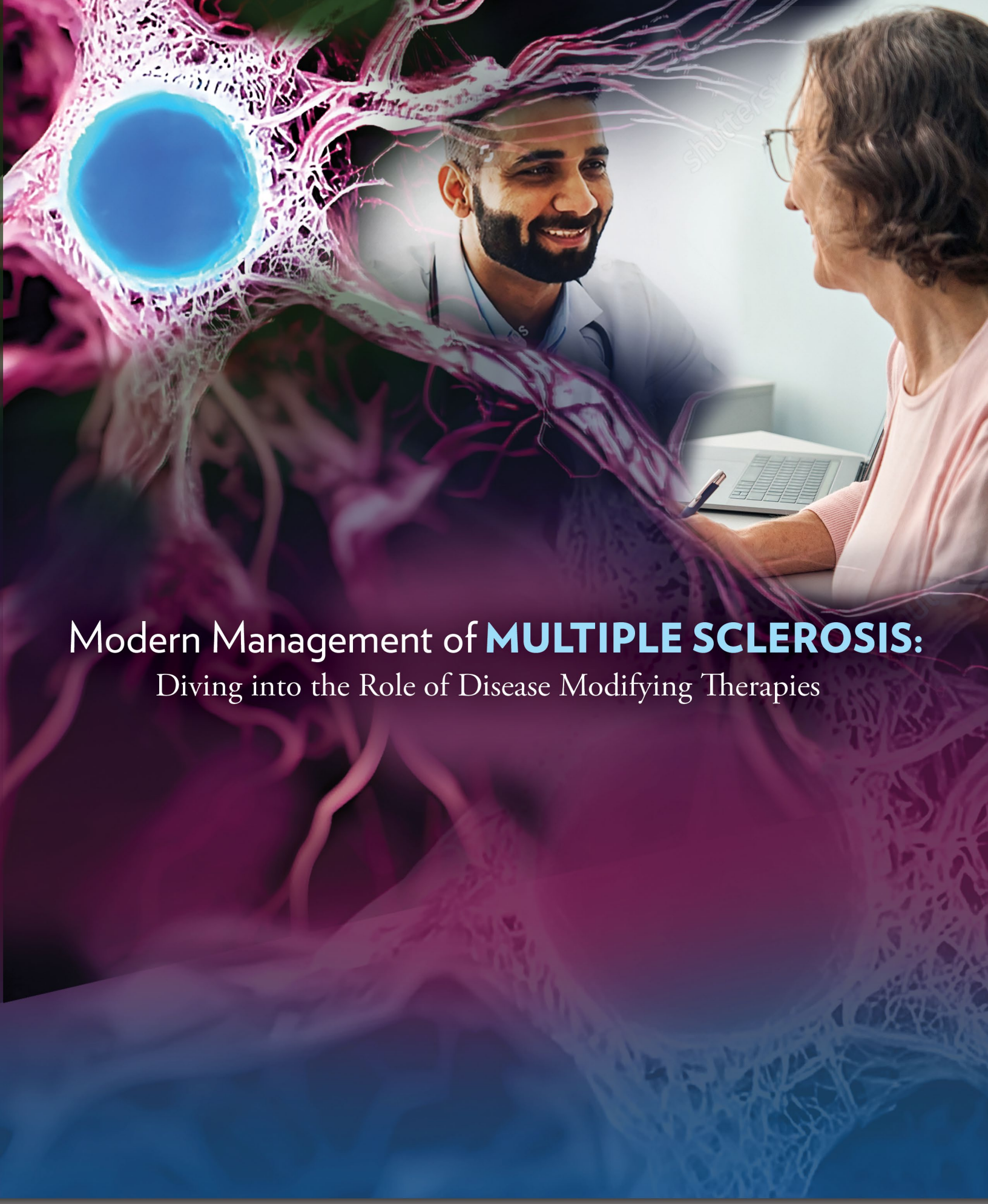

Modern Management of **MULTIPLE SCLEROSIS:**

Diving into the Role of Disease Modifying Therapies

MED LEARNING GROUP

This activity is provided by Med Learning Group.
This activity is supported by an educational grant from Novartis.

Modern Management of Multiple Sclerosis: Diving into the Role of Disease Modifying Therapies

PROGRAM CHAIR
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PROGRAM OVERVIEW

Multiple sclerosis is a chronic, immune-mediated disease of the central nervous system that leads to progressive neurological disability and significant reductions in a patient's quality of life. While the diagnosis of MS has improved, difficulties remain in recognizing certain forms of MS and selecting the appropriate treatment approach. The treatment landscape for MS has rapidly evolved over the past two decades to include a number of disease-modifying therapies, which, while highly significant in their ability to slow disease progression and improve quality of life, nonetheless still face challenges related to suboptimal implementation and adherence. This program will discuss the pathophysiology of MS and its treatment implications, review current data on DMTs, describe evidence- and guideline-based treatment strategies, and help clinicians incorporate shared decision-making and collaborative care to improve outcomes in patients with MS.

