

Counseling Points™

Enhancing Patient Communication for the MS Nurse

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Assessing the Efficacy of Disease-modifying Therapy in the Long-term—One Patient at a Time

A Roundtable Discussion

It is fair to say that a large number of patients diagnosed with multiple sclerosis (MS) choose to begin treatment with one of the currently available injectable disease-modifying therapies (DMTs). They start therapy with high hopes and rightly so—after all, it was only just under 20 years ago that we had no disease-specific therapies to offer patients. Nevertheless, we need to temper these high hopes with realistic expectations. As we have emphasized in previous issues of *Counseling Points™*, these agents do not cure MS or even reverse the neurological deficits that patients have accumulated prior to initiation of therapy. However, there is a growing body of evidence that DMTs can alter the natural history of the disease, at least in the short term, in as much as they



reduce the frequency and severity of relapses, decrease inflammatory activity in the brain and spinal cord as measured by magnetic resonance imaging (MRI), and delay the progression of disability.

It cannot be said often enough how important the role of the nurse is in educating patients with MS about their disease, its potential course, and how to manage it optimally. Being able to talk to

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Welcome to MS Counseling Points™

ENDORSED BY THE INTERNATIONAL ORGANIZATION OF MS NURSES

Dear Colleague,

Probably one of the toughest questions that a patient with multiple sclerosis (MS) can ask you is: How do I know if my injections are working? Unfortunately, there is no simple answer to that question, nor a response that applies to every situation. The currently available injectable disease-modifying therapies (DMTs) were tested in a series of randomized, controlled clinical trials using a set of measures of efficacy that are not always practical to apply in day-to-day practice. As we all know, the clinical setting is often very different from that of a rigorously conducted trial.

In this edition of *Counseling Points™* we tackle the tough issue of how to reassure patients that their DMT is working. We'll take a look at the natural history of MS before DMTs were introduced in the mid-1990s, and the effects, as reported in published studies and anecdotally, that these agents seem to have had on the disease course in the majority of patients. We'll also talk about the measures used to evaluate efficacy in clinical trials and the degree to which these measures are helpful in everyday practice.

One of the most important things to keep in mind when dealing with this or any other situation that arises with your patients is that you're not alone. If you work in a general neurology practice or a setting where you can't talk these issues through with other team members or experts in the arena of MS, remember to tap into the resources of the International Organization of Multiple Sclerosis Nurses (IOMSN). As detailed later in this issue, the IOMSN's focus extends beyond just that of nurses who are MS specialists, but offers support, education, and counseling to any nurse who sees patients with MS.



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patients about ways in which they can assess the efficacy of their therapy is crucial; thus, the focus of this issue is on practical advice for answering the dreaded question: How do I know if my therapy is working?

Setting the Stage

Before delving into this complex subject, it is important that we define some of the terms that tend to get bandied about when talking about measuring efficacy. The focus will be on those measures typically used in clinical trials: the occurrence of a relapse, the Kurtzke Expanded Disability Status Scale (EDSS) score, and MRI results.

Definition of Relapse

What constitutes a relapse? The formal definition of a relapse—or, as it is sometimes called, an exacerbation or attack—is the new onset of neurological problems that are separated in space and time from a prior episode.¹

- By *space*, the definition refers to a new central nervous system (CNS) lesion that produces new symptoms (e.g., leg numbness as opposed to optic neuritis).² If the symptoms are the same as the patient has experienced before or an existing neurological deficit worsens, he or she is described as having a relapse if the symptoms last more than 48 hours. However, some clinicians use 24 to 48 hours as the criterion for a relapse.

- By *time*, the definition refers to symptoms that last for more than a day and are separated by at least 30 days from a previous relapse.²

What a patient describes as a relapse can differ from this formal definition. It is also worth mentioning that the symptoms should be in the absence of an infectious or metabolic process, as these can cause a return of old symptoms or symptoms suggestive of a relapse. For example, a patient with a urinary tract infection may experience stiffness in the lower extremities and think she is having a relapse. This phenomenon is often referred to as a “pseudo-relapse.”

The formal definition of a relapse is the new onset of neurological problems that are separated in space and time from a prior episode.

EDSS Score

The EDSS is an ordinal scale ranging from 0.0 (meaning the patient shows no deficits) to 10.0 (death due to MS) (Figure 1).³ It is largely a measure of ambulatory ability.

