RWJBarnabas HEALTH

MULTIPLE SCLEROSIS (MS)

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A presentation for HealthTrust Members

Speaker Disclosures

- The presenter has no real or perceived conflicts of interest related to this presentation.

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Learning Objectives

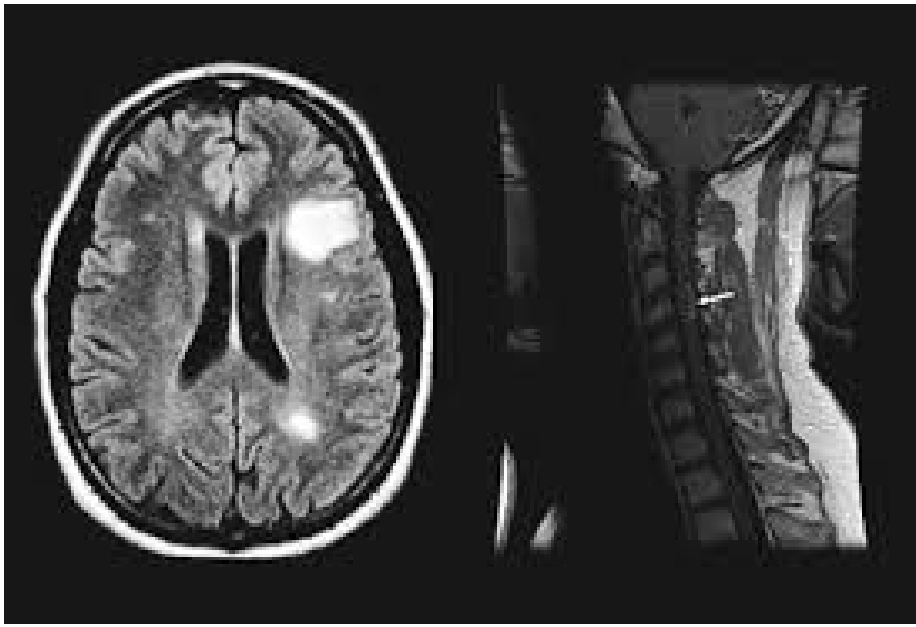
- Pharmacists & Nurses:
  - Describe immune dysregulation as pathogenesis of MS
  - Identify therapeutic goals and outcome measures for a patient started on MS therapy
  - Compare and contrast disease-modifying agents in terms of efficacy, safety, ease of administration, place in therapy, and patient-specific considerations

Learning Objectives

- Pharmacy Technicians
  - Describe risk factors and symptoms of MS
  - Identify routes of administration for disease modifying therapies for MS

Multiple Sclerosis

- Chronic, progressive autoimmune disease affecting the white matter of the central nervous system
- Diagnosis of exclusion
- Numerous affected areas of brain and spinal cord (CNS)-> **multiple** symptoms that accrue over time
- Characterized lesions developing over **location and time**
- No cure
- Associated with 7–10 year reduction in life expectancy



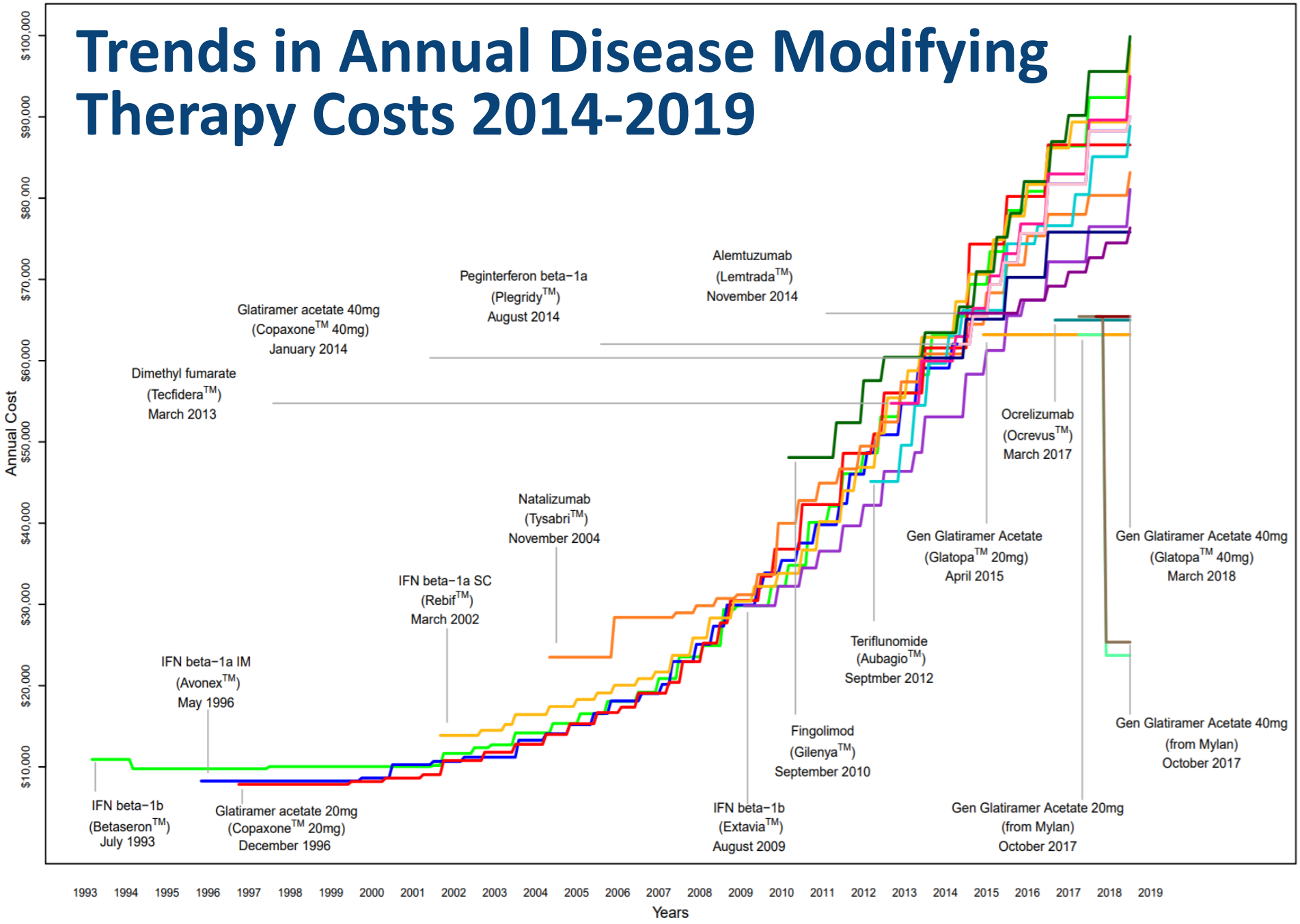
Steinman L, et al. S *Nat Rev Immunol* 2003;3(6):483-92.
Burkill S, et al. *Neurology* Aug 2017, 89 (6) 555-562.

Epidemiology

- Afflicts 2.5 million people worldwide
  - 500,000 patients in North America
  - 10,000 new cases per year
- $20,000–$100,000 annual treatment cost
  - Median cost of $88,853 in 2019
- Incidence
  - Typical age of onset 15 to 45 years
  - 1 in 200 women
  - More common in women ratio of 2-3:1 (women:men)

Ascherio A, et al. *Semin Neurol* 2008;28:17-28.
Hartung DM, et al. Leave Behind Access to MS Medications [Internet]. National MS Society. Washington, DC; 2019.

Trends in Annual Disease Modifying Therapy Costs 2014-2019



Hartung DM. Leave Behind Access to MS Medications [Internet]. National MS Society. Washington, DC; 2019 [cited 2019Oct28].

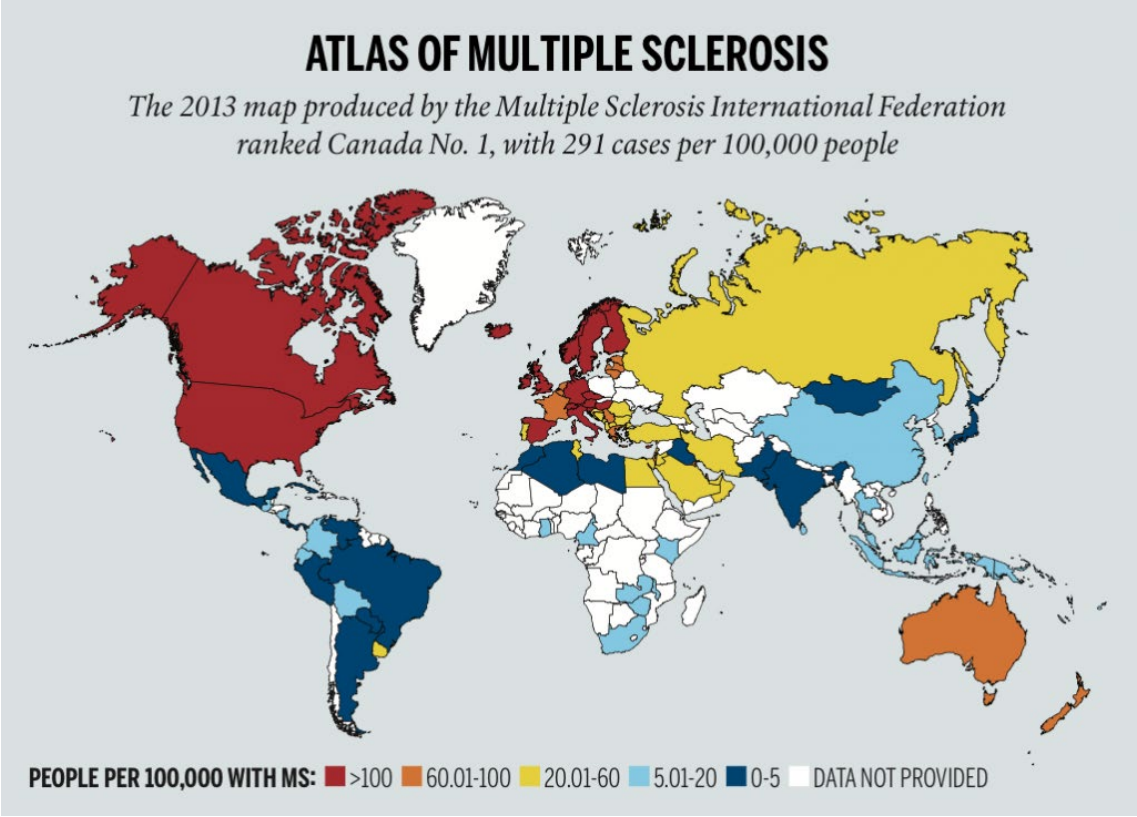
Etiology

- Overwhelming evidence that MS is a primary disorder of immune dysregulation
  - T and B cells are found within demyelinating lesions
  - Central nervous system (CNS)-antigen specific immune responses in MS patients
  - Disease responds to treatment with immune modulation
- Known genetic risk factors
  - Female (2-3:1)
  - Immunologically relevant genes (not regularly screened)
    - HLA-DRB1*15
    - Heterozygous 3:1 risk
    - Homozygous 6:1 risk
  - Single nucleotide polymorphisms
    - Over 200 associated with increased risk, closely related to regulating immune function

Source: Thompson AJ, et al. *Lancet Lond Engl*. 2018;391(10130):1622-1636.