TARGET AUDIENCE

This initiative is designed to meet the educational needs of neurologists, neuroimmunologists, nurse practitioners, and physician assistants involved in the diagnosis and management of patients with multiple sclerosis.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Describe the pathophysiology of multiple sclerosis (MS) and its implications for evolving treatment strategies
- Evaluate clinical data on current and investigational disease-modifying therapies (DMTs) and apply best practices for selecting appropriate treatments based on emerging efficacy and safety endpoints
- Develop treatment approaches to prevent or manage adverse effects associated with DMTs
- Implement evidence-based practices, including shared decision-making and collaborative care, to improve outcomes for patients with MS

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Faculty Member	Disclosures
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This activity is supported by an educational grant from Novartis.

Agenda

30 min.	**Didactic Review**
	Navigating the Treatment Landscape in Multiple Sclerosis (MS):
	• AAN Guidelines – initiating DMTs in MS
	• Issues in treatment-naïve patients with MS
	• Current DMTs (injectable, oral, monoclonal antibodies)
	• Choosing among DMTs
	• Current issues/questions
	  ○ Assessing efficacy and tolerability
	  ○ Treatment barriers and adherence
	  ○ Switching DMTs
	• Emerging DMTs (BTK inhibitors, frexalimab, CAR-T, etc)
	• Aging in MS
	• Summary

20 min.	**Case Discussions** A patient presents with new numbness and tingling that began in her feet and ascended to mid-waist over 7 days • Workup and diagnosis • Review of first-line treatment options The patient returns, now on treatment for >1 year; surveillance brain MRI shows 3 new lesions • What issues need to be evaluated? • Pros and cons of changing DMT • DMTs in pregnancy • Incorporate the patient preferences for shared treatment decision-making
10 min.	**Q&A and Post-Test**

Modern Management of Multiple Sclerosis: Diving into the Role of Disease Modifying Therapies

Patricia K. Coyle, MD, FAAN, FANA
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Disclosures

- **Dr Coyle** discloses the following:
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  - **Contracted research/grant support:** Cleveland Clinic, CorEvitas LLC, Genentech/Roche, NINDS, Sanofi Genzyme
  - **May reference the following off-label or investigational uses:** BTK inhibitors, CNS repair strategies
- During the course of this lecture, the presenter may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications
- All relevant financial relationships have been mitigated

This activity is supported by an educational grant from Novartis.

Learning Objectives

- Describe the pathophysiology of multiple sclerosis (MS) and its implications for evolving treatment strategies.
- Evaluate clinical data on current and investigational disease-modifying therapies (DMTs) and apply best practices for selecting appropriate treatments based on emerging efficacy and safety endpoints.
- Develop treatment approaches to prevent or manage adverse effects associated with DMTs.
- Implement evidence-based practices, including shared decision-making and collaborative care, to improve outcomes for patients with MS.

Modern Management of Multiple Sclerosis: Diving into the Role of Disease-Modifying Therapies

- Current treatment landscape
- DMT guidelines
- Assessing efficacy, tolerability
- Treatment barriers/adherence
- Switching DMTs
- Emerging DMTs

MS Revolution

- MS is a homogeneous continuum
- Biologic (vs clinical) definitions are needed
- All MS has 2 CNS inflammatory processes
  - Focal inflammation underlies relapsing MS
  - Smoldering intra-CNS inflammation with neurodegeneration underlies progressive MS
- Progression is the same process in all MS
- MS worsens by progression independent of relapse activity (PIRA) > relapse-associated worsening (RAW); aging, comorbidities, ↓ CNS reserve

CNS = central nervous system; MS = multiple sclerosis.

Current Treatment Landscape

- Personalized and ultimately precision-based approach
- Multiple DMTs
  - 10 MOA's
  - Multiple agents including generics, biosimiliars, brand name (>20 agents)
- Multifaceted therapeutic approach
  - Optimized management of symptoms, relapses
  - Enhance CNS reserve; manage comorbidity
  - DMTs
- Emphasis on early treatment, high efficacy

MOA = mechanism of action.

AAN Guidelines: Initiating MS DMT

- AAN endorses access to all DMTs; discuss at dedicated visit; evaluate/counsel on adherence
- Use shared decision-making, this is ongoing dialogue; understand readiness for treatment, AEs
- Realistic expectations; recognize new symptoms
- Counsel on comorbid disease, adverse health choices, drug interactions
- Offer DMT to patients with:
  - CIS with ≥2 MRI lesions
  - Active relapsing forms of MS
  - PPMS (ocrelizumab) who are likely to benefit
- Ongoing monitoring (includes reproductive plans)
- Endorse high-efficacy DMT for highly active MS

AAN = American Academy of Neurology; AE = adverse event; CIS = clinically isolated syndrome; MRI = magnetic resonance imaging; PPMS = primary progressive multiple sclerosis.

