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, pseudo-relapses, and disease management of veterans with multiple sclerosis (MS). It is an accompaniment to VHA Directive 1011.06 and 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 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.
   B. CIS is diagnosed after a single episode of neurological symptom(s) indicative of demyelinating or inflammatory disease of the brain or spinal cord. Symptoms of CIS may be monofocal (e.g. optic neuritis), or multifocal (e.g. optic neuritis plus unilateral weakness).
   C. Persons with CIS may not go on to develop MS. If lesions seen on MRI brain are similar to MS, there is a high risk of conversion to MS.
   D. Persons with CIS who start on a disease modifying therapy (DMT) may delay or prevent a second neurological episode or minimize future disability. Several DMTs are now FDA-approved for CIS: glatiramer, interferon beta-1a intramuscular (IM) and interferon beta-1b subcutaneous (SC).

2. MANAGEMENT OF MS RELAPSES
   A. **Definition of relapse:** A relapse is the acute appearance of at least one neurological symptom that is present for more than 24 hours in the absence of fever, infection, other significant physiological stress or severe psychological distress.
   B. **Pseudo-relapse:** A pseudo-relapse is new or worsening 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 or progression of disease. Pseudo-relapses should be ruled out in patients with acute neurological symptoms. Symptoms resolve with treatment of the underlying cause.
   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 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 **12 ½ tabs/dose**.
   - Prednisone **20 mg** form: Take **31 ¼ 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. High-dose steroid treatment, whether IV or oral, may be followed by a short oral steroid taper, although there is no clear evidence that this taper is necessary or beneficial.

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

   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 may be helpful.
3. MANAGEMENT OF MULTIPLE SCLEROSIS DISEASE PROCESS

A. **Relapsing forms of MS:** The goals of disease modification in relapsing MS are to reduce the frequency of relapses, reduce occurrence of new lesions and slow disease progression.

   a) **Disease-modifying therapies (DMTs) for relapsing MS.**
      - Reduce rate of relapses.
      - May slow rate of disease progression.
      - Will not restore lost function.
      - Are not recommended for women who are pregnant or plan to become pregnant.
      - Most are not FDA-approved for progressive forms of MS with relapses. Mitoxantrone is FDA-approved for SPMS; however, it has a significant risk profile in addition to requiring lifetime follow-up monitoring. It is rarely used in current practice.

B. **Primary progressive MS (PPMS):** 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.

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. **DMT choices:**

a) **Injectable (SC or IM) DMTs.**
   - Daclizumab (Zinbryta SC)
   - Glatiramer (Copaxone SC, Glatopa SC)
   - Interferon beta 1-a (Avonex IM, Rebif SC, Plegridy SC)
   - Interferon beta 1-b (Betaseron SC, Extavia SC)

b) **Oral DMTs.**
   - Dimethyl fumarate (Tecfidera)
   - Fingolimod (Gilenya)
   - Teriflunomide (Aubagio)

c) **Infusion DMTs.**
   - Alemtuzumab (Lemtrada)
   - Natalizumab (Tysabri)
   - Novantrone (Mitoxantrone)
   - Ocrelizumab (Ocrevus)

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. [https://www.pbm.va.gov/apps/VANationalFormulary/](https://www.pbm.va.gov/apps/VANationalFormulary/)
   - Alemtuzumab (Lemtrada)
   - Daclizumab (Zinbryta)
   - Dimethyl Fumarate (Tecfidera)
   - Fingolimod (Gilenya)
   - Natalizumab (Tysabri)
b) **Drug Monographs.** Provide a comprehensive drug review for making formulary decisions. 
https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp

- Alemtuzumab (Lemtrada)
- Daclizumab (Zinbryta)
- Dimethyl Fumarate (Tecfidera)
- Fingolimod (Gilenya)
- Interferon Beta-1a, Pegylated, SC (Plegridy)
- Natalizumab (Tysabri)
- Ocrelizumab (Ocrevus)
- Teriflunomide (Aubagio)


c) **Guidance for Disease Modifying Therapy Selection in MS.** This document is intended to complement the Criteria for Use documents and to assist in prioritizing the selection of disease modifying therapies used in the treatment of relapsing MS and primary progressive MS. 
https://www.pbm.va.gov/PBM/clinicalguidance/GuidanceforDiseaseModifyingTherapySelectioninMultipleSclerosis.pdf