Etiology

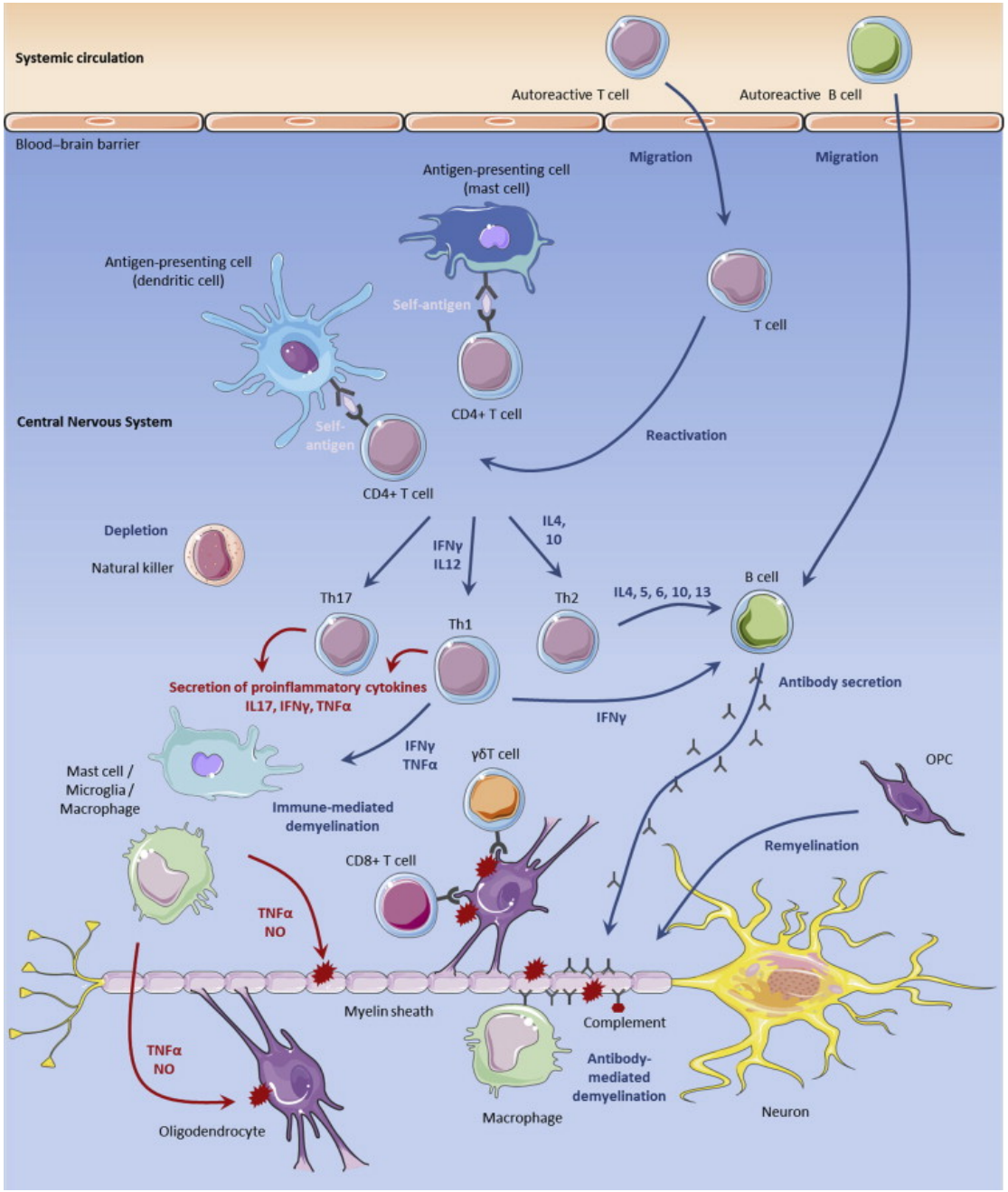
- Environmental
  - Epstein-Barr Virus
    - Doubles risk
  - Sun exposure
  - Low vitamin D
  - Geography
  - Smoking
  - Obesity
  - High salt intake
  - Urban environments



Sources: Evans C, et al. Neuroepidemiology. 2013;40(3):195-210.
Disanto G, et al. *Mult Scler Houndmills Basingstoke Engl*. 2013;19(10):1355-1358.
Kucukali C, et al. *NeuroMolecular Medicine* 2015;17:83-96.

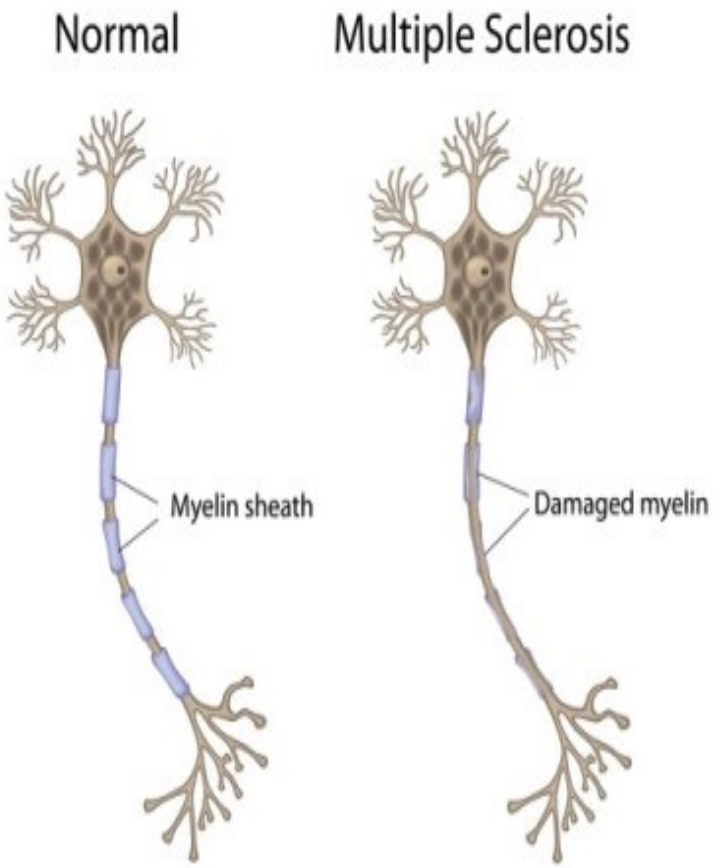
Pathophysiology

- B cells and T cells are activated in the plasma
- Cross the blood brain barrier
- Mediate cytokines and antibody production
- Attack oligodendrocytes leading to demyelination and axonal loss



Source: Steinman L, et al. S *Nat Rev Immunol 2003;3(6)*:483-92.

Demyelination



- Myelin Sheath made up of oligodendrocytes
- Demyelination inhibits normal impulse conduction AND renders the axons susceptible to damage, which becomes irreversible when they are severed
- Axonal damage correlates to disability

Source: Thompson AJ, et al. *Lancet Lond Engl*. 2018;391(10130):1622-1636.

Clinical Presentation

Demyelination & axonal damage

Primary Symptoms

Complications from Primary Symptom

Secondary Symptoms

Effect of MS on daily life

Tertiary Symptoms

Clinical Presentation

Primary Symptoms/signs	Secondary symptoms	Tertiary symptoms
Visual complaints/optic neuritis	Recurrent Urinary Tract Infections	Financial
Gait problems	Urinary calculi	Personal
Paresthesias	Decubiti	Social
Pain	Depression	Vocational
Spasticity	Upper Respiratory Infections	Emotional
Heat sensitivity (Uthoff phenomenon)	Poor nutrition	
Ataxia		
Speech difficulty		
Psychological/cognitive change		
Lhermitte's sign		
Fatigue/weakness		
Bowel/bladder dysfunction		
Sexual dysfunction		
Tremor		

Sources:Thompson AJ, et al. *Lancet Lond Engl.* 2018;391(10130):1622-1636.
Alexander RG, et al. *Neurology* Apr 2018, 90 (17) 777-788.

POLLING QUESTION 1:

All of the following are risk factors associated with the development of MS EXCEPT:

A. Epstein Barr Virus
B. Norwegian descent
C. Low Vitamin E
D. Smoking
E. Urban environment

QUESTION 1 RESPONSE:

All of the following are risk factors associated with the development of MS EXCEPT:

A. Epstein Barr Virus
B. Norwegian descent
C. **Low Vitamin E**
D. Smoking
E. Urban environment

Diagnostic Criteria

- Diagnosis of exclusion through clinical symptoms
  - Especially upon presentation with symptoms of MS
- Additional resources:
  - Magnetic resonance imaging (MRI) (not to be used in isolation)
    - Measures disease activity and progression
    - Lesion number, size and volume
  - Computed tomography (CT) (to rule out other conditions)
  - Cerebrospinal fluid (CSF) (to test for oligoclonal bands)
    - Indicate chronic inflammation within the CNS
- Document all signs & clinical certainty
  - To allow for review of diagnosis for later in life

Source: Alexander RG, et al. *Neurology* Apr 2018, 90 (17) 777-788.

Assessment Scales

- McDonald Criteria
  - Assists with diagnosis
    - Brain MRI, cerebrospinal (CSF), and clinical symptoms

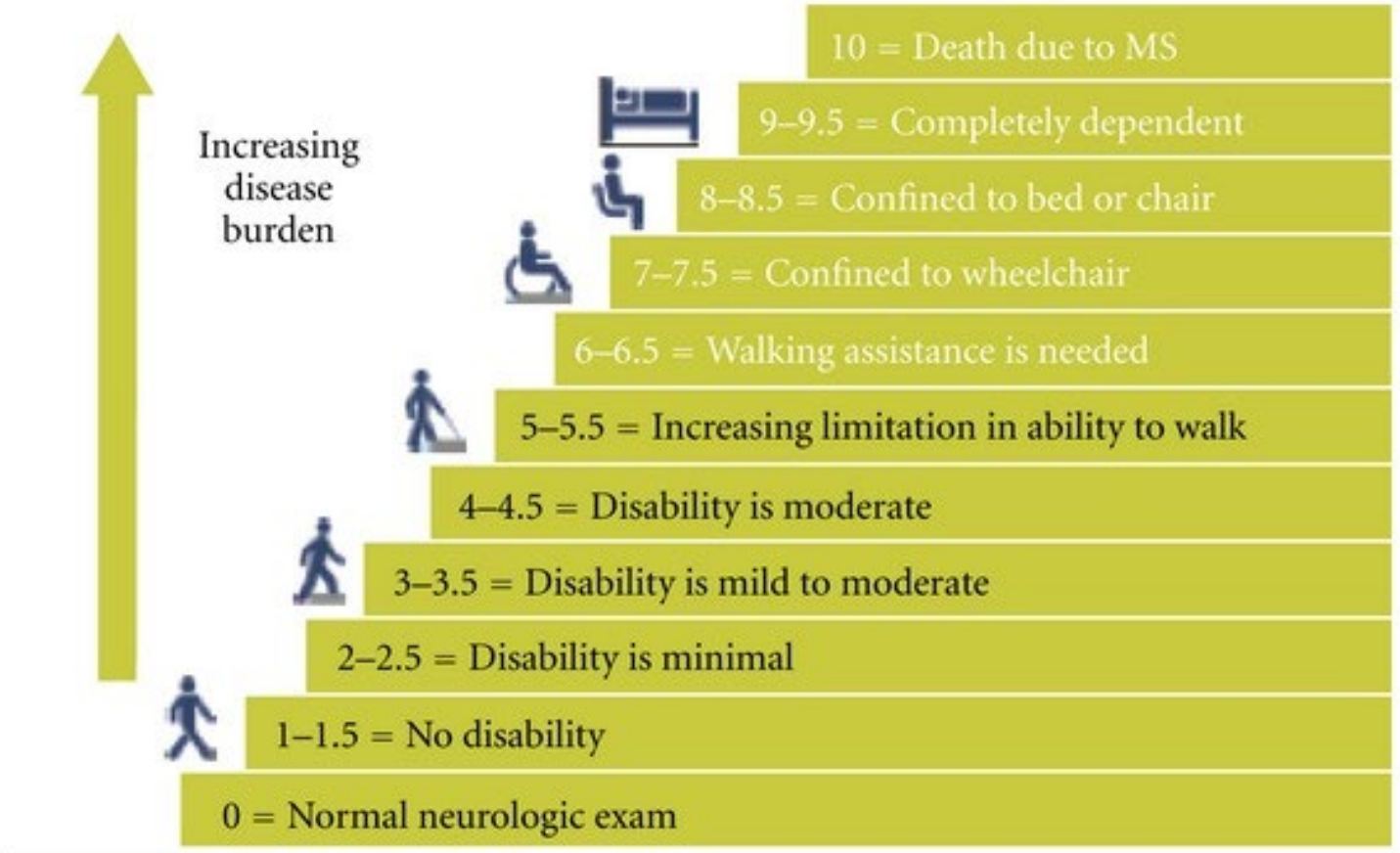
- Kurtzke Expanded Disability Status Scale (EDSS)
  - Evaluates neurologic functions
  - Limitations in measuring cognition, fatigue & affect
  - Value range: 0 (no disability) to 10 (death)
    - 6 (requires assistance to walk)