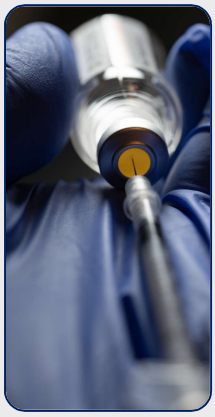
Rae-Grant A, et al. *Neurology*. 2018;90:777-788.

Issues for Treatment-Naïve MS

- Education, realistic expectations
- Use of shared decision-making
- High efficacy is fine
- Treat-to-target concept
- Remember there is finite time to efficacy (10 weeks)
- Plans to monitor should be clear-cut

Rae-Grant A, et al. *Neurology*. 2018;90:777-788.

Current DMTs



Needle immunomodulators

Oral immunosuppressives

High-efficacy monoclonal antibodies

Audience Response Question

Which of the following is generally considered to be the highest efficacy class of DMT for MS?

a) Needle DMTs (eg, interferon-β, glatiramer acetate)

b) Fumarates (dimethyl, diroximel, monomethyl)

c) B-cell depleting agents (eg, ofatumumab, ocrelizumab)

Needle DMTs

Interferonβ

- INFβ-1b 250 mcg SC QOD
- INFβ-1a 30 mcg IM weekly
- INFβ-1a 22 or 44 mcg SC TIW
- Pegylated INFβ-1a 125 mcg SC or IM Q2W

Glatiramer acetate (GA)

- 20 mg SC QD and 40 mg SC TIW formulations
- Three products in US (brand and generics)

Attributes

- Immunomodulatory (not immunosuppressive); no progressive multifocal leukoencephalopathy
- Long-term experience
- Minimal safety and modest tolerability concerns
- Safest DMTs for pregnancy
- Recent GA anaphylaxis box warning

IFNβ = interferon beta; IM = intramuscular; Q2W = every 2 weeks; QD = once daily; QOD = every other day; SC = subcutaneous; TIW = three times a week.

Cocco E, et al. *Mult Scler*. 2015;21:433-441. Jokubaitis VG, et al. *Ann Neurol*. 2016:80:89-100. Cree BA, et al; University of California, San Francisco MS-EPIC team. *Ann Neurol*. 2016;80:499-510. Comi G, et al. *Lancet*. 2017;389:1347-1356.

Oral DMTs

S1P-receptor modulators

- Fingolimod 0.5 mg daily
- Second generation
  - Siponimod 2 mg and 1 mg QD
  - Ozanimod 1 (0.92) mg QD
  - Ponesimod 20 mg QD

Fumarates

- Dimethyl fumarate 240 mg BID (2 caps)
- Generic DMF
- Diroximel fumarate 462 mg BID (4 caps)
- Monomethyl fumarate 190 mg BID (4 caps)

Teriflunomide

- 7 mg, 14 mg PO daily

Cladribine

- 3.5 mg/kg (1.75 mg/kg annually x 2)

Attributes

- Convenient delivery (no needle)
- Efficacy as good or better than with injectables
- Cladribine is induction therapy

BID = twice daily; DMF = dimethyl fumarate; PO = by mouth (oral); S1P = sphingosine 1-phosphate.

Yang JH, et al. *Front Neurol*. 2022;13:824926.

Monoclonal Antibodies

Natalizumab (anti-α4 integrin)	Alemtuzumab (anti-CD52)	Anti-CD20s	Attributes
▪ 300 mg IV monthly	▪ 12 mg QD for 5 days, then 12 mg QD for 3 consecutive days no more than annually	▪ Ocrelizumab 600 mg IV or 920 mg SC Q6M ▪ Ofatumumab 20 mg SC Q4W (after loading x 3) ▪ Ublituximab 450 mg IV Q6M	▪ Highest efficacy

CD = cluster of differentiation; IV = intravenous; Q4W = every 4 weeks; Q6M = every 6 months.

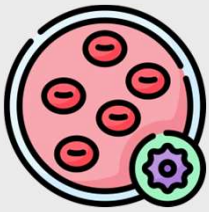
Yang JH, et al. *Front Neurol*. 2022;13:824926. Ocrelizumab/hyaluronidase (Ocrevus Zunovo®) PI, 8/2025 (www.gene.com/download/pdf/ocrevus_zunovo_prescribing.pdf). Ublituximab (Briumvi®) PI, 1/2026 (www.tgtherapeutics.com/label-prescribing-info/uspi-briumvi.pdf). URLs accessed 2/24/26.

DMT AEs

- Injection reactions
- WBC abnormalities
- ↑ Infection risk
- GI issues
- Liver issues

Current DMTs and Approach

- **Increasing use of anti-CD20s (B cell lytic agents) due to excellent control of relapsing MS**
  - However, there are concerns about long-term infection rate
- Major treatment needs recognized in 2 areas: progressive MS and CNS repair
  - Ocrelizumab is single approved agent for PPMS
  - Positive study for siponimod in SPMS
    - It worked in those patients closer to relapsing phase
    - Siponimod is approved for relapsing forms of MS



NINDS = National Institute of Neurological Disorders and Stroke; SPMS = secondary progressive multipole sclerosis.

