, poor adherence was attributed to: “forgot

to take” (>55%), “didn’t feel like it” (>20%), and “tired of shots” (>15%). How many of these reasons are masking some anxiety toward injections is not known (Figure 1).

Patient Responsibility and Cost

It is well-established that the out-of-pocket expenses accrued by a patient will affect adherence. Curkendall et al examined insurance claims of self-insured employer health plans (n = 2285) and calculated that the average out-of-pocket expenses accrued by patients with rheumatoid arthritis for anti-TNF agents were \$7.84 ± \$14.15 per week.²⁵ This study also showed that adherence was inversely proportional

■ **Table 1.** Oral Agents for Multiple Sclerosis

Oral Agent	Mechanism of Action	Status	Expected dosing
Dalfampridine ⁵	Potassium channel blocker	Approved for use by the FDA	10.0 mg twice daily
Laquinimod ^{6,7}	Immunomodulator	Granted fast-track review by the FDA	0.6 mg daily
Cladribine ^{2,10,29}	Purine nucleoside analogue prodrug	FDA issued a refuse-to-file letter for the New Drug Application due to reports of patients developing solid malignancies	3.5 or 5.25 mg/kg over 96 weeks
Fingolimod ^{1,11,24}	Partial sphingosine 1-phosphate–receptor agonist	FDA advisory committee recommends approval for the treatment of relapsing-remitting MS	0.5 mg daily

FDA indicates US Food and Drug Administration; MS, multiple sclerosis.

to weekly out-of-pocket expenses. For every \$5.50 increase in weekly out-of-pocket expenses, therapy was reduced by 1 week. A recent study by Gleason et al used a database of commercially insured individuals (>13 million persons) and found 2791 patients with MS beginning high-cost therapy.²⁶ The researchers divided the members into 7 groups based on their annual out-of-pocket expenses (\$0-\$100, \$101-\$150, \$151-\$200, \$201-\$250, \$251-\$350, \$351-\$500, or >\$500). As shown in **Figure 2a** and **Figure 2b**, adherence decreased as out-of-pocket expenses increased. There was a dramatic increase in nonadherence with the highest costs. The minimal increases at the lower cost differentials indicate that small increases in the cost of injectable medicines may have smaller effects on patient adherence. The same may not be true for oral medications. A recent study presented at the Academy of Managed Care Pharmacy’s 2010 Annual Meeting and Showcase examined insurance records for patients taking new oral anticancer agents (n = 1909) and observed that costs may be more tightly linked to poor adherence, with abandonment rates rising with each copay step.²⁷ Abandonment rates were 4.9% (77 of 1562) in the \$0-\$100 group, 6.5% (2 of 31) in the \$101-\$200 group, 16.1% (9 of 56) in the \$201-\$500 group, and 28.8% (75 of 260) in the >\$500 group. Whether or not a similar pattern will be observed with newer oral MS agents remains to be seen; however, the authors cautioned that health insurers should consider the potential impact of member cost share on abandonment rates when designing pharmacy benefits. Similar results have been observed with oral antidiabetic agents.²⁸ The authors of the diabetes study calculated that every \$10 increase in copay rates resulted in a 26% relative increased risk of treatment discontinuation or switching. For patients with lower out-of-pocket expenses (<\$10 or \$10-\$20), the time to discontinuing or switching therapy was longer (200.56 ± 137.98 days and 196.44 ± 136.29 days,

respectively) compared with those who had higher out-of-pocket expenses (\$20-\$30 or >\$30) (179.18 ± 131.63 days and 170.9 ± 131.10 days, respectively).

Oral Agents for MS

Of the new generation of oral agents for MS, there are 4 that show particular promise: dalfampridine, laquinimod, cladribine, and fingolimod (**Table 1**).^{1,2,5-7,10,11,29} These agents were discussed in detail in the previous article.²⁴ A brief summary of our current knowledge on the efficacy and safety of these agents in MS is located below.

