Multiple Sclerosis

CHAPTER 16

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Definition and etiology:

Multiple Sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system (CNS) characterized by focal demyelination, axonal injury, and neurodegeneration [1]. MS is defined by episodes of focal neurological deficits that affect different areas of the brain, spinal cord, or optic nerves[2,3]. MS most commonly starts with a relapsing–remitting course but may transition into a progressive phase marked by gradual accumulation of disability in the disease course [4]. Five distinct phenotypes of MS are recognized: 1) Radiologically Isolated Syndrome (RIS), 2) Clinically Isolated Syndrome (CIS), 3) Relapsing Remitting Multiple Sclerosis (RRMS), 4) Primary Progressive Multiple Sclerosis (PPMS), and 5) Secondary Progressive Multiple Sclerosis (SPMS)[5,6]. The etiology of MS is complex and multifactorial, with genetic susceptibility and environmental triggers converging to cause immune-mediated CNS injury [7,8]. MS risk is strongly associated with the HLA-DRB1*15:01 gene, which confers a roughly threefold increase in risk [9]. Over 200 additional genetic loci have been identified, each with modest effects, indicating a polygenic architecture with no single gene sufficient to cause disease [10]. Known environmental risk factors for MS are Epstein-Barr virus (EBV) infection [11], low vitamin D [12], smoking [13], and childhood obesity [14].

Epidemiology

Multiple sclerosis (MS) is the most common immune-mediated demyelinating disease of the central nervous system and is considered the leading cause of non-traumatic neurological disability in young adults[15,16]. An estimated 2.2–2.8 million people are living with MS worldwide [17]. The typical age of onset for MS is between 20 and 40 years [18]. Pediatric-onset MS (POMS) is defined by onset before age 18 years and accounts for about 3–10% of cases [19]. Late-onset MS (LOMS) is defined as onset after age 50 years. It represents around 5% of cases and has a more progressive disease at the onset [20]. MS affects women more often than men, with an estimated female-to-male ratio of 3:1[21]. Prevalence of MS increases with distance from the equator, highlighting the role of environmental risk factors such as vitamin D deficiency and ultraviolet B exposure [22,23]. The overall incidence and prevalence of MS have risen in many regions in the past 50 years. This may be due to the improved diagnostic criteria and access to care, greater survival with the introduction of disease-modifying therapies, or possibly a true change in disease risk and biology over time[24].

Pathophysiology

A complex interplay between adaptive and innate immune cells drives the pathophysiology of MS. It is driven by autoreactive T cells, B cells, and myeloid cells that breach the blood–brain barrier (BBB) and infiltrate the CNS, causing focal demyelinating lesions and axonal damage. T cells release proinflammatory cytokines, initiating an autoimmune attack on the myelin sheet [25]. CD4 T cells (Th1, Th17) induce demyelination via cytokine (including IFN-γ, TNF-α, and IL-17) release, which in turn recruits and activates macrophages and microglia [26]. Within the CNS, CD4 T cells are reactivated by antigen-presenting cells (B cells), amplifying the course of neuroinflammation and tissue damage [27]. CD8 T cells outnumber CD4 T cells in active MS lesions, especially at the edges of chronic active lesions. CD8 T cells induce cytotoxicity by killing oligodendrocytes and neurons, leading to demyelination and axonal loss [28]. B cells are central to MS pathogenesis; they act as antigen-presenting cells[29] and produce pro-inflammatory cytokines such as IL-6 and TNF-α that promote Th1/Th17 differentiation and inhibit regulatory T cells [30]. B cells differentiate into plasma

cells that produce pathogenic antibodies, including intrathecal oligoclonal bands (OCBs), which are a hallmark of MS and reflect chronic CNS inflammation [31]. In addition, B cells form ectopic meningeal lymphoid follicles, sustaining chronic CNS inflammation and contributing to smoldering disease activity [32]. Macrophages and microglia have dual functions in tissue injury and repair [33]. They contribute to demyelination and axonal injury via the secretion of pro-inflammatory cytokines and reactive oxygen species [34]. Chronic microglial activation at the rims of MS lesions and in the normal appearing white matter causes smoldering inflammation and neurodegeneration, correlating with clinical disability in progressive MS [35,36]. Conversely, microglia also clear myelin debris [37]and secrete growth factors that support remyelination [38]. In MS, astrocytes' function shifts from homeostatic support to reactive inflammatory cells. They produce pro-inflammatory cytokines (IL-1β, TNF-α, GM-CSF) and chemokines (CCL2, CXCL10) that recruit and activate immune cells, leading to the breakdown of BBB [39,40]. Reactive astrocytes drive excitotoxicity by disrupting glutamate uptake, secreting complement and other neurotoxic factors such as nitrous oxide. They impede remyelination by inhibiting the differentiation of oligodendrocyte precursor cells [41] (Figure 1).

