

# Importance of Adherence to and Persistence with Prescribed Treatments in Patients With Multiple Sclerosis

a report by

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## Introduction

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system (CNS), characterized by cognitive dysfunction and increasing physical disability. The pathogenesis of MS is mediated by T-cells and other immune factors, including antibodies, complement, and mediators of the innate immune responses.<sup>1</sup> Environmental triggers are thought to influence the onset of MS in genetically susceptible individuals.<sup>1</sup>

In the US, it has been estimated that MS affects 250,000 to 350,000 people, and more than one million people worldwide.<sup>2,3</sup> MS is typically diagnosed during early adulthood, with a median onset age of 28.<sup>4</sup> The early age of onset, the chronic nature of the disease, and the accumulation of physical disability contribute to devastating economic and personal burdens in patients with MS. Fifty per cent of patients with MS require an assistive walking device by 15 years from diagnosis, and 83% after 30 years.<sup>5,6</sup>

The current treatment of MS consists of lifelong disease and symptom management. Disease-modifying therapies (DMTs), including intramuscular (IM) interferon beta-1a (IFN $\beta$ -1a), subcutaneous (SC) IFN $\beta$ -1a, SC IFN $\beta$ -1b, and glatiramer acetate, form the basis of treatment of relapsing MS. DMTs cannot cure MS; however, they can reduce the frequency and severity of relapses and resulting disability. Over two years, patients who receive DMTs can expect a 30% decrease in relapse rate<sup>7-10</sup> and those who receive IFN $\beta$  may experience a slowing of sustained disability progression.<sup>7,9</sup> In general, the IFN $\beta$  products are equally effective in reducing disability in the short-term; however, based on available data, glatiramer acetate does not affect disability and has a mild and delayed effect on disease parameters assessed by magnetic resonance imaging (MRI). Considering these therapeutic benefits, eligible patients should receive a DMT as soon as possible after a diagnosis of relapsing MS. Other treatments, such as corticosteroids and immunosuppressants, are used concomitantly with DMTs during stages of breakthrough or continued breakthrough disease.<sup>11,12</sup>

To achieve the maximum benefit from DMTs, patients with MS must adhere closely to their prescribed therapeutic regimen (adherence), and they must continue treatment throughout the course of the disease (persistence). As with other pharmacological treatments, DMTs cannot be effective in patients who do not adhere to them over a reasonable length of time.<sup>13</sup> Promoting high levels of adherence and persistence should therefore be major aims of therapy. It is interesting to note that discontinuation rates within the first six months of treatment range from 9% to 20% in clinical practice,<sup>13,14</sup> whereas rates reported during clinical trials of MS ranged from 7% to 15%.<sup>7,9,10</sup> This difference may be partly due to the fact that patients in clinical trials receive a more intense follow-up than patients seen in clinical practices.

## Treatment Barriers in Patients with MS

The first step toward improving adherence to DMTs is to gain a clear understanding of the complex and diverse patient-related, treatment-related, and disease-specific barriers to adherence.<sup>15,16</sup> Special challenges associated with adherence in patients with MS include an unpredictable disease course, physical disability, feelings of hopelessness, and cognitive impairment. Furthermore, because DMTs do not produce immediate results, treatment adherence can be more challenging than adherence to a therapy that does produce immediate results (e.g. insulin for diabetes).

Patient-related treatment barriers vary among patients. The principal barriers include communication problems, knowledge deficits, physical impairment, social or cultural variables, financial concerns, emotional distress, psychological disorders, and cognitive deficits. For example, physical impairment may result in poor hand to eye coordination or tremor, which can be an obstacle to self-injection. Cognitive deficits may interfere with a person's ability to understand treatment rationale, and emotional distress and depression are strong impediments to taking medications.<sup>17</sup> Knowledge deficits can cause unrealistic treatment expectations. A study of patients beginning treatment with IFN $\beta$ -1b reported that unrealistic expectations were highly predictive of treatment non-adherence.<sup>14</sup>



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Other barriers of adherence to DMTs relate to the frequency of dosing, injection-related side effects, and other treatment-related side effects. The literature clearly shows that factors such as drug regimen complexity (e.g. frequent administration) and adverse effect intensity or frequency can have an unfavorable impact on adherence.<sup>18–22</sup> Furthermore, administration of high-dose IFN $\beta$  products may be associated with a higher rate of adverse events.

