VA MULTIPLE SCLEROSIS CENTERS OF EXCELLENCE CONSENSUS STATEMENT
RELAPSE and DISEASE MANAGEMENT in MULTIPLE SCLEROSIS

1. REASON FOR ISSUE
This Multiple Sclerosis Centers of Excellence (MSCoE) Consensus Statement addresses clinically isolated syndrome, relapses and relapse management, and disease management of Veterans with multiple sclerosis (MS). It is an accompaniment to VHA Directive 1011.06 and the MSCoE Program Guide.

2. BACKGROUND
The MSCoE were established in 2003 with a mandate to establish a national network for the care of Veterans with MS. As part of that mandate, the MSCoE has developed consensus statements to assist VA providers caring for Veterans with MS.

MS is a unique disease in the VA system due to its onset in young adulthood and common connection with military service. MS can be difficult to diagnose due to its variable presentations. It is also challenging to manage due to its dynamic and unpredictable course, progressive nature, variable symptoms, required monitoring, costly and potentially high-risk treatments, and its radically changing face over the 4 to 5-decade course of the disease. To adequately care for Veterans with MS requires a multidisciplinary team, including neurologists, physiatrists, internists, primary care providers, nurses, occupational therapists, physical therapists, psychologists, recreation therapists, social workers, urologists, vocational counselors, and other providers who are knowledgeable about the care of MS.

3. RESPONSIBLE OFFICE
The Directors of the MSCoE are responsible for the contents of this Consensus Statement. Questions may be referred to the MSCoE leadership through the website contacts (www.va.gov/ms).

4. REVIEW
This MSCoE Consensus Statement is scheduled for review every two years, or earlier in case of major practice or medication changes.

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RELAPSE and DISEASE MANAGEMENT in MULTIPLE SCLEROSIS

This Multiple Sclerosis Centers of Excellence (MSCoE) Consensus Statement provides guidance to VA providers on MS relapse and disease management for Veterans with MS. This Consensus Statement is a document that presents the current MSCoE opinion on treatment approaches which may be used in MS relapse and disease management throughout the MS Regional and Support Programs of the MSCoE Network. Note that not all approved United States Food and Drug Administration (FDA) treatments in use in the community are discussed.

1. MANAGEMENT OF CLINICALLY ISOLATED SYNDROME
   A. Definition of clinically isolated syndrome (CIS): A term that describes symptoms of a typical MS relapse in a person not previously diagnosed with MS and who do not meet criteria for a diagnosis of MS.
   B. Typical relapses (see section 2) are events indicative of demyelinating or inflammatory disease of the brain or spinal cord. Symptoms may be monofocal (e.g. optic neuritis), or multifocal (e.g. optic neuritis plus unilateral weakness).
   C. Persons with a first neurological event typical for MS may be diagnosed with MS based on 2017 McDonald Criteria for the Diagnosis of MS. Supportive evidence for an MS diagnosis are simultaneous presence of enhancing and non-enhancing typical lesions on brain and spinal cord MRI, and/or the presence of oligoclonal bands in cerebral spinal fluid that are not found in serum. See section 3 for management of MS. Of note, the ~15% of people with MS who have primary progressive MS do not experience typical relapses at disease onset and use other criteria for diagnosis.
   D. Persons with a typical relapse who don’t meet MS diagnostic criteria have the diagnosis of CIS. People with CIS may or may not go on to develop MS. If lesions are seen on brain and/or spine MRI that are similar to MS lesions, there is a high risk of conversion to MS.
   E. Only person with CIS and high risk of conversion to MS are offered MS disease modifying therapy (DMT). DMT may delay or prevent a second neurological episode or minimize future disability. Nearly all DMTs FDA-approved for relapsing forms of MS are also approved for CIS.
   F. Persons with low risk of conversion to MS are followed with regular neurological exams and periodic MRIs to see if new relapses or typical MS lesions on MRI develop over time that would then indicate a conversion to MS and need for DMT.

