Multiple sclerosis

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Key points

- Multiple sclerosis (MS) is an autoimmune disorder characterized by multifocal demyelination and axon loss that affect the brain and spinal cord.
- Patients present with neurologic deficits in differing locations presenting at differing times.
- Common symptoms of first or subsequent attacks include monocular or binocular visual loss and ocular motor deficit resulting in diplopia, hemiparesis, paraparesis, gait ataxia, and appendicular ataxia; these findings can be present alone or in varying combinations.
- Following an initial demyelination episode, MS may follow one of three different courses: relapsing remitting, primary progressive, or secondary progressive after a relapsing-remitting phase.
- The cause of MS is not known, but exogenous and endogenous predisposing factors are believed to exist.
- The diagnosis is established on the basis of clinical features, supportive imaging study findings, and the results of paraclinical tests and laboratory studies.
- Acute attacks are usually treated with high-dose corticosteroids, and disease-modifying therapies are now initiated after one clinically isolated event.
- Immunomodulators are used to treat chronic disease.
- The prognosis has been linked to various clinical features, including patient age at onset, the lesion 'load' on magnetic resonance imaging (MRI) of the brain at onset, and the extent of recovery following a relapse.

Background

Description

- MS is characterized by destruction of the myelin sheath and subsequently causes axon loss within the central nervous system (CNS).
- Young adults are affected.
- Patients can present with any of a variety of protean neurologic symptoms disseminated in space (multiple CNS locations) and time (multiple episodes); common presentations are optic neuritis, incomplete transverse myelitis, and oculomotor disturbances, all as initial demyelination events, with subsequent limb weakness, limb sensory loss, and fatigue.
- The disease course is characterized by relapses and remissions or progression.
• The diagnosis is usually confirmed by MRI

• There are three essential subtypes dependent on the nature of the disease course:
  o Relapsing-remitting MS, which is characterized by acute-onset, self-limiting attacks of neurologic dysfunction, usually with recovery of previous function, although some patients may have some residual, additional disability
  o Secondary progressive MS, which usually develops from existing relapsing-remitting MS, with a reduction in the rate of new attacks but with a slow deterioration in function without an acute episode
  o Primary progressive MS, which is characterized by steady functional decline from the outset, without acute attacks

• These three subtypes can be further divided into the following:
  o Clinically isolated syndrome
    ▪ Monophasic presentation with suspected underlying inflammatory demyelinating disease
    ▪ Typically involves a single optic nerve, the spinal cord, or brainstem
    ▪ Brain MRI findings may be normal, or single or multifocal demyelination may be seen
    ▪ Presence of asymptomatic brain lesions is associated with a higher probability of fulfilling the criteria for MS
  o Radiologically isolated syndrome
    ▪ Patients have classic MRI findings of MS without the clinical symptoms of MS
    ▪ It has been shown that 33% of patients with abnormal brain MRI findings will go on to have definite MS within 5 years; factors predictive of conversion to MS exist

• Treatment is aimed at reducing relapses, slowing disease progression, and relieving symptoms

• Interferon-β, glatiramer acetate (copolymer-1), and natalizumab have been shown to reduce the frequency of relapses and the long-term accumulation of disability

Epidemiology

Incidence and prevalence:

• MS occurs in temperate climates and is rare near the equator

• Incidence is 30 to 80 cases per 100,000 persons per year in the northern U.S. and 0.5 to 2.9 cases per 100,000 persons per year in the southern U.S.
Prevalence increases with increasing latitude in both hemispheres. The prevalence is 100 cases per 100,000 persons in the northern U.S., Canada, and northern Europe and 20 cases per 100,000 persons in the southern U.S. and southern Europe.

Demographics:

- MS primarily occurs in young adults, with approximately two thirds of patients presenting between the ages of 20 and 40; presentation before adolescence and in elderly patients is unusual.
- The disease is twice as common in women as it is in men.
- In the U.S., MS is more commonly seen in white patients. Incidence is lower in black patients and Japanese-American patients, but those who live in the northern U.S. are more at risk than those who live in the south.
- There is evidence to suggest that several genes contribute to susceptibility to MS. Myelin basic protein gene is associated with MS in human leukocyte antigen (HLA)-DR4- and HLA-DR5-positive Italians and Russians. Among persons with an affected first-degree relative, 4% will develop MS, a 20-fold to 40-fold increase over that of the general population. Approximately 20% of patients with MS have an affected relative. Those highest at risk have been noted to be siblings.
- The highest incidence of MS is reported in the temperate climate of the northern U.S., Canada, and northern Europe, with a steady decrease as the equator is approached. Some studies indicate that the prevalence is higher in rural areas. People who migrate from a high-risk, temperate zone to a low-risk, equatorial zone carry part of the risk from their country of origin if the migration occurs after 15 years of age, but early-life migration reduces the risk.
- Some studies suggest that MS is more frequent in higher socioeconomic groups.

Causes and risk factors

Causes:

- The causes of MS are not completely understood.
- An autoimmune attack on CNS myelin is the central pathogenetic event.

Risk factors:

- Polygenic influences are important contributing factors.
- Some evidence suggests a role for viral infection in early life as a predisposing factor; minor viral infections frequently precipitate relapses.
- Trauma is a controversial factor that likely only increases the relapse rate to a small degree, if at all.
- The relapse rate increases by approximately one third in the immediate postpartum period, although the rate decreases to a similar degree during the last two trimesters of pregnancy.
Screening

- Mass screening for MS is not indicated or justified, as the incidence of the disease is too low, and subjecting the entire population of young adults to MRI is not practical or feasible
- However, screening of concerned siblings of affected patients may be justified

Prevention

To date, no causative factor has been specifically implicated in the etiology of MS, and, therefore, no specific recommendations regarding prevention can be made.

Diagnosis

Summary approach

- MS is considered when a patient presents with a neurologic deficit of subacute onset, especially in young to middle age
- Common symptoms of first or subsequent attacks include monocular or binocular visual loss and ocular motor deficit resulting in diplopia, hemiparesis, paraparesis, gait ataxia, and appendicular ataxia; these findings can be present alone or in varying combinations
- Establishing the diagnosis is straightforward in a young adult with relapsing and remitting disease whose symptoms and signs can be attributed to white matter lesions in the CNS, but it is much more difficult in the early stages of the disease, when the symptoms may be minimal and the clinical signs very subtle
- The following laboratory investigations are suggested:
  - MRI of the brain and/or spine
  - Analysis of the cerebrospinal fluid (CSF)
  - Measurement of the serum vitamin B12 level to exclude subacute combined degeneration of the spinal cord
  - Measurement of the erythrocyte sedimentation rate (ESR) to exclude autoimmune vasculitic diseases, such as systemic lupus erythematosus (SLE) and polyarteritis nodosa
  - HIV testing

Clinical presentation

Symptoms

Presentation may be insidious or dramatic, with one or several of the following:

- Weakness in one or more limbs
- Visual blurring due to optic neuritis
- Sensory disturbances
- Diplopia
- Incoordination, dysarthria, and intention tremor
- **Trigeminal neuralgia**
- Bladder or bowel symptoms, usually urgency or incontinence
- Fatigue

