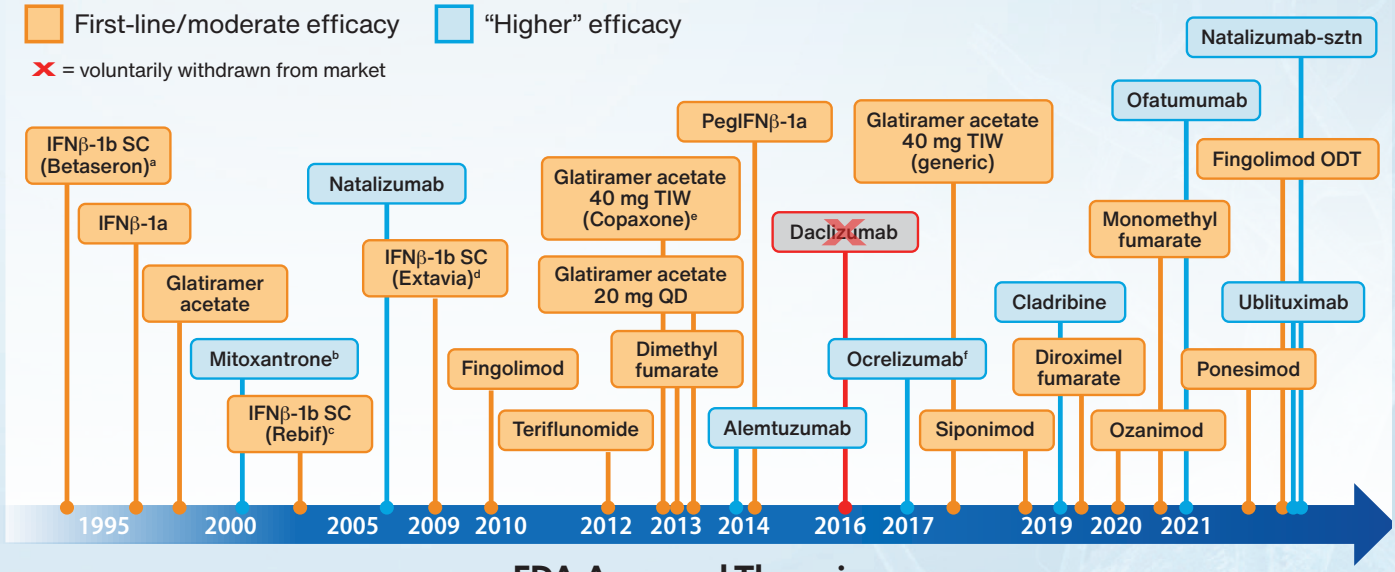
DISEASE-MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS

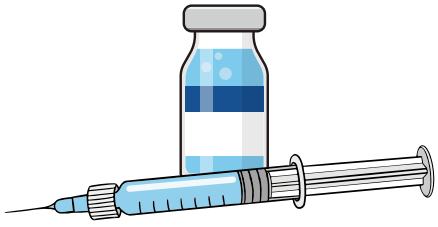
FDA-Approved Therapies for MS

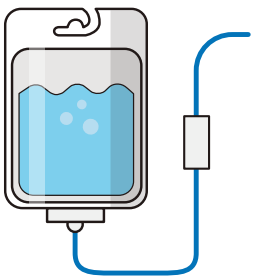


[a]Bayer HealthCare Pharmaceuticals. [b]Not used often in modern MS treatment. [c]Merck Serono. [d]Novartis Pharmaceuticals Corporation. [e]Teva Pharmaceutical Industries. [f]Rituximab also used off-label.

