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Winter 2010

Volume 5, Number 4

## Update on Clinically Isolated Syndrome



This continuing education publication is supported by an educational grant from Teva Neuroscience.

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Barbara Bishop has received honoraria for serving as a speaker for Bayer HealthCare and Teva Neuroscience.

Brenda Brelje has received honoraria for serving as a consultant to Teva Neuroscience.

Tracy Walker has received honoraria for serving as a speaker for Bayer HealthCare, Biogen Idec, EMD Serono/Pfizer, Novartis, and Teva Neuroscience.

**Planners and Managers:** The following planners and managers have no conflicts of interest to disclose:

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# Counseling Points™

## Update on Clinically Isolated Syndrome

### Continuing Education Information

#### Target Audience

This educational activity is designed to meet the needs of nurses who treat patients with multiple sclerosis (MS).

#### Purpose

To provide MS nurses with the latest information on clinically isolated syndrome and early MS, acknowledging the nurse's role in patient counseling.

#### Learning Objectives

*Upon completion of this educational activity, the participant should be able to:*

- Describe the latest clinical and radiographic findings in clinically isolated syndrome (CIS) and early multiple sclerosis (MS)
- Describe current disease management recommendations for CIS treatment
- Review discussions with patients regarding when to initiate treatment
- Discuss potential barriers to starting treatment in CIS

#### Continuing Education Credit

This continuing nursing education activity was approved by the Wisconsin Nurses Association Continuing Education Approval Program Committee, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 1.0 contact hours.

Approximate time to complete this activity is 1 hour.

This program expires January 4, 2012.

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Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any medications, diagnostic procedures, or treatments discussed in this publication should not be used by clinicians or other health care professionals without first evaluating their patients' conditions, considering possible contraindications or risks, reviewing any applicable manufacturer's product information, and comparing any therapeutic approach with the recommendations of other authorities.

# welcome

Dear Colleague,

What we know about clinically isolated syndrome (CIS) is changing at a rapid pace as new data from research studies add to our knowledge base. It can be difficult for clinicians—especially those who aren't based in large multiple sclerosis (MS) centers—to keep up with these changes, so *MS Counseling Points*<sup>TM</sup> continues to develop educational activities on CIS.

Clinical trials have shown that a large majority of patients diagnosed with CIS go on to develop clinically definite MS (CDMS). As this publication explains, many factors can help us discern which patients have the greatest likelihood of converting to CDMS. The Food and Drug Administration (FDA) has approved several disease-modifying therapies (DMTs) for use in MS and CIS, and trial data show that, for the majority of patients, conversion to MS as defined by McDonald criteria can be significantly delayed if they start a DMT early in the course of their disease. In addition, many clinical trials are underway to test newer agents in people with a single clinical episode and/or magnetic resonance imaging (MRI) evidence suggestive of MS.

As MS nurses, we are witnessing diagnosis of this disease at earlier stages than ever before. CIS often occurs in a young, Internet-savvy population, yet the availability of balanced, meaningful information about CIS on the Web is lacking. Successfully counseling patients with CIS can present significant challenges for the MS nurse, including the challenge of convincing patients to begin treatment even while the diagnosis remains uncertain.

Treatment of CIS has resulted in a much more hopeful and positive outlook today than our “watch and wait” approach of many years ago. Patients have good and expanding choices for therapies, and most have an excellent prognosis for minimizing relapses and disability for many years to come.

*Amy Perrin Ross*

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# Update on Clinically Isolated Syndrome

In cases of clinically isolated syndrome (CIS) or suspected multiple sclerosis (MS), the “wait and see” approach that once was viable no longer serves patients well. Studies show that as many as 88% of patients with CIS will convert to clinically definite MS (CDMS), many within just a few years.<sup>1</sup> The data also clearly show that starting patients with CIS on immunomodulatory therapy can significantly delay conversion to CDMS and thus potentially delay the onset of permanent neurologic damage.<sup>2-5</sup>

If we could pinpoint exactly when MS begins, which patients will develop CDMS, and which patients will respond well to therapy, much of the battle would be

won. Many promising research paths are now leading in those directions. For now, however, the MS clinician has to evaluate patients presenting with CIS using the available information and make judgment calls based on current insights.