**Signs**

- Hemiparesis, paraparesis, or occasionally monoparesis or quadriparesis
- Ocular motor deficit without ptosis; a common presentation is internuclear ophthalmoplegia, with impaired adduction of an eye with gaze to the opposite side. Nystagmus is common and is often worsened with direction of gaze
- Spasticity in one or more limbs, with exaggerated tendon reflexes and upgoing plantar responses
- Sensory deficit that does not conform to single neural or dermatomal distributions
- Ataxic gait and/or limb ataxia
- Visual deficit in one or both eyes
- Afferent pupillary defect with severe optic nerve involvement

**Examination**

- Do a full neurologic examination, checking motor strength and sensation in all limbs and looking for limb ataxia
- Check extraocular movements, as nystagmus and internuclear ophthalmoplegia are common findings
- Observe the patient's affect. Depression (in children and adolescents or in adults) is common
- Look for increased reflexes and presence of Babinski sign (upgoing toes), as MS causes upper motor neuron findings
- Check the patient's motor tone, as spastic increased tone is common
- Look for a tremor that increases in amplitude when the patient reaches toward a target. Action tremor is a common finding due to disruption of cerebellar outflow systems

**Questions to ask**

**Presenting condition:**

- *Have you had similar symptoms in the past?* Previous episodes are typical of the remitting-relapsing course of MS
• **Have you had any visual blurring?** Visual symptoms due to optic nerve involvement are a common initial manifestation

• **Have you had any difficulties emptying your bladder?** Bladder dysfunction is another common finding in patients with MS

• **Have you had any shooting electrical sensation in the arms?** Electricity-like impulses traveling down the arm on flexion of the neck are known as Lhermitte sign

• **Where did you live before the age of 15?** MS is most common in the Northern latitudes, and the risk seems to be established before the age of 15

**Contributory or predisposing factors:**

• **Have you had any recent infections?** This is more suggestive of acute disseminated encephalomyelitis or Guillain-Barré syndrome

**Family history:**

• **Does anyone in your family have a similar illness?** Fifteen percent of patients with MS have a positive family history. The most commonly affected relative is a sibling

**Associated disorders**

• **Trigeminal neuralgia** is an uncommon manifestation of MS due to brainstem plaques irritating central trigeminal pathways

• Depression (in children and adolescents or in adults)

**Laboratory evaluation**

• **MRI of the brain and/or spinal cord** will provide findings supporting the diagnosis in more than 90% of patients

• **Examination of the CSF** (obtained by lumbar puncture), including testing for oligoclonal bands, immunoglobulin G (IgG)/albumin index, and myelin basic protein, is normally done by a specialist

• **Visual, auditory, and somatosensory evoked potential testing** may detect clinically silent lesions. Often the visual evoked potential is abnormal, even if an episode of optic neuritis has resolved

• **Head computed tomography (CT) scan with intravenous contrast** is done immediately if MRI is not available. CT scan findings are often normal in patients with MS but can eliminate some of the other possible diagnoses, including most strokes, hemorrhages, and tumors

• Screening blood tests often done as part of specialist evaluation of general health include the following:
  o **Complete blood count (CBC) and comprehensive metabolic panel** to detect metabolic and electrolyte abnormalities
- **Antinuclear antibody (ANA) testing and ESR** to look for vasculitis and other autoimmune diseases
- **Vitamin B12** measurement to determine if a deficiency is present
- **Human immunodeficiency virus (HIV) testing**

**MRI of the brain and/or spinal cord**

**Description**
- Used to evaluate volumetric abnormalities that, although nonspecific, may occur in patients with MS
- Detects clinically silent lesions in addition to clinically overt lesions

**Normal result**
- Absence of multifocal T2 abnormalities

**Comments**
- Many infectious, neoplastic, inflammatory, and ischemic illnesses can produce multifocal T2 abnormalities. Findings particularly suggestive of MS include more than three lesions; diameter larger than 6 mm; oval shape; and location in the periventricular area, corpus callosum, and posterior fossa
- Lesions result from increased tissue water content due to demyelinated plaques
- Enhancement with gadolinium can be used to differentiate between new and old lesions
- Highly sensitive, with lesions seen in more than 90% of patients with MS
- Monitors disease activity more sensitively than clinical examination
- Expensive and not tolerated by patients who are claustrophobic, although open MRI may be an option

**CSF examination**

**Description**
- CSF is usually obtained by lumbar puncture, which is done by a neurologist
- CSF analysis can support a diagnosis of MS and helps exclude neoplasm and infection

**Normal results**
- Normal protein level
- Leukocyte count <5/μL
- No increased intrathecal synthesis of normal IgG/albumin index
- Absence of oligoclonal bands
• Absence of myelin basic protein

Comments
• Findings are abnormal in 85% to 95% of patients with MS but may be normal, especially early in the disease course
• Elevated CSF protein level is nonspecific and of limited diagnostic value
• Autoimmune CNS inflammation may produce lymphocytic pleocytosis, an elevated CSF leukocyte count (seldom >50/μL) with a lymphocytic predominance occurring during acute exacerbations in one third of patients with MS
• Elevated IgG index and synthesis rate is present in 70% to 90% of patients with MS and is a marker of active disease
• Synthesis of immunoglobulins in the CNS compartment within the blood-brain barrier causes higher than normal ratios of CSF to serum γ-globulin
• Synthesis of particular immunoglobulin species within the CNS compartment causes appearance of oligoclonal bands in the CSF, which is supportive of the diagnosis of MS in the appropriate clinical context but cannot confirm the diagnosis
• Presence of myelin basic protein is not believed to be as sensitive or as specific for MS as previously assumed
• The procedure is mildly invasive
• Specificity is good but not perfect. Infections and inflammatory and other CNS illnesses can cause abnormal findings. Up to 8% of CSF samples from patients without MS show oligoclonal bands

Visual, auditory, and somatosensory evoked potential testing

Description
• Brain electrical responses to repeated visual, auditory, and somatosensory stimuli are recorded and time averaged, usually by a neurologist
• Confirms the presence of neurologic impairment in clinically unaffected brain systems
• Facilitates evaluation of multiple areas of the CNS, including visual brainstem and spinal cord pathways

Normal result
• No delay in transmission of visual, auditory, or tactile signals

Comments
• Delayed transmission of visual, auditory, or tactile signals results from loss of myelin, slowing conduction in nerve fibers
Although an abnormal result correlates with central demyelination, the test lacks specificity for MS. Sensitivity is typically 80% to 90%

There is a small percentage of false-positive results

Electrical jolts during somatosensory testing cause mild discomfort

Head CT scan with intravenous contrast

Description

- Should be done if MRI is not available

Normal result

- Absence of regions of lucency that enhance with contrast

Comments

- Increased tissue water content due to demyelinated plaques results in the appearance of regions of lucency that enhance with contrast
- Less expensive but much less sensitive than MRI
- Not tolerated by patients who are claustrophobic

CBC and comprehensive metabolic panel

Description

- Venous blood samples for assessing general health and organ function
- Although these tests will not identify the cause of an MS-like presentation, determination of integrity of general health is essential for diagnosis and treatment

Normal ranges

CBC:

- Leukocyte count: 4,500 to 11,000/μL
  - Differential count:
    - Neutrophils—segmented: 1,800 to 7,800/μL
    - Neutrophils—bands: 0 to 700/μL
    - Lymphocytes: 1,000 to 4,800/μL
    - Monocytes: 0 to 800/μL
    - Eosinophils: 0 to 450/μL
    - Basophils: 0 to 200/μL
- Erythrocyte count: 3.9 to 5.5 × 10^6/μL
- Hemoglobin: 14.0 to 17.5 g/dL
- Hematocrit: 41% to 50%
- Platelet count: 150 to 350 × 10^3/µL

Comprehensive metabolic panel:
- Sodium: 136 to 142 mEq/L
- Potassium: 3.5 to 5.0 mEq/L
- Chloride: 96 to 106 mEq/L
- Bicarbonate: 21 to 28 mEq/L
- Calcium (total): 8.2 to 10.2 mg/dL
- Blood urea nitrogen: 8 to 23 mg/dL
- Creatinine: 0.6 to 1.2 mg/dL
- Fasting plasma glucose: 70 to 110 mg/dL
- Protein (total): 6.0 to 8.0 g/dL
- Albumin: 3.5 to 5.0 g/dL
- Bilirubin (total): 0.3 to 1.2 mg/dL
- Alanine aminotransferase: 10 to 40 U/L
- Aspartate aminotransferase: 10 to 30 U/L
- Alkaline phosphatase: 30 to 120 U/L

Comments
- Immune deficits, which can predispose patients to MS-like diseases, can produce abnormalities on CBC, including a reduction in the leukocyte count
- Infections may produce an increase in the leukocyte count and/or alteration in the differential count
- Renal and/or hepatic failure can predispose patients to certain infections and metabolic conditions that may be mistaken for MS
- Renal and/or hepatic insufficiency can limit treatment options if MS is confirmed

ANA testing and ESR

Description
- Used to screen for some vasculitides that can present with multifocal infarctions and can be mistaken for MS
Normal results

ANA testing:
- Absence of ANA

ESR:
- Male patients: 1 to 15 mm/h
- Female patients: 0 to 20 mm/h

Comments
- Results are nonspecific, but abnormal findings require follow-up
- The presence of ANA is associated with several autoimmune diseases but is most commonly seen in patients with SLE
- Moderate elevations in the ESR occur with inflammation but also with anemia, infection, pregnancy, and advanced age. Elevated ESR can be seen in patients with CNS vasculitis or temporal arteritis, but a normal ESR does not rule out the diagnosis of MS. Patients with temporal arteritis present with a temporal headache and are at risk for stroke and visual loss; this condition should not be confused with MS, unless an untreated patient presents with headache and neurologic deficit

Vitamin B12

Description
- Venous blood sample

Normal range
- 160 to 950 pg/mL

Comments
- Vitamin B12 deficiency can present with confusion; ataxia; and/or myelopathy, which can have a subacute to chronic onset or even an acute appearance (eg, after nitrous oxide administration). The myelopathic presentation can be mistaken for MS
- Vitamin B12 deficiency is most common in elderly patients due to impaired absorption and in vegetarians due to decreased intake

HIV testing

Description
- Serum or plasma sample
- Single-use diagnostic system rapid HIV test

Normal result
Absence of HIV antibodies

Comments

- High sensitivity (99.9%) and specificity (99.6%)
- Must be done by a trained laboratory technician
- Positive results must be confirmed with standard serologic testing

Differential diagnosis

Acute disseminated encephalomyelitis

- Also known as postinfectious or postimmunization encephalomyelitis
- Characterized by multiple demyelinating lesions in the brain and/or spinal cord
- Usually presents approximately 2 weeks after viral infection or vaccination; precipitating viral infections include measles, chickenpox, rubella, mumps, and influenza
- Typically presents with limb weakness, convulsions, coma, and fever
- Differentiated from MS by the absence of new lesions on brain MRI in a clinically stable patient and by the absence of relapse or new symptoms, especially 3 months following the initial symptoms and discontinuation of steroid therapy

Neuromyelitis optica

- Also known as Devic syndrome
- An autoimmune, inflammatory disorder that produces inflammation of the optic nerve (optic neuritis) and the spinal cord (myelitis)
- Typically associated with a spinal cord lesion extending over three or more vertebral segments, which can lead to varying degrees of weakness or paralysis in the legs or arms, loss of sensation, and/or bladder and bowel dysfunction
- Has a relapsing course in more than 90% of patients
- Associated with a highly specific serum autoantibody marker (NMO-IgG), which targets the water channel aquaporin 4

SLE

- SLE is an autoimmune disease in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes
- Occurs in young adults, like MS
- Can present with hemiparesis, paraparesis, seizures, cranial nerve palsies, cerebellar ataxia, or chorea
- Usually associated with musculoskeletal symptoms and dermatologic manifestations
CNS symptoms may be caused by several processes, including cerebral vasculitis, cerebral vasculopathy without inflammation, hypercoagulable state due to antiphospholipid antibodies, and direct autoimmune attack on brain parenchyma.

Polyarteritis nodosa

- **Polyarteritis nodosa** is a necrotizing vasculitis of small and medium arteries.
- Can present with mononeuropathy, hemiparesis, seizures, and polyneuropathy.
- Usually associated with fever, weight loss, and arthralgia.
- Laboratory investigations show an elevated leukocyte count, ESR, and C-reactive protein level.

Guillain-Barré syndrome (acute infective polyneuritis)

- **Guillain-Barré syndrome** is the most common acquired demyelinating polyneuropathy.
- Often follows a viral infection.
- Commences with sensory symptoms and then progresses to motor weakness.
- Weakness is maximal 3 weeks after onset.
- Caused by autoimmune demyelination of peripheral nerve system myelin, whereas MS compromises CNS myelin.
- Usually not confused with MS because peripheral demyelination produces hyporeflexia and weakness, with decreased tone, and is associated with deficits confined to distributions of a polyneuropathy. In contrast, MS produces lesions of central localization, without hyporeflexia.

Progressive multifocal leukoencephalopathy

- Usually associated with immunosuppressive illnesses, including leukemia, lymphoma, and HIV infection; now known to occur in patients who have taken natalizumab or other monoclonal antibodies, such as rituximab.
- Caused by JC virus infection of the CNS.
- Nonremitting and generally fatal within 3 to 6 months, although there are now known cases of patients who have survived.
- Widespread, multifocal white matter demyelination, usually not gadolinium enhancing, is seen on CT scan and MRI.
- There is no known medication approved by the U.S. Food and Drug Administration for this indication, although various medications have been tried.

Subacute combined degeneration of the spinal cord

- Caused by vitamin B12 deficiency.
- May be associated with megaloblastic anemia.
Paraparesis, quadriparesis, and encephalopathy are the most common signs. Deficit may develop after nitrous oxide exposure. A symmetric polyneuropathy, also due to vitamin B12 deficiency, may occur simultaneously.