NINDS. MS, 12/17/2025 (www.ninds.nih.gov/health-information/disorders/multiple-sclerosis-ms). Siponimod (Mayzent®) PI, 8/2025 (www.novartis.com/us-en/sites/novartis_us/files/mayzent.pdf). URLs accessed 2/24/26.

Choosing Between DMTs

- Important to determine what matters to the individual patient with MS
  - You want adherence/compliance
- Considerations involve:
  - Drug factors (efficacy, safety, AEs, monitoring, convenience, delivery, pregnancy impact)
  - Patient factors (adherence, age, comorbidities, risk tolerance)
  - MS factors (clinical subtype, disease severity, disease prognosis, genetics)
- High-efficacy agents should be used in highly active/poor prognosis MS
  - Optional in other cases

Current DMT Issues

- No practical treatment biomarkers (blood tests preferred)
- No guidance on optimal duration to treat (Can relapsing DMT be stopped?)
- Most DMTs have moderate efficacy
- Age-related factors
  - Response diminishes with advanced age
- Comorbid conditions are an ↑ factor
- Ongoing risk:benefit analysis required
- AEs may limit use
- CNS penetration, route of delivery, immune targets may be key

Assessing Efficacy and Tolerability

- Regular visits
- Defined laboratory monitoring; monitoring program explained to patient and agreed to ahead of time
  - Blood work (1–2 x annually)
  - Annual brain MRI without contrast, after baseline MRI at 3 to 6 months
  - Spinal imaging every few years
- Communication encouraged

Treatment Barriers/Adherence Issues

- Treatment barriers and adherence issues include:
  - Realistic expectations
  - Clear communication
  - Pregnancy issues
  - Risk-benefit analysis
  - Depression assessment
  - Trust
  - Preexisting bias
  - Lack of social support
  - Economics
  - Cognitive status
- Should be considered/discussed pre-DMT and ongoing post-DMT

AAN Guidelines: Switching DMT

- Discuss switch if over 1 year there is ≥1 relapse, increased disability on exam, or ≥2 new MRI lesions
- When switching for breakthrough activity, consider disease activity level, adherence, AE profile, MOA
- Consider injection fatigue, medication AEs, persistent laboratory abnormalities, pregnancy, persistent neutralizing mAbs against natalizumab
- Counsel on PML risk, infection/malignancy uncertainty, natalizumab antibodies; rebound (natalizumab → fingolimod)

mAb = monoclonal antibody; PML = progressive multifocal leukoencephalopathy.

Rae-Grant A, et al. *Neurology*. 2018;90:777-788

Treatment Issues: Switching

- Reason for switching matters and may include:
  - Breakthrough activity
  - Needle fatigue
  - Change in risk
  - Pregnancy issues
  - Tolerability
  - Lab abnormality

- Breakthrough activity warrants switch to new MOA, high-efficacy agent

Novel Potential DMTs

- Oral BTK inhibitors
- IV frexalimab (anti-CD40L mAb given monthly)
- Obexelimab
- CAR-T therapy (modify personalized T cells in a one-time infusion)
  - Can target more than 1 antigen
- Intranasal human anti-CD3 mAb
- Oral vidofludimus calcium (Nurr-1 activation, DHODH inhibition)
- CNS repair strategies
- GLP-1
- Aging

BTK = Bruton's tyrosine kinase; CAR-T = chimeric antigen receptor-T (cell); DHODH = dihydroorotate dehydrogenase; GLP-1 = glucagon-like peptide-1; Nurr-1 = nuclear-receptor-related 1 protein.

Oral BTK Inhibitor

- Targets B cells and myeloid cells
- Blocks cell activation but does not kill the cell
- Can penetrate into CNS and targets microglia
- BTK inhibitors differ in:
  - Selectivity
  - Mode of binding
  - Target occupancy
  - Inhibitor potency
  - CNS penetrance
- 4 approved for B cell cancers; 1 (remibrutinib) approved for urticaria

BTK Inhibitor Update

Evobrutinib

- 2 phase 3 relapsing trials failed (vs teriflunomide on ARR)

Tolebrutinib

- Positive phase 3 nonrelapsing SPMS HERCULES trial vs placebo (31% ↓ progression risk)
- 2 phase 3 relapsing trials negative vs teriflunomide (but CDW impact)
- 1 phase 3 PPMS PERSEUS negative vs placebo

Not FDA approved for MS
ARR = annualized relapse rate; CDW = confirmed disability worsening.

Montalban X, et al. *Lancet Neurol.* 2024;23:1119-1132. Fox RJ, et al. *N Engl J Med.* 2025;392:1883-1892. Oh J, et al. *N Engl J Med.* 2025;392:1893-1904. Sanofi press release, 12/15/2025 (www.sanofi.com/assets/dotcom/pressreleases/2025/2025-12-15-06-05-00-3205094-en.pdf). Accessed 2/25/26. Cree BAC, et al. *Curr Opin Neurol.* 2022;35:262-270.