DMTs by Route of Administration

INJECTION	ORAL	IV INFUSION
Glatiramer acetate (SC)	Cladribine	Alemtuzumab
IFN β-1a (IM or SC)	Dimethyl fumarate	Natalizumab
IFN β-1b (SC)	Diroximel fumarate	Ocrelizumab
PegIFN β-1a (SC)	Fingolimod	Ublituximab
Ofatumumab (SC)	Ozanimod	
	Siponimod	
	Ponesimod	
	Teriflunomide	
	Monomethyl fumarate	





INJECTABLE THERAPIES

Agent	MOA	Indication	Administration Route/Schedule	Most Commonly Reported AEs	Special Warnings/ Precautions for Use	Monitoring	Relative Reduction in Relapses or Disease Progression
Glatiramer acetate	Not fully understood; increases production of anti-inflammatory cytokines (Th2) and decreases production of proinflammatory cytokines (Th1)	Relapsing MS (CIS, RRMS, or active SPMS)	SC 3 times weekly or once daily	Injection-site reactions, vasodilatation, rash, dyspnea, chest pain	Lipoatrophy, skin necrosis, anaphylaxis	No specific laboratory tests, skin surveillance	**ARR:** 29% vs placebo **CDW:** not investigated
IFN β-1a	Reduces antigen presentation and T-cell proliferation; alters cytokine and MMP expression and restores suppressor function	Relapsing MS (CIS, RRMS, or active SPMS)	IM once weekly or SC 3 times weekly	Injection-site reactions (high dose), flu-like symptoms, headache, abdominal pain, depression, transaminitis, hematologic abnormalities	Suicidal ideation, anaphylaxis, hepatic injury, provocation of rheumatic conditions, congestive heart failure, blood dyscrasias, seizures, autoimmune hepatitis, skin necrosis (high-dose)	CBC with differential, LFTs, TFTs, IFN neutralizing antibodies (if clinically warranted), skin surveillance	**ARR:** 32-33% vs placebo **CDW:** 37-38% vs placebo
IFN β-1b			SC every other day	Injection-site reactions, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, asthenia			**ARR:** 31% vs placebo **CDW:** no effect
PegIFN β-1a	Distinguished from other formulations by the addition of a PEG chain to the IFN β-1a molecule	Relapsing MS (CIS, RRMS, or active SPMS)	SC every 2 weeks	Injection-site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection-site pain, asthenia, injection-site pruritus, arthralgia	Same as above	Same as above	**ARR:** 36% vs placebo **CDW:** 38% vs placebo
Ofatumamab	Anti-CD20 mAb; binds the receptor on pre-B and mature B lymphocytes, resulting in antibody-dependent cellular cytolysis and complement-mediated lysis	Relapsing MS (CIS, RRMS, or active SPMS)	SC once monthly (after 3 weekly loading doses)	Upper respiratory tract infections, headache, injection-related reactions, local injection-site reactions	Infections, injection-related and hypersensitivity reactions, reduction in immunoglobulins	Immunoglobulin levels (before, during, and after treatment until B-cell repletion)	**ARR:** 50% vs teriflunomide **CDW:** 46% vs teriflunomide

Adapted for educational purposes only from Jakimovski D, et al. 2024.