- Scores in the range of 1.0 to 3.5 are determined by various functional system scores.
- Scores in the range of 4.0 to 7.0 are determined by a patient’s ability to walk.

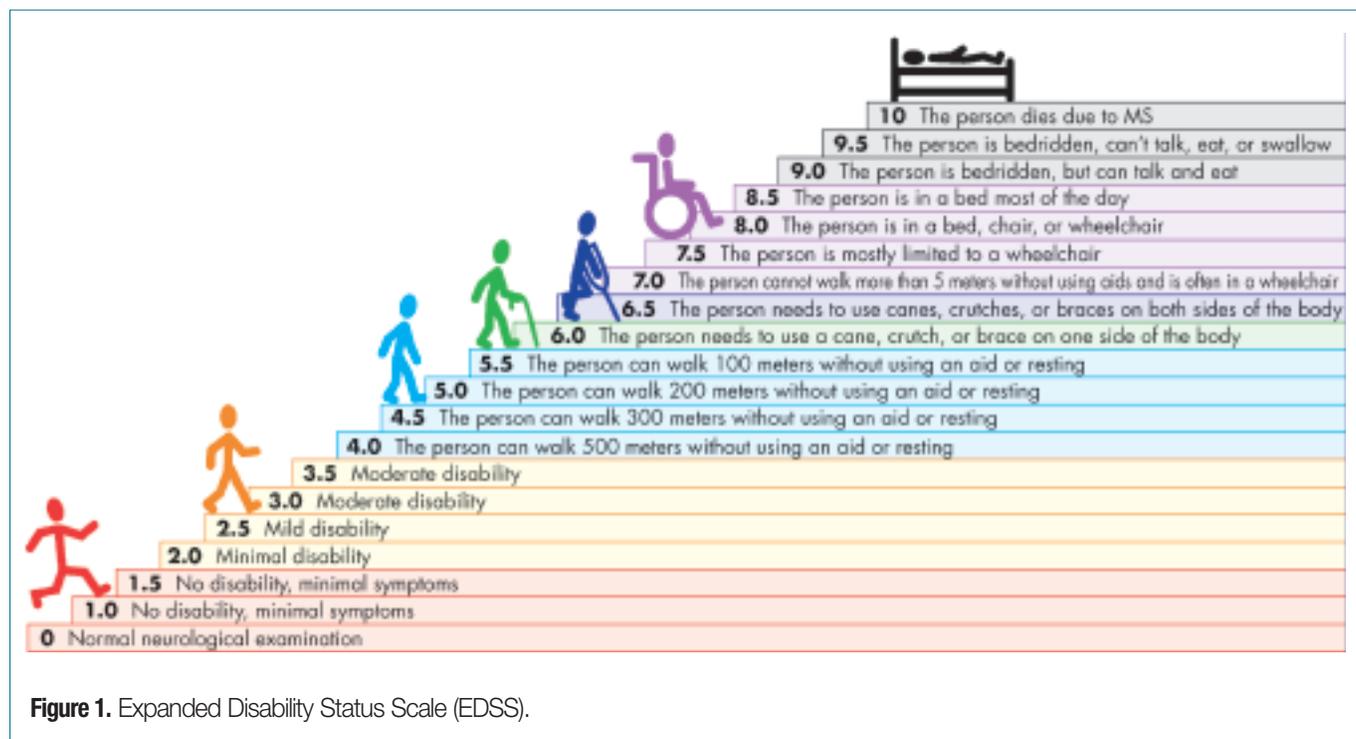


Figure 1. Expanded Disability Status Scale (EDSS).

- Scores greater than 7.0 indicate patients who are unable to walk.
- Scores in the range of 7.5 to 8.5 are determined mostly by a patient's arm function. Thus, patients with scores greater than 8.5 cannot use their arms or legs.³

As discussed later in this issue, the EDSS is not ideal for use in everyday practice. When it is implemented by an experienced clinician, however, it can provide some useful information about a patient's functional and ambulatory status. In many clinical settings where it is not practical to perform a full EDSS test, the 25-foot timed walk is used as a sensitive measure of change.