Clinical Presentation and Disease Course

MS presents with highly variable neurological symptoms depending on the location of the demyelinating lesions in the CNS. Common clinical manifestations include painful vision loss, sensory disturbances (e.g., numbness, paresthesia), weakness, gait impairment, double vision, vertigo, bladder and bowel dysfunction (urgency, frequency, urge incontinence, and constipation), fatigue, and cognitive impairment [42–46]. MS has several distinct clinical courses, each with unique characteristics. Clinically Isolated Syndrome (CIS) is the first clinical episode of neurological symptoms consistent with CNS demyelination, lasting typically >24 hours [47]. Most MS patients are diagnosed with the relapsing-remitting form of MS (RRMS) at the onset. It is characterized by acute attacks of focal neurological symptoms (relapses) followed by partial or complete recovery (remissions) [48]. A small subset of MS patients (around 10-15%) present with continuous worsening of neurological symptoms from onset without relapses (primary progressive MS, PPMS). Secondary progressive multiple sclerosis (SPMS) is defined by gradual, irreversible disability accumulation independent of relapses, typically following an initial relapsing-remitting phase [49,50]. Patients with MS accumulate disability via two distinct processes: 1) Relapse-Associated Worsening (RAW) is disability that originates from incomplete recovery after a relapse, 2) Progression Independent of Relapse Activity (PIRA) is disability that accrues gradually without clinical relapses [51,52]. RAW is primarily driven by acute inflammatory demyelination and axonal injury, while PIRA reflects chronic, smoldering inflammation and subsequent neurodegeneration. PIRA is linked to axonal loss, brain atrophy, and chronic microglial activation behind the closed BBB, and is less responsive to traditional anti-inflammatory therapies, highlighting the need for treatments targeting neurodegeneration and CNS-resident immune cells in MS [53,54].

Assessment and Diagnosis

The assessment and diagnosis of MS rely on 1) clinical evaluation, a focused history, and detailed neurological exam, 2) Magnetic Resonance Imaging (MRI) to visualize demyelinating lesions in the CNS, and 3) lumbar puncture for cerebrospinal fluid analysis. It is important to exclude mimics such as neuromyelitis optica, acute disseminated encephalomyelitis, small vessel disease, and other inflammatory or genetic conditions [55,56]. McDonald's diagnostic criteria (Table 1) provide a unified framework for diagnosing MS across ages and phenotypes by integrating clinical, MRI, and