## CIS and MS Criteria

To receive a diagnosis of CDMS, the most current diagnostic criteria require that a patient have had two or more clinical attacks, or one attack combined with magnetic resonance imaging (MRI) evidence of dissemination in time and/or space (**Table 1**).<sup>6</sup> These revised criteria allow for earlier diagnosis compared with the previous

**Table 1. Revised McDonald Criteria for Clinically Definite MS (CDMS)<sup>6</sup>**

Clinical Presentation	Additional Data Needed
<ul style="list-style-type: none"> <li>• ≥2 attacks (relapses)</li> <li>• ≥2 objective clinical lesions</li> </ul>	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
<ul style="list-style-type: none"> <li>• ≥2 attacks</li> <li>• 1 objective clinical lesion</li> </ul>	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> <li>• MRI</li> <li>• or positive CSF and ≥2 MRI lesions consistent with MS</li> <li>• or further clinical attack involving different site</li> </ul>
<ul style="list-style-type: none"> <li>• 1 attack</li> <li>• ≥2 objective clinical lesions</li> </ul>	Dissemination in time, demonstrated by: <ul style="list-style-type: none"> <li>• MRI</li> <li>• or second clinical attack</li> </ul>
<ul style="list-style-type: none"> <li>• 1 attack</li> <li>• 1 objective clinical lesion (monosymptomatic presentation, CIS)</li> </ul>	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> <li>• MRI</li> <li>• or positive CSF and ≥2 MRI lesions consistent with MS</li> </ul> <b>and</b> Dissemination in time, demonstrated by: <ul style="list-style-type: none"> <li>• MRI</li> <li>• or second clinical attack</li> </ul>
Insidious neurological progression suggestive of MS (primary progressive MS)	1 year of disease progression (retrospectively or prospectively determined) and two of the following: <ol style="list-style-type: none"> <li>a. positive brain MRI (9 T2 lesions or ≥4 T2 lesions with positive VEP)</li> <li>b. positive spinal cord MRI (2 focal T2 lesions)</li> <li>c. positive CSF</li> </ol>

CIS=clinically isolated syndrome; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; VEP=visually evoked potential. Adapted with permission from: Polman CR, et al. *Ann Neurol*. 2005;58:840-846.

2001 criteria, which called for two clinical attacks and a more complete MRI picture.<sup>7</sup> However, the criteria leave the initial clinical event—or MRI evidence in the absence of clinical signs or symptoms—in the gray area known as CIS.

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*Many experts argue that CIS is too broad of a term because it can encompass either clinical or MRI findings without distinguishing between them.*

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Many experts argue that CIS is too broad of a term because it can encompass either clinical or MRI findings without distinguishing between them.<sup>8,9</sup> While it might have been unusual at one time to see a patient with MRI findings of MS before he or she exhibited symptoms, these situations are now being encountered when people have brain MRI scans for other reasons (i.e., headache) and the results show signs consistent with MS.<sup>10</sup>

In a consensus document on differential diagnosis of MS, an international panel of MS experts recently pointed out that the term CIS does not differentiate between patients with lesions on MRI and those without, although these two groups of patients have distinctly different prognoses.<sup>8</sup> The authors proposed a breakdown of CIS subcategories based on whether there was MRI or clinical evidence, and whether clinical findings were monofocal (limited to one area, such as optic neuritis [ON]) or multifocal. The proposed subcategories include:

- Type 1.** Monofocal presentation with at least one asymptomatic MRI lesion.
- Type 2.** Multifocal presentation with at least one asymptomatic MRI lesion.
- Type 3.** Monofocal presentation; normal-appearing MRI.
- Type 4.** Multifocal presentation; normal-appearing MRI.
- Type 5.** MRI suggestive of MS but no clinical presentation suggesting demyelinating disease.<sup>8</sup>

Patients with at least one asymptomatic MRI lesion characteristic of demyelination (Types 1 and 2) have a

higher probability of later meeting criteria for MS, and this prognosis correlates with the number and location of these lesions.<sup>11</sup> In contrast, patients with a monofocal clinical presentation and no lesions on MRI (Type 3) have a low risk for developing MS.<sup>12</sup> The scenario in Type 4 (multifocal clinical presentation but no MRI lesions) is rare and would suggest the possibility of other diagnoses.<sup>8</sup> Because Type 5 (MRI evidence only) is a relatively recent phenomenon, more study and observation is needed before prognostic predictions can be made.<sup>8</sup>

## How Often Should MRI Be Done in CIS?

Frequent MRI scans in the first year after a CIS diagnosis can help to facilitate early and accurate diagnosis of definite MS.<sup>13</sup> Proposed 2009 updates to the Consortium of Multiple Sclerosis Centers (CMSC) MRI guidelines for patients with CIS are listed in **Table 2**.<sup>14</sup>

The question of how often to repeat an MRI in patients with CIS has not been clearly defined in the CMSC guidelines. In most cases, MRI should be repeated 3 to 6 months after the baseline study, depend-

### Table 2. Revised Clinical Guidelines for Brain and Spinal Cord MRI in MS<sup>14</sup>

#### For Patients with a CIS and suspected MS

*Recommendations for baseline evaluation:*

- Brain MRI with gadolinium
- Spinal cord MRI if there is persistent uncertainty about diagnosis and/or findings on brain MRI are equivocal
- Spinal cord MRI if presenting symptoms or signs are at the level of the spinal cord

*Recommendations for a follow-up evaluation:*

- Brain MRI with gadolinium to demonstrate new disease activity

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CIS=clinically isolated syndrome; MRI=magnetic resonance imaging; MS=multiple sclerosis.