MRI Scans

On MRI, gadolinium-enhancing lesions represent the breakdown of the blood-brain barrier and indicate the presence of active inflammation.³ Enhancing lesions can also be signs of destruction of CNS myelin and transection of axons. Lesions detected on T₂-weighted MRI may reflect edema in an active lesion or a chronic inactive lesion with a variable degree of axon loss. In addition, the greater the number of T₂ lesions (i.e., the lesion burden) the greater the degree of brain atrophy and the frequency of new enhancing lesions.³ T₁ hypointense lesions are a marker for tissue destruction and are associated with greater progression of clinical disability and increased axonal loss.³

The Natural History of MS

One way of assessing the efficacy of DMTs is to look at the natural history of MS before the introduction of this class of agents in the 1990s. Early hallmark studies of the natural history of MS were published by Weinshenker and colleagues in the late 1980s. In one study, it was suggested that the average number of relapses experienced by patients with MS is 0.1 to 1 per year.⁴ However, this correlates with the stage of the disease at which relapses are measured, as the frequency tends to diminish over time. The most relevant finding from these studies in this day and age where we have treatments that are at least partially effective is that 30% of patients with MS reached a Disability Status Scale (DSS, an earlier version of the EDSS) score of 6.0 within 10 years of the onset of their disease.⁵ This means that these patients had some difficulty with walking. In a follow-up report, by 15 years after disease onset, 50% of patients had reached EDSS score 6.0 and

10% had reached EDSS score 8.0 (meaning they were restricted to bed without effective use of their arms).⁶ Remember, however, that these data come before the era when DMTs were available.

Can we tell if DMTs affect the natural history of MS? The answer to this question varies. Some experts are reluctant to compare data from clinical trials with natural history data. Indeed, such comparisons should always be made with caution. In most natural history studies, patient assessments are performed infrequently and patient populations are probably less well defined than in clinical trials.⁷ In addition, quite often any disability data reported are in effect "snapshot" assessments, (i.e., compiled only at a single point in time).⁷ With those caveats in mind, it is still interesting to look at the data available on the effects of the injectable DMTs on relapses and disability.

In clinical trials, the injectable DMTs compared with placebo reduced relapses by about 30%.⁸ Interestingly, although the number of relapses while on treatment was substantially lower than the number reported in the 2 to 3 years prior to enrollment, the number of relapses was also lower among the control subjects.⁸ One possible explanation for this finding is that relapses were defined more rigorously and objectively in clinical trials.⁹ Keep in mind, however, that in the real world, some patients tend to describe any flare-up as a relapse.

Data presented at the annual American Academy of Neurology meeting in 2006 suggested that patients who had been taking interferon β -1b, administered subcutaneously (SC) every other day for up to 16 years, had slower disease progression compared with those who had not been on long-term therapy.¹⁰ Among the patients who reached EDSS level 6.0, those on long-term (≥ 12 years) interferon β -1b treatment reached this endpoint after a median of 13 years compared with 7 years for patients on short-term treatment (≤ 1.6 years).¹⁰ It should be noted that this is one of those "snapshot" situations because the patients were not followed after completion of the original trial; rather, the investigators only evaluated how patients were doing at a point in time some years after the trial ended.

A retrospective evaluation of patients originally treated in the interferon β -1a once-weekly pivotal clinical trial (given via intramuscular injection) was recently published. Among 160 patients at an 8-year follow-up assessment, 42% and 29.1%

of the original placebo and treated patients reached an EDSS score of ≥ 6.0 , respectively.¹¹

Trial data confirm that the earlier a DMT treatment is started, the greater the benefit.

The 10-year results of a prospective, open-label study of glatiramer acetate were published in 2006 and also showed a significant slowing of disease progression.⁷ Through November 2003, 108 patients had taken the drug for up to 12 years (mean 10.1 years). Sixty-two percent were described as having stable or improved EDSS scores, defined as an increase of ≤ 0.5 point, no change, or a decrease in EDSS score from the onset of treatment.⁷ The proportion of patients who progressed to predefined EDSS thresholds was much lower than what would be predicted based on MS natural history data.^{6,12,13} Eight percent reached an EDSS score of 6.0 and only 1% a score of 8.0. Clinicians feel comfortable with the validity of these data from this ongoing study, in which

International Organization of MS Nurses

Established 12 years ago by a group of nurses who specialize in caring for patients with multiple sclerosis (MS), the International Organization of MS Nurses (IOMSN) is an invaluable resource for specialist MS nurses and those who may only occasionally see patients with this disease.