BTK Inhibitor Update (cont.)

Fenebrutinib

- Positive phase 3 PPMS FENtrepid (noninferior to ocrelizumab; best impact on 9HPT)
- 2 phase 3 relapsing trials + vs teriflunomide; 51% to 59% ↓ in ARR

Remibrutinib

- 2 relapsing REMODEL 1, 2 phase 3 trials ongoing vs teriflunomide (April 2026)
- REMASTER phase 3 SPMS ongoing vs placebo
- RESHAPE phase 3B remibrutinib vs ocrelizumab: ocrelizumab switch to remibrutinib, or maintain

Not FDA approved for MS
9HPT = nine-hole peg test.

Roche PR, 3/1/2026 (https://www.roche.com/media/releases/med-cor-2026-03-02). Ciccone I. *NeurologyLive*. 11/12/2025 (www.neurologylive.com/view/fenebrutinib-hits-key-phase-3-marks-relapsing-primary-progressive-ms). Wiendl H, et al. *Neurology*. 2022;98(18 suppl):2562. Novartis PR 2/19/2026 remibrutinib REMASTER (www.novartis.com/clinicaltrials/study/nct07225504). Ciccone I. *NeurologyLive*. 2/6/2026 (www.neurologylive.com/view/phase-3b-reshape-study-evaluates-risk-benefit-switching-from-ocrelizumab-btk-inhibitor-remibrutinibNeurologyLive). Novartis PR 2/19/2026 remibrutinib RESHAPE (www.novartis.com/clinicaltrials/study/nct06846281). Cree BAC, et al. *Curr Opin Neurol*. 2022;35:262-270. URLS accessed 2/26/26.

BTK Inhibitor Update (cont.)

Orelabrutinib

- Ongoing phase 3 PPMS, SPMS trials

BIIB091

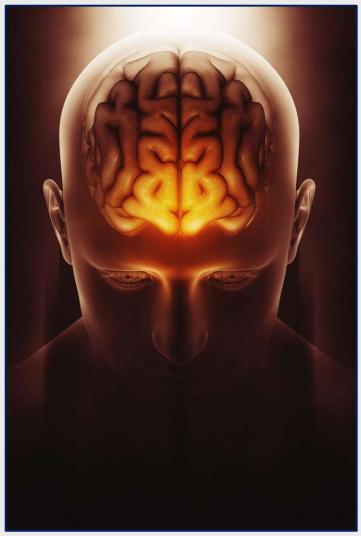
- Phase 2 trial FUSION for relapsing MS; monotherapy vs combination + DRF

Not FDA approved for MS
DRF = diroximel fumarate.

Zenas BioPharma PR, 10/8/2025 (https://investors.zenasbio.com/node/7571/pdf). MedPath. BIIB091 Phase 2 trial (https://trial.medpath.com/news/7782f77627ec1f07/biogen-completes-phase-2-trial-of-biib091-for-relapsing-multiple-sclerosis). Gallagher D. *NeurologyLive*. 2023 (www.neurologylive.com/view/phase-2-fusion-trial-btk-inhibitor-biib091-diana-Gallagher. Cree BAC, et al. *Curr Opin Neurol*. 2022;35:262-270. URLs accessed 2/26/26.

BTK Inhibitor Issues in MS

- No current approved DMT for MS
- Liver toxicity concern
- Is CNS penetration, microglia targeting critical?
- Potential uses
  - Monotherapy for progressive MS
  - Sequential B cell lytic DMT, followed by BTK inhibitor
  - Combination therapy



Frexalimab

- Antagonist second-generation mAb binds to human CD40L
  - Blocks CD40/CD40L costimulatory signaling pathway
  - Immune checkpoint for adaptive and innate immune responses
  - Critical for T cell-dependent Ab response; costimulation between T cells and APCs; suppresses effector function of macrophages, dendritic cells
  - Given IV 1200 mg monthly
- Positive phase 2 trial
- Phase 3 trials ongoing
  - FREXALT 1, 2 relapsing MS vs teriflunomide; FREVIVA nonrelapsing SPMS
  - FREXCITE (SC vs IV frexalimab)

Not FDA approved for MS

Ab = antibody; APC = antigen-presenting cell; BBB = blood-brain barrier; CMSC = Consortium of Multiple Sclerosis Centers.

Vermersch P, et al. *N Engl J Med.* 2024;390:589-600. Vermersch P, et al. CMSC 2023; abstract LB02. (https://cmsc.confex.com/cmsc/2023/meetingapp.cgi/Paper/9072). Krieger S, et al. CMSC 2024; poster DMT52 (https://congress.sanofimedical.com/s3fs-public/2024-05/Frexalimab%20in%20Relapsing%20Multiple%20Sclerosis%20and%20Non-Relapsing%20Secondary%20Progressive%20Multiple%20Sclerosis%20Design%20of%20Phase%203%20Frexalt%20and%20Freviva%20Trials.pdf?VersionId=cdoRyCnURvj4Q8BjtlO1rgcJ7AfILLP). Meglio M. *NeurologyLive.* 2/6/2026 (www.neurologylive.com/view/cd40l-inhibitor-frexalimab-enters-phase-3-frexite-trial-non-relapsing-secondary-progressive-multiple-sclerosis). URLs accessed 2/24/26.