Sources: Polman CH, et al. *Ann Neurol* 2011;69:292-302.
Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173.

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
…in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
2 or more attacks and clinical evidence of 1 lesion	DIS shown by one of these criteria: • Additional attack implicating different CNS site • 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
1 attack and clinical evidence of 2 or more lesions	DIT shown by one of these criteria: • Additional clinical attack • Simultaneous presence of both enhancing and non-enhancing MS typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) • CSF oligoclonal bands
…in a person who has steady progression of disease since onset	
1 year of disease progression	DIS shown by at least two of these criteria: • 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) • 2 or more T2 spinal cord lesions • CSF oligoclonal bands

Source: Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173.

Extended Disability Severity Scale



EDSS indicates expanded disability status scale; MS indicates multiple sclerosis.

Source: Kurtzke JF, et al. *Neurology* 1983;33:1444-1452.

POLLING QUESTION 2:

Which of the following provides evidence for Multiple Sclerosis?

- MRI lesions in the brain
- CT scan of the brain
- History of optic neuritis
- Presence of oligoclonal bands in serum

QUESTION 2 RESPONSE:

Which of the following provides evidence for Multiple Sclerosis?

- **MRI lesions in the brain**
- CT scan of the brain
- **History of optic neuritis**
- Presence of oligoclonal bands in serum

Types of MS

- Clinically isolated syndrome (CIS)
- Relapsing-remitting MS (RRMS)
- Secondary-progressive MS (SPMS)
- Primary-progressive MS (PPMS)
- Progressive-relapsing MS (PRMS)
- Relapse: a neurologic deficit associated with an acute inflammatory demyelinating event that lasts at least 24 hours

Source: Alexander RG, et al. *Neurology* Apr 2018, 90 (17) 777-788.

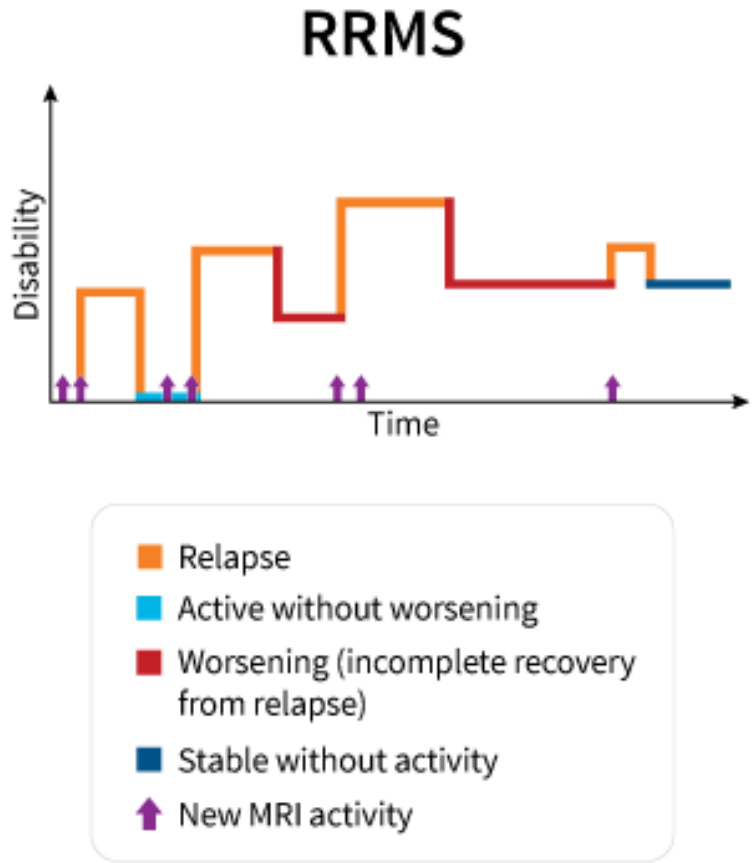
Clinically Isolated Syndrome (CIS)

- First and only clinical episode of symptoms suggestive of MS
- Develops acutely or sub-acutely, lasts at least 24 hours
- Absence of fever or infection
- Symptoms resemble an MS episode without a diagnosis of MS
  - No MS-like lesions on a brain MRI
  - Low likelihood of developing MS

Souroces: Dobson R, et al. *European Journal of Neurology* 2019, 26: 27–40.
Angelo G, et al. *Neurol Ther* (2018) 7:189–194.
Lublin FD, et al. *Neurology*. 2014;83(3):278-286.

Relapsing-Remitting MS (RRMS)

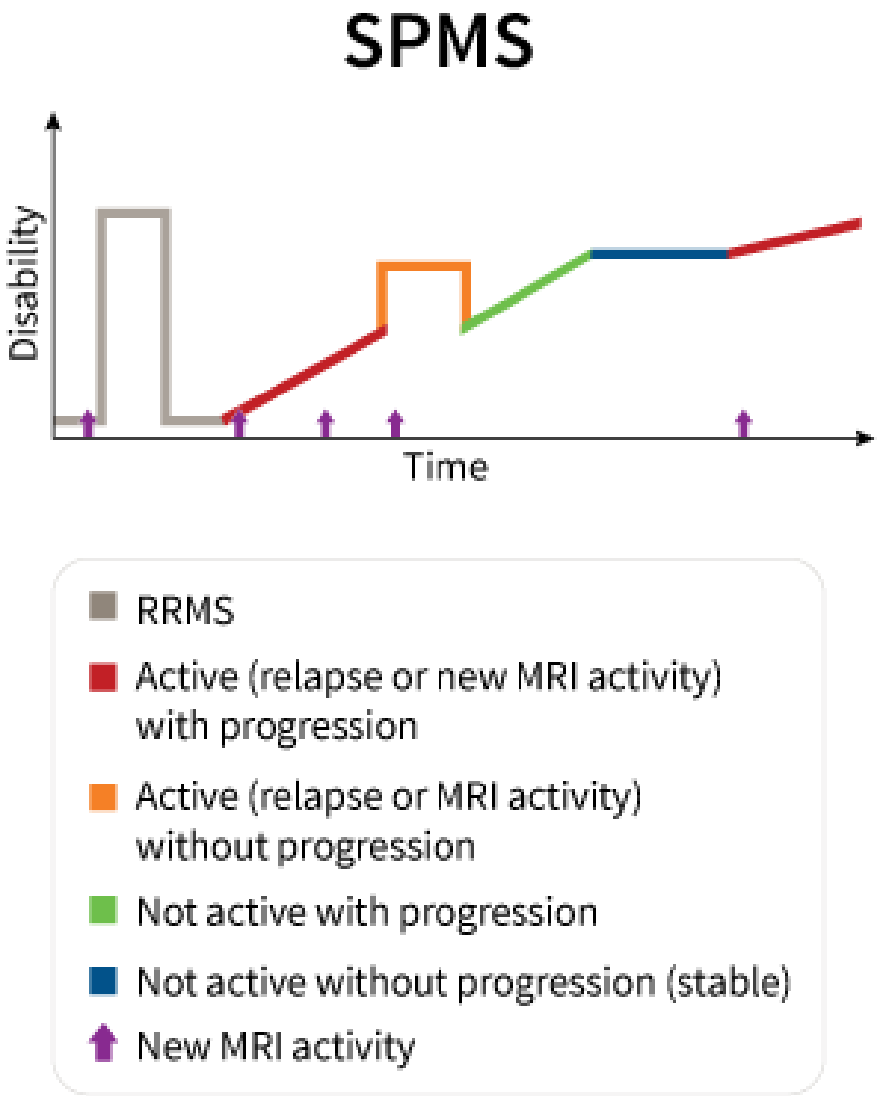
- 80% of patients have RRMS upon presentation



Sources: Dobson R, et al. *European Journal of Neurology* 2019, 26: 27–40.
Angelo G, et al. *Neurol Ther* (2018) 7:189–194.
Lublin FD, et al. *Neurology*. 2014;83(3):278-286.

Secondary Progressive MS (SPMS)

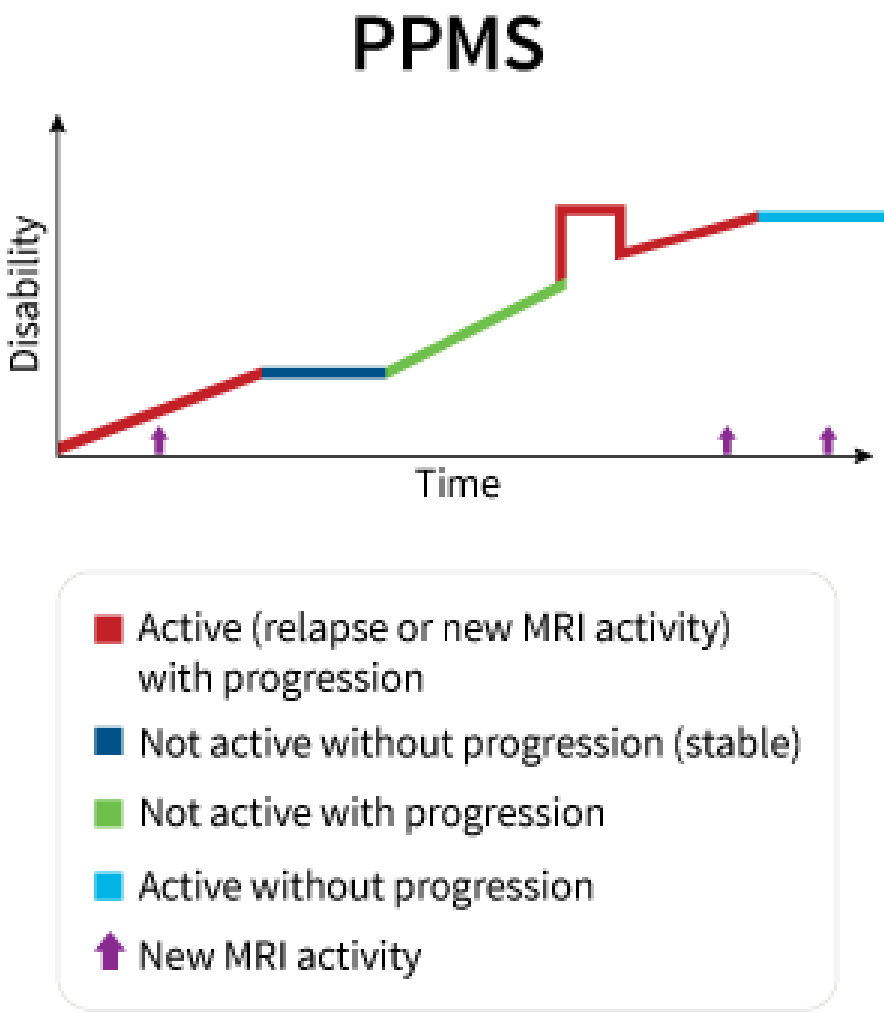
- RRMS transitions to SPMS overtime with worsening neurologic function
- 50% of patients develop SPMS during the first 10 years of illness



Sources: Dobson R, et al. *European Journal of Neurology* 2019, 26: 27–40.
Angelo G, et al. *Neurol Ther* (2018) 7:189–194.
Lublin FD, et al. *Neurology*. 2014;83(3):278-286.