2. MANAGEMENT OF MS RELAPSES
   A. Definition of relapse: A relapse (also called “flare” and “exacerbation”) is an acute worsening of an old symptom or the appearance of a new symptom that is present for more than 24 hours in the absence of fever, infection, and other significant physiological or psychological stress. Typically, relapses are associated with a
new and/or enhancing lesion on MRI indicating a breakdown in blood-brain barrier with focal inflammation. Typical relapses worsen and then improve either to baseline or incompletely over a period of days to weeks, less often over months.

B. **Pseudo-relapse:** A pseudo-relapse is a worsening of neurological symptoms associated with a trigger such as infection, elevated or low body temperature, pain, fatigue, trauma, menses, or other stressors. The symptoms are not related to increased disease activity (i.e., new or enhancing lesions on MRI). Pseudo-relapses should be ruled out in patients reporting an acute change in neurologic function. Symptoms resolve with treatment of the underlying cause alongside rehabilitation therapy.

C. **Determining if a relapse requires treatment:** Relapse treatment has not been shown to alter the long-term course of MS but only to shorten recovery time. Treatment is not indicated for every incident. Potential benefits must be weighed against potential adverse effects. Relapses with significant disability, such as ambulation impairment or loss of vision, usually warrant treatment. Relapses with little or no disability (e.g. sensory loss or myokymia) may not warrant treatment. Factors such as prior adverse reactions to corticosteroids should also influence the decision as to whether treatment should be given.

D. **Relapse treatment:** The standard treatment for relapses associated with significant disability is a short course of intravenous (IV) or oral corticosteroids.

a) **Intravenous corticosteroid treatment.** Intravenous treatment remains the most widely used route for corticosteroid administration in acute relapses. The most common regimens are:

- 1,000 mg of intravenous methylprednisolone (IV MP) daily for 3 to 5 days.
- Intravenous dexamethasone (Decadron) may be used in place of IV MP at 160-180 mg/day for 3 to 5 days.

Intravenous steroids may be administered in several settings, including a VA Medical Center (VAMC), Community Based Outpatient Clinic (CBOC), non-VA infusion center, or the Veteran’s home.

b) **Oral corticosteroid treatment.** A growing body of evidence supports the safety and efficacy of the use of an equivalent dose of oral prednisone. Studies indicate no difference in response between oral and IV routes. The primary limitation in the use of oral treatment at present is that a large number of pills is required using current formulations of prednisone.

- Oral equivalent of 1,000 mg IV methylprednisolone is 1,250 mg prednisone/day in two divided doses (625 mg dose in a.m. and 625 mg dose in p.m.).
- Prednisone **50 mg** form: Take 12½ tabs/dose.
- Prednisone **20 mg** form: Take 31¼ tabs/dose.
- Omeprazole or similar medication is helpful to increase gastric tolerance.
Insomnia is a common side effect of steroid treatment, and a sedative medication may be indicated. Monitor glucose in diabetics and those at high risk of diabetes. There is no evidence that a steroid taper is beneficial and therefore is not recommended.

c) **Plasma exchange.** For severe MS relapses, plasma exchange may be considered.

d) **Rehabilitation.** Physical and/or occupational therapy should be considered in every relapse including pseudo-relapse.

Treatment of a relapse does not affect the long-term course of MS. Response may be seen within a few days, but may take longer. There is no significant difference in the degree of remission at 1 year between those who did and did not receive treatment. Depending on degree of residual impairment, rehabilitation is nearly universally helpful to maintain function during a relapse and prevent disuse complications.

3. **MANAGEMENT OF MULTIPLE SCLEROSIS DISEASE PROCESS**

   A. **Relapsing forms of MS:** The goals of DMT in relapsing MS are to reduce the frequency of relapses, reduce occurrence of new lesions, and slow disease progression. These DMTs are approved for CIS, relapsing remitting MS, and secondary progressive MS with active relapses (clinical relapses and/or new/enhancing lesions on interval MRI scans).

   a) **Disease-modifying therapies (DMTs) for relapsing forms of MS.**

      • Reduce rate of relapses.
      • Slow rate of disability worsening.
      • Will not restore lost function.
      • Limit new activity (lesions) seen by MRI.
      • May not be recommended for women who are pregnant or plan to become pregnant (see specific DMT considerations).