Dalfampridine

Dalfampridine is a potassium channel blocker approved by the US Food and Drug Administration (FDA) for treatment of MS in January 2010. Dalfampridine has a unique indication, specifically for improving walking in patients with MS. It is not indicated to reduce relapses or slow disease progression. Dalfampridine (above the recommended dosage of 10 mg twice daily) is associated with an elevated risk for seizures.³⁰

Laquinimod

The immunomodulator laquinimod is structurally similar to linomide, and it is currently being evaluated in 2 phase 3 trials. It has been granted fast-track review status by the FDA. In a phase 2b, double-blind, placebo-controlled study and 2 subsequent extension trials, laquinimod was more effective than placebo in reducing the cumulative number of gadolinium-enhancing lesions.^{4,6,7} The incidence of serious adverse events was 5.1% for laquinimod 0.3 mg/day, 2.8% for laquinimod 0.6 mg/day, and 4.9% for placebo.⁴ In the 24-month open-label extension trial, laquinimod was well tolerated and the most frequently reported adverse events were nasopharyngitis (25.8%), back pain (12.4%), and headache (8.1%).⁷

Cladribine

The disease-modifying agent cladribine is a purine nucleoside analogue prodrug. Its active metabolite, 2-chlorodeoxyadenosine triphosphate, disrupts cellular metabolism and inhibits DNA synthesis and repair, and subsequently causes apoptosis.² CLARITY (CLAdRIbine Tablets in Treating MS Orally) was a 96-week, phase 3 trial that showed cladribine to be superior to placebo in lowering relapse rates in patients with MS. However, CLARITY also revealed significant safety concerns: 4 patients receiving cladribine were diagnosed with solid malignancies during the study. Cladribine was also associated with lymphopenia and neutropenia, and it is teratogenic.^{2,3,9} In November 2009, the FDA issued a refuse-to-file letter for the New Drug Application (NDA) for cladribine.¹⁰ The NDA was resubmitted in June 2010.²⁹

Fingolimod

Fingolimod is a sphingosine 1-phosphate–receptor modulator. In a 24-month, phase 3, double-blind, placebo-controlled study (FREEDOMS [FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis] trial), fingolimod significantly reduced the relapse rate and risk of disability progression compared with placebo.¹¹ In a 12-month, double-blind study that compared fingolimod with IFNB-1a, patients receiving fingolimod had greater reductions in relapse rates and improved MRI outcomes, although disability progression was similar between the 2 treatment groups.¹ Two deaths and 4 cases of breast cancer occurred in patients receiving fingolimod compared with no deaths or cases of breast cancer in the IFNB-1a group. The incidence of localized skin cancer was also higher in those given fingolimod. It is uncertain whether treatment with fingolimod was related to these adverse events.¹

Oral Agents and Adherence

In terms of adherence, oral drugs have a potential advantage over injected therapies. Generally, they are perceived to be better tolerated, physically and psychologically. Studies involving patients with diabetes³¹ or cancer³² have shown that patients prefer receiving medication in the form of inhaled or tablet preparations, rather than an injectable one. In patients with cancer, 63% preferred tablets compared with 24% who preferred an injection.³² Among the patients receiving an injectable medication, 38% were anxious about receiving injections, whereas 17% felt that their anxiety or dislike of needles might lead them to avoid injections. In contrast, most patients (94%) taking oral agents did not think it interfered with their daily lives, although 13%

reported that they deliberately did not take their tablets on occasion.

Whether the same preference and behavior will hold true for oral MS agents has yet to be studied, but it is likely that oral agents will be the preferred formulation of most patients. One possible problem with oral medications is that they may be perceived as less effective than injections. This was recently seen by Halfdanarson and Jatoi,³³ who commented that many of the patients' perceptions of oral chemotherapy agents, including their perceptions of their efficacy, are inaccurate and may lead to poor adherence.