The ultimate goal of the IOMSN is to improve the lives of all patients affected by MS through the provision of appropriate health care services. The organization achieves this goal, in part, by offering a mechanism by which members can share information on practice positions and resources and by providing a forum for discussion and collaboration on issues that concern MS nurses. The IOMSN encourages collaboration with other nursing organizations and welcomes all nurses who care for patients with MS to tap into the resources it offers.

The best way to contact the IOMSN is to visit their website at www.iomsn.org and complete the feedback form. Someone will contact you to answer your questions and identify your needs.

patients are followed in a prospective fashion and examined every 6 months.

Trial data also confirm that the earlier a DMT treatment is started, the greater the benefit. For instance, 68% of patients enrolled in the pivotal trial of interferon β -1a given via subcutaneous injection three times weekly presented for a follow-up visit at 7 to 8 years after baseline.¹⁴ Of these, 72% were receiving interferon β -1a. Patients who had originally been randomized to receive 44 μ g three times weekly showed less EDSS progression and a lower relapse rate than those who were originally randomized to receive placebo and were switched to active treatment after 2 years.¹⁴ Importantly, the time to reach an EDSS score of 6.0 was less among those who had been on active treatment since baseline.

From these limited data and anecdotal reports, it seems safe to say that the current DMTs have a favorable effect on the course of MS. Nevertheless, each individual patient is different and will not always respond to therapy in the same way that others do.

Evaluating Efficacy in Clinical Practice

When talking about efficacy with patients, it is important to emphasize that the majority of patients respond well to the initial DMT they are prescribed. The time taken for the effects of the DMT to take hold vary from patient to patient and are dependent on a patient's level of adherence to the drug schedule. Thus, we would recommend that nurses not even consider the possibility of a suboptimal response for any changes in the patient status until at least 6 months, if not a year, after the initiation of therapy.

The majority of patients respond well to the initial DMT they are prescribed.

Relapse Rate as a Marker of Treatment Efficacy

In our experience, the consensus is that relapse rate alone is not a particularly good marker of treatment efficacy. Often, patients want to know if a single attack reflects a suboptimal response, regardless of the duration of treatment or the number of relapses they experienced prior to initiating therapy. However, comparing the number of relapses experienced before initiation of a DMT with the number experienced after

is not ideal. Because patients are being treated earlier and earlier—in many cases after one clinically isolated episode—many patients may have had only a single attack or very few attacks before starting a DMT.⁸

As mentioned earlier, in reality, patients tend to describe any flare-up or symptom as a relapse. Hence, when patients come in concerned that their DMT is not working because they have experienced a transient tingling or numbness, it is critical to question them closely to determine whether they are experiencing a true relapse. Of course, this should be done without dismissing their very real fears and anxieties as over-reactions. However, at times like these, although it might sound a little pedantic, it is probably reassuring to patients if you make sure they understand the official definition of a relapse. It may not make them feel any better at the time, but it might prevent them from panicking that their therapy isn't working.

If patients have genuine relapses, it is crucial to put the specific relapse into perspective. How severe is it? Is it more or less severe than relapses experienced before the initiation of DMT? Is it lasting a longer or shorter time than those experienced at or before baseline? Does the patient require corticosteroid therapy and, if so, for how long? Does the patient's function return to baseline after symptoms have resolved? These are just some of the questions you need to ask to help determine if a suboptimal response to therapy is likely.

EDSS Score as a Marker of Treatment Efficacy

The EDSS is often criticized because it requires quite a bit of training and experience to use and is not sensitive to subtle changes, including cognitive deficits.³

Nevertheless, despite its shortcomings, the EDSS is easier to apply in everyday practice than more quantitatively derived composite measures of disability. It is important to remember that any change in the EDSS score associated with a relapse may only be a reflection of the severity of the relapse. The score may return to the pre-relapse level over 3 to 6 months and, thus, should not be used in isolation to determine a suboptimal response.⁸ However, a long-term increase in EDSS score (i.e., sustained for a year) of 1 point from a previous score of 3.0 to 5.5, or a 0.5 point increase from a previous score of 6.0 or greater in the absence of relapses, is noteworthy. This may mean that a patient with relapsing-remitting MS (RRMS) is transitioning to secondary-progressive MS (SPMS)

or that a patient with SPMS is having a suboptimal response to therapy. Changes in the EDSS score of patients with scores below 3.0 are too variable to be used in isolation to determine a suboptimal response.⁸

The day-to-day symptoms of MS such as fatigue and depression can affect patients' ability to walk and thus cause fluctuations in their EDSS score.

