Patients with multiple sclerosis (MS) now have a variety of disease-modifying therapies (DMTs) from which to choose. The upside of current DMTs is that they represent a huge advance over previous treatments for MS: Just 15 years ago, disease-specific treatments for MS were non-existent. The downside is that all of the available therapies are parenteral and have a variety of side effects. For the purposes of this discussion, we’ll focus on the four available injectable agents—key features of which are outlined in Table 1—because these are the ones that currently create problems with adherence.

We’ve all seen patients—whether they have hypertension, diabetes, or any number of other diseases—who just can’t seem to stick to their treatment regimens. Patients with MS are no different, and, in some cases, not only have to deal with the normal stresses associated with taking long-term medication, but also have to cope with gradually deteriorating motor and cognitive skills. While education, re-education, and frequent re-evaluation are the keys to promoting adherence, maintaining open lines of communication with patients is also essential—nonadherent patients are often depressed, stressed, and frankly, just plain embarrassed that they have let you or them-
Dear Colleague,

Patients diagnosed and living with multiple sclerosis (MS) face a variety of challenges. Not only must they come to grips with the idea that they have a chronic disease for which there is no cure, they also have to learn to cope with the often debilitating signs and symptoms of the disease. However, perhaps one of the toughest challenges is having to accept the fact that, at least at this time, the only disease-specific treatments available are parenteral agents.

In this issue of MS Counseling Points™, our panel tackles the tough issue of adherence to injectable disease-modifying therapies (DMTs). Barriers to adherence are discussed and we share strategies to overcome these barriers. All patients, those who are currently adherent and those who are not, need to be aware that although self-injection is just about the only option available to them, adherence to these therapies now will allow them to take advantage of newer and, hopefully, more user-friendly agents in the not-too-distant future. Thus, the current therapies are being used to check the progress of MS while we await new, improved therapies.

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selves down. Understanding without judgment is the best approach.

**What Is Adherence?**

Adherence is defined as the accumulation of time from initiation to discontinuation of therapy, as measured by time.

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**Adherence is a global term under the umbrella of which falls three distinct subcategories: acceptance, persistence, and compliance.**

We often bandy the word adherence around without really stopping to think what it means. Many are guilty of using the terms adherence and compliance interchangeably. In fact, adherence is a global term under the umbrella of which falls three distinct subcategories: acceptance, persistence, and compliance. Before patients can adhere to a treatment regimen they first have to accept the fact that they need treatment and that the treatment will help them. As will be discussed in more detail when we address barriers to adherence, patients with MS frequently find it hard to accept that they need to inject themselves daily, every few days, or weekly, particularly in the early stages of the disease when relapses can be infrequent and they suffer from very subtle, often intermittent, disability.

Once patients have embarked on a treatment regimen, persistence may fall by the wayside. One study reported that nearly 19% of patients stopped taking interferon β-1b via subcutaneous injection or β-1a via intramuscular injection within the first 6 months of therapy.¹ This occurs due to a variety of reasons, described later. The third component of adherence, compliance, refers to taking a medication properly—that is, the extent to which a patient acts in accordance with the prescribed dosing interval and dosing regime. The unit of measure for compliance is administered doses reported as a proportion (%) of prescribed doses per a defined period of time. Noncompliance is a major issue with patients with MS. Patients may lose track of which day their injection is due or may skip one or two injections now and then.

**Barriers to Adherence**

Once patients have overcome the hurdle of accepting

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<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Dosing Route/Frequency</th>
<th>Administration Mode</th>
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</thead>
<tbody>
<tr>
<td>Avonex®</td>
<td>Interferon β-1a</td>
<td>Intramuscular/once weekly</td>
<td>Premixed</td>
</tr>
<tr>
<td>Betaseron®</td>
<td>Interferon β-1b</td>
<td>Subcutaneous/every other day</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>Copaxone®</td>
<td>Glatiramer acetate</td>
<td>Subcutaneous/daily</td>
<td>Premixed, autoinjector</td>
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<tr>
<td>Rebif®</td>
<td>Interferon β-1a</td>
<td>Subcutaneous/3 times weekly</td>
<td>Premixed, autoinjector</td>
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they have MS, they must come to grips with the fact that four of the mainstay disease-specific treatments currently available require self-injection. In many cases, patients will be prescribed a DMT when their disease seems to be in remission—they have recovered from the initial attack and are not experiencing any symptoms. In this situation, it is often difficult for patients to commit to self-injecting and to persist with therapy. One would think that the main reason for discontinuation in the long-term would be not having had a relapse for some time and not experiencing any disability; however, in many cases patients are simply needle-phobic. Even after patients have been using a DMT for months or years, they sometimes decide to stop taking it or miss doses because of injection-related issues. Tremlett and colleagues reported a number of other reasons why patients stop therapy: They found that perceived lack of efficacy is a significantly more common reason among men than women (42% vs. 26%, respectively; \( P=0.008 \)) and among patients with a higher Expanded Disability Status Scale (EDSS) score (>3.5)—40% vs. 21% of patients with a lower score (\( P=0.002 \)). In addition, flu-like reactions were cited as reasons for discontinuation by significantly more patients with a higher EDSS score and longer duration of disease. It is clear that the degree of disability, duration of disease, and side effects influence a patient’s decision to stop therapy. Patients may also have unrealistic expectations of the benefits of therapy.