Source: Consortium of Multiple Sclerosis Centers. MRI Protocol for the Diagnosis and Followup of MS. Proposed 2009 revised guidelines. Available at: [www.ms-care.org](http://www.ms-care.org).



ing upon the patient’s risk and clinical presentation. Repeat MRI is performed to determine changes from baseline (e.g., new gadolinium-enhancing lesions or increased lesion load) to indicate separation in time and space.

## What Factors Predict Which Patients Will Develop CDMS?

Studies show that CDMS can be expected to develop in approximately 90% of patients with CIS, often within a few years.<sup>1,15,16</sup> Thirty percent of patients with CIS will progress to CDMS within 12 months.<sup>1</sup> Because the disease course is unpredictable at its onset, long-term observation and follow-up MRI studies are necessary.<sup>17</sup>

*Many studies have shown that early MRI findings are more predictive than clinical signs of future MS risk.*

If CIS is untreated, which patients are most likely to have a second clinical episode, and when? An increasing number of clues are being found to shed light on these questions.

## MRI and Laboratory Indicators of CIS Conversion

Many studies have shown that early MRI findings are more predictive than clinical signs of future MS risk. A longitudinal 14-year study by Brex and colleagues in patients with CIS revealed that 88% of those with an abnormal baseline MRI developed CDMS during that extended follow-up period.<sup>1</sup> In this study, the number of lesions at baseline did not correlate with CDMS conversion rates, but in another study by Barkhof and colleagues, patients with more than eight T2-weighted hyperintense lesions and at least one gadolinium-enhancing lesion on MRI did have a greater risk of converting to CDMS.<sup>18</sup>

The presence of oligoclonal IgG bands in cerebrospinal fluid (CSF) has also been shown to be highly specific and sensitive for early prediction of conversion to MS.<sup>19</sup> One study showed that 32 of 33 patients with

oligoclonal bands developed MS within a 6-year time frame, while only three of 19 patients without oligoclonal bands developed MS.<sup>20</sup>

Finally, a recently published study examined whether the presence of antimyelin antibodies in serum has prognostic significance in CIS.<sup>21</sup> In 103 untreated patients with CIS, positive MRI findings, and oligoclonal bands, the investigators analyzed serum for the presence of antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP). Patients who were positive for anti-MOG and anti-MBP antibodies had relapses more often and significantly earlier during the study period than patients without these antibodies (Table 3).<sup>21</sup>

**Table 3. Antimyelin Antibodies and Relapse Risk in CIS<sup>21</sup>**

Antibody Status	# with Relapse/ Total (%)	Mean Time to Relapse
Negative	9/39 (23%)	45.1 ± 13.7 months
Positive, anti-MOG and -MBP	21/22* (95%)*	7.5 ± 4.4 months
Positive, anti-MOG only	35/42* (83%)*	14.6 ± 9.6 months

\*P<0.001 compared with antibody seronegative patients. MBP=myelin basic protein; MOG= myelin oligodendrocyte glycoprotein.  
Source: Berger T, et al. *N Engl J Med.* 2003;349:139-145.

## Clinical Presentation and CIS Prognosis

Although early MRI findings appear to be more helpful in predicting risk of conversion to CDMS, clinical findings are not without significance. For instance, in a recent study by Nielsen et al involving 468 patients with a single clinical episode, time to CDMS was similar in those with a monofocal versus a multifocal presentation.<sup>22</sup> However, those with a monofocal presentation and more MRI signs (≥9 T2-weighted lesions or at least one gadolinium-enhancing lesion) were more likely to convert to CDMS.

**Table 4. Pivotal Clinical Trials of Disease-Modifying Therapy in CIS<sup>2-5</sup>**

Trial Name	Agents Tested	% Converting to CDMS		
		Placebo	Treatment	P value
CHAMPS <sup>2</sup>	IFN beta-1a (IM)	50%	35%	P=0.02
PreCISe <sup>3</sup>	Glatiramer acetate	43%	25%	P<0.0001
BENEFIT <sup>4</sup>	IFN beta-1b (SC)	45%	28%	P<0.0001
ETOMS <sup>5</sup>	IFN beta-1A (SC) (low-dose)	45%	34%	P=0.09

CIS=clinically isolated syndrome; CDMS=clinically definite multiple sclerosis; IFN=interferon; IM=intramuscular; SC=subcutaneous.

In the group with a multifocal presentation, MRI measures did not significantly predict conversion to CDMS.