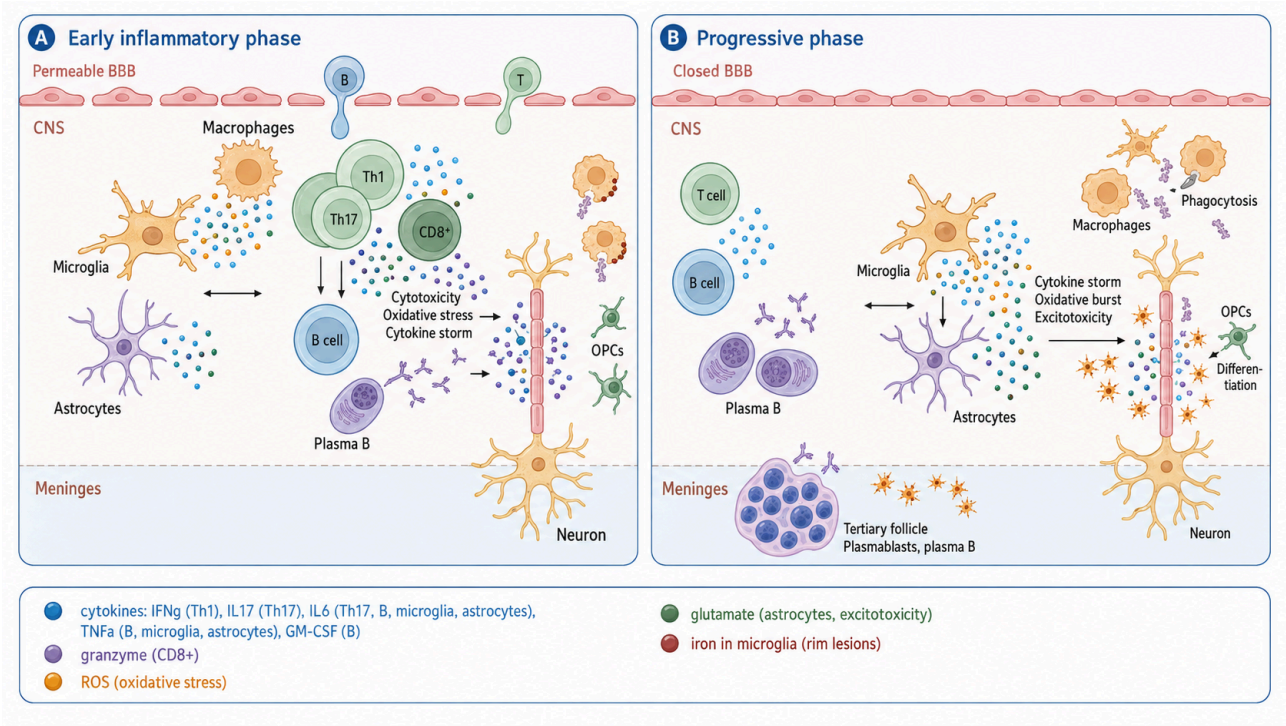


Figure 1. Pathophysiology of multiple sclerosis. (A) In the early inflammatory phase of MS, peripheral adaptive immune cells infiltrate the CNS through a disrupted BBB. These activated cells interact with each other and the resident cells of the CNS. They secrete cytokines (e.g., IFNγ by Th1, IL6/17 by Th17, GM-CSF, IL6, TNFα by B cells) and cytotoxic molecules (e.g., granzyme B by CD8+ T cells). B cells can further evolve into autoantibody-producing plasma cells. As a consequence, T and B cells activate macrophages and microglia, which produce cytokines, nitric oxide, and ROS. This cytotoxic pro-inflammatory environment breaks down the myelin sheaths around axons and induces energy failure in the axon. Macrophages and microglia can still clear the myelin debris, allowing for the recruitment of OPCs that will partially remyelinate the lesion. (B) In the progressive phase of MS, T and B cell infiltrates are reduced. Remarkably, plasmablasts and plasma B cells form tertiary follicle-like structures in the meninges. The BBB is closed and the inflammation is sustained by innate CNS-resident cells, i.e., microglia and astrocytes. They produce cytokines (TNFα, IL6) and release ROS, causing myelin damage. Although microglia are primed into a pro-inflammatory phenotype, their phagocytic capacities are reduced. These features also characterize the senescence associated phenotype of microglia and astrocytes. Myelin debris are improperly cleared, OPCs are less recruited and fail to differentiate. TNFα-mediated glutamate release from astrocytes results in excitotoxicity causing axonal damage. The ferrous iron released from the myelin, where it accumulates with age, is oxidized, which produces ROS, and incorporated by microglia, forming a phenotypical rim around the demyelinating lesions both in the white and gray matter. These successive events are self-sustained and enhanced by senescent processes, resulting in a major oxidative burst, causing mitochondrial dysfunction, mitochondrial DNA damage, energy failure and axonal loss. BBB, blood brain barrier; B, B cell; CNS, central nervous system; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MS, multiple sclerosis; OPC, oligodendrocyte progenitor cell; ROS, reactive oxygen species; T, T cell; Th, T helper cell; TNF, tumor necrosis factor.

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CSF findings[57]. Dissemination in space refers to the presence of 2 or more lesions in the typical regions in the CNS (periventricular, juxtacortical, infratentorial, spinal cord, and optic nerve) (Figure 2) [58,59]. The 2024 McDonald criteria (most recent version) formally incorporated two advanced MRI-based biomarkers (the central vein sign and paramagnetic rim lesions) (Figure 3) as optional diagnostic tools to enhance specificity when conventional MRI findings are insufficient [60]. CSF analysis is particularly helpful when MRI is inconclusive. Presence of OCBs or kappa-free light chains (KFLC) is indicative of intrathecal immunoglobulin synthesis and suggestive of MS diagnosis (OCBs are positive in 87–95% of established MS) [61]. Other emerging biomarkers for MS include serum biomarkers such as neurofilament light chain (NfL) and Glial Fibrillary Acidic Protein (GFAP) [62], Optic Coherent Tomography (OCT) to measure retinal nerve fiber layer thickness (correlates with brain atrophy and clinical progression) [63]and

Positron Emission Tomography (PET) as an advanced research-based imaging tool to detect chronic neuroinflammation (''smoldering lesions'')[64]and synaptic loss[65].