ORAL THERAPIES

Agent	MOA	Indication	Administration Route/Schedule	Most Commonly Reported AEs	Special Warnings/ Precautions for Use	Monitoring	Relative Reduction in Relapses or Disease Progression
Cladribine	Purine nucleoside analog structurally resembling deoxyadenosine; causes apoptosis or autophagy in dividing and resting lymphocytes	Relapsing MS (RRMS and active SPMS; not CIS)	2-year course: daily for 4 or 5 days in months 1 and 2	Upper respiratory tract infections, headache, lymphopenia	**Black box warnings for malignancies, risk of teratogenicity**	CBC with differential including lymphocyte count, cancer screening (standard), infections	**ARR:** 58% vs placebo **CDW:** 33% vs placebo
Dimethyl fumarate	Anti-inflammatory immune response through activation of Nrf2-dependent and -independent pathways	Relapsing MS (CIS, RRMS, or active SPMS)	Twice daily	Flushing, abdominal pain, diarrhea, nausea	Anaphylaxis and angioedema, PML, HSV and other opportunistic infections, lymphopenia, liver injury	CBC with differential, LFTs	**ARR:** 53% or 44% vs placebo* **CDW:** 28% or 21% vs placebo*
Diroximel fumarate	Has a chemical structure distinct from that of dimethyl fumarate, but is converted to the same active metabolite, monomethyl fumarate	Relapsing MS (CIS, RRMS, or active SPMS)	Twice daily	Same as dimethyl fumarate with improved GI tolerability	Same as dimethyl fumarate	Same as dimethyl fumarate	**ARR:** 79.5% vs baseline relapse rate **CDW:** not available
Fingolimod	S1PR modulator (S1PR 1, 3, 4, and 5); suppresses the exit of lymphocytes from lymph nodes	Relapsing MS (CIS, RRMS, or active SPMS)	Once daily	Headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, pain in extremity	Bradycardia, heart block, hypertension, risk of infections (herpetic, PML, cryptococcal), lymphopenia (absolute lymphocyte count <200 cells/mL), transaminitis, macular edema, cutaneous malignancies, respiratory effects, PRES	First-dose cardiac monitoring, eye and skin examinations, CBC with differential, LFTs, VZV, IgG prior to starting medication, PFTs (if clinically indicated)	**ARR:** 54% vs placebo **CDW:** 30% vs placebo
Monomethyl fumarate	Major active metabolite of dimethyl fumarate and diroximel fumarate	Relapsing MS (CIS, RMMS, or active SPMS)	Twice daily	Flushing, abdominal pain, diarrhea, nausea	Anaphylaxis, angioedema, PML, herpes zoster and other serious opportunistic infections, lymphopenia, liver injury	Same as dimethyl fumarate and diroximel fumarate	FDA approval based on bioequivalence with dimethyl fumarate data
Ozanimod	Selective S1PR1 and S1PR5 modulator	Relapsing MS (CIS, RRMS, or active SPMS)	Once daily	Upper respiratory tract infections, hepatic transaminase elevation, orthostatic hypotension, urinary tract infections, back pain, hypertension	Infections, PML, bradyarrhythmia and atrioventricular conduction delays, macular edema, pulmonary function decline, liver injury, increased blood pressure, cutaneous malignancy, fetal risk	Same as fingolimod except no need for first-dose monitoring	**ARR:** 38% vs IM interferon β-1a **CDW:** 5% vs IM interferon beta-1a (ns)
Ponesimod	Selective S1PR1 and S1PR5 modulator	Relapsing MS (CIS, RRMS, or active SPMS)	Once daily	Upper respiratory tract infections, hepatic transaminase elevation, hypertension	Same as above	Same as fingolimod	**ARR:** 30.5% vs teriflunomide **CDW:** 17% vs teriflunomide (ns)
Siponimod	Selective S1PR1 and S1PR5 modulator	Relapsing MS (CIS, RRMS, or active SPMS)	Once daily	Headache, hypertension, transaminase increases	Same as above	Same as fingolimod	In SPMS: **ARR:** 55% vs placebo **CDW:** 26% vs placebo
Teriflunomide	Selectively and reversibly inhibits DHO-DH, a key enzyme in de-novo pyrimidine synthesis required by rapidly dividing lymphocytes	Relapsing MS (CIS, RRMS, or active SPMS)	Once daily	Headache, diarrhea, nausea, alopecia, ALT elevation	**Black box warnings for hepatoxicity and embryofetal toxicity**; lymphopenia; latent tuberculosis; neuropathy; hypertension	CBC with differential, LFTs (monthly for first 6 months), PPD prior to starting, washout (if needed)	**ARR:** 35% vs placebo **CDW:** 26% vs placebo

*For both ARR and CDW, the first is from the DEFINE trial and the second is from the CONFIRM trial.
Adapted for educational purposes only from Jakimovski D, et al. 2024.