Obexelimab

- Humanized bifunctional mAb that binds to CD19, FCγRIIb
- Inhibits B cell activation
- Given at 250 mg SC weekly
- Positive 12-week phase 2 MOONSTONE relapsing/active SPMS trial
  - ↓ contrast lesion at 8, 12 weeks by 95% (0.01 vs 0.23)

Not FDA approved for MS
Okuda DT, et al. ACTRIMS 2026; LB1 (www.abstractsonline.com/pp8/#!/21408/presentation/974). Accessed 2/24/26

Chimeric Antigen Receptor (CAR-T) Cell Therapy

- Personalized therapy; significant immunotherapy breakthrough
- Leukapheresis to collect specific immune cells that are then genetically modified using viral vector to express CAR gene
- Modified CAR cells are expanded to millions of cells
- Lymphodepleting chemotherapy regimen
- CAR cells are infused back into patient
- Risk of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS)
- Currently focused on B cell antigens (CD19, BCMA)
  - Can target NK cells, macrophages, NK-T, neutrophils
- Successful in B cell malignancies, refractory immune disorders (SLE, RA)
- Patient is hospitalized 1–2 weeks

Not FDA approved for MS
BCMA = B-cell maturation antigen; NK = natural killer; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.
Conway SE, Galetta K. *Neurotherapeutics*. 2025;22:e00558.

Foralumab

- Human anti-CD3 monoclonal delivered by nasal spray
- 10 patients with nonactive SPMS who failed B cells therapy (continued PIRA)
- In expanded access program, 10 nonactive SPMS foralumab ↓ fatigue in 60%
- TSPO PET ↓ over 6 months microglial activation on PET at 3 and 6 months
- Phase 2A randomized double blind placebo-controlled study of nonactive SPMS
  - N = 54 planned
  - 50 mcg, 100 mcg vs placebo
  - Change in microglial activation on PET at 3 months
  - Age 18 to 75 years
  - 3-week cycles (3x weekly for 2 weeks); at-home dosing

Not FDA approved for MS

PET = positron emission tomography; PIRA = progression independent of relapses; TSPO = 18-kDa translocator protein.

Chitnis T, et al. *Neurol Neuroimmunol Neuroinflamm*. 2026;13:e200543. Meglio M. *NeurologyLive*. Foralumab 9/25/2025 (www.neurologylive.com/view/phase-2a-inform-ms-trial-study-anti-cd3-agent-foralumab-non-active-secondary-progressive-ms). NCT06292923 INFORM-MS (https://clinicaltrials.gov/study/NCT06292923). URLs accessed 2/27/26.

Vidofludimus Calcium

- New selective second-generation DHODH inhibitor (IMU-838)
- Being studied in relapsing and progressive MS
- Ongoing phase 2 relapsing (EMPhASIS) and progressive (CALLIPER) trials
- Two phase 3 (ENSURE 1, 2) (N = 2100) relapsing MS trials

Not FDA approved for MS

Fox RJ, et al. *Ann Clin Transl Neurol*. 2022;9:977-987. Fox RJ, et al. *Neurol Neuroimmunol Neuroinflamm*. 2024;11:2200208. NCT03846219 (EMPhAS(S)(https://clinicaltrials.gov/study/NCT03846219). NCT05054140 (CALLIPER)(https://clinicaltrials.gov/study/NCT05054140). NCT05134441 (ENSURE-1)(https://clinicaltrials.gov/study/NCT05134441). NCT05201638 (ENSURE-2)(https://clinicaltrials.gov/study/NCT05201638). URLs accessed 2/27/26.

CNS Repair Strategies

- Cell transplantation (stem cells and others)
- Neurotrophic factors
- Immune modulation
  - Remyelinating autoantibodies, blocking inhibitory factors
- Removal of glial scar
- Gene transfer
- Neuroprotective/antioxidant agents
- Remyelinating/energy agents (high-dose biotin)

Not FDA approved for MS

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in MS

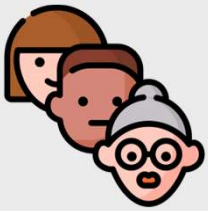
- Used in T2D, chronic weight management, cardiometabolic indications
- These agonists affect multiple neurobiologic pathways implicated in MS
- Can impact oxidative stress, mitochondrial dysfunction, glial activation, neuroinflammation, potentially myelin repair
- Trials starting in MS
  - TAG-MS: double blind, placebo-controlled randomized 96-week trial; 1° outcome brain volume
  - Observational study of ocrelizumab + GLP-1 agonists
- Nonacylated and nonpegylated agents cross BBB

Not FDA approved for MS
BBB = blood-brain barrier; T2D = type 2 diabetes mellitus.