Role of Managed Care Organizations in Appropriate Utilization and Access to New MS Agents

The key factors for placement of these new agents in formularies are 3-fold: (1) Are they safer than current agents? (2) Are they more effective than current agents? (3) Are they less expensive than current agents? At present, we do not entirely know the answers to these questions. However, some data are available. Cohen et al recently published data from the TRANSFORMS study.¹ This 12-month, double-blind, double-dummy study compared the efficacy and safety of oral fingolimod (0.5 mg or 1.25 mg daily) with IFNB-1a (30 µg intramuscularly once weekly) in patients with relapsing-remitting MS (n = 1153). Both doses of fingolimod were associated with significantly lower relapse rates versus IFNB-1a ($P < .001$ for both doses), but disability progression was not significantly different among groups. Both treatments were well tolerated.¹

It is likely that the oral medications will cost patients less out of pocket compared with the injectable medications because of the current tier system, in which most MCOs place injectable medications in specialty tiers. However, a recent trend is to place expensive oral cancer therapies in the highest tiers as well. If oral MS agents are placed in the more traditional third and fourth tiers, it is very likely that a positive impact on adherence will be seen in patients with MS²⁶ based on comparable data in oncology and diabetes.^{27,28,31,32} Furthermore, if patient adherence improves, total medical costs will likely decrease. A study by Birnbaum et al compared workers with MS receiving DMDs (n = 258) with those not receiving DMDs (n = 322).³⁴ Treatment with DMDs led to reduced medical and indirect costs (Table 2).

In the United States, the average annual cost for the direct care of MS is \$12,879 (2004 dollars).³⁵ Cost is largely dependent on the overall health of the patient, and among those patients reporting conditions such as abnormality of gait, ataxia, convulsions, malaise or fatigue, optic neuritis, or

■ Table 2. Comparison of Risk-Adjusted Medical and Indirect Costs With and Without Disease-Modifying Drugs in Employees With Multiple Sclerosis (n = 580)³⁴

Cost	Disease-Modifying Drugs		No Disease-Modifying Drugs		Cost Difference	P
	Risk-Adjusted Costs	Standard Deviation	Risk-Adjusted Costs	Standard Deviation		
Actual distribution of MS symptom-relief treatment						
Medical costs	\$4393	(\$5952)	\$6187	(\$8953)	\$1794	<0.0001
Indirect costs	\$2252	(\$2592)	\$3053	(\$3338)	\$801	<0.0001
Assuming no patients received MS symptom-relief treatment						
Medical costs	\$3166	(\$4125)	\$5557	(\$8014)	\$2392	<0.0001
Indirect costs	\$1302	(\$1290)	\$2173	(\$2207)	\$870	<0.0001
Assuming all patients received MS symptom-relief treatment						
Medical costs	\$4733	(\$6036)	\$6420	(\$9068)	\$1687	<0.0001
Indirect costs	\$2444	(\$2640)	\$3208	(\$3422)	\$764	<0.0001

MS indicates multiple sclerosis.
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spasms, total costs were significantly higher. The extent to which these conditions can be avoided by better adherence with oral medications remains to be seen.

Conclusion

The introduction of oral agents for MS has the potential to greatly impact patients, clinicians, and MCOs. Several factors will likely determine the extent to which third-party payers make these therapies available to patients. At present, it is expected that oral medications will require less out-of-pocket expenses for members compared with current injectable medications. This, in turn, will likely lead to improved adherence and ultimately reduce overall medical costs.

Preliminary results indicate that oral medications are as effective as, or possibly more effective than, current injectable formulations. It is hoped that improved outcomes will translate into higher real and perceived efficacy rates and contribute to improved adherence. Patients newly diagnosed with MS may prefer oral agents when they become available. It is difficult to predict their uptake at this time. In patients currently receiving therapy, clinicians may be more reluctant to alter successful therapy. The decision to switch established patients from injectable to oral medications will likely be a personal matter that takes into account the efficacy and tolerability of the patient’s existing therapy, their compliance history, and differences in out-of-pocket expenses.

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