IV THERAPIES

Agent	MOA	Indication	Administration Route/Schedule	Most Commonly Reported AEs	Special Warnings/ Precautions for Use	Monitoring	Relative Reduction in Relapses or Disease Progression
Alemtuzumab	Anti-CD52 mAb; results in depletion of CD52-bearing B and T cells	Relapsing MS including active SPMS (patients with inadequate response to ≥2 DMTs)	Year 1: 5 infusion days Year 2: 3 infusion days	Rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infections, fatigue, insomnia, upper respiratory tract infections, herpes viral infections, urticaria, pruritus, thyroid gland disorders, fungal infections, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, vomiting	**Black box warnings for autoimmunity, infusion reactions, stroke, and malignancies (REMS program);** infections (HSV, VZV, *Listeria*, PML), pneumonitis, cervicocephalic arterial dissection	Monthly CBC with differential, LFTs, urinalysis with urine cell counts, TFTs every 3 months	**ARR:** 49% vs interferon beta-1a **CDW:** 42% vs interferon beta-1a
Natalizumab	Anti-α4-integrin mAb; blocks α4-mediated adhesion of leukocytes on endothelial side of the blood-brain barrier to prevent transendothelial migration into the CNS	Relapsing MS (CIS, RRMS, or active SPMS)	Every 4 weeks	Headache, fatigue, arthralgia, urinary tract infections, lower respiratory tract infections, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, rash	**Black box warning for PML (REMS program);** infusion reactions, HSV, other infections, autoimmune hepatitis	CBC with differential, LFTs, serum JCV antibody (every 6 months), MRI, natalizumab antibodies (if clinically warranted)	**ARR:** 67% vs placebo **CDW:** 42% vs placebo
Ocrelizumab	Anti-CD20 mAb	Relapsing MS (CIS, RRMS, or active SPMS), PPMS	Initiation: days 1 and 15; maintenance every 6 months	Upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections	Severe infusion reactions, infections (PML, COVID-19), hepatitis B reactivation, questionable malignancies, immune colitis, pyoderma gangrenosum, babesiosis	Hepatitis B screening, CBC with differential, LFTs, PPD or tuberculosis spot/ QuantiFERON prior to starting, Ig levels over time	**ARR:** 46% vs interferon-beta 1a **CDW:** 40% vs interferon-beta 1a
Ublituximab	Anti-CD20 mAb	Relapsing MS (CIS, RRMS, or active SPMS)	Initiation: days 1 and 15; maintenance every 6 months	Infusion reactions, upper respiratory tract infections	Infusion reactions, infections, increased risk of hepatitis B reactivation, reduction in immunoglobulins, fetal risk	Hepatitis B screening, immunoglobulin levels (before, during, and after treatment until B-cell repletion)	**ARR:** 59% (ULTIMATE 1) and 49% (ULTIMATE 2) vs teriflunomide **CDW:** 16% vs teriflunomide (ns)