Shirani A, et al. *ACTRIMS* 2026; Scientific Session 3. Kaye AD, et al. *Cureus*. 2024;16:e67232.

Aging in MS

- About 50% of MS patients are ≥50 years of age
  - Peak prevalence is 45–64 years of age in Europe/North America
- Progression linked to aging
- MS shows premature biologic aging
  - Shorter telomeres
  - ↑ senescent markers
  - Altered DNA methylation
  - Accelerated metabolic aging
  - ↑ oxidative stress
  - Marked gut dysbiosis



DNA = deoxyribonucleic acid.

Kabakibo TS, et al. *Neurol Ther*. 2026; online ahead of print. van der Walt A, et al. *Nat Rev Neurol*. 2025;21:432-448.

Aging in MS (cont.)

Senescence may be targeted in the future

- Senolytic agents (induce apoptosis)
- Senomorphics inhibit without apoptosis

Sutter PA, et al. *Curr Opin Pharmacol*. 2022;63:102184.

Summary

- Multiple DMT options are available for relapsing MS
- Early use of high-efficacy DMT is now encouraged
- Therapy is needed for progressive MS, CNS repair

Case Discussion

Case Discussion: Emily

- Emily is a 25-year-old white female who works as an accountant and has been married for 3 years without having children
- She has always been healthy and is on no medication
- Emily presents with numbness and tingling that began in her feet and rose to her mid-waist over 7 days
- Examination shows:
  - T 10 sensory level
  - Diminished vibration in her lower extremities
  - Spared reflexes

Case Discussion: Considerations for Emily

What are your concerns?

What workup would you do?

Case Discussion: Workup and Diagnosis

- Emily's MRI scan shows several >3 mm lesions in the brain (including periventricular and infratentorial) that do not enhance
- There are 3 spinal cord lesions at C6, T2 and T9; only the T9 lesion enhances
- Emily's CSF shows 10 CSF-specific oligoclonal bands
- IgG to aquaporin 4 and MOG are negative
- Otherwise, her bloodwork just shows low level of 25-hydroxyvitamin D
- Emily is diagnosed with relapsing MS

CSF = cerebrospinal fluid; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein.

Case Discussion: Polling Question

What initial therapy should be considered for Emily?

a) Anti-CD20 monoclonal antibodies

b) Plasmapheresis

c) High-dose steroids

d) Oral MS DMT

Case Discussion: Initial Therapy

- High-dose corticosteroid (1 g IV or PO daily for 3 to 7 days) is usually offered for initial CNS inflammatory demyelinating attack
- Oral taper is typically not required
- Contrast lesions support use
- This approach may speed up Emily's recovery, but it is not considered a DMT
- Because of excellent bioavailability, high-dose oral steroids can substitute for IV delivery

Case Discussion: Initial Therapy

Would you recommend that Emily start a MS DMT?

Why or why not?

Case Discussion: DMT for Emily

- Emily has active MS
- This is early in the course of her disease
- Data support that treating MS early gives better results
- High-efficacy DMT is typically preferred to escalation DMT

Case Discussion: Polling Question

How would you discuss options for MS DMT with Emily?

a) Recommend one DMT

b) Present MS DMTs in distinct groups

c) Give her a list and ask her to choose

d) Briefly present each DMT option

Case Discussion: Pregnancy

- Because Emily has plans for future pregnancy, she wants to go on safest DMT possible
- Emily starts on GA 40 mg SC 3 times weekly

Case Discussion: Follow-Up

- Emily returns for a routine follow-up visit after she has been on glatiramer acetate for about a year.
- Her recent surveillance brain MRI shows 3 new lesions; enhancement was not done
- Emily complains about cosmetic issues at her injection sites
- She is also having problems with her tennis game

Case Discussion: New Issues

What issues now need to be evaluated?

Case Discussion: Switching DMTs

What are the pros and cons for changing Emily's DMT?

Case Discussion: Polling Question

Which of the following would you switch to, and why?

a) Anti-CD20

b) Interferon beta

c) Oral S1P receptor agents

d) Natalizumab

Case Discussion: DMT Use When Considering Pregnancy

What DMTs are attractive choices for those patients considering pregnancy?

DMTs in Pregnancy

- Glatiramer acetate and IFNβ; patient could continue or stop therapy
- B cell lytic agents typically are stopped (have long-lasting effect)
- Oral cladribine allows initiation periods
- Natalizumab and fingolimod have rebound concerns; fingolimod is contraindicated in pregnancy

McConville K, Bove R. *CNS Drugs*. 2026;40:305-331.

Summary: Current Consensus on MS DMT Use

Generally agreed that DMTs have better effect early in disease course

- **Later DMT treatment leads to ↑ disability in longer term**
- **DMT should be started as early as possible (<3–6 months post CIS acceptable)**
- **Advantage to using high-efficacy DMT from the beginning (registry data)**

Wiendl H, et al. *Ther Adv Neurol Disord*. 2021;14:1-39. Trojano M, et al. *Curr Opin Neurol*. 2022;35:271-277.