Spinal cord compression
- Presents with paraparesis/paraplegia or quadriparesis/quadriplegia, depending on the level and severity of the compression
- Accompanied by sensory changes, and a clear-cut sensory level often can be detected
- Usually associated with bladder or bowel involvement, saddle anesthesia, and decreased anal tone
- MRI of the relevant segment of the spinal cord will show the cause of the compression

Neurosyphilis
- The most common manifestation of tertiary syphilis
- May present with cranial nerve palsies, sensory ataxia, areas of paresthesia, and dementia
- Argyll Robertson pupil (constricted pupil that reacts to accommodation but not to light) may be seen on physical examination
- Serologic test results are positive for syphilis

Conversion disorders
- Focal and multifocal symptoms can easily be mistaken for MS. Transient symptoms that have resolved by the time of evaluation can be impossible to differentiate clinically from previous MS attacks
- A precipitating emotional stressor frequently is present
- Physical examination findings suggesting nonorganic deficits (inconsistencies and anatomic impossibilities) usually are present
- Caution must be exercised in diagnosing a nonorganic condition, as patients with transient or mild deficits may embellish the clinical presentation for the examiner
- MRI and lumbar puncture findings are usually normal, but normal MRI findings do not rule out demyelinating disease

Stroke
- **Focal or multifocal infarctions** can develop in young patients and be mistaken for MS; small-vessel disease is especially easy to confuse, even on MRI
- Patients with vascular risk factors, coagulopathy, vasculitis, or cardiac defects are predisposed to multifocal infarctions at a premature age
• Infarctions are more commonly confused with MS than hemorrhages, although multifocal hemorrhages can occur, especially in patients with coagulopathies

• Strokes usually have a more rapid onset of symptoms than MS, although differentiation can be difficult

• MRI in a patient with a deficit may show focal or multifocal lesions, which cannot be definitively determined to be small-vessel vascular disease or MS

• History is a key to differentiation, as the onset of symptoms is subacute in patients with MS

• Any cortical involvement of lesions makes a vascular cause most likely, although occasional plaques can have cortical involvement

Tumor

• Gradual onset of focal or multifocal deficits can be mistaken for MS, but the onset of deficit in patients with tumors is generally slower than in those with MS

• Some metastases can have an appearance similar to that of MS on MRI, although in cases of a large nodular lesion with cortical involvement, tumor is most likely

• Differentiation may be possible only with biopsy

Migraine

• Migraine presents with episodic headache, often in association with nausea and photophobia

• Transient neurologic deficits can occur in conjunction with aura, although these deficits are brief; the rapid onset and short duration allow differentiation from MS attacks

• May be mistaken for MS on the basis of multifocal signal abnormalities on T2 and fluid-attenuated inversion recovery imaging, although the clinical features are quite different. The presence of nonspecific white matter changes on MRI should not trigger evaluation and treatment for MS, unless there are symptoms and/or signs of previous MS-like attacks

HIV/acquired immunodeficiency syndrome (AIDS)

• Patients with AIDS can present with multifocal cerebral lesions from a variety of causes, including opportunistic infections. Cryptococcal meningitis, progressive multifocal leukoencephalopathy, and toxoplasmosis are particularly prevalent in HIV-infected patients

• AIDS and subsequent opportunistic infections can produce headache, confusion, and/or focal or multifocal deficits

• Differentiation from MS can be difficult, especially in patients with progressive multifocal leukoencephalopathy

Consultation

• Referral to a neurologist is indicated:
  o To confirm the diagnosis of MS when strongly suspected
To establish a long-term, disease-modifying treatment plan
  - When relapses occur in a previously stable patient
  - If the clinical course progresses rapidly

- Referral to an ophthalmologist is necessary to exclude primary ophthalmic causes in a patient presenting with monocular visual loss

**Treatment**

**Summary approach**

- MS is a chronic, potentially debilitating disease with no cure
- Treatments aim to reduce the frequency of relapses or exacerbations and hasten recovery from them, slow disease progression, provide symptomatic relief in patients with fixed deficits, and maximize independence and physical abilities at all stages of the disease

**Treatment of acute exacerbations**

- First-line therapy is high-dose intravenous methylprednisolone, usually administered daily for 5 days. This may be followed by a tapering dose of prednisone
- Oral high-dose prednisone can be considered in patients who cannot or will not take intravenous therapy, but there are fewer data supporting its use
- Plasma exchange is sometimes used in patients with severe demyelinating episodes, especially transverse myelitis, but should be done in consultation with a neurologist or neuroimmunologist
- In patients with acute optic neuritis, intravenous methylprednisolone is usually followed by oral corticosteroids
- Intravenous immune globulin (IVIG) is not recommended at present

**Disease-modifying therapies in patients with relapsing-remitting MS**

- First-line therapy is usually interferon-β1a/ interferon-β1b or glatiramer
- If one agent is ineffective in reducing relapses, then another should be used, but most patients are on a specific agent for a sufficient amount of time that an accurate indication of disease activity can be determined. This may take 6 to 12 months, depending on the clinical situation. There is generally no reason to discontinue a tolerated medication that appears to be effective
- Interferon-β1a, interferon-β1b, and glatiramer are also approved for patients who have experienced their first clinical episode and have MRI features consistent with MS. Early initiation of treatment with interferons or glatiramer should be considered in all patients following an initial episode of acute optic neuritis to reduce or delay the onset of definitive MS
- [Natalizumab](https://www.natalizumab.com) should be considered in patients who do not respond to or cannot tolerate interferons or glatiramer. Although natalizumab has been shown to be effective as maintenance therapy in patients with relapsing-remitting MS, it was removed from the U.S. market following
FDA approval because of a small risk of progressive multifocal leukoencephalopathy; the risk appears to increase the longer a patient has received the drug. Reevaluation of this risk led to the reintroduction of natalizumab under specific prescription regulations, and it is currently available through a special distribution program.

- **Fingolimod** was recently approved by the U.S. Food and Drug Administration for the treatment of relapsing forms of MS and has been shown to reduce relapses and delay the progression of disability.
- Scheduled pulsed corticosteroids, IVIG, or other immune-modulating agents should be considered in patients with refractory relapsing-remitting MS, although these agents are not routinely used in clinical practice and require consultation with a neurologist or neuroimmunologist.

**Treatment of primary progressive MS**

- Data to support the use of specific therapies are limited.
- There is no definitive evidence showing that β-interferons slow the progression of MS.
- Treatment should be coordinated in consultation with a neurologist or neuroimmunologist specializing in MS.

**Treatment of secondary progressive MS**

- Data to support the use of specific therapies are limited.
- Treatment should be coordinated in consultation with a neurologist or neuroimmunologist specializing in MS.
- Interferon-β or natalizumab should be considered in patients experiencing relapses.
- Regular pulsed corticosteroid therapy may be useful. The addition of cyclophosphamide to corticosteroid therapy may be of value in younger patients (under age 40), although the evidence for this is weak.
- Methotrexate may influence disease progression.
- **Mitoxantrone** is approved for use in patients with secondary progressive MS or progressive-relapsing MS. However, because of adverse effects and limitations on duration of use, it should be used only when other maintenance therapy has failed.

**Treatment of clinical manifestations of MS**

- **Counseling** may be needed to manage the psychological effects of MS.
- Patients should be given general information on the disease, its clinical course, and available treatment options.

Motor and coordination deficits:
- **Dalfampridine** is now approved by the FDA and has been shown to improve walking speeds in patients with any type of MS, although it is associated with a small risk of seizures and should be avoided in patients with renal disease.

- Gabapentin is sometimes used for muscle twitches associated with MS.

- **Physical and occupational therapy** can help to improve and maintain motor function. **Dietary modification and exercise**, as well as management of comorbid conditions that have been shown to increase the risk of physical disability (e.g., hypertension, diabetes, and hypercholesterolemia), are also beneficial.