Table 1. MS diagnosis based on McDonald Criteria 2024 [66]

Dissemination in Space (DIS) topographies (number of CNS anatomic sites involved)	Evidence of a typical MS attack
4-5	Allows MS diagnosis without additional DIT or CSF evidence
2-3	Requires one of the following: • DIT • Positive CSF analysis • CVS
1	Requires a combination of the following: • DIT or positive CSF analysis and • CVS or PRL
0	Unable to make a diagnosis

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Dissemination In Space (DIS): presence of lesions in the typical 5 anatomical regions in the central nervous system (periventricular, juxtacortical, infratentorial, spinal cord, and optic nerve)

Dissemination In Time (DIT): either clinical DIT: presence of second clinical relapse or MRI DIT: Simultaneous gadolinium-enhancing and non-enhancing lesions, or new T2/gadolinium-enhancing lesion on follow-up MRI

Cerebrospinal Fluid (CSF): either the presence of CSF-specific IgG oligoclonal bands (OCBs, intrathecal synthesis) or an elevated Kappa Free Light Chain (KFLC) index as an alternative to OCBs

Central Vein Sign (CVS): ≥6 lesions showing CVS (Select-6) supports the diagnosis of MS Paramagnetic Rim Lesion (PRL): ≥1 lesion showing PRL supports the diagnosis of MS