How MS presents clinically, such as with episodes of ON or transverse myelitis (TM), may also predict prognosis. In the Optic Neuritis Treatment Trial, 22% of patients with ON but normal brain MRI developed CDMS within 10 years after the initial event.<sup>23</sup> However, those who had even a single lesion consistent with demyelination had double the risk, with 56% converting to CDMS over 10 years. Another trial looked at patients with brainstem syndromes, ON, or TM, and showed that patients with any of these conditions and a normal brain MRI had an 11% chance of developing MS within 10 years, while those with an abnormal brain MRI at baseline had an 83% chance of developing MS.<sup>15</sup>

In addition, some characteristics of ON and TM may be predictive of prognosis. Thrower and colleagues observed that young adult females presenting with unilateral, painful ON but normal disc appearance on fundoscopy had a higher risk for future demyelinating events than did those with the opposite characteristics, (e.g., males, bilateral presentation, painless neuropathy, or severe disc edema).<sup>24</sup> Similarly, patients presenting with incomplete TM, asymmetric symptoms, and nonedematous small cord lesions had a higher risk of developing MS than those with complete TM, symmetric symptoms, and multisegmental cord lesions.<sup>24</sup>

Clinical and demographic predictors for a second event within 1 year of a CIS diagnosis were identified by Mowry and colleagues.<sup>25</sup> These included non-white race/ethnicity and younger age. Although it may seem counterintuitive, these authors also found that having fewer functional systems involved in the initial clinical event was associated with a lower likelihood of converting to CDMS in the first year.

*Four large-scale, blinded trials, some with ongoing extensions, have been conducted to evaluate how DMT affects conversion of CIS to CDMS.*

Smoking has also been shown to affect time to CDMS conversion. A group of investigators followed 129 untreated patients with CIS over 36 months and showed that 75% of smokers developed CDMS during that time period, versus 51% of nonsmokers ( $P=0.008$ ). In addition, smokers had a significantly shorter time interval to their first relapse.<sup>26</sup>

### Treatment Delays Conversion to CDMS

Four large-scale, blinded trials, some with ongoing extensions, have been conducted to evaluate how DMT affects conversion of CIS to CDMS (**Table 4**).

CHAMPS was a 3-year trial enrolling 382 patients with clinical CIS and at least three suspicious brain MRI lesions.<sup>2</sup> Patients were randomized to receive either placebo or intramuscular (IM) interferon beta-1a, and the primary endpoint was time to second clinical relapse. At the interim analysis, 35% of patients receiving interferon therapy met the criteria for CDMS versus 50% of patients receiving placebo, representing a 49% reduction in risk ( $P=0.02$ ). Because of this result, the trial was stopped after the interim analysis. An extension study, CHAMPIONS, crossed all patients over to active therapy and compared the groups after another 2 years.<sup>27</sup> Those receiving DMT from the start of the trial had a 36% risk of developing CDMS, versus 59% for those who originally received placebo ( $P=0.03$ ).

PreCISe was a 3-year, randomized, double-blind trial enrolling 481 patients with an initial demyelinating event, monofocal presentation, and at least two T2-weighted lesions.<sup>3</sup> This study compared the effects of glatiramer acetate treatment with placebo over 36 months or until conversion to CDMS. Patients converting to CDMS were placed on active treatment for an additional 2-year extension study. Interim PreCISe results showed that 43% of the placebo group had converted to CDMS versus 25% in the glatiramer acetate group ( $P<0.0001$ ). The time it took for 25% of the patients to convert to CDMS was extended by 115% in the glatiramer acetate-treated group (722 days versus 366 days for placebo). In addition, treatment reduced the number of new T2 lesions by 58% ( $P<0.0001$ ).<sup>3</sup>

The BENEFIT trial enrolled patients with a first demyelinating event and at least two clinically silent brain MRI lesions and evaluated the time to CDMS diagnosis over 2 years among those treated with subcutaneous (SC) interferon beta-1b ( $n=292$ ) and those receiving placebo ( $n=176$ ).<sup>4</sup> Among those receiving the active treatment, 28% had a second attack confirming a CDMS diagnosis during the study period, versus 45% of those in the placebo group; this represented a 50% risk reduction ( $P<0.0001$ ) (**Figure 1**). When the data were analyzed using the latest McDonald criteria to define CDMS, an even greater percentage (85%) of placebo-treated patients

had converted in 2 years, versus 46% in the treatment group ( $P<0.00001$ ). The BENEFIT results showed that, for those with CIS who were untreated, conversion to CDMS was rapid: 51% of untreated patients met McDonald criteria for CDMS by 6 months.<sup>4</sup>

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*Treatment of CIS significantly delays conversion to CDMS for most patients, may delay the onset of progressive forms of the disease, and for most patients ultimately delays or prevents some of the permanent neurologic damage that occurs in MS.*