- **Intermittent urinary catheterization** may be useful in dealing with urinary retention associated with MS.

**Muscle spasticity:**

- Physical and occupational therapy with range-of-motion exercises can be helpful.

- **Muscle relaxants**, such as baclofen or tizanidine, may be needed to reduce spasticity. Surgery to insert an intrathecal baclofen pump may be beneficial in nonambulatory patients with spasticity that is resistant to oral baclofen.

- **Diazepam** is a powerful treatment for spasticity but is usually only used if baclofen or tizanidine have not been effective.

- **Botulinum toxin** injections into selected muscle groups can help in reducing spasticity for a specific purpose (e.g., leg scissoring that impedes care or hand contractures).

**Bladder dysfunction:**

- Medical treatment of spastic bladder, using routine medications, occasionally is helpful.

- Intermittent catheterization may be needed in patients with spinal cord lesions.

**Fatigue:**

- **Amantadine** or modafinil is used.

**Medications**

- Methylprednisolone
- Interferon-β
- Glatiramer
- Natalizumab
- Mitoxantrone
- Fingolimod
- Amantadine
Modafinil
Muscle relaxants
IVIG
Dalfampridine
Botulinum toxin

**Non-drug treatments**

**Intermittent urinary catheterization**

- Intermittent catheterization as opposed to the use of an indwelling catheter helps prevent recurrent [urinary tract infections](#).
- Patients must be taught how to self-catheterize in a hygienic manner. Those who are severely disabled by MS may lack the manual dexterity to perform this task.
- The patient's urine should be checked frequently to ensure that no infection is present.

**Physical and occupational therapy**

- Rehabilitative measures are useful in maintaining mobility, preventing contractures, and helping patients with MS maintain their independence and can aid in deferring the bedridden stage of the disease.
- However, there is a risk that excessive activity may exhaust the patient.
- Hydrotherapy in cool water is reported to be the most effective form of physiotherapy in patients with MS.

**Evidence**

There is some evidence from small randomized trials that rehabilitation therapy improves disability in patients with progressive MS.

- An RCT comparing multidisciplinary inpatient rehabilitation versus waiting list (no treatment) in 66 patients with progressive MS found that patients who received a short period (average of 25 days) of inpatient rehabilitation experienced a significant improvement in their level of disability and handicap compared to those in the control group. [46] *Level of evidence:* 1

- An RCT comparing 3 weeks of inpatient physical rehabilitation versus home exercise in 50 ambulatory patients with MS found that those receiving inpatient rehabilitation experienced a significant improvement in disability compared to those performing exercises at home. [47] *Level of evidence:* 1

- An RCT comparing 6 weeks of individualized outpatient rehabilitation versus no therapy in 111 patients with progressive MS found that those receiving rehabilitation experienced significant improvement in their level of disability compared to those in the control group, although impairment was unaffected. [48] *Level of evidence:* 1
A small controlled clinical trial comparing 5 hours of outpatient rehabilitative treatment per week for 12 months versus waiting list (no treatment) in 46 patients with progressive MS found that patients receiving rehabilitation had a reduced frequency of fatigue and MS symptoms. \[49\]  
*Level of evidence: 2*

References

**Dietary modification and exercise**

- The value of a low-fat diet in patients with MS is not proven, but it will have beneficial general health effects
- Patients should be advised to avoid saturated fats (eg, butter and animal fats)
- Yoga and exercise may help to reduce fatigue

**Evidence**

There is some evidence that exercise improves muscle function and mobility in patients with MS.

- A systematic review identified nine RCTs evaluating exercise therapy in a total of 260 patients with MS not presently experiencing an exacerbation. Six RCTs compared exercise therapy versus no exercise therapy, and three RCTs compared different exercise regimens. Meta-analysis of the trial data was not possible because of the different outcomes measured. However, qualitative analysis showed strong evidence that exercise therapy resulted in significant improvements in muscle power, exercise tolerance, and mobility. Additionally, there was moderate evidence that exercise improved patient mood. \[50\]  
*Level of evidence: 1*

**Counseling**

- Should include measures aimed at stress reduction
- Likely to help patients and their care providers cope with the effects of MS

**Evidence**

- A small, single-blind study compared neuropsychological counseling versus standard psychotherapy in 15 patients with MS and marked cognitive impairment and behavior disorder. Pre- and posttreatment assessments of personality and social behavior showed that patients who received neuropsychological counseling had a significant positive response on measures of social behavior compared to those who received standard counseling. \[51\]  
*Level of evidence: 2*

**References**

**Special circumstances**

**Patient satisfaction/lifestyle priorities**

Patients should be encouraged to continue to maintain as active a lifestyle as possible without compromising their safety.
Consultation

Patients with MS should be referred for management when an acute exacerbation occurs or when symptoms are chronically progressing.

Follow-up

Plan for review:

- In some patients, the period of remission may last several years. Patients with clinically isolated syndrome and definite MS should be seen regularly by a neurologist to document response to therapy and progression of disease. Repeat MRI of the brain and spine and additional laboratory tests may be necessary, depending on treatment and clinical course.

- Patients with an acute exacerbation should return for a follow-up visit once they have been weaned off of corticosteroids to avoid early relapse; recurrences may be decreased with the use of disease-modifying therapies, including interferon-β, glatiramer, natalizumab, and fingolimod.

Prognosis:

- Following an initial demyelination episode, defined MS may take one of the following three forms:
  - Relapsing-remitting MS, which is characterized by recovery of previous function following attacks, although some patients may have some residual additional disability.
  - Secondary progressive MS, which is characterized by a slow deterioration in function without an acute episode.
  - Primary progressive MS, which is characterized by a steady functional decline from the outset, without acute attacks.

- MS follows an unpredictable course, with some cases being clinically silent throughout the patient's life and only diagnosed incidentally at autopsy and others being fatal within weeks of initial presentation.
  - The usual pattern after the initial attack is of gradually progressing disease with remissions and exacerbations; the average relapse rate is 0.3 to 0.4 per year.
  - Average survival has increased to approximately 35 years in recent decades. Up to one third of patients are still working and two thirds of patients are still ambulatory approximately 25 years after diagnosis.
  - As a general rule, presentation with sensory symptoms (blurred vision or paresthesia) tends to indicate a benign course, whereas the presence of pressure sores, intractable spasticity with contractures, and recurrent urinary tract infections indicates significant disease progression with little likelihood of significant recovery.
  - One study found that progression of disability in patients with relapsing-remitting MS or secondary progressive MS may be more favorable than originally reported. The study
also found that once a clinical threshold of disability was reached, the rate of progression of disability increased

- Death from MS itself is rare. Death is usually caused by related infections: urinary tract infections, pressure sores leading to septicemia, and respiratory tract infections are common

- Disability can be lessened by the use of immunomodulating agents, most of which are supported by long-term data. Steroid therapy for MS attacks does not appear to have a major, long-term effect on disability. However, aggressive steroid therapy for optic neuritis does alter visual outcomes

Terminal illness:

- Treatment of MS in the terminal stages should be directed toward symptom control
- Interferons and possibly even steroids should be discontinued
- Any advance directives that the patient may have established (eg, a wish not to be given any antibiotics for life-threatening infections when the condition is terminal) should be taken into account

Clinical complications:

- Partial or total loss of vision in one eye due to optic neuritis
- Bladder dysfunction (often associated with impotence in male patients)
- Spasticity and contractures
- Mental deterioration
- Ataxia and impaired mobility
- Impaired mobility due to limb weakness

Patient Education

- Patients should be advised that the disease course is highly variable and often relatively benign
- Appropriate counseling and support services should be made available
- Because MS is postulated to be an immune-modulated disorder, patients should be instructed to avoid unnecessary vaccinations

Online information for patients

- American Academy of Family Physicians: FamilyDoctor.org: Multiple Sclerosis
- American Academy of Neurology: Multiple Sclerosis
- Multiple Sclerosis Association of America
- Multiple Sclerosis International Federation
Corticosteroids may speed functional recovery in patients with acute exacerbations of MS, and their use is endorsed by expert opinion.