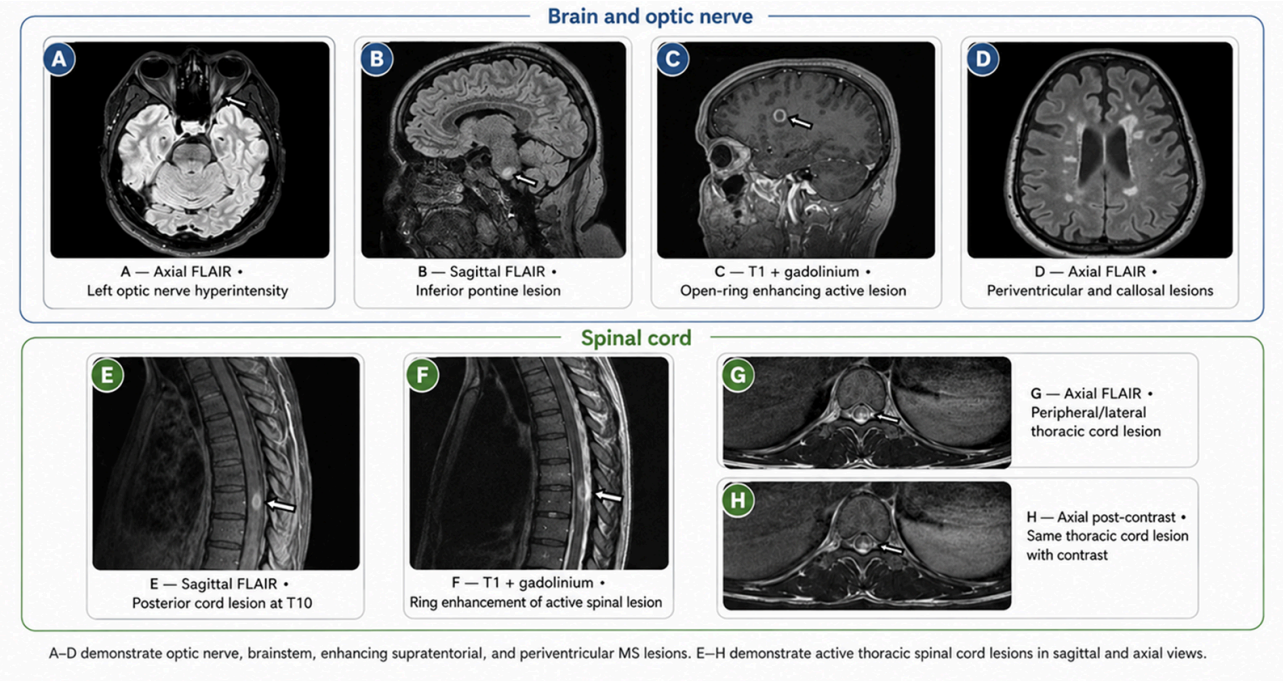


Figure 2- MRI sequences showing MS lesions in typical regions in the central nervous system (CNS), including optic nerve, brain stem, periventricular, and spinal cord. **(A)** Axial FLAIR sequence showing a hyperintense signal on the left optic nerve in a 35 year old patient with clinically isolated syndrome who presented with left optic neuritis, **(B)** Sagittal FLAIR sequence demonstrates a typical MS lesion in the left inferior pons in a 21 year old woman with newly diagnosed MS, **(C)** T1 Gadolinium sequence in the same patient shows a MS lesion with open ring brain enhancement in the supratentorial brain consistent with an active MS lesion, **(D)** Axial FLAIR sequence shows several typical periventricular and corpus callosum lesions in a 54 year old patients with established diagnosis of relapsing remitting MS (RRMS), **(E)** Sagittal FLAIR MRI of spinal cord demonstrates a posterior cord lesion at T10 in a 28 year old patient with transverse myelitis as first presentation of RRMS, **(F)** T1 Gadolinium sequence showing ring enhancement indicative of an active lesion and **(G, H)** Axial FLAIR sequences of the same lesion without and with contrast demonstrating a thoracic cord lesion occupying the peripheral/lateral aspect of the cord, a classic finding for MS.

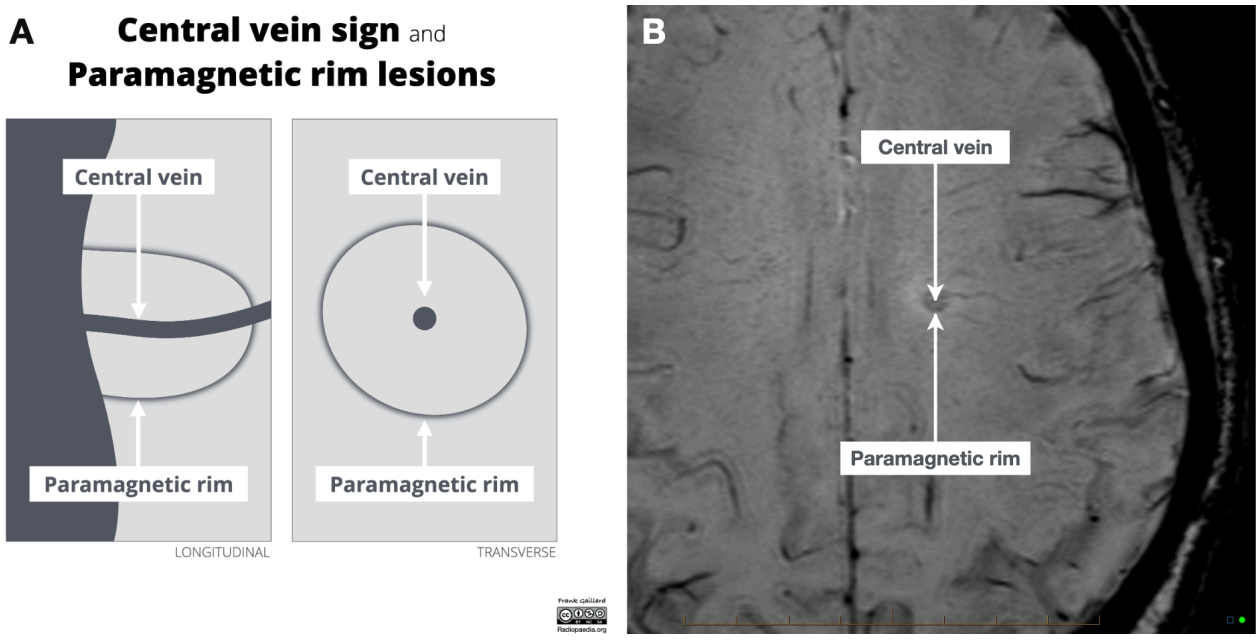


Figure-3. A) A schematic showing the central vein sign and paramagnetic rim in a typical MS lesion, B) Axial Susceptibility-Weighted Imaging (SWI) showing ovoid lesion in left centrum semiovale with c*entral vein sign* and an '*iron rim*' of hemosiderin (Taken from: https://radiopaedia.org/cases/central-vein-sign-and-paramagnetic-rim-lesion-illustration?lang=us, https://radiopaedia.org/articles/paramagnetic-rim-lesion?lang=us). Case credit to Frank Gaillard.

Neuropsychiatric aspects of Multiple Sclerosis (MS)