Primary Progressive MS (PPMS)

- Disease **progression from onset** with minor improvements
  - 10-15% of patients have primary progressive MS at onset
- Less inflammation
- Lesions more commonly seen on spinal cord than brain
- Difficult to diagnose
  - Diagnosed at later age
  - Often results in more symptoms
- More common in males than females
  - Worse prognosis for males



Dobson R, et al. *European Journal of Neurology* 2019, 26: 27–40.
Angelo G, et al. *Neurol Ther* (2018) 7:189–194.
Lublin FD, et al. *Neurology*. 2014;83(3):278-286.

Disease Course

Relapsing Remitting (RRMS)	Secondary Progressive (SPMS)	Primary Progressive (PPMS)	Progressive-relapsing (PRMS)
			
Exacerbation/Attack (lasts at least 24hrs) followed by **Remission**	Exacerbation/Attack And Remission difficult to identify	Progressive disease from the onset	Progressive disease from outset, with additional "relapses" and recovery
No disease progression between attacks	Disability accumulates progressively	Disability accumulates progressively	Disease progresses between relapses
	Less responsive to typical therapy		

Source: Dobson R, et al. *European Journal of Neurology* 2019, 26: 27–40.
Angelo G, et al. *Neurol Ther* (2018) 7:189–194

Goals of Therapy

- Modify disease course
  - Reduce brain lesions & atrophy
- Treat exacerbations
- Improve overall quality of life
  - Manage symptoms
- Improve function & safety

Source: Dobson R, et al. *European Journal of Neurology* 2019, 26: 27–40.
Angelo G, et al. *Neurol Ther* (2018) 7:189–194.

ACUTE EPISODE MANAGEMENT

Acute Episode Definition

- Defined as:
  - Primary symptom exacerbation lasting at least 24 hours
  - Optic neuritis (acute inflammation of the optic nerve resulting in pain and vision loss)
  - Increased limitation on activities
- Separated from last attack by at least 1 month

Acute Episode Management

- First line: corticosteroids
  - Methylprednisolone IV 500 mg – 1000 mg daily for three–five days
  - Methylprednisolone PO 500 mg – 2000 mg daily for three–five days
- Rationale
  - Decreases edema and inflammation associated with demyelination
    - Restores blood brain barrier
- Refractory:
  - Plasma Exchange (PLEX) – every other day x 7 treatments
  - IVIG
  - Adrenocorticotropic hormone (ACTH)

Which of the following patients would benefit from a short course of high dose steroids?

Millie Larson

- 72 y/o female with relapsing remitting MS diagnosed 2 years ago and is on interferon therapy. PMH significant for hx of diabetes and frequent URI. Presents to her PCP with a 2 week history of paresthesia in her left arm.

Gwen Cummings

- 25 y/o female diagnosed with CIS 5 years ago where her clinical symptoms were right sided weakness in her legs. She now presents with complaints of visual changes and is found to have optic neuritis.

Ali Ibrahim

- 43 y/o male who was diagnosed with progressive relapsing MS 6 months ago when he was started on glatiramer injections. He continues to have LE spasticity, which has caused several falls during this past month. He experiences fatigue as the day progresses.

POLLING QUESTION 3:

Which of the following patients would benefit from a short course of high dose steroids?

A. Ms. Larson
B. Ms. Cummings
C. Mr. Ibrahim

QUESTION 3 RESPONSE:

Which of the following patients would benefit from a short course of high dose steroids?

A. Ms. Larson

B. **Ms. Cummings**

C. Mr. Ibrahim

CHRONIC MANAGEMENT OF MS

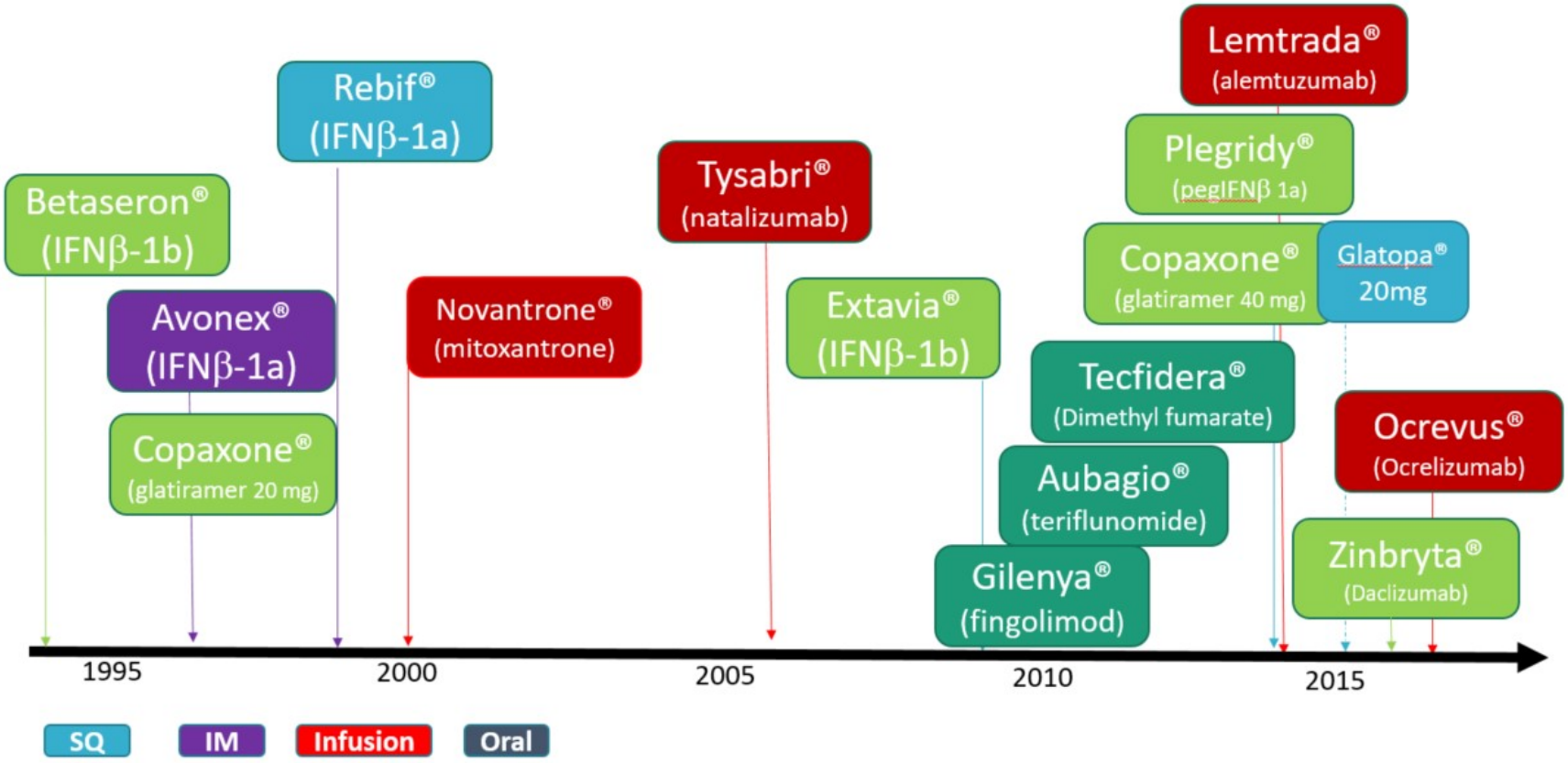
Disease Modifying Therapy (DMT)

- Alter disease course
- Goals:
  - Reduce number of attacks “Relapse Rate”
  - Delay progression of disease disability
- Minimum of 3–6 months to assess efficacy
  - Consider alternative treatment if relapse occurs

FDA Approved DMTs

Injectable	Oral	Infusion
• Interferon beta-1a (Avonex©) • Interferon beta-1b (Betaseron©) • Interferon beta-1b (Extavia©) • Peginterferon beta-1a (Plegridy©) • Interferon beta-1a (Rebif©) • Glatiramer acetate (Copaxone©) • Glatiramer acetate (Glatopa©)	• Cladribine (Mavenclad©) • Teriflunomide (Aubagio©) • Fingolimod (Gilenya©) • Dimethyl fumarate (Tecfidera©)	• Natalizumab (Tysabri©) • Alemtuzumab (Lemtrada©) • Ocrelizumab (Ocrevus©) • Mitoxantrone (Novantrone©)

Approval Dates



Source: Floriana DA, et al. *BMJ* 2018; 363 :k4674.