A systematic review identified six RCTs examining the use of methylprednisolone (four trials) or adrenocorticotropic hormone (two trials) versus placebo in 377 patients with an acute exacerbation of MS. Meta-analysis of these studies showed that both methylprednisolone and adrenocorticotropic hormone significantly reduced the number of patients whose symptoms were worse or unimproved within 5 weeks of treatment compared to placebo. The evidence favored intravenous methylprednisolone, with no significant difference between a 5-day or a 15-day treatment course. [1] Level of evidence: 1


Intravenous methylprednisolone is superior to oral corticosteroids in the treatment of acute optic neuritis.

A large RCT compared treatment with oral prednisolone for 14 days versus treatment with intravenous methylprednisolone for 3 days followed by oral prednisolone for 11 days versus placebo in 456 patients with acute optic neuritis. Treatment with intravenous methylprednisolone resulted in significantly faster rates of recovery of visual function compared to either oral prednisone alone or placebo. Patients receiving oral prednisone alone had a significantly greater risk of recurrent attacks of optic neuritis. [3], [4] Level of evidence: 1

Follow-up data from the aforementioned RCT showed that, at 2 years, 7.5% of patients receiving intravenous methylprednisolone had definite MS compared to 14.7% of patients receiving oral prednisone and 16.7% of patients receiving placebo. [5] Level of evidence: 1

Interferon-β

There is evidence that early treatment with interferon-β1 reduces the probability that a person with a first demyelinating event will go on to have definite MS.

An RCT compared interferon-β1 versus placebo in 383 patients presenting with an acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis, or brainstem or cerebellar syndrome) and evidence of previous subclinical demyelination on brain MRI. All patients initially received corticosteroids. Treatment with interferon-β1 resulted in significantly reduced rates of
conversion to definite MS compared to placebo. Additionally, there was a reduction in the accumulation of new and/or enlarging lesions on MRI. [6] Level of evidence: 1

- In an extension of the aforementioned RCT, all of the original participants were offered treatment with interferon-β1a, and the outcomes of patients originally assigned to treatment with interferon-β1awere compared with those of patients who originally received placebo. The cumulative probability of developing definite MS was significantly reduced in the patients who received interferon-β1a initially compared to those who received placebo initially and then opted for interferon-β1atreatment subsequently. [7] Level of evidence: 1

- Another RCT compared interferon-β1aversus placebo in 308 patients presenting with a first episode of neurologic dysfunction suggestive of MS within the previous 3 months and brain MRI findings strongly suggestive of MS. Treatment with interferon-β1a resulted in a significantly lower rate of conversion to definite MS, a significant delay in conversion to MS among those patients who did progress, and fewer new lesions on MRI. [8] Level of evidence: 1

Interferon-β1a and interferon-β1bhave been shown to reduce the frequency of relapses in patients with relapsing-remitting MS.

- A systematic review identified seven RCTs comparing recombinant interferon-β1a/interferon-β1bversus placebo in patients with active relapsing-remitting MS. Treatment with interferon resulted in a modest but significant reduction in the occurrence of exacerbations and disease progression over 2 years. However, if the patients receiving interferon who were lost to follow-up were assumed to have experienced disease progression or relapse (the worst-case scenario), the significance of these effects was lost. [9] Level of evidence: 1

- One of the RCTs included in the aforementioned systematic review compared low-dose interferon-β1bversus high-dose interferon-β1bversus placebo in 372 patients with relapsing-remitting MS. Treatment with high-dose interferon-β1bsignificantly reduced the clinical relapse rate, and there was a trend toward an effect on other measures of disease activity, including a reduction in MRI lesion burden and in disease progression. [10] Level of evidence: 1

- Another RCT comparing interferon-β1aversus placebo in 301 patients with relapsing-remitting MS found that treatment with interferon-β1aresulted in significantly lower clinical attack rates, reduced MRI lesion burden, and a reduction in the Kurtzke Expanded Disability Status Scale score over 2 years. [11] Level of evidence: 1

- A third RCT comparing two subcutaneous dosing regimens of interferon-β1aversus placebo in 560 patients with relapsing-remitting MS found that treatment with either dose of interferon-β1asignificantly reduced the clinical attack rate and the MRI lesion burden. [12] Level of evidence: 1

- Data from RCTs comparing dosing regimens suggest that higher or more frequent doses of interferon-β are superior to once-weekly treatment. [13], [14] Level of evidence: 1

The effectiveness of interferon-β on disability in patients with primary progressive MS remains unclear.

- A systematic review found that there are limited data on the effect of interferon-β treatment on primary progressive MS. Only two single-center, placebo-controlled trials have been conducted,
both of which showed that treatment with interferon-β was not associated with reduced disability progression in patients with primary progressive MS. However, the trial population was too small to allow definitive conclusions regarding efficacy. Larger research studies need to be done in patients with primary progressive MS to determine whether interferon-β is effective in this population. [15] Level of evidence: 1

There is some evidence to suggest that interferon-β slows disease progression in patients with secondary progressive MS.

- An RCT comparing interferon-β1b, 8 million IU every other day, versus placebo in patients with secondary progressive MS found that treatment with interferon-β1b prolonged the time to sustained progression of disability by between 9 and 12 months, significantly reduced the risk of progression, and reduced the risk of becoming wheelchair bound. [16] Level of evidence: 1

- An RCT comparing subcutaneous interferon-β1a versus placebo in patients with secondary progressive MS found no significant difference in confirmed progression of disability between groups, but patients receiving interferon had a significantly reduced risk of relapse. [17] Level of evidence: 1

- An RCT comparing interferon-β1a versus placebo in patients with secondary progressive MS found that active treatment reduced progression, as measured by the MS Functional Composite (consisting of a 25-foot timed walk, nine-hole peg test, and the paced auditory serial addition test) score, after 2 years. However, this outcome has not been assessed in other trials, and its significance is not clear. No significant difference in Expanded Disability Status Scale scores was found between the two groups. [18] Level of evidence: 1

Glatiramer

Treatment with glatiramer is beneficial in reducing the relapse rate in patients with relapsing-remitting MS, and its use is endorsed by expert opinion.