Results of one study showed that adverse events were the primary reason for non-adherence to therapy in patients who received high-dose IFN $\beta$  formulations.<sup>23</sup> Another recent post-marketing Italian study of 1,481 patients treated with IFN $\beta$ -1b (Betaferon) and IFN $\beta$ -1a (Avonex) showed similar clinical benefits (including an increase in the percentage of relapse-free patients and a decrease in annual relapse rate) between the two treatment groups. The Betaferon group (every-other-day injection), however, had a higher incidence of side effects and a treatment discontinuation rate of 41.1%, while the Avonex group had a discontinuation rate of 15.3%.<sup>24</sup>

Importantly, the route or frequency of administration or the pH of the drug may affect injection-related side effects. These three factors account for major differences among the available DMTs. Intramuscular (IM) IFN $\beta$ -1a is administered once weekly, SC IFN $\beta$ -1a three times weekly, SC IFN $\beta$ -1b every other day, and SC glatiramer acetate every day. Furthermore, the pH of IM IFN $\beta$ -1a and SC IFN $\beta$ -1b is mildly basic, whereas that of SC IFN $\beta$ -1a is acidic. The acidic pH of SC IFN $\beta$ -1a is necessary to provide stability of the formulation and is considered a possible cause of injection-site pain; however, results from one study suggest other causes.<sup>25</sup> Injection-site reactions are rare and mild after IM IFN $\beta$ -1a administration, whereas higher incidences of injection-site reactions have been associated with SC IFN $\beta$ -1a and -1b.<sup>7–9</sup> Skin necrosis has also been associated with SC IFN $\beta$ -1b.<sup>26</sup> The administration of SC glatiramer acetate has been associated with a number of injection-related side effects including pain, inflammation, erythema, pruritus, induration, lipoatrophy, and immediate post-injection systemic reactions.<sup>10,27</sup>

### Improving Adherence

Traditionally, adherence to therapy has been improved in part by managing adverse events. Although there have been no well-controlled studies of adverse effect management, the collective experience of the clinical community is useful in guiding the management of common adverse events associated with DMTs.<sup>28–31</sup>

Flu-like symptoms, which are commonly observed during treatment with IFN $\beta$ , may include fever, chills,

sweating, and muscle aches; these symptoms usually appear two to eight hours after injection and resolve within 24 hours.<sup>31</sup> The severity of flu-like symptoms tends to decrease with continued dosing.

The management of flu-like side effects primarily involves a gradual dose titration and, if required, co-administration of a non-steroidal anti-inflammatory drug (NSAID) 30 minutes before injection.<sup>28,30</sup> Low-dose corticosteroids may be used in patients who do not respond to NSAIDs. A recent randomized study comparing the efficacy of corticosteroids and ibuprofen or acetaminophen for the treatment of IFN $\beta$ -associated flu-like syndrome (FLS) showed that all three interventions had a similar effect on the primary outcome (FLS index expressed as area under the curve). When the FLS index was evaluated as mean value, however, a significant benefit was seen with 400mg of ibuprofen given before, and six and 12 hours after, the injection.<sup>32</sup> IFN $\beta$  may be initiated at 25% of the recommended dose for the first week followed by 50% of the dose the next week.<sup>31</sup> Patients should also be advised to administer IFN $\beta$  in the evening so that the majority of adverse events occur during sleep.<sup>31</sup>

The most common reasons for dose titration of glatiramer acetate include chest pain or pressure, episodes of shortness of breath, anxiety or panic attacks, lightheadedness, and hot flashes.<sup>28</sup> If these symptoms occur, glatiramer acetate should be administered at 25% of the recommended dose and increased by the same amount weekly until the full dose is achieved. This type of dose fractionation allows patients who would otherwise have discontinued treatment to remain adherent. Unfortunately, some patients will experience these reactions on an idiosyncratic basis.

The management of injection-site reactions primarily involves rotating the injection site and improving the injection technique. Practical techniques to minimize skin-related adverse events include:

- washing hands thoroughly;
- thoroughly cleansing the injection site;
- waiting for alcohol to dry before injecting;
- completely penetrating the needle into the skin surface;
- using shorter needles for IM injection in lean patients; and
- smoking cessation.<sup>28</sup>

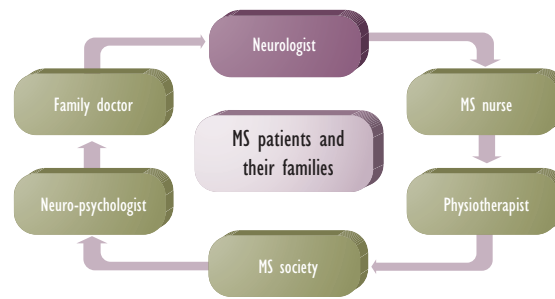
To ease pain, the injection site may be iced for 30 to 60 seconds before cleansing. Topical corticosteroids (1% to 2% hydrocortisone) may be applied for post-injection erythema. Patients should allow medications to warm to room temperature before injecting.<sup>29</sup>