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The ETOMS trial compared low-dose (22 mg once weekly) SC interferon beta-1a with placebo in patients with one clinical event and multiple lesions on MRI indicative of MS.<sup>5</sup> Treatment reduced the risk of CDMS during the 2-year study period (34% for interferon versus 45% for placebo;  $P=0.09$ ) and also reduced the number of new lesions and total area of myelin damage. Investigators have noted that the low dose used (one-sixth of that typically used in relapsing-remitting MS) probably accounted for the lower degree of protection.<sup>5</sup>

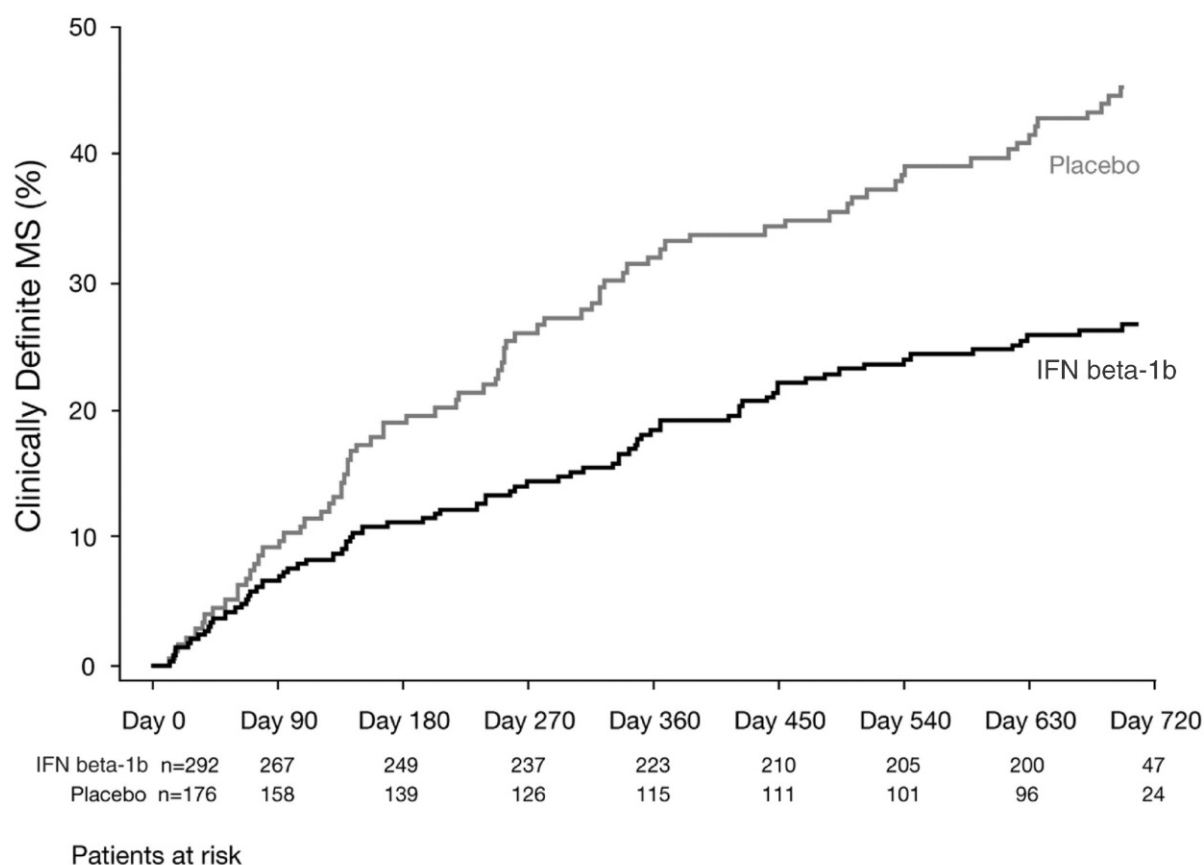
### Newer Study Results on the Effects of Early Treatment

Ongoing evaluation of data from offshoot studies stemming from the original CIS pivotal trials continues to provide more information about treatment benefits for CIS. For example, data from the BENEFIT trial suggest that treatment with interferon beta-1b in CIS may result in better preservation of cognitive functioning than delayed treatment.<sup>28</sup>

Follow-up data from the PreCISe trial of glatiramer acetate in CIS show that early treatment may protect against neuronal/axonal injury. Comparisons of N-acetylaspartate (NAA), a marker of neuronal mitochondrial function, demonstrate that treatment with glatiramer acetate in CIS results in increased NAA levels, which may confer neuroprotection, compared with placebo, which results in a decline in NAA consistent with that demon-



**Figure 1. The BENEFIT trial and the probability of developing clinically definite MS.<sup>4</sup>**



IFN beta-1b=interferon beta-1b.