   B. **Primary progressive MS (PPMS):** PPMS is defined as slow accumulation of disability due to central nervous system demyelination and does not have typical relapses described above. The goal of MS disease modification in PPMS is to reduce the rate of disease progression. Currently only one DMT, ocrelizumab, is FDA-approved for PPMS. Treatment for PPMS is an active area of research.

   C. **Secondary progressive MS (SPMS):** Approximately 10-20 years after diagnosis, most people with relapsing remitting MS will transition to SPMS. In this phase, there is slow accumulation of disability with fewer and then eventually no more typical relapses. For those with ongoing relapses (defined above), medications for relapsing forms of MS may be used. If there are no longer relapses, symptomatic therapy only is indicated.
Treatment for non-relapsing SPMS is an active area of research.

4. **CONSIDERATIONS FOR DISEASE MODIFYING THERAPY (DMT) USE:**

   A. **General considerations for DMT use:**
      - Appropriate candidates for DMTs should start as early as possible after diagnosis.
      - DMT use for relapsing forms of MS is not limited by age, relapse frequency, or disability level.
      - MS DMTs are often classified by route of administration, yet there are important distinctions and variations in efficacy between agents within each classification.

   B. **Considerations for specific DMT selection:**
      - Aggressiveness of disease.
      - DMT risk/benefit profile.
      - Veteran preference for specific dosing route (injection vs. oral) and/or frequency.
      - Likelihood of adherence to dosing frequency and recommended monitoring.
      - Prior DMTs used, if any.
      - Relevant comorbidities.

   C. **FDA Approved DMT choices:**
      a) **Injectable (SC or IM) DMTs.**
         - Glatiramer Acetate (Copaxone SC, Glatopa SC, Glatiramer Acetate Injection)
         - Interferon beta 1-a (Avonex IM, Rebif SC, Plegridy SC)
         - Interferon beta 1-b (Betaseron SC, Extavia SC)
      b) **Oral DMTs.**
         - Cladribine (Mavenclad)
         - Dimethyl fumarate (Tecfidera)
         - Diroximel fumarate (Vulmerity)
         - Fingolimod (Gilenya)
         - Siponimod (Mayzent)
         - Teriflunomide (Aubagio)
      c) **Infusion DMTs.**
         - Alemtuzumab (Lemtrada)
• Natalizumab (Tysabri)
• Novantrone (Mitoxantrone) (rarely used)
• Ocrelizumab (Ocrevus)

d) **Not FDA approved for MS.**
• Rituximab (Rituxan) (off label, used instead of ocrelizumab)

D. **VHA Pharmacy Benefits Management guidance:** Information, recommendations, and guidance is provided by VHA PBM. Some information may only be accessed through a VA computer or portal. Some medications may not warrant a current need for the guidance outlined below or the information has been archived.

a) **Criteria for Use.** Provide recommendations based on current medical evidence and expert opinion from clinicians. Some agents do not have a CFU because there is significant clinical experience regarding the safety and efficacy of the medication. Agents that have been approved recently, have demonstrated safety concerns in clinical trials, and/or have complex monitoring/administration guidance will have a CFU so that the appropriate patient is selected for therapy and the drug is given in a safe/effective manner. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.


b) **Drug Monographs.** Provide a comprehensive drug review for making formulary decisions.

   [www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp](http://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp)

c) **Guidance for Disease Modifying Therapy Selection in MS.** This document is intended to complement the CFU documents and to assist in prioritizing the selection of disease modifying therapies used in the treatment of relapsing MS and primary progressive MS.

   [www.pbm.va.gov/PBM/clinicalguidance/GuidanceforDiseaseModifyingTherapySelectioninMultipleSclerosis.pdf](http://www.pbm.va.gov/PBM/clinicalguidance/GuidanceforDiseaseModifyingTherapySelectioninMultipleSclerosis.pdf)