Neuropsychiatric symptoms are common and clinically significant in MS. They often emerge early in the disease course (sometimes before the first demyelinating event) and contribute to the functional decline and reduced quality of life [67,68]. Cognitive impairment affects approximately 40–70% of patients. The most common affected domains are information processing speed, working memory, executive function, and episodic memory[69,70]. Cognitive deficits correlate strongly with whole-brain atrophy and cortical and deep gray matter volume loss (e.g., thalamus)[71,72]. Mood disorders are highly prevalent in MS. The lifetime rate of major depression approaches 30–50%, and anxiety disorders affect more than 30% of patients[73–75]. Psychiatric symptoms are often underdiagnosed and undertreated in MS[75]. The American Academy of Neurology (AAN) recommends that clinicians consider the Beck Depression Inventory (BDI) and a 2-question screening tool to screen for depressive disorders in individuals with MS (Level C recommendation). The 2-question screen asks about depressed mood and diminished interest or pleasure; an affirmative response to either question constitutes a positive screen. Regarding the BDI, a cut-point of 13 produced 71% sensitivity, 79% specificity, 70% PPV, and 79% NPV for major depressive disorder (MDD). The General Health Questionnaire (GHQ) is possibly effective and may be considered for identifying individuals with broadly defined emotional disturbances (Level C). Clinicians may consider using the Center for Neurologic Study Emotional Lability Scale (CNS-LS) to screen for pseudobulbar affect (Level C) [76].Depression in MS is associated with worse cognitive performance, reduced treatment adherence and productivity, greater fatigue, and poor quality of life[77,78]. Social cognition deficits, including impaired emotion recognition and theory of mind, are increasingly recognized and may contribute to interpersonal and occupational difficulties in MS[79,80]. Fatigue—reported by up to 80% of patients—interacts bidirectionally with mood and cognition and is a major determinant of functional status and employment[81,82]. Emerging neuroimaging evidence establishes that depression, anxiety, and fatigue in MS are not purely reactive psychological responses but have distinct neuropathological substrates involving specific brain regions and networks. Several MRI studies demonstrate that depression in MS patients correlates with structural changes in the frontotemporal and limbic system[83]. Depressed MS patients show higher lesion volume in the temporal lobe, arcuate fasciculus, superior frontal, and parietal regions—areas representing projection zones of the basal limbic system[84,85] . MS patients with fatigue have significantly lower volumes of deep gray matter structures (e.g., bilateral thalamus, putamen, and nucleus accumbens) compared to healthy controls[86] . PET imaging studies have shown that regional microglial activation in the substantia nigra is linked with fatigue in MS[87]. Routine screening for mood disorders and anxiety is recommended as part of comprehensive MS care with attention to the bidirectional relationships between these domains and their shared and distinct structural underpinnings.

Treatments

The therapeutic landscape of MS has evolved dramatically in the past two decades. Over 20 disease-modifying therapies (DMTs) are currently approved for the treatment of MS. Current MS therapies are categorized into three groups by their efficacy: 1) low-efficacy (interferons, glatiramer acetate, and teriflunomide) reducing risk of relapses by ≈20–40%, 2) medium-efficacy (fumarates, S1P modulators, and cladribine) reducing risk of relapse by about 40-50%, and 3) high-efficacy (natalizumab, alemtuzumab, ocrelizumab, ofatumumab and ublituximab) reducing risk of relapses by 50% and more[88,89]. Early use of high-efficacy DMTs is preferred to prevent irreversible damage and long-term disability accumulation[90]. High-efficacy DMTs carry greater risks (e.g., infections,

infusion reactions) and require careful monitoring[91]. Most of the current treatments are approved and effective for RRMS, and treatment options for progressive MS remain very limited[92]. In addition to disease-modifying treatments, symptom management plays a key role in the optimal care of MS patients. Despite recent advances in MS immunotherapy, DMTs have modest effect on neuropsychiatric manifestations such as depression, anxiety, and fatigue[93–95]. Evidence-based guidelines recommend routine screening and treatment of depression and anxiety using pharmacotherapy (e.g., SSRIs), exercise, cognitive-behavioral therapy (CBT), and mindfulness-based approaches[96]. An individualized approach is recommended when choosing an antidepressant for patients with MS. SSRIs (e.g., sertraline, fluoxetine, escitalopram) are usually first-line treatments, but may worsen sexual dysfunction, which is already common in MS [97]. SNRIs (e.g., duloxetine, venlafaxine) offer dual benefit in patients with comorbid neuropathic pain [98]. Bupropion may be considered when fatigue is prominent, as it is activating and has minimal sexual side effects. However, it lowers the seizure threshold [99]. Mirtazapine is useful for patients with insomnia and weight loss, but its sedating properties may exacerbate MS-related fatigue [100]. Tricyclic antidepressants (TCAs) should be avoided as the first treatment option and used with caution as their anticholinergic effect may worsen cognitive dysfunction, urinary retention, and constipation symptoms of MS [97]. Certain important drug-drug interactions exist between some MS treatments and commonly used neuropsychiatric medications. Monoamine oxidase (MAO) inhibitors such as selegiline, phenelzine, and linezolid are contraindicated in MS patients taking ozanimod (a S1P receptor modulator). There was initial theoretical concern about serotonin accumulation when combining ozanimod with SSRIs/SNRIs. However, the DAYBREAK open-label extension trial (n=2257, of whom 274 used an SSRI/SNRI concurrently with ozanimod) found no increase in adverse events related to serotonin accumulation [101]. Combining QT-prolonging antidepressants (e.g. TCA, high-dose citalopram) with fingolimod and Siponimod increase cardiovascular risks, including bradycardia and AV block. Patients may require close cardiac monitoring (ECG to monitor Q-T interval) if combination therapy cannot be avoided [102,103].