Reprinted with permission from Kappos L, et al. *Neurology*. 2006;67:1242-1249.

strated in historical control studies.<sup>29,30</sup>

Of promise, among the agents being evaluated for future use in MS, many of them have studies specifically enrolling subjects with CIS to test the treatments' safety and efficacy.

## Discussing DMT with Patients

As the data described here collectively demonstrate, clinicians have an increasingly clearer picture of what CIS is, which patients have the highest risk of MS, and the benefits of starting therapy after a first clinical episode. Treatment of CIS significantly delays conversion to CDMS for most patients, may delay the onset of progressive forms of the disease, and for most patients ultimately delays or prevents some of the permanent neurologic damage that occurs in MS.

As many MS clinicians find, discussing treatment of CIS with patients is a bit like leading a horse to water. Some people may be eager to do whatever they can to help themselves as soon as possible. Many others will proceed more cautiously and may want to wait for further signs of disease progression. Still others will reject DMT outright. This latter group may have a number of reasons, such as financial constraints, a hope of finding alternative treatments, belief they have a wrong diagnosis or a “benign” disease course, or an unwillingness to adopt an injectable therapy.

Yet another group, growing in numbers, consists of patients who are waiting for some of the newer “pipeline drugs” for MS to become available before they begin therapy. Several of the new therapies not yet approved for MS are taken orally, making them particularly attractive

to these patients, who are unaccustomed to using injected therapies. Many, including some oral therapies and the newer monoclonal antibodies in the pipeline, have shown high efficacy rates in recent trials, but may require the patient to accept a tradeoff of higher documented safety risks, along with other unknown risks that may emerge over time.<sup>31,32</sup>

People who experience a more dramatic onset of clinical symptoms—such as those who experience vision loss with an episode of ON—may be more motivated to begin an effective therapy immediately compared with those who have vague clinical symptoms such as numbness and tingling. Some people quite naturally make the argument, “My condition is not bad enough yet” to warrant treatment. This is where it is crucial to educate patients about the essential goal of DMT in MS, which is to reduce the *risk* of future deterioration—not to erase damage that already exists. MS clinicians want to help patients avoid getting to the point where their condition is “bad enough” that they wish they had done more sooner. An analogy might be made to cancer chemotherapy, in which early treatment, however difficult, is always preferable to waiting until the cancer has become advanced.

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*It is crucial to educate patients about the essential goal of DMT in MS, which is to reduce the risk of future deterioration—not to erase damage that already exists.*

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Of course, patients with CIS are in a good position to enter clinical trials for new MS agents. According to an estimate by Richert, there are more than 136 ongoing clinical trials involving new and existing drug regimens for MS, requiring a large influx of eligible patients to test them for safety and efficacy.<sup>33</sup> Many of these trials are designed for CIS or newly diagnosed CDMS patients who are still treatment naïve. Suitability for these trials depends on the patient’s lifestyle, proximity to trial centers, and the particulars of the trial design. For example, patients should be aware that most clinical trials involving

**Table 5. Financial Assistance Programs Offered by Manufacturers of DMTs\***

Drug Name	Manufacturer	Contact for Financial Assistance Program
Avonex®	Biogen Idec	Access Program 800-456-2255
Betaseron®	Bayer Healthcare	Betaseron Patient Assistance Program 800-788-1467
Copaxone®	Teva Neuroscience	Shared Solutions 800-887-8100
Rebif®	Serono	MS Lifelines 877-447-3243

\*Therapies approved for multiple sclerosis and clinically isolated syndrome.  
DMTs=disease-modifying therapies.

CIS or MS can be expected to involve multiple MRIs at more frequent intervals than would normally be done in clinical practice.

Because of the early disease stage involved in CIS, many patients may prefer a therapeutic intervention that least disrupts their lifestyle. Similarly, due to the uncertain nature of CIS, many clinicians may be hesitant to recommend an agent with unknown long-term effects and may opt for a well-tolerated agent with a demonstrated safety record.

### Barriers to Starting Treatment for CIS

Even for patients who are willing to start therapy, a number of barriers often stand in the way of early treatment in CIS. Delays in diagnosis are still a factor preventing many patients from getting the treatment they need. Clinicians outside of MS centers, including neurologists, may be reluctant to make a diagnosis of CIS and even more reluctant to initiate therapy in these cases.<sup>25</sup> Many will take a conservative “wait and see” stance despite clear evidence that waiting does not serve the patient in the long run. Patients in areas of the country without access to a nearby MS center may be particularly subject to

delays in diagnosis, as are patients with atypical presentations of CIS.

Lack of adequate insurance coverage, financial limitations, and fear of the stigma of an MS diagnosis on insurance or employment records are major factors that prevent many patients with CIS from receiving early treatment. Many people simply do not have the financial resources or the insurance coverage to pay for an expensive DMT. Although assistance programs are available (**Table 5**), in early disease stages the patient may be less motivated to pursue these services.