Selection Considerations

- Age & gender
  - Child bearing age
- Co-morbidities & viral exposure
- Prior or concurrent medications, previous DMT
  - Cumulative risk of immunosuppression
- Severity & stage of MS
  - Induction vs. Escalation strategy
- Adherence to therapy (dosage form, frequency)
  - >25% of MS patients discontinue injectable therapy within 2 years
    - Severe side effects
- Patient preference
- Relative efficacy & toxicity profile
- Accessibility
- Cost

Main Guidelines

- ECTRIMS = European Committee for Treatment & Research in Multiple Sclerosis
- EAN = European Academy of Neurology
- ABN = Association of British Neurologists
- AAN = American Academy of Neurology

American Academy of Neurology

- Initiate DMTs for:
  - Relapsing forms of MS with recent clinical relapses or MRI activity
  - A single clinical demyelinating event and 2 or more brain lesions characteristic of MS
- Preventing disease progression with RRMS
  - Dimethyl fumarate
  - Fingolimod
  - Teriflunomide
  - IFN-β-1a 30 µg IM weekly
  - IFN-β-1a 44 µg subcutaneous 3 times weekly
  - Mitoxantrone
  - Natalizumab
  - Pegylated interferon (IFN)
  - Cladribine

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

American Academy of Neurology

- Highly active MS (relapsing activity, MRI markers)
  - Alemtuzumab
  - Fingolimod
  - Natalizumab
- Preventing disease progression with PPMS
  - Mitoxantrone
  - Ocrelizumab
- Preventing disease conversion from CIS
  - Glatiramer acetate
  - IFN-β-1a subcutaneous 3 times weekly

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

American Academy of Neurology

- Consider switching:
  - One or more relapses or two or more new MRI lesions
  - Side effects or persistent laboratory test abnormalities
    - Change to noninjectable or less frequent injectable DMTs for intolerable side effects
  - Patients treated with natalizumab who are John Cunning Virus (JCV) positive
- Consider stopping:
  - Secondary progressive MS who have inactive disease and are non-ambulatory for at least 2 years
  - Before conception and during pregnancy unless the risk of MS disease activity outweighs the benefits

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

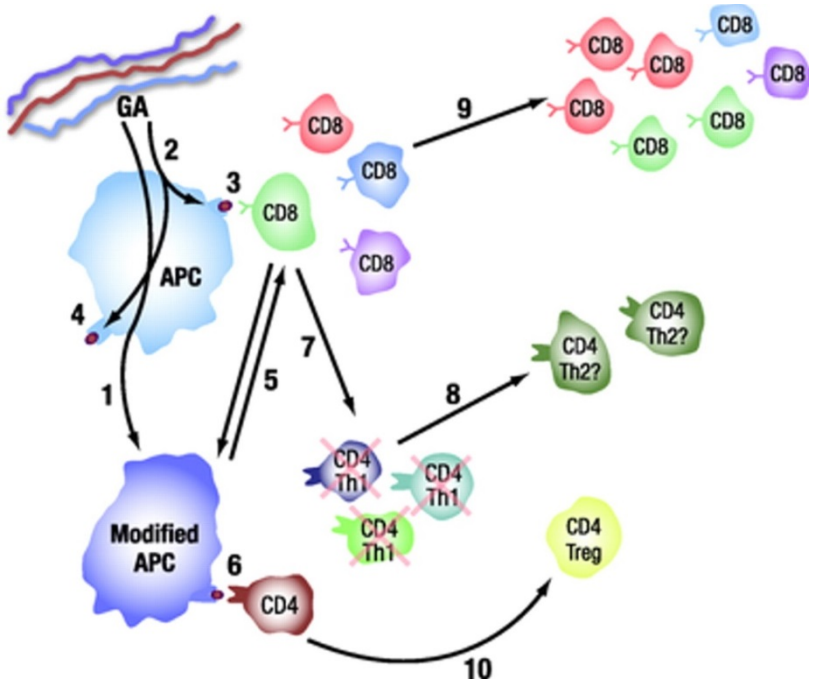
American Academy of Neurology

		CIS	Relapsing MS			Progressive MS	
Phenotype		**1st attack suggestive of MS**	Inactive	Active	Highly active	SPMS	PPMS
			No clinical attacks and stable MRI	1 relapse in the previous year and/or new T2 gadolinium-enhancing lesions on MRI	1 relapse and new gadolinium-enhancing lesions and/or significant increase in T2 lesions while on DMTs 2 or more relapses in the previous year and MRI activity in patients not on DMT	Steady increase in neurological disability independent of relapses following an initial relapse course	Steady increase in neurological disability independent of relapses from disease onset
Treatment	DMT	• **Glatiramer acetate** • **Interferon beta**	Active monitoring with clinical assessment and MRI	• Dimethyl fumarate • Fingolimod • Teriflunomide • Interferon beta • Mitoxantrone • Natalizumab • Pegylated interferon (IFN) • Cladribine	• Alemtuzumab • Fingolimod • Natalizumab	No licensed treatments	• Ocrelizumab • Mitoxantrone
	Standard	• Offer high-dose corticosteroids for management of acute disabling relapses after ruling out infections • Offer treatment for ongoing symptoms such as bladder disturbances, constipation, spasticity, and pain • Promote brain health including smoking cessation, regular exercise, healthy diet and weight loss if appropriate • Treat comorbidities including depression, hypertension, diabetes and osteoporosis					

Angelis DF, et al. BMJ. 2018 Nov 27;363:k4674.

Glatiramer Acetate

- Mechanism of Action:
  - Mixture of 4 amino acids antigenically similar to myelin basic protein (MBP)
  - Inhibit binding of myelin binding protein (MBP) peptide to T cell receptor complex



Source: Michael KR, et al. *Neurology* Jan 2010, 74 (1 Supplement 1) S25-S30.
Copaxone (glatiramer acetate) [Package Insert]. North Wales, PA: Teva Pharmaceuticals; July 2019.

Glatiramer Acetate

- Dosing:
  - 20 mg subcutaneously (SQ) every day or
  - 40 mg SQ three times per week (if intolerable side effects)
- FDA approval
  - For the treatment of adults with CIS and RRMS in adults
    - May be 1st or 2nd line depending on patient specific factors
  - Approved 1996

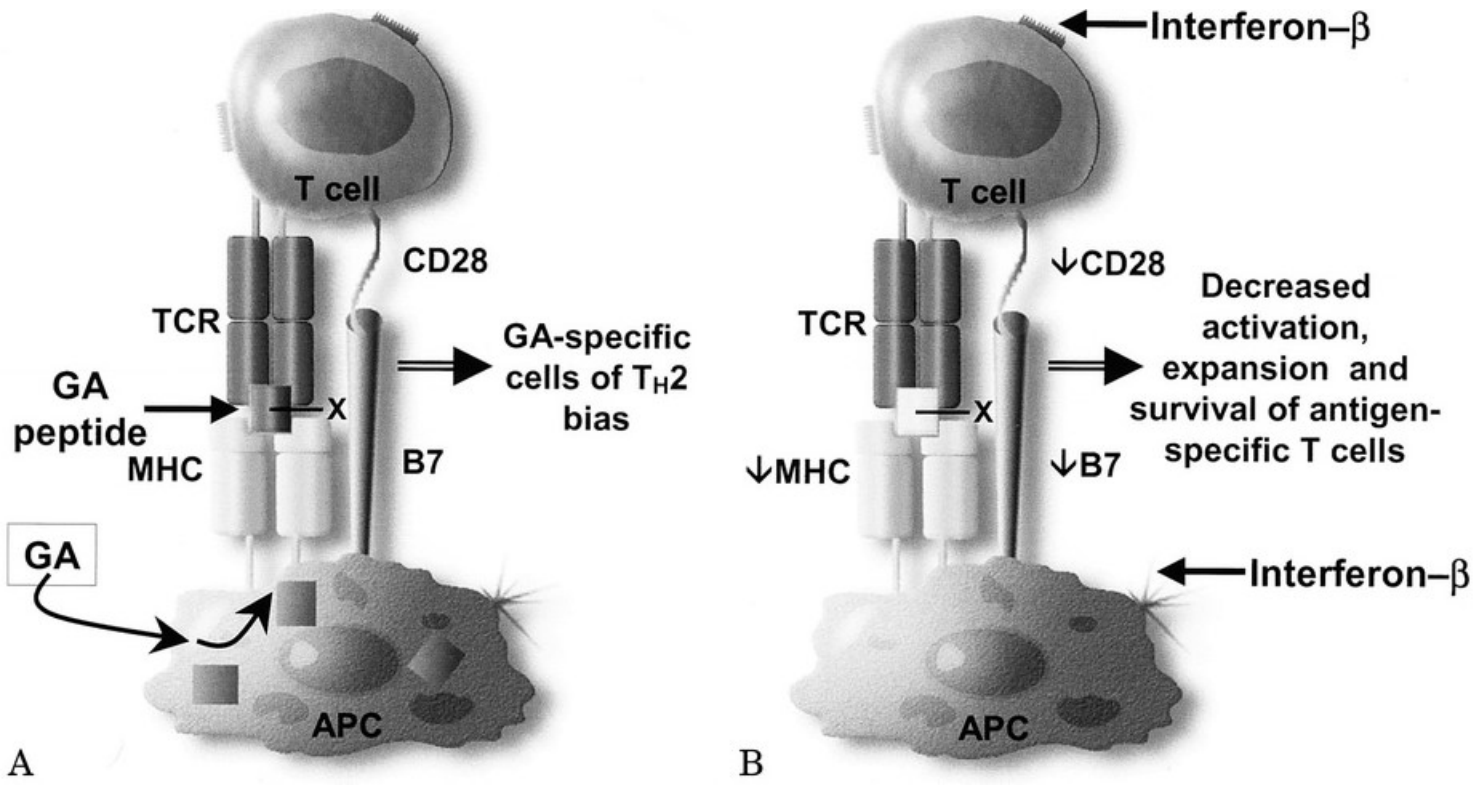
Source: Copaxone (glatiramer acetate) [Package Insert]. North Wales, PA: Teva Pharmaceuticals; July 2019.

Glatiramer Acetate

- Adverse effects:
  - Injection site reactions (redness, pain, swelling), flushing, shortness of breath, rash, chest pain
- Warnings:
  - Chest pain
  - Post-injection site reactions
  - Lipoatrophy at injection site
- Pregnancy category B

Copaxone (glatiramer acetate) [Package Insert]. North Wales, PA: Teva Pharmaceuticals; July 2019.

Glatiramer Acetate vs. Interferon Beta



Yong VW, et al. *Neurology* Sep 2002, 59 (6) 802-808.

Interferon Beta-1a (Avonex©)

- MOA: increases suppressor T-cell activity, decreases cytokines and antigen presenting cells (APCs)
- Dosing:
  - 30 mcg intramuscularly (IM) (into a large muscle) once weekly
- FDA indication
  - Treatment of CIS and RRMS to slow the physical disability and to reduce exacerbations in adults
  - Patients with a first clinical episode and a relevant MRI
  - Approval 1996

Source: Avonex (interferon beta-1a) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.

Interferon Beta-1a (Rebif©)

- MOA: increases suppressor T-cell activity, decreases cytokines and APCs
- Dosing:
  - Target: 44 mcg subcutaneously (SQ) three times per week
    - Reduced: 22 mcg SQ three times per week for intolerable side effects
- FDA indication
  - Treatment of RRMS to slow the physical disability and to reduce exacerbations in adults
  - Approval 2002

Souroce: Rebif (interferon beta-1a) [Package Insert]. Rockland, MA: EMD Serono Inc; July 2019.

Interferon Pegylated Beta-1a (Plegridy©)

- MOA: increases suppressor T-cell activity, decreases cytokines and APCs
- Dosing:
  - 125 mcg subcutaneously every 14 days
- FDA indication
  - Treatment of adults with RRMS
  - Approval 2014

Source: Plegridy (peginterferon beta-1a) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.

Interferon Beta-1a (Avonex© and Rebif©)

- Adverse effects:
  - **Headache, flu-like symptoms (chills, fever, muscle pain, fatigue weakness), injection site pain & inflammation**
- Warnings:
  - Depression and suicide
  - Leukopenia
  - Hypersensitivity reactions
  - Post-injection site reactions
  - Seizures
  - Drug-induced autoimmune thrombotic microangiopathy
  - Hepatic impairment
  - Cardiovascular disease
- Pregnancy category C

Sources: Avonex (interferon beta-1a) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.
Rebif (interferon beta-1a) [Package Insert]. Rockland, MA: EMD Serono Inc; July 2019.