Cognitive rehabilitation and compensatory strategy training help to improve processing speed and executive function[104]. Fatigue in MS is often multifactorial; other notable causes for fatigue include low mood, poor sleep, medication side effects, and medical conditions such as anemia and thyroid disease. Pharmacologic options such as modafinil and stimulants are often used in clinical practice with variable efficacy. Evaluation by an occupational therapist can help develop individualized behavioral strategies and practical energy-conservation techniques to optimize daily functioning[105] (Table-2) Optimal care for MS is multidisciplinary and requires integrating neurology, psychiatry, rehabilitation, and psychosocial support[106].

Table 2. Summary of common psychiatric symptoms and conditions in MS and the current evidence-based management strategies.

Condition	Pharmacological Treatment	Non-Pharmacological Treatment	Key Evidence / Notes	References
Depression	SSRIs (e.g., sertraline, fluoxetine), SNRIs; sertraline showed similar efficacy to CBT in a comparative trial (mean dose ~139 mg/d)[1]	CBT (in-person, telephone, or internet-delivered); tailored CBT showed clinically meaningful reductions in BDI-II scores (adjusted OR 3.62, p=0.01)[2]	Some MS treatments (corticosteroids and interferons) may cause depression[3,4], AAN guideline (Level C) supports telephone-administered CBT; pharmacotherapy is widely used, but MS-specific RCT evidence remains limited (LevelU)[5]	1. Mohr D.C et al, J Consult Clin Psychol. 2001 Dec;69(6):942-9 2. Kirapoulos L.A et al, J Affect Disord. 2026 Oct 1;410:121917 3. Pinto E.F, Curr Neuropharmacol. 2016;14(7):743-8 4. Morrow S.A. J Affect Disord. 2015 Nov 15:187:142-6 5. Minden SL et al, Neurology. 2014 Jan 14;82(2):174-81
Anxiety	SSRIs/SNRIs (first-line per general psychiatry guidelines); no MS-specific pharmacotherapy RCTs with robust evidence[1]	CBT (individual or group; in-person or internet-delivered); internet-CBT showed 30% avg. reduction in GAD-7 (g=0.37)[2]; structured exercise programs also reduce anxiety[3,4]	MS-specific pharmacotherapy trials are lacking; management follows general psychiatry recommendations; CBT plus relaxation training showed large effect sizes (d=0.85, p<0.05)[1,5]	1. Minden SL et al, Neurology. 2014 Jan 14;82(2):174-81 2. Gandy M et al, J Affect Disord. 2026 Jun 15:403:121403 3. Fahy A et al, PLoS One, 2025 Nov 10;20(11):e0336493 4. Flemig K.M et al, Mult Scler. 2021 Dec;27(14):2267-2279 5. Foley F.W et al, J Consult Clin Psychol 1987 Dec;55(6):919-22
Pseudobulbar affect (PBA)	Dextromethorphan/quinidine (20/10 mg BID) (FDA-approved); reduced PBA episode rate by ~49% vs placebo[1]; amitriptyline (limited data, n=12)[2]	–	DM/Q is the only FDA-approved treatment for PBA (AAN guidelines, Level C), well tolerated, with dizziness as the main dose-related side effect; other drugs (e.g., SSRIs, TCAs) are used in clinical practice. There are no randomized controlled trials of these other agents[3]	1. Pioro E.P et al, Ann Neurol. 2010 Nov;68(5):693-702. 2. Schiffer R.B et al, N Engl J Med. 1985 Jun 6;312(23):1480-2 3. Minden SL et al, Neurology. 2014 Jan 14;82(2):174-81