A word of caution about using the EDSS: Because it is largely a measure of ambulatory ability, it is important that a patient's walking ability is measured accurately. It is not always practical or feasible because of time and space constraints to walk patients the required distances to perform an accurate assessment. Thus, in situations where you have to rely on patients' reports of their walking ability, it is useful to offer them some reference points. For example, knowing that a standard football field is 100 meters in length or measuring the distance from the street or the parking area to the clinic and having patients assess their ability to walk this distance can be helpful. If the patient does not actually walk the required distances but simply reports how far they can walk, this should be noted. In addition, the day-to-day symptoms of MS such as fatigue and depression can affect patients' ability to walk and thus cause fluctuations in their EDSS score; thus, it is important to request that patients perform walking assessments on several different days and at different times of day to get an accurate picture of mobility.

MRI Findings as a Marker of Treatment Efficacy

It is difficult to define what constitutes excessive MRI activity that may be an indicator of suboptimal response to therapy. It has been suggested that the presence of three or more enhancing lesions, or two or more new T₂ lesions on scans performed 3 months apart might be predictive.⁸ Certainly, in the absence of clinical problems, findings on random MRIs cannot be interpreted in isolation.

At present, the consensus is that MRI findings should not be used as a sole indicator of a suboptimal treatment response.⁸ Following diagnosis and initiation of therapy, an

MRI should be performed when there is unexpected clinical worsening or it is suspected from clinical findings that the patient is not responding to therapy.¹⁵

Real-world Markers

When patients are first prescribed a DMT, it is essential to not only set realistic expectations about their medication, but also to teach them to identify markers of success, rather than measures of failure. For example, if a patient previously had to take a lot of time off from work and after 6 months to a year of therapy has missed hardly a day, that's a positive sign. Other potential markers of success are ability to ambulate, energy level, capacity for exercise, ability to socialize, and general quality of life.

When patients are first prescribed a DMT, it is essential to not only set realistic expectations about their medication, but also to teach them to identify markers of success, rather than measures of failure.

Of course, if patients don't achieve predefined markers of success, they will probably assume that their therapy is not working. Thus, if patients are having to take more time off from work than usual, are finding it harder to cope with work, or if they are having trouble driving or performing any of those activities that make their lives normal, they will probably put it down to a suboptimal response. Before jumping straight to the conclusion that there's a problem with the DMT, however, nurses should ensure that patients are adhering to their therapies. Clinicians also need to find out if anything else is going on in their patients' lives that could be causing undue stress. This includes assessment of the home situation, relationship issues, sleep patterns, and drug side effects. The increased use of medications to manage symptoms such as sexual or bladder dysfunction can be an indicator of disease progression. If everything else seems normal and patients claim to be fully adherent yet there are subtle and not so subtle indicators that they are becoming more disabled, then it may be time to have the physician perform a thorough assessment to evaluate whether or not a change

of therapy is appropriate. If a change does become necessary, it is important to emphasize that patients should not become disillusioned with DMT altogether and that there are many success stories of patients stabilizing after a drug switch.

Summary

Compared with 20 years ago, the future looks bright for patients with MS. There are now a number of DMTs available and more on the horizon. While the currently available therapies are not a cure and are only partially effective, the vast majority of patients gain control of their disease.

The goal of DMT therapy is to prevent future disability, not to reverse deficits that are already present. This makes it hard to assess the efficacy of DMTs because each patient's degree of disability tends to fluctuate over time and is affected by a number of factors. Researchers and clinicians tend to look at substitute targets for treatment efficacy, such as number and frequency of relapses and MRI activity. Although relapses are of great concern to patients, they do not relate particularly well to future disability.⁸ MRI activity is also not a particularly good marker of future disability. Nevertheless, these markers are often used when evaluating response to therapy.⁸

In everyday practice, it is important to educate patients to identify markers of success rather than look for markers of failure. Thus, the ability to perform normal daily activities is probably as good an indicator of treatment success as measures such as the relapse rate and the EDSS score.