Interferon Beta-1a (Plegredy©)

- Adverse effects:
  - Flu-like symptoms (chills, fever, muscle pain, fatigue, weakness) following injection, elevated hepatic enzymes, low white blood count
- Warnings:
  - Depression and suicide
  - Hepatic injury
  - Hypersensitivity reactions
  - Low peripheral blood counts
  - Thrombotic microangiopathy
  - Seizures
  - Chronic heart failure
- Pregnancy category C

Source: Plegridy (peginterferon beta-1a) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.

Interferon Beta-1b (Extavia© and Betaseron©)

- MOA: increases suppressor T-cell activity, decreases cytokines and APCs
- Dosing:
  - 0.25 mg SQ every other day
- FDA indication
  - Treatment of MS to slow the physical disability and to reduce exacerbations in adults
  - Patients with a first clinical episode and a relevant MRI
  - Betaseron: approval 1993 for RRMS
  - Extavia: approval 2009 for CIS and RRMS

Source: Extavia (interferon beta-1b) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2019. Betaseron (interferon beta-1b) [Package Insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; August 2019.

Interferon Beta-1b (Extavia© and Betaseron©)

- Adverse effects:
  - Flu-like symptoms (chills, fever, muscle pain, fatigue, weakness) following injection, headache, injection site reactions (swelling redness, pain)
- Warnings:
  - Depression and suicide
  - Leukopenia
  - Hypersensitivity reactions
  - Post-injection site reactions
  - Thrombotic microangiopathy
  - Seizures
  - Hepatic impairment
  - Cardiovascular disease
- Pregnancy category C

Sources: Extavia (interferon beta-1b) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2019. Betaseron (interferon beta-1b) [Package Insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; August 2019.

Interferons

- Monitoring
  - Complete blood count (CBC), liver function test (LFT) baseline, then at 1 month, then every 3 months for 1 year, then every 6 months
  - Depression screening, cardiac and thyroid function tests

Interferon Counseling Points

- Injection technique
  - Monitoring for injection site irritation
  - Rotate injection site
  - Apply cold packs before or after
  - Hydrocortisone cream
- Flu-like symptoms
  - APAP/NSAIDS before or after injection
  - Lasts ~24 hrs, transient (1–3 months)
  - Taper to full dose over 1–2 months

	Rebif© (interferon beta-1a)	Avonex© (interferon beta-1a)	Betaseron© (interferon beta-1b)	Extavia© (interferon beta-1b)	Copaxone© (glatiramer acetate)
Route of injection	SQ	IM	SQ	SQ	SQ
Dosing frequency	3 times per week	Once per week	Every other day	Every other day	20 mg Every day or 40 mg 3x/week
Number of injections per year	156	52	182	182	365 Or ~156
Prefilled, preassembled syringes	YES	YES	NO	NO	YES
Auto-injector available	YES	YES	YES	YES	YES
Storage	Store in refrigerator OR at room temp up to 30 days	Store in refrigerator OR at room temp up to 7 days	Store at room temp OR refrigerate and use within 3 hours if already reconstituted	Store at room temp OR refrigerate and use within 3 hours if already reconstituted	Store in refrigerator OR at room temp up to 30 days
Protect from Light	YES	YES	NO	NO	YES

POLLING QUESTION 4:

Which of the following is mismatched?

a) Avonex- inject into muscle
b) Betaseron- must be stored in refrigerator
c) Interferon-1a – protect from light
d) Glatiramer acetate- inject everyday

QUESTION 4 RESPONSE:

Which of the following is mismatched?

a) Avonex- inject into muscle

b) Betaseron- must be stored in refrigerator

c) Interferon-1a – protect from light

d) Glatiramer acetate- inject everyday

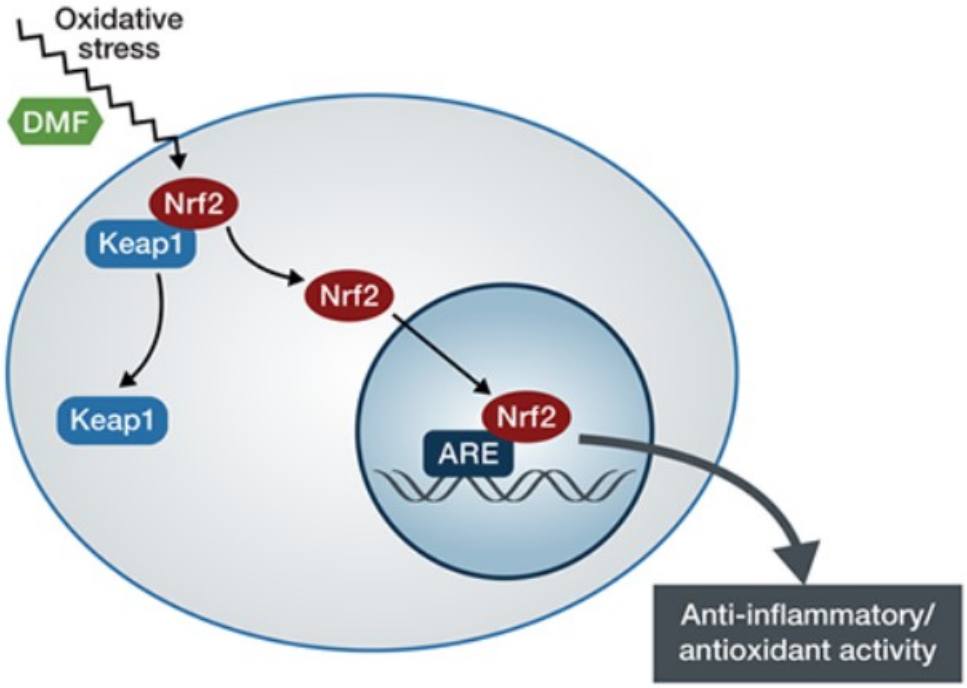
American Academy of Neurology

		CIS	Relapsing MS			Progressive MS	
Phenotype		1st attack suggestive of MS	Inactive	**Active**	Highly active	SPMS	PPMS
			No clinical attacks and stable MRI	**1 relapse in the previous year and/or new T2 gadolinium-enhancing lesions on MRI**	1 relapse and new gadolinium-enhancing lesions and/or significant increase in T2 lesions while on DMTs 2 or more relapses in the previous year and MRI activity in patients not on DMT	Steady increase in neurological disability independent of relapses following an initial relapse course	Steady increase in neurological disability independent of relapses from disease onset
Treatment	DMT	• Glatiramer acetate • Interferon beta	Active monitoring with clinical assessment and MRI	• **Dimethyl fumarate** • **Fingolimod** • **Teriflunomide** • **Interferon beta** • **Mitoxantrone** • **Natalizumab** • **Pegylated interferon (IFN)** • **Cladribine**	• Alemtuzumab • Fingolimod • Natalizumab	No licensed treatments	• Ocrelizumab • Mitoxantrone
	Standard	• Offer high-dose corticosteroids for management of acute disabling relapses after ruling out infections • Offer treatment for ongoing symptoms such as bladder disturbances, constipation, spasticity, and pain • Promote brain health including smoking cessation, regular exercise, healthy diet and weight loss if appropriate • Treat comorbidities including depression, hypertension, diabetes and osteoporosis					

Angelis DF, et al. BMJ. 2018 Nov 27;363:k4674.

Dimethyl fumarate (Tecfidera©)

- MOA: activates the NF-E2-related factor-2 (Nrf2) pathway resulting in anti-inflammatory effects



Source: Tecfidera (dimethyl fumarate) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.

Dimethyl fumarate (Tecfidera©)

- Dosing
  - Initial: 120 mg capsule orally twice daily
  - After 7 days increase the dose to the ongoing (maintenance) dose of 240 mg capsule orally twice daily
- FDA indication
  - For the treatment of adults with RRMS in adults
  - Approval 2013
- Monitoring
  - Baseline: full blood count (FBC), LFTs, urea, electrolytes, creatinine (UEC) and MRI
  - Follow-up: FBC, LFTs, UEC and MRI every 3 months

Source: Tecfidera (dimethyl fumarate) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.

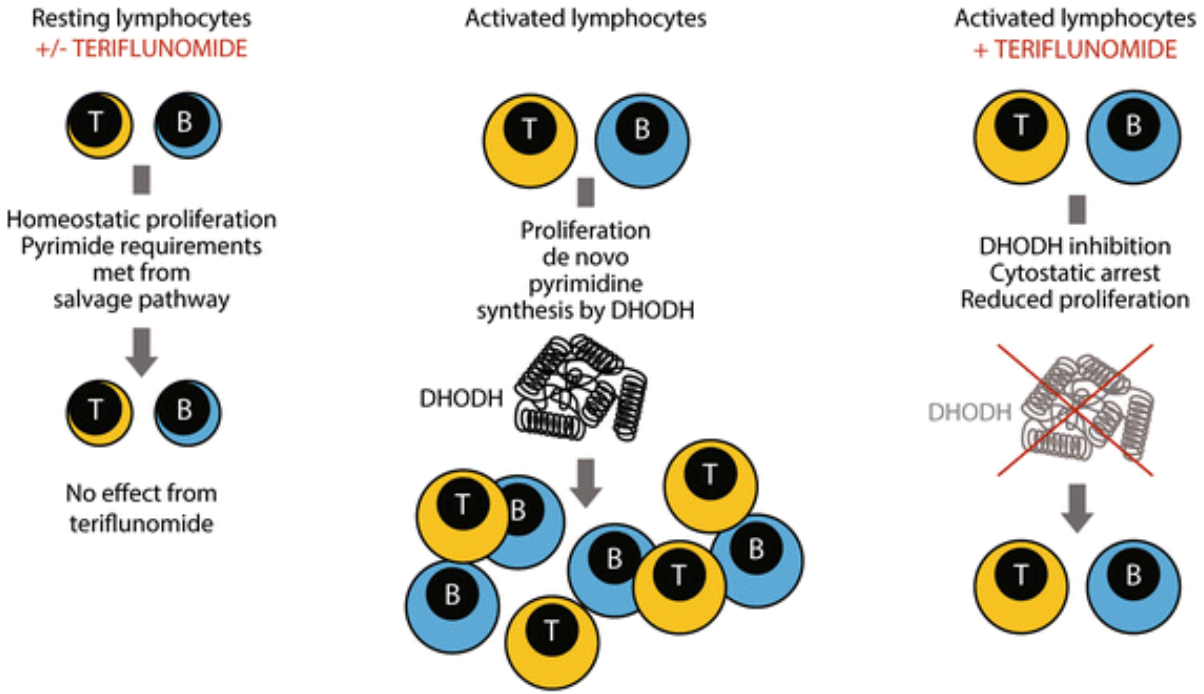
Dimethyl fumarate (Tecfidera©)

- Adverse effects:
  - Flushing (sensation of heat or itching and a blush on the skin), gastrointestinal issues (nausea, diarrhea, abdominal pain)
- Warnings:
  - Allergic reactions
  - Leukopenia
  - Progressive multifocal leukoencephalopathy (PML)
  - Hepatic impairment
  - Flushing/skin irritation
- Pregnancy category C

Source: Tecfidera (dimethyl fumarate) [Package Insert]. Cambridge, MA: Biogen Idec Inc; July 2019.

Teriflunomide (Aubagio©)

- MOA: inhibits pyrimidine synthesis in activated lymphocytes by inhibiting dihydroorotate dehydrogenase (DHODH) which halts cell cycles



Sources: Michael K. Racke, Amy E. Lovett-Racke, Nitin J. Karandikar. Neurology Jan 2010, 74 (1 Supplement 1) S25-S30.
Aubagio (teriflunomide) [Package Insert]. Cambridge, MA: Genzyme Corporation; July 2019.