Flu-like reactions were cited as reasons for discontinuation by significantly more patients with a higher EDSS score and longer duration of disease.

Beyond persistence, lack of compliance is a major problem. In the Global Adherence Project (GAP) study, Devonshire and colleagues reported the reasons cited for noncompliance among 2,649 patients with MS. They found that 12% of patients forgot to inject, 5% were too tired, and 5% had trouble with side effects. Compliance was also lower in those patients who had more cognitive deficits. GAP was a global, multicenter, cross-sectional, observational study that investigated factors that influence nonadherence to MS therapies. Patients were evaluated through a validated MS quality-of-life scale, as well as a self-reported questionnaire that collected data on disease status, treatment, and factors that may have affected adherence to treatment during the course of their therapy.

As the disease fluctuates, patients may find their ability to comply with a treatment regimen also fluctuates. Some patients experience problems with fine motor skills due to tremor; thus, they may find it difficult to reconstitute their medication or to perform the actual injection. If patients experience severe fatigue or depression (two key features of MS), they may not have the energy to self-inject routinely. In addition, cognitive deficits can interfere with a patient’s ability to first, remember to inject, and second, perform the task. Finally, family or support circumstances may change—patients who had a family member or caregiver available to administer injections may no longer have access to this resource.

A factor that influences both persistence and compliance is access to medication. More and more often, formulary or insurance coverage changes mean that patients may be required to pay hefty copayments for their medication. In some instances, patients may stop therapy altogether because of the economic burden or may choose to skip some injections. Alternatively, they may go without therapy while they are switching to another agent that requires smaller copayments.

Perhaps one of the major reasons patients do not persist or comply with therapy is a lack of understanding of the importance of DMT. As mentioned earlier, if patients feel healthy or believe that their disease is progressing despite therapy they might be more inclined to skip doses or discontinue therapy altogether. Many patients with MS are not aware of
the subclinical nature of the disease processes, which can lead to a laissez-faire attitude or disillusionment with therapy.

**One of the major reasons patients do not persist or comply with therapy is a lack of understanding of the importance of DMT.**

**Addressing Barriers to Adherence**

It cannot be overemphasized that education is the key to overcoming many of the barriers to adherence. Education is important from day one and should be an ongoing process. This is an area where nurses can make a major difference. A nurse’s role is not only to teach patients how to self-inject, but to make sure patients understand why it is important to start therapy and continue it, even in the absence of relapses and disease progression or perceived efficacy.

**Education is the key to overcoming many of the barriers to adherence.**

One useful approach to helping patients understand the importance of adherence is to explain and illustrate the concept of subclinical activity. It is well-known that although patients may not be experiencing any signs and symptoms of MS, underlying inflammatory disease activity continues, as seen on repeat magnetic resonance imaging (MRI). For those patients who cite lack of efficacy of a DMT as a reason for not persisting or noncompliance, you should point out that while the available agents decrease the incidence of relapses by approximately 30% to 50%, relapses may still occur—but they will be less frequent and less severe with treatment. Treatment also decreases MRI activity by 50% or more.² It is this subclinical activity that may cause damage that becomes additive and results in progressive disability later on.

Although patients may not be experiencing any signs and symptoms of MS, underlying inflammatory disease activity continues.

When first prescribing a DMT, it is a good idea to sit down with patients and develop a management model. This model should involve identifying realistic expectations and encouraging patients to make a commitment to sticking to their therapy. At follow-up visits, you should revisit patients’ expectations and together address any issues that have arisen about any aspect of their disease management.

Needle phobia can be problematic. That’s where patience and understanding on the nurse’s part comes in. You can help patients overcome this phobia by putting them in touch with other patients who have gone through the same thing and are successfully self-injecting routinely. In addition, you can recommend measures to avoid painful injection-site reactions (for a full discussion of this topic see Volume 1, Issue 2 of *Counseling Points™*). Flexibility is important. Stress to patients that they must rotate injection sites and strictly adhere to this rotation. Sometimes patients have difficulties with one or more sites and rather than drop them from the rotation they will persevere and inject improperly or, even more likely, omit their injection on the day that they are due to use the troublesome site. Reassure patients that it is okay to drop a site and help them explore other sites that can be added.