Condition	Pharmacological Treatment	Non-Pharmacological Treatment	Key Evidence / Notes	References
Cognitive impairment	Stimulants (L-amphetamine, modafinil) show benefits in selective cognitive domains[1-3]; donepezil and memantine did not show efficacy in RCTs[4,5]	Cognitive rehabilitation: Modified Story Memory Technique (Class I evidence; medium-to-large effect on verbal learning); computerized programs (RehaCom, BrainHQ, Attention Process Training) show small-to-large effects[6]	Disease-modifying therapies have not demonstrated clear cognitive benefits (evidence limited to uncontrolled observational studies)[7]; cognitive training is helpful, but the effects may wane, suggesting a need for booster sessions[6,8]	1. Morrow S.A et al, J Neurol. 2009 Jul;256(7):1095-102 2. Ford-Johnson L et al, Rehabil Psychol. 2016 Feb; 61(1):82-91 3. Sumawsky J.F et al, Mult Scler. 2011 Sep;17(9):1141-5 4. Krupp L.B et al, Neurology. 2011 Apr 26;76(17):1500-7 5. Lovera J.F et al, Mult Scler. 2010 Jun;16(6):715-23 6. Benedict R et al, Lancet Neurol. 2020 Oct;19(10):860-71 7. Landmeyer N.C et al, Neurology. 2020 Jun 2;94(22):e2373-e2383 8. Lampit A et al, Neurorehabil Neural Repair. 2019 Sep;33(9):695-706
Fatigue	no FDA-approved pharmacotherapy for MS fatigue, some studies support off label use of Modafinil (100–200 mg/d)[1-3]; amantadine also used off-label (200mg/d)[4]	CBT (telephone-delivered or in-person); COMBO-MS trial showed CBT, modafinil, and combination therapy all produced clinically meaningful fatigue reduction (>60% of participants improved); CBT preferred when sleep hygiene is poor[1]	NICE guidelines recommend modafinil; CBT effects maintained at 24-week follow-up; sleep hygiene moderates treatment response[5]	1. Braley T et al, Lancet Neurol. 2024 Nov;23(11):1108-18 2. Rammohan K.W et al, J Neurol Neurosurg Psychiatry. 2002 Feb;72(2):179-83 3. Lange R et al, J Neurol. 2009 Apr;256(4):645-50 4. Krupp L.B et al, Neurology. 1995 Nov;45(11):1956-61 5. https://www.nice.org.uk/guidance/ng220
Bipolar disorder (BD)	Mood stabilizers (lithium, valproate), atypical antipsychotics (per general psychiatry guidelines)[1]	–	Lifetime prevalence of BD in MS is ~13% vs 1–4.5% in general population[2]; no MS-specific treatment trials exist; management follows standard psychiatric practice; corticosteroids may precipitate manic symptoms[1, 3]	1. Minden SL et al, Neurology. 2014 Jan 14;82(2):174-81 2. Joffe Rt et al, Arch Neurol. 1987 Apr;44(4):376-8 3. De Bock M et al, World J Biol Psychiatry. 2024 Mar;25(3):161-174
Psychosis	Use of atypical antipsychotics (per general psychiatry guidelines)[1]	–	Prevalence 2–3% in MS vs 1.8% general population[2]; corticosteroid and interferon-β may induce psychosis[3]; AAN guideline notes insufficient evidence for MS-specific treatment recommendations (Level U)[1]	1. Minden SL et al, Neurology. 2014 Jan 14;82(2):174-81 2. Patten S.B et al, Neurology. 2005 Oct 11;65(7):1123-5 3. Kim J.S et al, J Clin Neurol. 2024 Feb 26;20(2):153-165

Chapter Summary

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) with both inflammatory (relapses, focal lesions) and neurodegenerative components (brain atrophy, gradual worsening of symptoms).

Diagnosis of MS requires fulfilling certain diagnostic criteria, such as dissemination in space supported by MRI findings and CSF analysis (McDonald 2024 diagnostic criteria); it is important to exclude mimics (e.g., neuromyelitis optica, vascular, and other CNS inflammatory disorders).

Clinical phenotypes of MS: The most common form is relapsing remitting MS (RRMS). Primary Progressive MS (PPMS) and Secondary Progressive MS (SPMS) reflect progressive phenotypes of MS. Disability accrues via two mechanisms: Relapse-Associated Worsening (RAW) and Progression Independent of Relapses (PIRA).

Neuropsychiatric symptoms are core features of MS. They may precede or occur in parallel to neurological disability.

Cognitive impairment (40–70%) in MS primarily affects processing speed, working memory, and executive function, and it correlates with thalamic and cortical atrophy.

Mood disorders and fatigue are highly prevalent in MS: depression (30–50%), anxiety (>30%), and fatigue (≈80%) are major drivers of quality of life, adherence to medication, and occupational function.

Management of MS requires early initiation of disease-modifying therapy to limit inflammation-related injury and disability progression, plus routine screening and treatment of depression, anxiety, cognitive dysfunction, and fatigue within a multidisciplinary model.

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