Thank you!

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Multiple Sclerosis:
Diagnosis, Management, and Implications of Disease-Modifying Therapy

Resource	Address
Arachchige ASPM, El Choueiri J, Pellicanò F, et al. A review of multiple sclerosis: From pathophysiology to latest therapeutic advances. *AIMS Neurosci*. 2025;12:514-538.	https://pmc.ncbi.nlm.nih.gov/articles/PMC12782939/
Burkhard A, Toliver J, Rascati K. Association between multiple sclerosis disease severity and adherence to disease-modifying therapies. *J Manag Care Spec Pharm*. 2021;27:915-923.	https://pmc.ncbi.nlm.nih.gov/articles/PMC10391086/
Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: An expert opinion. *J Neurol*. 2022;269:5382-5394.	https://pmc.ncbi.nlm.nih.gov/articles/PMC9489547/
Henderson M, Horton DB, Bhise V, Pal G, Bushnell G, Dave CV. Initiation patterns of disease-modifying therapies for multiple sclerosis among US adults and children, 2001 through 2020. *JAMA Neurol*. 2023;80:860-867.	https://pubmed.ncbi.nlm.nih.gov/37428482/
Higuera L, Carlin CS, Anderson S. Adherence to disease-modifying therapies for multiple sclerosis. *J Manag Care Spec Pharm*. 2016;22:1394-1401.	https://pubmed.ncbi.nlm.nih.gov/27882830/
Khan G, Hashim MJ. Epidemiology of multiple sclerosis: Global, regional, national and sub-national-level estimates and future projections. *J Epidemiol Glob Health*. 2025;15:21.	https://pubmed.ncbi.nlm.nih.gov/39928193/
Langer-Gould AM, Smith JB, Gonzales EG, Piehl F, Li BH. Multiple sclerosis, disease-modifying therapies, and Infections. *Neurol Neuroimmunol Neuroinflamm*. 2023;10:e200164.	https://pubmed.ncbi.nlm.nih.gov/37813594/
Montalban X, Lebrun-Frénay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *Lancet Neurol*. 2025;24:850-865.	https://pubmed.ncbi.nlm.nih.gov/40975101/
Ragab S, Fouda BH, Sarhan AA, et al. Multiple sclerosis patients' journey delay in diagnosis and treatment: A multicenter study. *BMC Neurol*. 2025;25:377.	https://pubmed.ncbi.nlm.nih.gov/40898140/
Roberts M, Andrews A. An overview of multiple sclerosis: Diagnosis, causes and symptom management. *Nurs Stand*. 2025;40:40-45.	https://pubmed.ncbi.nlm.nih.gov/40785404/
Sabatino JJ Jr, Cree BAC, Hauser SL. New horizons for multiple sclerosis therapy: 2025 and beyond. *Ann Neurol*. 2025;98:317-328.	https://pmc.ncbi.nlm.nih.gov/articles/PMC12278195/
Samjoo IA, Drudge C, Walsh S, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: A systematic review and network meta-analysis. *J Comp Eff Res*. 2023;12:e230016.	https://pmc.ncbi.nlm.nih.gov/articles/PMC10508312/

Tafti D, Ehsan M, Xixis KL. Multiple sclerosis. *StatPearls*. Updated March 20, 2024.	https://www.ncbi.nlm.nih.gov/books/NBK499849/
Tenembaum S, Hartung HP. Multiple sclerosis: Advances and challenges in diagnosis. *Curr Opin Neurol*. 2025;38:197-204.	https://pubmed.ncbi.nlm.nih.gov/40145196/
Vollmer BL, Wolf AB, Sillau S, et al. Evolution of disease modifying therapy benefits and risks: An argument for de-escalation as a treatment paradigm for patients with multiple sclerosis. *Front Neurol*. 2022;12:799138.	https://pubmed.ncbi.nlm.nih.gov/35145470/
Wu X, Wang S, Xue T, et al. Disease-modifying therapy in progressive multiple sclerosis: A systematic review and network meta-analysis of randomized controlled trials. *Front Neurol*. 2024;15:1295770.	https://pubmed.ncbi.nlm.nih.gov/38529035/

Resources and Societies

Resource	Address
American Academy of Neurology	https://www.aan.com
Brain and Spine Foundation	https://www.brainandspine.org.uk/health-information/fact-sheets/multiple-sclerosis/
Multiple Sclerosis Association of America	https://mymsaa.org/
National Institute of Neurological Disorders and Stroke	https://www.ninds.nih.gov/health-information/disorders/multiple-sclerosis-ms
National Multiple Sclerosis Society	https://www.nationalmssociety.org/
World Health Organization	https://www.who.int/news-room/fact-sheets/detail/multiple-sclerosis

All URLs accessed February 26, 2026