Teriflunomide (Aubagio©)

- Dosing
  - 7 mg or 14 mg capsule orally once daily
- FDA indication
  - For the treatment of adults with RRMS
    - Decrease relapse rates, disability progression, MRI evidence
  - Approval 2010
- Monitoring
  - Baseline: FBC, LFTs, tuberculosis (TB) and blood pressure (BP)
  - Follow-up: FBC, LFTs, TB and BP every 2 weeks for the first 6 months then every 8 weeks

Source: Aubagio (teriflunomide) [Package Insert]. Cambridge, MA: Genzyme Corporation; July 2019.

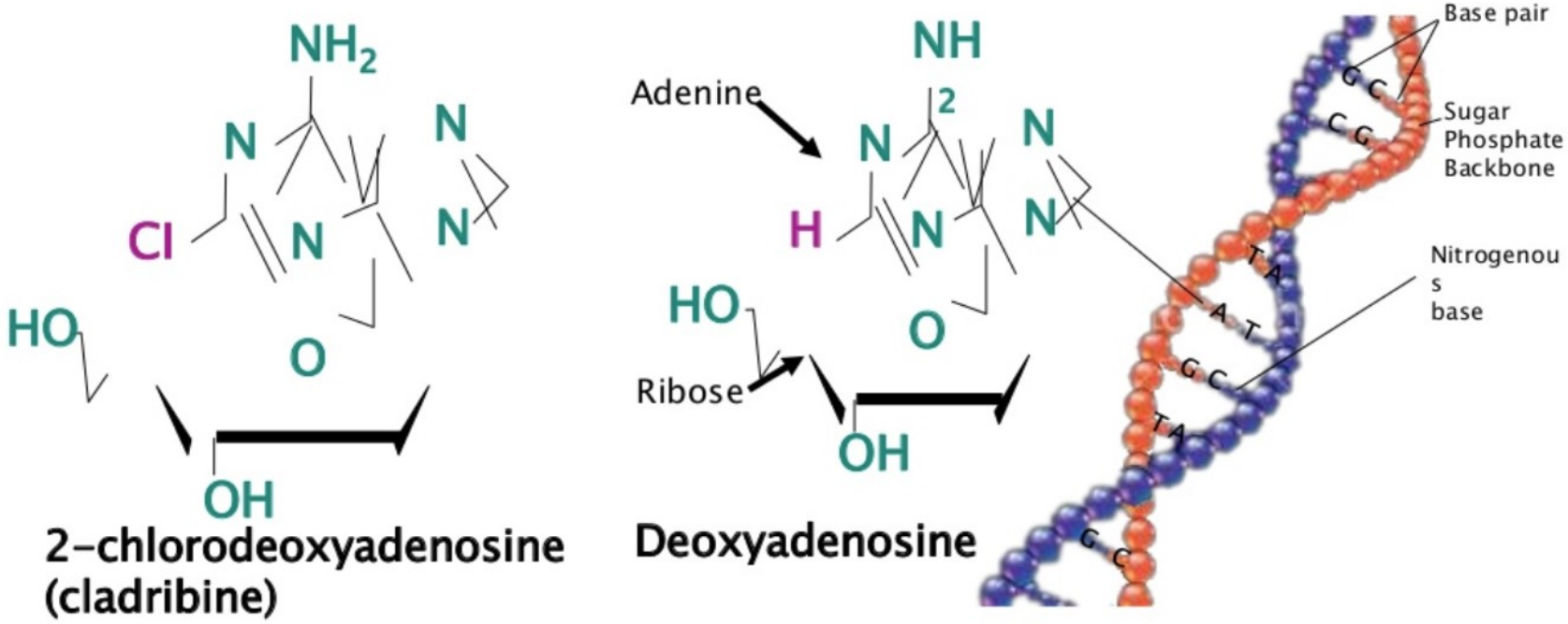
Teriflunomide (Aubagio©)

- Adverse effects:
  - Headache, hair thinning, diarrhea, nausea, abnormal liver tests
- Warnings:
  - In blood for 2 years
  - Allergic reactions
  - Leukopenia
  - Avoid live vaccinations
  - Tuberculosis screening
  - Peripheral neuropathy
  - Acute kidney failure (hyperkalemia)
  - Hypertension
  - Malignancy
  - Interstitial lung disease
- Pregnancy category **X**

Source: Aubagio (teriflunomide) [Package Insert]. Cambridge, MA: Genzyme Corporation; July 2019.

Cladribine (Mavenclad©)

- MOA: cytotoxic effects on B and T lymphocytes, shuts down DNA synthesis, leading to a depletion of lymphocytes



Sources: Caron DA, et al. Proc Natl Acad Sci USA 1980;77:6865-9.
Mavenclad (cladribine) [Package Insert]. Rockland, MA: EMD Serono Inc; April 2019.

Cladribine (Mavenclad©)

- Dosing
  - Two treatment courses once per year for two years
  - Two cycles: 4–5 days long and about one month apart
  - Weight based dosing
- FDA indication
  - Treatment of adults with RRMS and SPMS
    - Typically reserved for inadequate response (salvage therapy)
  - Approval 2019
- Monitoring
  - CBC at baseline and at 2 & 6 months after initiation
  - HIV, TB, hepatitis B & C, varicella zoster virus and pregnancy before annual courses
  - Skin exams annually

Source: Mavenclad (cladribine) [Package Insert]. Rockland, MA: EMD Serono Inc; April 2019.

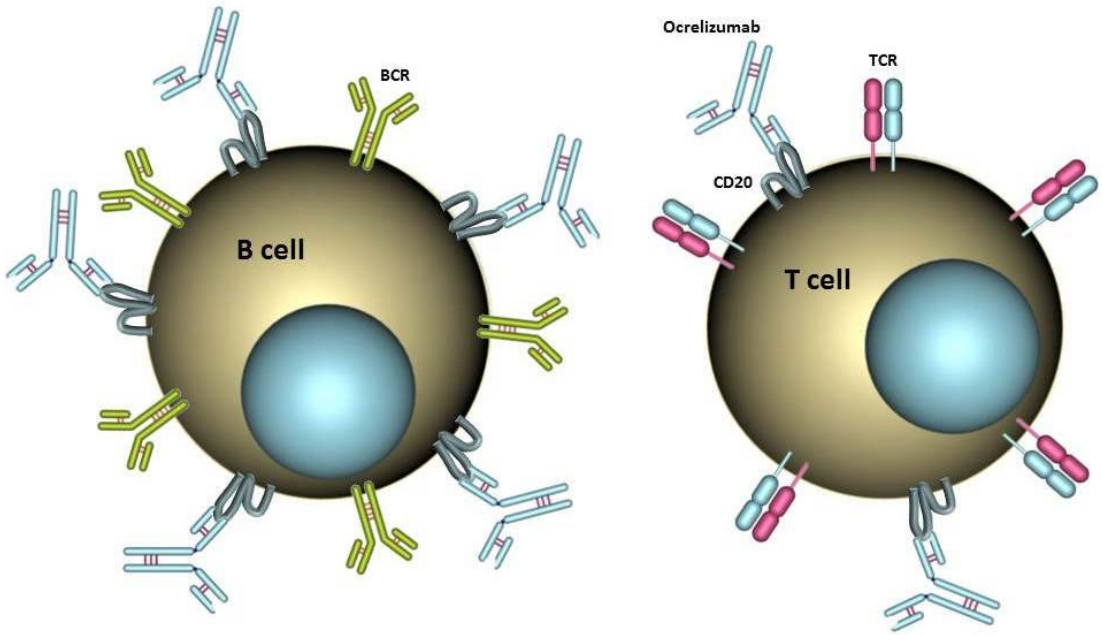
Cladribine (Mavenclad©)

- Adverse effects:
  - Upper respiratory infection, headache, low white blood cell count
- Warnings:
  - Teratogenic
  - Bone marrow suppression
  - Malignancy
  - Increased risk of infection
  - PML
  - Avoid live vaccination
  - Hepatotoxicity
  - Cardiotoxicity
- Pregnancy category **X**

Source: Mavenclad (cladribine) [Package Insert]. Rockland, MA: EMD Serono Inc; April 2019.

Ocrelizumab (Ocrevus©)

- MOA: Monoclonal antibody. CD20 directed cytolytic antibody



Source: Gingele, S, et al. *Cells* 2019, *8*, 12.
Ocrevus (ocrelizumab) [Package Insert]. South San Francisco, CA: Genetech Inc; July 2019.

Ocrelizumab (Ocrevus©)

- Dosing
  - 600 mg IV every 6 months (first dose: 300 mg IV on day one and 300 mg IV 2 weeks later)
- FDA indication
  - Treatment of adults with RRMS or PPMS
    - Generally reserved in RRMS patients with inadequate response to >2 MS medications
  - Approval 2017
- Monitoring
  - Before: HBsAG and anti-HBc for Hepatitis B
  - Continued Hepatitis B every 3 months during treatment
  - Vaccinations at least 6 weeks prior

Source: Ocrevus (ocrelizumab) [Package Insert]. South San Francisco, CA: Genetech Inc; July 2019.

Ocrelizumab (Ocrevus©)

- Adverse effects:
  - Infusion reactions (most commonly itchy skin, rash, throat irritation, flushed face or fever, headache)
  - Increased risk of infections (respiratory tract, skin & herpes)
- Warnings:
  - Infusion related reactions (premedicate 30-60 minutes prior)
    - Methylprednisolone 100mg + diphenhydramine +/ acetaminophen
  - Increased risk of infections
  - Hepatitis B virus reactivation
  - Progressive multifocal leukoencephalopathy (PML)
  - Increase in malignancies (breast cancer)
- Pregnancy category: not known

Source: Ocrevus (ocrelizumab) [Package Insert]. South San Francisco, CA: Genetech Inc; July 2019.