It is important to remember that DMT is usually successful and, in most cases, you should not even consider a response as suboptimal until 6 to 12 months after therapy has started. When counseling patients who are concerned about the possibility of a suboptimal response to treatment, the nurse's role is to be a cheerleader, while at the same time not dismissing patients' concerns as an overreaction. As "cheerleaders," part of our role is to foster hope. The late Linda Morgante, RN, MSN, MSCN, was a strong proponent of establishing realistic hope in MS. She believed that hope can be the driving force in MS care and the IOMSN has adopted this philosophy in all of its activities. As has been said by others, hope sees the invisible and achieves the impossible, embodies our vision of the future, and gives us promise for tomorrow.

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MS Counseling Points™

Assessing the Efficacy of Disease-modifying Therapy in the Long-term—One Patient at a Time

- Set realistic expectations at the initiation of therapy.
- Ask patients to identify markers of success, rather than measures of failure.
- Reassure patients that the majority of patients do well on a disease-modifying therapy (DMT).
- Don't consider that a patient is having a suboptimal response to a DMT until at least 6 months to a year after initiation of therapy.
- Make sure patients know what constitutes a true relapse.
- Evaluate the nature of a relapse (e.g., severity, duration, and need for corticosteroids).
- Keep in mind that the true value of the Expanded Disability Status Scale (EDSS) score is as a measure of ambulation. It does not measure more subtle deficits such as cognitive problems.
- Do not rely on the findings of random magnetic resonance imaging (MRI) scans as indicators of suboptimal response to treatment.
- Evaluate the degree of patient adherence with therapy before assuming a suboptimal response to therapy has occurred.
- Ask patients about their capacity to perform their normal day-to-day activities when a suboptimal response is suspected.

Do Relapses Contribute to Sustained Worsening of Disability?

In this study, researchers investigated whether or not relapses contribute to future sustained disability, by looking at the correlation of time to an increase in the Expanded Disability Status Scale (EDSS) score sustained for 6 months with the occurrence of prior relapses. The patients studied were a subset of 256 subjects with relapsing-remitting multiple sclerosis (RRMS) from the placebo arms of 20 randomized, controlled, clinical trials. The researchers concluded that although relapses may result in EDSS progression, there was no consistent effect of relapses on the subsequent development of a sustained increase in EDSS score during a typical clinical study observation period.

Young, PJ, Lederer C, Eder K, et al. Relapses and subsequent worsening of disability in relapsing-remitting multiple sclerosis. *Neurology*. 2006;67:804-808.



Low Rate of Relapse and EDSS Progression in 22-year Study of Glatiramer Acetate

This article presents results for patients with RRMS who were enrolled in a controlled pilot study of the safety and efficacy of glatiramer acetate (GA) and continued to be treated in an open-label compassionate use study for up to 22 years. Forty-six patients were enrolled; as of October 2004, 18 patients continued to be in the study. The mean EDSS score increased by 0.9 ± 1.9 from the pretreat-

Most patients maintained improved or stable EDSS scores.

ment score (3.0 ± 1.8 , $P=0.076$). Most patients maintained improved or stable EDSS scores. The annualized relapse rate decreased to 0.1 ± 0.2 from 2.9 ± 1.4 pretreatment ($P<0.0001$). The drug was well-tolerated, as evidenced by patients' willingness to self-inject GA for up to 22 years. The findings of this study support the results of the GA extension study (Ford CC, et al. *Mult Scler*. 2006;12:309-320), in which relapse rates were reduced by $>80\%$ and EDSS score increased by only 0.5 points for patients who were treated with GA continuously for >10 years.

Miller A, Spada V, Beerkircher D, et al. Long-term (up to 22 years), open-label, compassionate-use study of glatiramer acetate in relapsing-remitting multiple sclerosis. *Mult Scler*. 2007; epub ahead of print. Doi:10.1177/1352458507085029.