Although the management of side effects is vital, the optimal strategy toward improving adherence requires additional measures involving a multidisciplinary team (see *Figure 1*). Each member of the healthcare team must strive to develop and maintain a quality relationship with the patient, because doing so will have a significant positive effect on treatment outcomes.<sup>33</sup> Patients report that the manner in which they are treated by their healthcare team has a substantial impact on whether or not they follow medical advice.<sup>33</sup> One study reported that the highest rates of adherence to the DMT occurred at clinics that emphasized cooperation and promoted less formal relationships with their patients.<sup>34</sup>

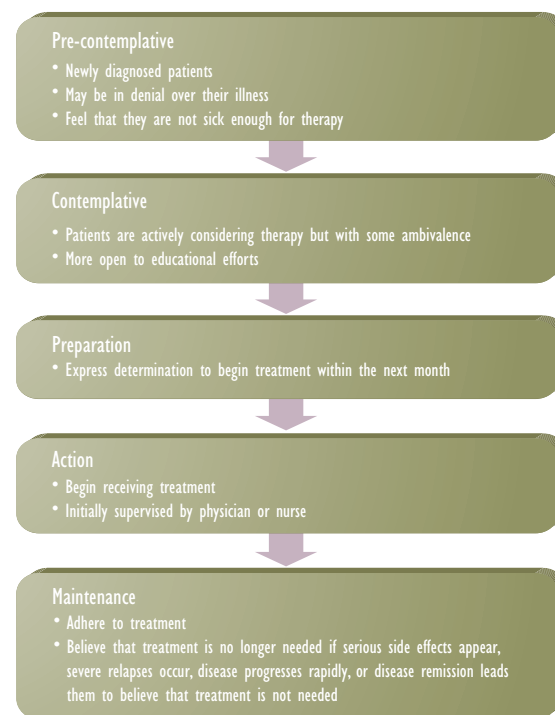
All members of the healthcare team must strive to do as much as possible to improve patient adherence. Neurologists should regularly question their patients to identify possible treatment barriers by assessing the severity and incidence of adverse events and the perceived benefits of DMTs. Patients must be involved as much as possible in treatment decisions and be educated about MS and its treatment. Patients should be encouraged to inform family and friends about their condition and the suggested treatment. Although some patients may refuse to be adherent despite all efforts, it is important to continue working with these patients and offer other services such as psychotherapy or rehabilitation. MS nurses can help to identify areas of difficulty as well as provide education, including comprehensive initial training, support, and advocacy.

The development of strategies to encourage the continued use of DMTs may be tailored according to the trans-theoretical model of change (see *Figure 2*).<sup>16</sup> This model is based on the premise that patient attitudes and beliefs are dynamic; therefore, their acceptance or adherence to treatment can change over time. Healthcare providers can intervene at any point throughout these stages by tailoring their messages to the appropriate stage of behavior. Although patients do not always move through these stages in a linear fashion, the goal of intervention is to prepare patients to move into the subsequent stage in the model. This is primarily accomplished by providing information tailored to the attitude of the patient. For example, patients in the pre-contemplative stage must gain an understanding of their disease state and be able to verbalize personal barriers to treatment before moving to the contemplative stage; therefore, interventions must address educational and personal barriers to treatment. During the contemplative stage, patients must be able to describe the process of MS therapy, including potential benefits and side effects of the DMT, before moving on. Once patients enter the preparation stage, a plan of action should be developed and initiated to advance to the action stage. Individuals in the action stage should commit to remain on therapy for six months, unless side

**Figure 1: A Multidisciplinary Approach to Improving Adherence**



**Figure 2: Trans-theoretical Model of Behavior in Patients with Multiple Sclerosis**



effects are intolerable or the physician decides that treatment should be discontinued.<sup>16</sup>

**Summary**

Adherence is an important modifier of treatment efficacy in the long term. Managing patient expectations, teaching excellent injection technique, and counseling patients to manage side effects are crucial for the long-term success of DMTs in patients with MS. Whereas the efficacy profiles of current DMTs are similar, convenience and tolerability vary according to treatment and should be considered when choosing the type of MS therapy. Selecting a treatment with an uncomplicated dosing regimen and a favorable adverse event profile may substantially increase the likelihood of adherence to therapy. ■

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