When patients come in for follow-up visits, nurses should not only evaluate them physically but should also attempt to assess their mental and cognitive status. Depression is common among patients with MS and, in many cases whether or not it is coupled with fatigue, can lead to nonadherence. If your patients appear depressed, consider referring them to a counselor/psychologist for a formal evaluation. You
should also be alert for signs of cognitive deficits because these can interfere with patients’ ability to adhere to therapy. You should suggest to all patients, irrespective of their cognitive status, that they post an injection reminder in a location in their home where they won’t miss seeing it. For example, many patients find it helpful to put a reminder near their toothbrush.

At least annually, you should re-evaluate patients’ injection technique. Patients may think that they are doing it properly but it is not uncommon to find that their technique needs some brushing up. Improper administration of therapy can contribute to nonadherence as much as missing doses.

When fatigue seems to be a problem for patients, it often helps if you recommend they self-inject in the morning. Patients who inject at night are often tired and tend to skip doses. Anecdotally, patients who take glatiramer acetate for injection, which is administered daily, can be more adherent if the injection becomes part of a morning routine.

Patients with comorbidities such as diabetes or arthritis frequently find it more difficult than others to adhere to therapy. When evaluating patients, it is important to take any comorbidities into account and, working with specialists in other areas, ensure that treatment is optimized not only for MS but other conditions as well.

For patients who have trouble gaining access to medications or who have difficulty self-injecting, referring them to a company-sponsored support program (see Table 2) can often be helpful. These programs offer excellent telephone and on-site support.

 Patients with comorbidities such as diabetes or arthritis frequently find it more difficult than others to adhere to therapy.

Some patients who live in more remote areas must rely on visiting nurses from non-specialized services. To ensure that visiting nurses are equipped to teach proper injection procedures and administer injections, as well as answer questions patients may have, consider conducting regular in-service programs to update them about MS therapies and the importance of adherence. Getting off to a good start is crucial, and visiting nurses play a vital role in ensuring this happens.

Referring patients to local support groups, such as those conducted by the National Multiple Sclerosis Society (www.nmss.org), can be useful. In these settings, patients can share their problems and help each other identify solutions, allowing them to realize that they are not the only ones going through this.

Finally, one of the most important keys to overcoming adherence problems is to keep the lines of communication wide open. Be available, even if it is via voicemail or e-mail, to listen to patients’ concerns. Nonjudgmental listening and counseling can go a
long way in helping patients deal with whatever issues that have led them to not persist with therapy or to be noncompliant.

**Conclusions**

As would be expected with therapies that require self-injection, nonadherence remains a problem for patients with MS. Being aware of barriers to adherence is the first step in helping patients address these barriers. As has been said many times before, MS is not a sprint, but a marathon—and adhering to currently available therapies might mean that patients will be in a better position to take advantage of new therapies as they emerge.

**References**


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**The Psychological Side of Adherence**

Psychological theories provide some insight into the phenomenon of adherence. One particular model that appears to relate to why some patients adhere better than others to treatment regimens is self-efficacy. As defined by Bandura, self-efficacy is a judgment made by people about their ability to organize and implement a new stressful or unexpected course of action. People’s perception of this ability can help determine whether or not this task will be accomplished. This perception influences the amount of time and energy they are willing to put into completing a task, particularly an unpleasant one such as self-injecting. Successful completion of tasks enhances self-efficacy. Thus, patients who are prepared to persevere with preparing and administering their injections are more likely to gain a reinforced, indeed greater, sense of self-efficacy compared with patients who give up too easily. Fraser and colleagues demonstrated that a single unit increase in the total Multiple Sclerosis Self-Efficacy Scale (MSSE) score, which measures in part how convinced patients are that they will be able to perform a certain task, correlates with an increased probability of adherence. Measurement on the control and function subscales of the MSSE found that patients who adhered to therapy had a significantly greater belief in their ability to control their disease and their ability to function.

The self-efficacy theory bolsters the need to educate patients about the preparation and administration of injectable DMTs and encourage hands-on practice. The more patients believe they are able to self-inject, the more likely they are to be successful at self-injecting.
MS Counseling Points™

Adherence to Disease-modifying Therapy—Recognizing Barriers and Offering Solutions

• Educate, re-educate, and re-evaluate frequently.
• Maintain open lines of communication with your patients.
• Remember that adherence is a global term under the umbrella of which falls three distinct subcategories: acceptance, persistence, and compliance.
• Note the key reasons for discontinuing therapy: perceived lack of efficacy, increased levels of disability, and side effects.
• Note the key reasons for noncompliance: forgetfulness, fatigue, and side effects.
• Make sure patients understand why it is important not only to start therapy but to continue it, even in the absence of relapses and disease progression or perceived efficacy.
• Develop a management model that identifies realistic expectations for patients.
• Recommend measures to avoid painful injection-site reactions.
• Assess patients’ mental and cognitive status.
• Suggest to all patients, irrespective of their cognitive status, that they post a reinjection reminder in a location in their home where they won’t miss it.
• Re-evaluate a patient’s injection technique at least once a year.
• When fatigue seems to be a problem, recommend patients self-inject in the morning.
• Take any comorbidities into account and, working with specialists in other areas, ensure that treatment is optimized not only for MS but other conditions as well.
• Refer patients to a company-sponsored support program.
• To ensure that visiting nurses are equipped to teach proper injection procedures and administer injections, as well answer patient questions, conduct regular in-service programs to update them about MS therapies and the reasons why adherence is important.
• Refer patients to local support groups.
Adherence to Self-Injected MS Therapy Influenced by Individual Factors