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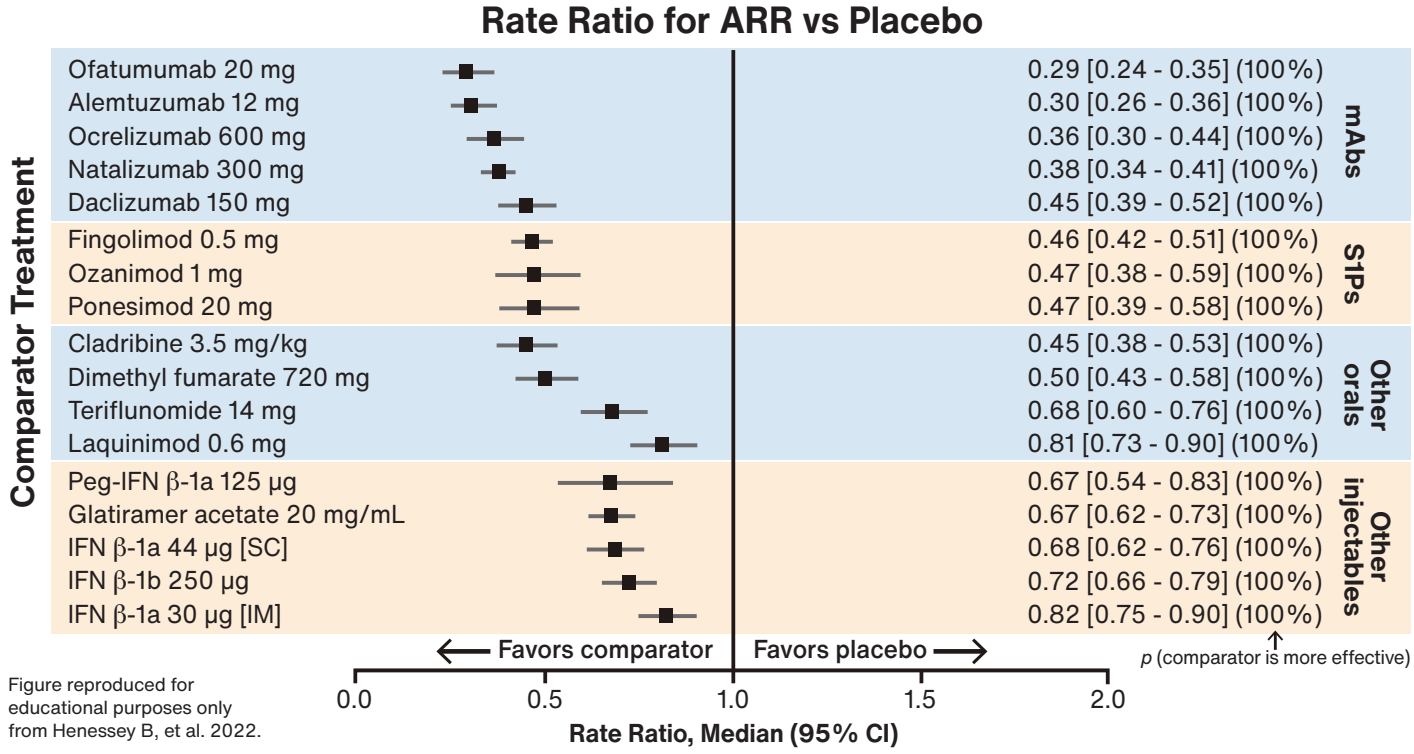
Comparative Efficacy of DMTs: ARRs



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Practices and Principles of Treatment With DMTs

Who should receive DMT?

- Everyone with a diagnosis of clinically definite RRMS should be offered DMT

Importance of early DMT:

- Start DMT as soon as possible after MS diagnosis for all patients with RRMS
- Observational data show DMT use reduces long-term risk of disease progression in MS
- DMTs may slow disability progression in RRMS patients, particularly in the short term (eg, 2 to 3 years)

Goals of DMT:

- Prevent MS relapses (attacks)
- Reduce neurological impairment and disability accumulation over time
- Minimize brain inflammation and injury

Effective monitoring and management of DMTs:

- Regular monitoring (clinical and subclinical) is central to managing MS
- Monitoring can improve adherence to DMTs
- Patient engagement is more likely with regular monitoring
- Regular monitoring can help identify subtherapeutic responses to treatment