- An RCT comparing treatment with glatiramer versus placebo in 251 patients with relapsing-remitting MS who had two or more relapses in the previous 2 years found that glatiramer significantly reduced the relapse rate (1.19) compared to placebo (1.68). [19] Level of evidence: 1

- Follow-up data on the patient cohort in the aforementioned RCT showed that significantly fewer patients receiving glatiramer experienced increased disability over 2 years compared to those receiving placebo. [20] Level of evidence: 1

- Another RCT comparing glatiramer versus placebo in 249 patients with relapsing-remitting MS found that treatment with glatiramer resulted in a 35% reduction in the total number of enhancing lesions on MRI and a reduction in the clinical attack rate compared to placebo. [21] Level of evidence: 1

- Guidelines from the American Academy of Neurology state that glatiramer has been shown to reduce the attack rate and possibly slows sustained disability progression in patients with relapsing-remitting MS, and, thus, it is appropriate to consider the use of glatiramer in this patient population. [2] Level of evidence: 3
Glatiramer may be effective in decreasing the risk of developing definite MS in patients with clinically isolated syndrome.

- An RCT comparing glatiramer versus placebo in 481 patients presenting with a first event of CNS demyelination found that glatiramer decreased the risk of conversion to clinically definite MS by 45% and delayed conversion to clinically definite MS compared to placebo. [22] Level of evidence: 1

**Natalizumab**

Natalizumab may be beneficial in reducing the relapse rate and delaying disease progression in patients with relapsing-remitting MS, but caution regarding its use is warranted due to the risk of progressive multifocal leukoencephalopathy.

- An RCT comparing natalizumab, 300 mg intravenously per month, versus placebo in 942 patients with relapsing-remitting MS found that treatment with natalizumab significantly reduced the clinical relapse rate (by 68%), the number of new or enlarging lesions on MRI (by 83%), and disability progression (by 42%) compared to placebo. [23] Level of evidence: 1

- Another RCT compared treatment with natalizumab plus interferon-β1a versus continued treatment with interferon-β1a alone in 1,171 patients with relapsing-remitting MS experiencing relapse while receiving treatment with interferon-β1a. The addition of natalizumab to the existing interferon regimen resulted in significant reductions in the clinical relapse rate (by 54%) and the risk of sustained disability progression (by 24%); the accumulation of lesions on MRI also was reduced. [24] Level of evidence: 1

- Natalizumab may be associated with an increased risk of progressive multifocal leukoencephalopathy, with one study suggesting a risk of approximately 1 in 1,000 patients receiving the drug for a mean of 17.9 months. Initial reports led to voluntary withdrawal of natalizumab from the market in 2005, with reappraisal of data leading to its reintroduction with a black box warning in June 2006. [25] Level of evidence: 2

**Mitoxantrone**

Mitoxantrone may be of some benefit in selected patients with rapidly advancing MS that is unresponsive to other therapies, although significant cardiotoxicity may limit its use.

- A systematic review identified four RCTs evaluating the role of mitoxantrone in a total of 270 patients with relapsing-remitting MS or progressive MS. Treatment with mitoxantrone significantly reduced relapse rates (at both 1 and 2 years), the proportion of patients with sustained disease progression, and mean disability scores. [26] Level of evidence: 1

- One of the RCTs included in the aforementioned review compared mitoxantrone, 20 mg monthly, plus methylprednisolone versus methylprednisolone alone in an unblinded fashion in 42 patients with active MS. Disease activity, as assessed by MRI, and annual clinical relapse rates were significantly reduced in the patients receiving mitoxantrone. [27] Level of evidence: 1

- The largest RCT included in the systematic review compared two doses of intravenous mitoxantrone, 12 mg/m² or 5 mg/m² every 3 months, versus placebo over 24 months in 194
patients with secondary progressive MS or worsening relapsing-remitting MS. Multivariate analysis showed that treatment with the higher dose of mitoxantrone resulted in improvements in clinical outcome, as measured by a composite score, and produced a significant reduction in both the clinical attack rate and progression of disease. [28] Level of evidence: 1

- However, treatment with mitoxantrone is associated with an increased risk of cardiac toxicity, particularly with cumulative doses exceeding 100 mg/m², which may prevent long-term use. A study reviewing the records of 1,378 patients with MS from three clinical trials of mitoxantrone for signs and symptoms of cardiac dysfunction and left ventricular ejection fraction test results found an incidence of heart failure less than 0.2% in patients who received a mean cumulative dose of 60.5 mg/m² of mitoxantrone. The researchers recommend continued monitoring of patients with MS who are receiving mitoxantrone in order to determine whether the incidence of heart failure increases with higher cumulative doses and prolonged follow-up. [29] Level of evidence: 2

- Guidelines from the American Academy of Neurology state that mitoxantrone may have a beneficial effect on disease progression in patients with MS whose condition is deteriorating and that mitoxantrone probably reduces the clinical attack rate and attack-related MRI outcomes. However, the guidelines also note that the potential toxicity of mitoxantrone is considerable, and that due to the limited evidence of benefit, its use should be reserved for patients with rapidly advancing disease that has failed to respond to other therapies. [21], [30] Level of evidence: 3

**Fingolimod**

- A 2-year, double-blind RCT compared two doses of oral fingolimod, 0.5 mg/d or 1.25 mg/d, versus placebo in 1,272 patients with relapsing-remitting MS, 1,033 of whom completed the study. The cumulative probability of disability progression (confirmed after 3 months) was 17.7% among patients receiving 0.5 mg of fingolimod, 16.6% among patients receiving 1.25 mg of fingolimod, and 24.1% among patients receiving placebo. Both fingolimod doses improved the relapse rate, the risk of disability progression, and end points on MRI compared to placebo. [31] Level of evidence: 1

- A 1-year, double-blind, double-dummy RCT assigned 1,292 patients with relapsing MS who had not received any natalizumab in the previous 6 months to treatment with fingolimod, 0.5 mg or 1.25 mg, or interferon-β1a, 30 μg intramuscularly once weekly, for up to 12 months. The annualized relapse rate and the number of new and newly enlarging T2 lesions were significantly lower in patients receiving fingolimod than in those receiving interferon-β1a. [32] Level of evidence: 1

**Amantadine**

- A systematic review found little evidence of the efficacy and tolerability of amantadine in reducing fatigue in patients with MS. Five RCTs met the inclusion criteria, all of which reported small and inconsistent improvements in fatigue. However, the overall quality of the trials was poor, leading the reviewers to conclude that good-quality RCTs are needed. [33] Level of evidence: 1
- A double-blind RCT comparing amantadine, pemoline, and placebo in 93 patients with MS found that amantadine was superior to placebo in improving fatigue, with 70% of patients receiving amantadine experiencing improvement. [34] Level of evidence: 1

**Modafinil**

- A single-blind, prospective, phase 2 trial comparing modafinil versus placebo in patients with MS found that treatment with 200 mg/d of modafinil significantly improved fatigue in the short term, as measured by self-rating scales. [35] Level of evidence: 2
- A prospective, 3-month, open-label study evaluated the effect of modafinil on symptoms of fatigue in patients with MS. Treatment was initiated at a single daily dose of 100 mg and increased in nonresponders by 100-mg increments up to a maximum daily dose of 400 mg. Only 4% of patients required a dose higher than 200 mg. Fatigue scores were significantly improved at 3 months compared with baseline. [36] Level of evidence: 2