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*In the United States, three therapies are FDA-approved for reducing relapses in patients with CIS: glatiramer acetate (Copaxone®) and two interferon products (Avonex® and Betaseron®).*

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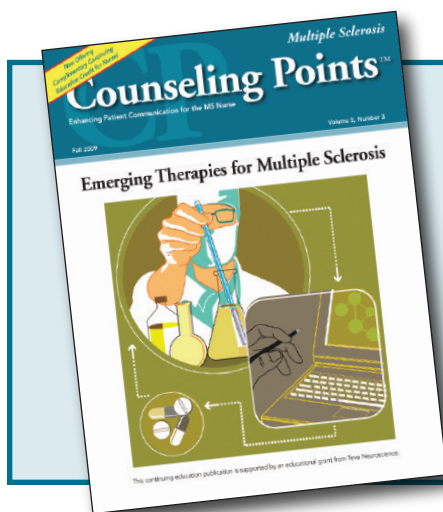
Another snag is the frustrating lack of an ICD-9 billing code that differentiates CIS from MS itself. Some clinicians may opt to use codes based on symptoms, such as paresthesias, rather than going straight to an MS billing code. The implications for long-term insurance coverage and pre-existing conditions may be unclear, thus the clinician may hesitate to “put a label” on a patient whose diagnosis remains uncertain. However, failure to identify an MS-related diagnosis may also make it more difficult to obtain approval for insurance payment for a DMT. In the United States, three therapies are FDA-approved for

reducing relapses in patients with CIS: glatiramer acetate (Copaxone®) and two interferon products (Avonex® and Betaseron®).

## Educating the Patient with CIS

The Internet has become the main source of information, certainly for young people but also for much of the population. Unfortunately, the available information on the Internet about CIS is limited and may be overwhelming or confusing. Few good, balanced resources are available to explain—in language appropriate for those who are not MS-savvy—what CIS means, what the risks are, and why early treatment is beneficial.

MS nurses can help people with CIS balance the fear of the unknown and the shock of this looming diagnosis with the significant hope we have today for a very different long-term outlook. MS is still strongly associated with the “wheelchair stigma,” a particularly frightening image to a young person. But what patients with a 30-year history of MS have unfortunately had to endure is not an accurate picture of what the majority of CIS patients will now encounter, given the opportunity for appropriate treatment and allocation of our health care resources. Although not all CIS and MS patients have a good response to early treatment, with a greater variety of therapies under evaluation employing different mechanisms of action, many more people at all stages of MS will be able to be treated successfully.



Other editions of  
*MS Counseling Points*<sup>TM</sup>  
can be found at [www.iomsn.org](http://www.iomsn.org).

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# CP Counseling Points™

## Update on Clinically Isolated Syndrome

- Clinically isolated syndrome (CIS) is defined as a first neurologic episode consistent with demyelination or inflammation in the central nervous system.
- As many as 88% of patients presenting with CIS will develop clinically definite MS (CDMS), many within a few years.
- Many factors have been studied to determine which patients are at higher risk for developing CDMS, including magnetic resonance imaging (MRI) findings, the presence of oligoclonal bands in cerebrospinal fluid, and other serum and clinical markers.
- Four pivotal clinical trials have been conducted to evaluate the benefits of disease-modifying therapy (DMT) in CIS. The results show that early treatment during CIS can delay the risk of conversion to CDMS by approximately 50% in the first few years and reduce MRI measures of disease activity.
- The CIS pivotal trials point out how quickly clinical status can change in CIS, with 51% of one untreated (placebo) group developing CDMS within the first 6 months of starting the study.
- Three MS DMTs are currently approved by the FDA for the treatment of CIS. These include glatiramer acetate (Copaxone®) and two interferon products (Avonex® and Betaseron®).
- Many barriers can stand in the way of early DMT for patients with CIS, including delays in diagnosis, unwillingness of the clinician to diagnose or treat CIS, unwillingness of the patient to begin an injected therapy, and financial factors such as lack of insurance coverage for therapies.
- In discussing treatment of CIS with patients, it is critical to emphasize that the essential goal of DMT is to reduce the risk of future deterioration—not to erase damage that already exists.
- MS nurses can help people with CIS balance the fear of the unknown and the shock of a looming MS diagnosis with the significant hope we have today for a very different long-term outlook.



# Counseling Points™

## Update on Clinically Isolated Syndrome

### Continuing Education Posttest

To receive contact hours, please read the program in its entirety, answer the following posttest questions, and complete the program evaluation. A certificate will be awarded for a score of 80% (8 correct) or better. A certificate will be mailed within 4 to 6 weeks. There is no charge for the CE credit.