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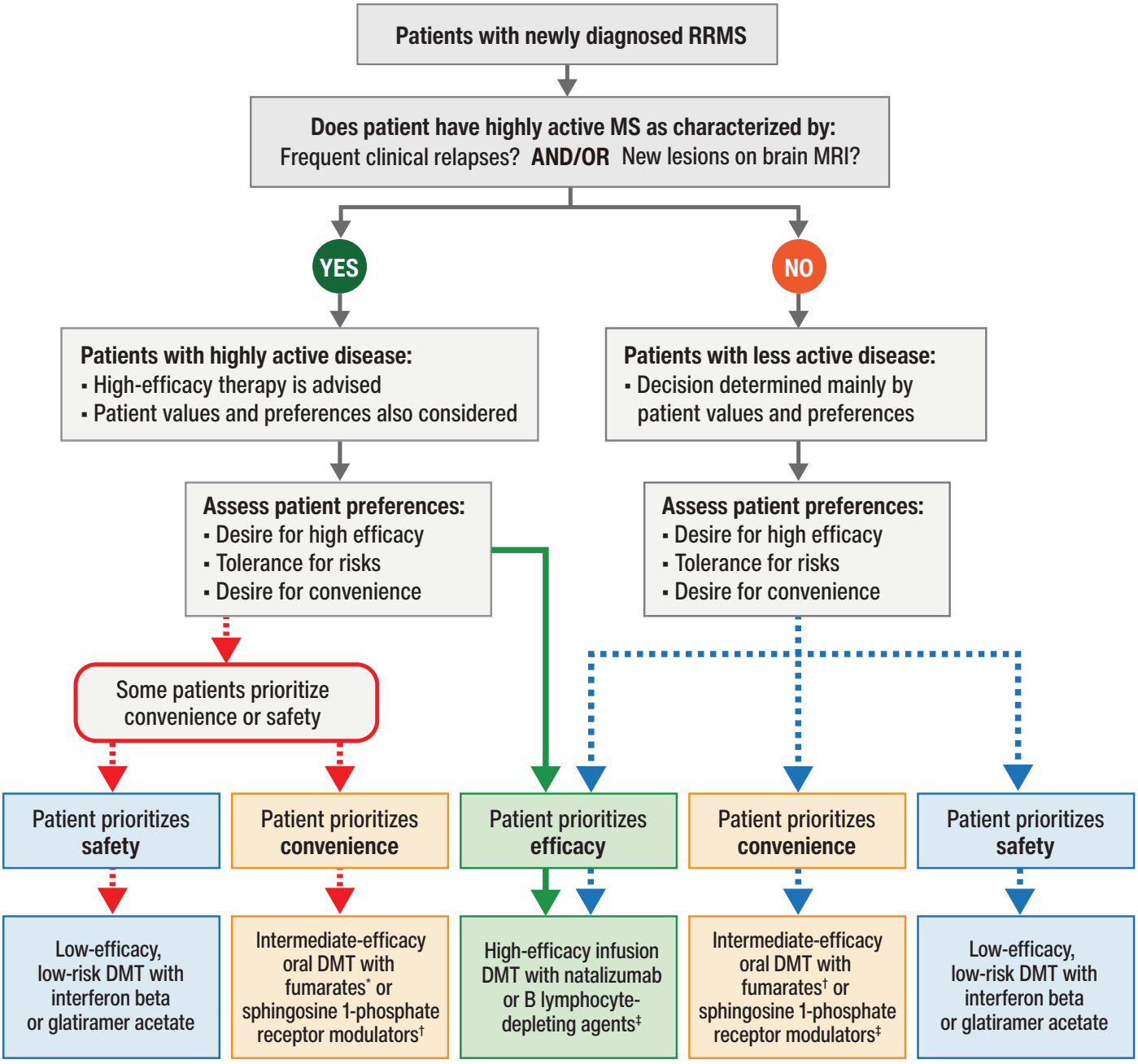
Initial DMT for RRMS



*Fumarates include dimethyl fumarate, diroximel fumarate, and monomethyl fumarate.
†Sphingosine 1-phosphate receptor modulators include fingolimod, siponimod, and ozanimod.
‡B lymphocyte-depleting agents include ocrelizumab, rituximab, ofatumumab, and alemtuzumab.