**Muscle relaxants**

- A systematic review including 23 placebo-controlled RCTs and 13 comparative studies of antispasticity agents, not limited to baclofen, in patients with MS concluded that the efficacy and tolerability of antispasticity agents is poorly documented, and no recommendations can be made regarding their use. [37] Level of evidence: 1
- Another systematic review found that there is limited evidence of the effectiveness of baclofen, tizanidine, and diazepam in the treatment of spasticity in patients with MS. [38] Level of evidence: 1
- A prospective, double-blind RCT evaluating oral tizanidine in 187 patients with MS found that tizanidine produced a significant reduction in spastic muscle tone compared to placebo. Within the effective dose range of 24 to 36 mg administered daily in three doses, tizanidine achieved a 20% mean reduction in muscle tone. Approximately 75% of patients with all degrees of spasticity reported subjective improvement, without an increase in muscle weakness, but there was no improvement in activities of daily living depending on movement. [39] Level of evidence: 1
- A multicenter, double-blind, 15-week RCT evaluated the use of tizanidine for spasticity secondary to MS. Primary efficacy parameters were muscle tone scores on the Ashworth Scale and type and frequency of muscle spasms, as recorded in patient diaries. According to patient diaries, tizanidine produced a significantly greater reduction in spasms and clonus than placebo, but there were no significant differences between groups in Ashworth Scale scores or in other secondary efficacy parameters. [40] Level of evidence: 1
- A small, crossover RCT comparing intrathecal baclofen versus placebo (intrathecal saline) in 20 patients with MS or spinal cord injuries and spasticity resistant to oral baclofen, 19 of whom were not ambulatory, found that intrathecal baclofen significantly improved spasticity and reduced the frequency of spasms. [41] Level of evidence: 1

**IVIG**
There is some evidence that treatment with IVIG reduces the risk of subsequent events in patients with an initial demyelination event.

- An RCT comparing IVIG, 2-g/kg loading dose followed by 0.4 g/kg administered once every 6 weeks for 1 year, versus placebo in 91 patients with features clinically consistent with a demyelination event (confirmed by MRI) found that treatment with IVIG significantly reduced the risk of a second demyelination event at 1 year (cumulative probability, 26%) compared to placebo (50%). [42] Level of evidence: 1

**Dalfampridine**

- A randomized, placebo-controlled, phase 3 trial comparing dalfampridine versus placebo in 301 patients with MS found that walking speed improved significantly more from baseline in patients receiving dalfampridine than in those receiving placebo. Significantly more patients receiving dalfampridine consistently showed improvement on timed 25-foot walk compared to those receiving placebo (34.8% vs 8.3%), and this improvement was seen in patients with all four major types of MS. The magnitude of improvement in walking speed was independent of concomitant treatment with immunomodulatory drugs for MS. [43] Level of evidence: 1

- A review of three RCTs found that extended-release dalfampridine significantly improved walking speed in patients with MS compared to placebo, and improvements were sustained above baseline for up to 2.5 years of treatment. Consistent improvements in walking speed were shown to be associated with improvements on a patient self-assessment of ambulatory disability. [44] Level of evidence: 2

**Botulinum toxin**

- A systematic review found good evidence that botulinum toxin is effective in reducing spasticity and is associated with functional benefit in patients with MS. [38] Level of evidence: 1

- A review article states that botulinum toxin provides short-term improvement of function and spasticity in patients with MS. [45] Level of evidence: 3

**Physical and occupational therapy**

There is some evidence from small randomized trials that rehabilitation therapy improves disability in patients with progressive MS.

- An RCT comparing multidisciplinary inpatient rehabilitation versus waiting list (no treatment) in 66 patients with progressive MS found that patients who received a short period (average of 25 days) of inpatient rehabilitation experienced a significant improvement in their level of disability and handicap compared to those in the control group. [46] Level of evidence: 1

- An RCT comparing 3 weeks of inpatient physical rehabilitation versus home exercise in 50 ambulatory patients with MS found that those receiving inpatient rehabilitation experienced a significant improvement in disability compared to those performing exercises at home. [47] Level of evidence: 1

- An RCT comparing 6 weeks of individualized outpatient rehabilitation versus no therapy in 111 patients with progressive MS found that those receiving rehabilitation experienced significant
improvement in their level of disability compared to those in the control group, although impairment was unaffected. [48] Level of evidence: 1

- A small controlled clinical trial comparing 5 hours of outpatient rehabilitative treatment per week for 12 months versus waiting list (no treatment) in 46 patients with progressive MS found that patients receiving rehabilitation had a reduced frequency of fatigue and MS symptoms. [49] Level of evidence: 2

**Dietary modification and exercise**

There is some evidence that exercise improves muscle function and mobility in patients with MS.

- A systematic review identified nine RCTs evaluating exercise therapy in a total of 260 patients with MS not presently experiencing an exacerbation. Six RCTs compared exercise therapy versus no exercise therapy, and three RCTs compared different exercise regimens. Meta-analysis of the trial data was not possible because of the different outcomes measured. However, qualitative analysis showed strong evidence that exercise therapy resulted in significant improvements in muscle power, exercise tolerance, and mobility. Additionally, there was moderate evidence that exercise improved patient mood. [50] Level of evidence: 1

**Counseling**

- A small, single-blind study compared neuropsychological counseling versus standard psychotherapy in 15 patients with MS and marked cognitive impairment and behavior disorder. Pre- and posttreatment assessments of personality and social behavior showed that patients who received neuropsychological counseling had a significant positive response on measures of social behavior compared to those who received standard counseling. [51] Level of evidence: 2

**References**

Evidence references


CrossRef


CrossRef


Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive


Guidelines

The American College of Radiology has produced the following:

The American College of Radiology and the American Society of Neuroradiology have produced the following:

- **ACR–ASNR Practice Guideline for the Performance and Interpretation of Magnetic Resonance Imagine (MRI) of the Brain**. Reston, VA: American College of Radiology; 2008

The American Academy of Neurology has produced the following:


The National Multiple Sclerosis Society has produced the following:
Guidelines for Administration of Human Papillomavirus (HPV) Vaccine (Gardasil®) to Multiple Sclerosis Patients - UPDATED

The European Federation of Neurological Societies has produced the following:


The National Institute for Health and Clinical Excellence (UK) has produced the following:


The following consensus statement on the role of CSF analysis in the diagnosis of MS has been produced:


The following consensus statement on the differential diagnosis of MS has been produced:


The following consensus statement on the use of disease-modifying agents in patients with MS has been produced:


The American Academy of Family Physicians has produced the following:


Further reading

• Polman CH, Uitdehaag BMJ. New and emerging treatment options for multiple sclerosis. Lancet Neurol. 2003;2;563-6
• Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. JAMA. 2004;291:2367-75
FAQ

- **Do all patients with optic neuritis or transverse myelitis develop MS?** No, most patients with isolated areas of demyelination do not go on to develop MS, although the percentage of risk is debatable.

- **Do all MS attacks have to be treated with corticosteroids?** No, treatment with corticosteroids seems to reduce the duration of the current attack but does not have a definite effect on the frequency of subsequent attacks.

- **Can corticosteroids be administered orally?** Corticosteroids for MS attacks are typically administered intravenously. Oral steroids are believed to be less effective, especially in the treatment of optic neuritis.

- **Is MRI required in all patients in whom MS is suspected?** CT scan is not sufficiently sensitive for the detection of demyelinating disease to be of assistance in diagnosing MS. MRI can be very helpful, and the use of contrast can show active plaques.

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