This study, conducted by investigators at Henry Ford Hospital, looked at potential factors in medication nonadherence. The study followed 252 HMO-insured patients with relapsing-remitting multiple sclerosis over 2 years from 2004-2006. Claims data were used to assess the amount of injectable medication patients kept on hand for the treatment period. Additional assessments of relapse rates and quality of life were performed using medical chart abstractions and patient surveys, respectively.

Results indicated that mean drug adherence among patients with two or more dispensings of drug was 84% overall (95% CI 81%-87%). Significant differences in adherence rates were discernable on the basis of three major factors: race, age, and income level. White patients were significantly more likely to adhere to therapy compared with African-American patients (80% vs. 62%). Likewise, greater adherence was skewed towards older age (46.7 vs. 42.9 years) and higher income. Only 76% of patients given surveys returned them, but among those, the adherence rate was higher than normal (92%).


Enhanced Patient Support Program Improves 90-Day Adherence to Copaxone

Nurses from Teva Neuroscience Inc.’s Shared Solutions program—a therapy support program for patients who have filled a prescription for glatiramer acetate (Copaxone®)—presented their investigations addressing ways to identify patients at high risk for early discontinuation of immunomodulatory therapy. Their study design also looked to improve adherence among these patients through enrollment in a new Shared Solutions program called Shared Solutions PLUS® (Personalized Lasting Unique Support). The program employs several specific interventions aimed at preventing discontinuation of therapy.

Among 4,451 patients who initiated Copaxone treatment between October 2006 and December 2006, the algorithm accurately predicted 78% of those at high risk of nonadherence within the first 90 days.

Over 4 years, an algorithm was developed to identify those patients most at risk for early discontinuation. A list of patient characteristics was compiled from the literature and the clinical experience of nurses in the program. Using multivariate regression analyses, each characteristic was assessed for its value in predicting discontinuation of Copaxone therapy. A 37-item questionnaire was then developed that helped identify the patients with those characteristics. Among 4,451 patients who initiated Copaxone treatment between October 2006 and December 2006, the algorithm accurately predicted 78% of those at high risk of nonadherence within the first 90 days.
Among 1,767 of the high-risk patients enrolled in the Shared Solutions PLUS program through the initial 90 days of treatment, the results showed an 87% continuation rate. The authors noted that as a result of the predictive algorithm and the PLUS program, they were able to maintain an additional 446 patients per year on Copaxone treatment beyond the 90-day period. Thus, only 8% of the total 4,451 patients who were tracked for this study discontinued Copaxone treatment—a significant improvement over the 11% of 5,433 patients reported by the original Shared Solutions program.

Parker D, Beach B. A care plan to improve adherence to Copaxone (glatiramer acetate) among patients at risk of nonadherence. Teva Neuroscience, Inc., Kansas City, MO, USA. Poster S75.

Age and Cost Factors Associated with Adherence to MS Immunomodulatory Therapy

Using pharmacy claims data analysis for the year 2004, this study looked at patients given a prescription for glatiramer acetate. The investigators looked at several factors that would influence adherence, including age, gender, urban vs. rural home setting, average cost share for the drug (ranging from $10-$50), having an average drug supply of 84 days-90 days vs. less, depression, and consultation with a neurologist. Regression models were developed to show the relationship of these factors to adherence to immunomodulatory drug therapy, measured as <85% vs. >85%.

Factors found to be significant for a positive influence on adherence were age 45+ years, an average drug supply of 90 days, and patients’ sharing of responsibility of less than $50. These same factors were consistent regardless of whether patients were new or existing users of the drug therapy; however, among existing users, having a 90-day drug supply was associated with a greater chance of adherence than other factors alone. Comorbid depression exerted a negative influence on adherence only in the existing-user group, despite a higher prevalence of depression among new users.

Factors associated with adherence to MS immunomodulatory therapy. Caremark, Northbrook, IL, USA. Poster S21.

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Factors associated with adherence to MS immunomodulatory therapy. Caremark, Northbrook, IL, USA. Poster S21.
MS Counseling Points™

Adherence to Disease-modifying Therapy—Recognizing Barriers and Offering Solutions

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