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**Via the Web:** Applicants can access this program at the International Organization of MS Nurses' website, [www.IOMSN.org](http://www.IOMSN.org). Click on Counseling Points and follow the instructions to complete the online posttest and application forms.

#### PLEASE SELECT THE BEST ANSWER

- For most patients with clinically isolated syndrome (CIS) that includes magnetic resonance imaging (MRI) evidence, experts now recommend that the best course of action is:**
  - perform an MRI every 6 months until clinically definite multiple sclerosis (CDMS) can be confirmed
  - wait until new clinical symptoms appear to confirm the diagnosis
  - begin treatment with disease-modifying therapies (DMTs)
  - none of the above
- For CDMS, current diagnostic (revised McDonald) criteria require all of the following EXCEPT:**
  - 2 or more clinical attacks (relapses) and 2 or more objective clinical lesions
  - 2 or more attacks plus dissemination in space
  - 1 attack plus family history of MS
  - 1 attack plus 1 objective clinical lesion and dissemination in time/space
- CIS may be too broad of a term because:**
  - it includes patients with comorbid MS and other neurologic syndromes
  - it does not distinguish between patients with MRI findings and those with clinical findings
  - it includes patients with early MS and CDMS
  - it includes patients with brain MRI and spinal MRI findings but not clinical signs of MS
- In the proposed update to the Consortium of MS Centers' MRI guidelines, a baseline evaluation includes all of the following except:**
  - brain MRI with gadolinium, but spinal cord MRI is not indicated
  - brain MRI with gadolinium
  - spinal MRI if there is persisting uncertainty about diagnosis
  - spinal MRI if presenting symptoms are at the level of the spinal cord
- Early MRI findings are more predictive of future MS risk than are clinical signs of MS risk.**
  - True
  - False
- All of the following have been shown to predict higher risk of CDMS EXCEPT:**
  - oligoclonal bands in cerebrospinal fluid
  - positive antibodies against myelin basic protein in serum
  - smoking history
  - greater number of functional systems involved in initial clinical event
- In the PreCISe study, \_\_\_\_% of glatiramer acetate-treated patients converted to CDMS status, versus 43% of those treated with placebo.**
  - 10%
  - 25%
  - 30%
  - 45%
- In the BENEFIT study, approximately \_\_\_\_% of untreated (placebo) patients had converted to CDMS within a 6-month period.**
  - 30%
  - 40%
  - 50%
  - 60%
- Barriers preventing patients with CIS from receiving DMTs include all of the following EXCEPT:**
  - lack of data showing benefit for early treatment
  - lack of insurance coverage for treatment
  - delays in diagnosis
  - stigma of MS and fear of prematurely "labeling" patients
- In counseling patients with mild symptoms and CIS about starting a DMT, the MS clinician should stress that:**
  - experts recommend waiting until more clinical symptoms appear before starting therapy
  - patients should wait until an oral therapy is available before starting therapy
  - the goal of DMT is to prevent symptoms from becoming worse
  - patients must have a diagnosis of CDMS in order for insurance to pay for their medication

# Counseling Points™: Program Evaluation Form

## Update on Clinically Isolated Syndrome

Using the scale provided, Strongly Agree = 5 and Strongly Disagree = 1, please complete the program evaluation so that we may continue to provide you with high quality educational programming. Please fax this form to **(201) 612-8282**.

5 = Strongly Agree      4 = Agree      3 = Neutral      2 = Disagree      1 = Strongly Disagree

**At the end of this program, I was able to:** *(Please circle the appropriate number on the scale.)*

- 1. Describe the latest clinical and radiographic findings in clinically isolated syndrome (CIS) and early multiple sclerosis (MS) ..... 5 4 3 2 1
- 2. Describe current disease management recommendations for CIS treatment ..... 5 4 3 2 1
- 3. Review discussions with patients regarding when to initiate treatment ..... 5 4 3 2 1
- 4. Discuss potential barriers to starting treatment in CIS ..... 5 4 3 2 1

**To what extent was the content...**

- 5. Well-organized and clearly presented ..... 5 4 3 2 1
- 6. Current and relevant to your area of professional interest ..... 5 4 3 2 1
- 7. Free of commercial bias ..... 5 4 3 2 1

**General Comments**

8. As a result of this continuing education activity (check only one):

I will modify my practice. (If you checked this box, how do you plan to modify your practice?) \_\_\_\_\_

I will wait for more information before modifying my practice.

The program reinforces my current practice.

Suggestions for future topics/additional comments: \_\_\_\_\_

**Follow-up**

As part of our continuous quality improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please check one:

Yes, I would be interested in participating in a follow-up survey.

No, I would not be interested in participating in a follow-up survey.

There is no fee for this educational activity.

**Posttest Answer Key**

1	2	3	4	5	6	7	8	9	10

**Request for Credit** *(Please print clearly)*

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