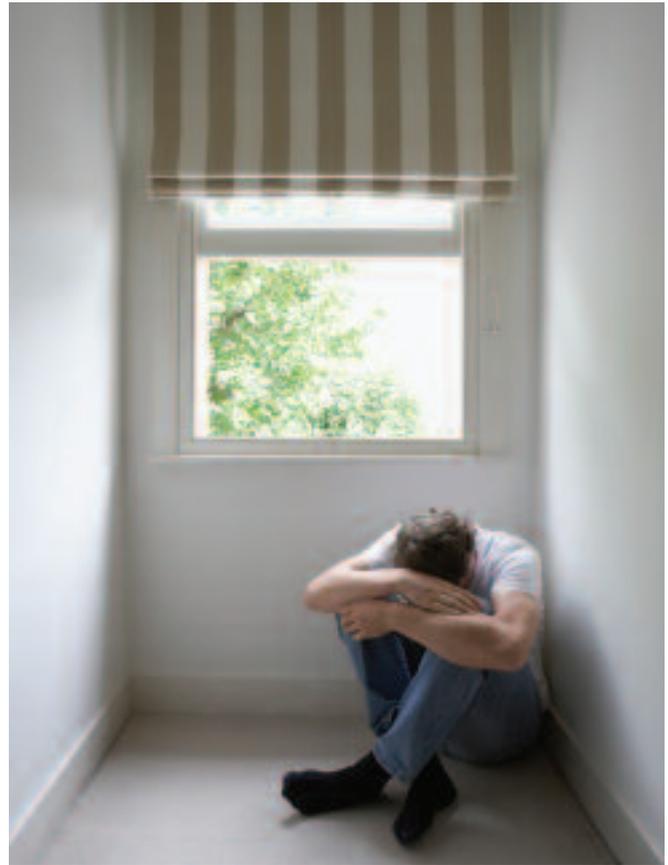
Use of Antidepressants Increased Among MS Patients

Depression has long been reported as a comorbid condition with MS, but the actual use of antidepressants in this population has not previously been specifically investigated. A study by Kessing et al reported in the January 2008 issue of *International Clinical Psychopharmacology* examined the use of antidepressant therapy for patients with MS compared with those with osteoarthritis and the general population. The investigators reviewed the data from nationwide case registries in Denmark from 1995 to 2000 for their cohort, which included 417 patients with diagnosed MS and 12,127 patients diagnosed with osteoarthritis. Patients with MS purchased three times more antidepressants than patients with osteoarthritis, and more than four times more antidepressants compared with the general population. These increased rates of use of antidepressants were consistent across all subgroups of patients, regardless of age, gender, socioeconomic status, or time since diagnosis.

Kessing LV, Harhoff M, Andersen PK. Increased rate of treatment with antidepressants in patients with multiple sclerosis. *Int Clin Psychopharmacol*. 2008;23:54-59.

Family History Provides Clues to MS Risk

A case-controlled study of 298 women with MS enrolled in the much larger Nurses Health Study I and II was conducted to determine the strength of a suggested link between a family history of autoimmune disorders or allergy and the risk of developing MS. The patients in the cohort were asked to complete a questionnaire, the results of which were compared to a control group of 1,248 healthy women. Another subset of 248 women with a history of



breast cancer was used for comparison. As expected from previous studies indicating a familial pattern, patients with MS were more likely to report a family history of MS (odds ratio [OR] 9.7, 95% CI: 6.1-15.3). Only a modest increase in overall risk of MS (OR 1.4, 95% CI: 1.0-1.8) was found among women who reported a family history of other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, hyperthyroidism, and type 1 diabetes. A similar increased risk was not associated with a family or personal history of allergy. The investigators concluded that more research needs to be done to investigate the possibility of a genetic predisposition to autoimmunity in general, which may influence an individual's risk of developing MS.

Alonso A, Hernan MA, Ascherio A. Allergy, family history of autoimmune diseases, and the risk of multiple sclerosis. *Acta Neurol Scand*. 2008;117:15-20.

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Program Evaluation

Using the scale below, please complete the program evaluation so that we may continue to provide you with high-quality educational programming:

Excellent ⑤ Good ④ Satisfactory ③ Fair ② Poor ①

How would you rate the:

Overall quality of *Counseling Points™*? ^ ⑤ ④ ③ ② ①

Readability of *Counseling Points™*? ⑤ ④ ③ ② ①

Usefulness of the information presented in *Counseling Points™*? ⑤ ④ ③ ② ①

Value of the *Counseling Points™* summary (page 8)? ⑤ ④ ③ ② ①

Do you believe you will be better able to communicate with patients after having read the information presented in *Counseling Points™*?

Yes No

We would appreciate your comments and suggestions on how we can improve future issues of *Counseling Points™*.

What future topics would you like to see addressed in *Counseling Points™*?

Are there any other comments, suggestions, or thoughts about *Counseling Points™* that you would like to share?



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