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Considerations for Initiating and Switching DMT

▪ Preferences ▪ Risk tolerance ▪ Comorbidities ▪ Reproductive status ***Vaccination status***	**Patient-related factors**	**Disease-related factors**	▪ Severity ▪ Phenotype ▪ Prognostic signs ▪ The risks of not treating or undertreating the disease itself
▪ Efficacy ▪ Safety[a] ▪ Tolerability ▪ Monitoring needed ▪ Dosing route and frequency	**Treatment-related factors**	**System-related factors**	▪ Insurance coverage ▪ Access to services

[a]JCV antibody status.

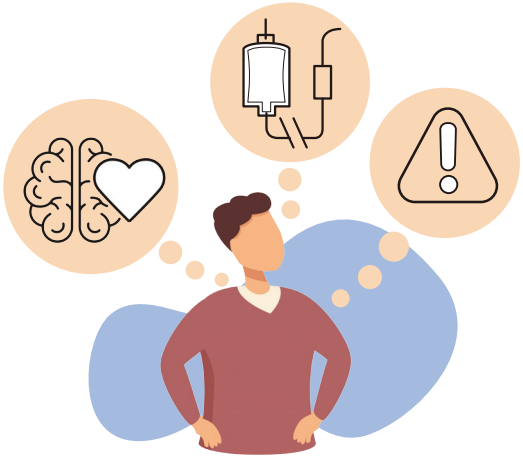
Additional Reasons to Consider Switching Treatments

- **Breakthrough disease activity (zero-tolerance policy?):**
  - Definite relapses
  - Examination changes suspicious for disability progression
  - MRI activity (new/enlarging T2 lesions, Gd lesions), even when asymptomatic
- **JCV antibody seroconversion**
- **Poor adherence**
- **Family planning**
- **Vaccination considerations**
- **Intolerable and severe medication side effects**

For detailed guidelines on starting, switching, and stopping DMTs in MS, scan the QR code

or visit the AAN Practice Guidelines at: https://www.aan.com/Guidelines/home/GuidelineDetail/898

Understanding Patients' Priorities



DMT decisions should be shared and well informed.

- Treatment priorities of the patient may differ from priorities of the MS care clinician
- People with MS often rank emotional well-being above functional status (vs neurologists)
- In medication selection, patients often rank route of administration as the #1 consideration
- A 1% risk of a serious side effect can reduce patient preference of a particular DMT by 5-fold
- Perceived benefits and risks of a DMT may depend on the way these treatments are presented to the patient

DISEASE-MODIFYING THERAPIES
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Abbreviations

AE: adverse event
ALT: alanine aminotransferase
ARR: annualized relapse rate
CBC: complete blood count
CDW: confirmed disability worsening
CIS: clinically isolated syndrome
CNS: central nervous system
DHO-DH: dihydro-orotate dehydrogenase
DMT: disease-modifying therapy
FDA: US Food and Drug Administration
Gd: gadolinium
GI: gastrointestinal
HSV: herpes simplex virus
IFN: interferon
IgG: immunoglobulin G
IM: intramuscular
IV: intravenous
JCV: John Cunningham virus
LFT: liver function test
mAb: monoclonal antibody
MMP: matrix metalloproteinase
MOA: mechanism of action
MRI: magnetic resonance imaging
MS: multiple sclerosis
ODT: orally disintegrating tablets
PEG: polyethylene glycol
PegIFN: pegylated interferon
PFT: pulmonary function test
PML: progressive multifocal leukoencephalopathy
PPD: purified protein derivative
PRES: posterior reversible encephalopathy syndrome
QD: daily
REMS: Risk Evaluation and Mitigation Strategy
RRMS: relapsing-remitting MS
S1PR: sphingosine-1-phosphate receptor
SC: subcutaneous
SPMS: secondary progressive MS
TFT: thyroid function test
Th1: T helper 1
Th2: T helper 2
TIW: 3 times weekly
VZV: varicella zoster virus

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