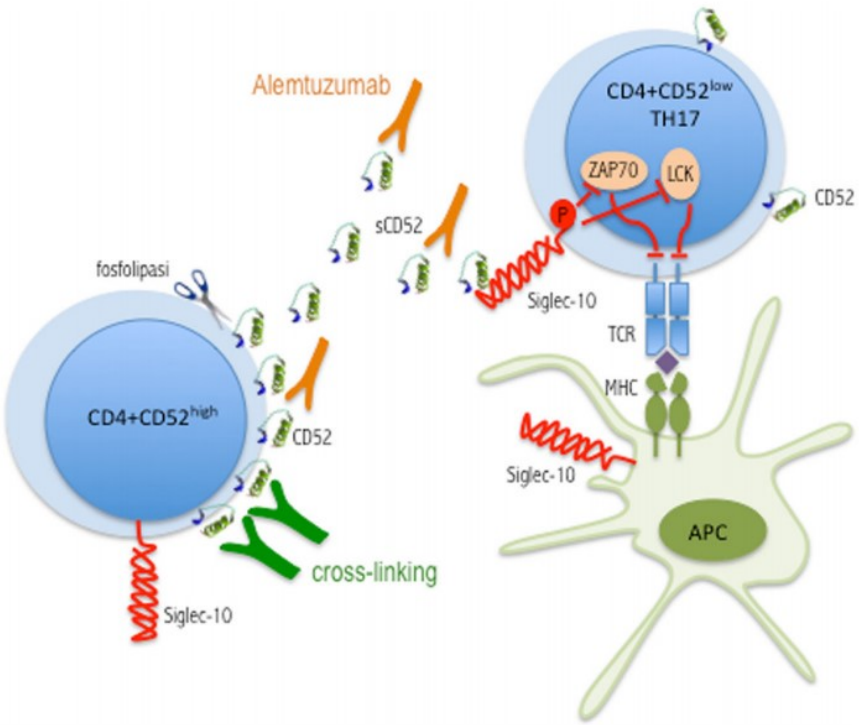
American Academy of Neurology

		CIS	Relapsing MS			Progressive MS	
Phenotype		1st attack suggestive of MS	Inactive	Active	**Highly active**	SPMS	PPMS
			No clinical attacks and stable MRI	1 relapse in the previous year and/or new T2 gadolinium-enhancing lesions on MRI	**1 relapse and new gadolinium-enhancing lesions and/or significant increase in T2 lesions while on DMTs** **2 or more relapses in the previous year and MRI activity in patients not on DMT**	Steady increase in neurological disability independent of relapses following an initial relapse course	Steady increase in neurological disability independent of relapses from disease onset
Treatment	DMT	• Glatiramer acetate • Interferon beta	Active monitoring with clinical assessment and MRI	• Dimethyl fumarate • Fingolimod • Teriflunomide • Interferon beta • Mitoxantrone • Natalizumab • Pegylated interferon (IFN) • Cladribine	• **Alemtuzumab** • **Fingolimod** • **Natalizumab**	No licensed treatments	• Ocrelizumab • Mitoxantrone
	Standard	• Offer high-dose corticosteroids for management of acute disabling relapses after ruling out infections • Offer treatment for ongoing symptoms such as bladder disturbances, constipation, spasticity, and pain • Promote brain health including smoking cessation, regular exercise, healthy diet and weight loss if appropriate • Treat comorbidities including depression, hypertension, diabetes and osteoporosis					

Angelis DF, et al. BMJ. 2018 Nov 27;363:k4674.

Alemtuzumab (Lemtrada©)

- MOA: Monoclonal antibody directed at CD52, causes depletion of lymphocytes



Source: Gallo et al. Multiple Sclerosis and Demyelinating Disorders (2017) 2:7.
Campath (alemtuzumab) [Package Insert]. Cambridge, MA: Genzyme Corporation; November 2018.

Alemtuzumab (Lemtrada©)

- Dosing
  - Initial: 12 mg IV per day for five consecutive days
  - Followed by 12 mg IV per day on three consecutive days one year later
- FDA indication
  - For the treatment of adults with RRMS in adults
  - Salvage therapy for patients with inadequate response to two or more disease modifying therapies
  - Approval 2014

Source: Campath (alemtuzumab) [Package Insert]. Cambridge, MA: Genzyme Corporation; November 2018.

Alemtuzumab (Lemtrada©)

- Monitoring
  - Pre-infusion: proper vaccinations, screenings (HPV, TB), baselines
  - Post-infusion:
    - Thyroid function every 3 months until 48 months
    - CBC monthly for 48 months
    - Kidney function monthly for 48 months
    - Urinalysis monthly for 48 months
    - Skin exam annually for cancer
- Adverse effects: extensive
  - REMS program

Source: Campath (alemtuzumab) [Package Insert]. Cambridge, MA: Genzyme Corporation; November 2018.

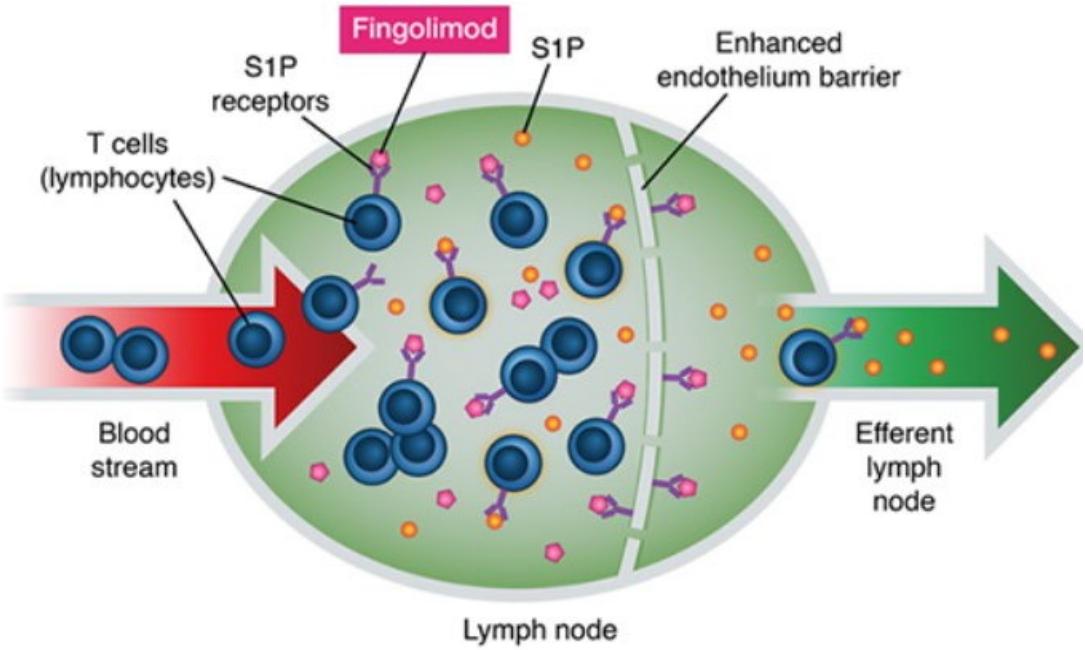
Alemtuzumab (Lemtrada©)

- Warnings:
  - Fatal autoimmune reactions
    - Immune thrombocytopenia
    - Anti-glomerular basement membrane disease
  - Fatal infusion related reactions
  - Increased cancer risk
  - Increased risk of stroke
  - Thyroid dysfunction
  - Pancytopenia
  - Increased risk of infection
- Pregnancy: Category X
  - Use contraception for 4 months after Lemtrada

Source: Campath (alemtuzumab) [Package Insert]. Cambridge, MA: Genzyme Corporation; November 2018.

Fingolimod (Gilenya©)

- MOA: blocks lymphocyte egress from lymph nodes and prevents them from entering the CNS



Source: Gilenya (fingolimod) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2019.

Fingolimod (Gilenya©)

- Dosing
  - 0.5 mg capsule orally once daily
- FDA indication
  - Treatment of adults and children (age 10) to slow the physical disability & to reduce exacerbations
  - Approval 2010
- Monitoring
  - EKG, BP and HR at baseline & hourly for 6 hours after treatment initiation
  - CBC and LFTs every 3 months for 6 months
  - Ophthalmologic and skin exams baseline, then 3-4 months after initiation & then annually

Source: Gilenya (fingolimod) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2019.

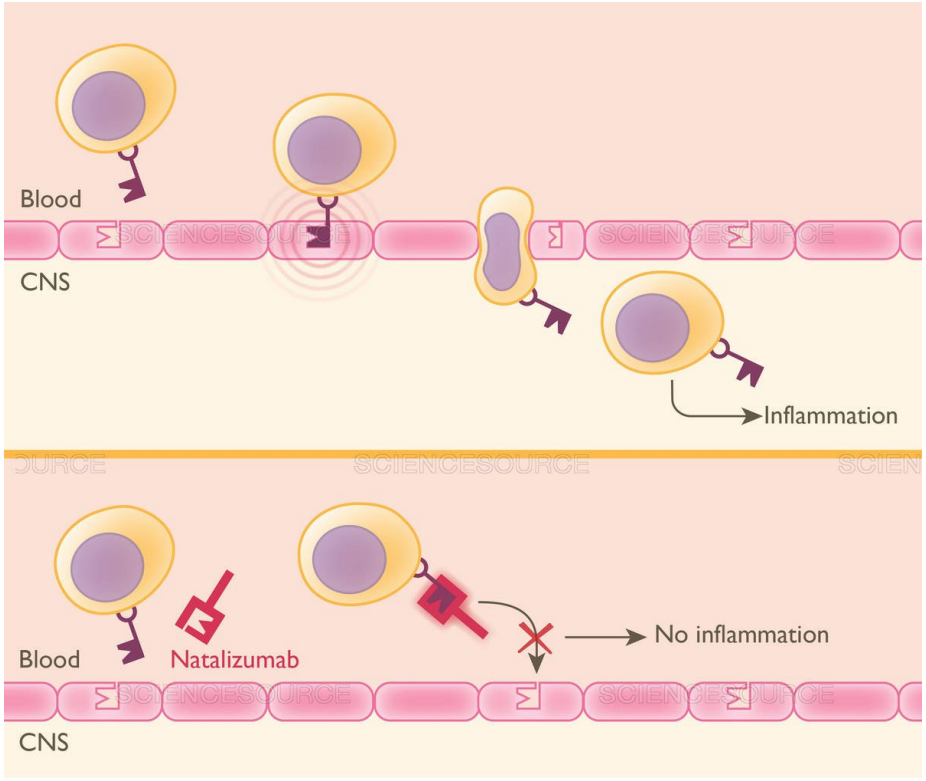
Fingolimod (Gilenya©)

- Adverse effects:
  - Headache, flu, diarrhea, back pain, abnormal liver tests, sinusitis, abdominal pain, pain in extremities, cough
- Warnings:
  - Allergic reactions
  - Bradycardia
  - Rebound MS symptoms
  - Hypertension
  - Leukopenia
  - Cancer
  - Live vaccinations (requires chicken pox)
  - Posterior Reversible Encephalopathy Syndrome (PRES)
  - Hepatic impairment
  - Macular edema
  - Progressive multifocal leukoencephalopathy (PML)
- Pregnancy category C: birth control for 2 months after

Source: Gilenya (fingolimod) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2019.

Natalizumab (Tysabri©)

- MOA: Attaches to VLA-1 and blocks activated lymphocytes from crossing BBB



Source: Tysabri (natalizumab) [Package Insert]. Cambridge, MA: Biogen Inc; August 2019.

Natalizumab (Tysabri©)

- Dosing
  - 300 mg IV once every 28 days in an approved facility
- FDA indication
  - Treatment of adults with RRMS as monotherapy
    - Greater relapse reduction vs interferons
  - Approval 2006
- Monitoring
  - Baseline: CBC, LFTs, HBV, and VZV
  - Anti-JCV before infusion and every 3 months for 6 months after infusions are complete

Source: Tysabri (natalizumab) [Package Insert]. Cambridge, MA: Biogen Inc; August 2019.

Natalizumab (Tysabri©)

- Adverse effects:
  - Headache, fatigue, joint pain, chest discomfort, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash
- Warnings:
  - Increased risk of infection
  - Hypersensitivity reaction
  - Progressive multifocal leukoencephalopathy (PML)
  - Hepatic impairment
- Only available through TOUCH program
- Pregnancy category X: REMS program

Source: Tysabri (natalizumab) [Package Insert]. Cambridge, MA: Biogen Inc; August 2019.

American Academy of Neurology

		CIS	Relapsing MS			Progressive MS	
Phenotype		1st attack suggestive of MS	Inactive	Active	Highly active	SPMS	PPMS
			No clinical attacks and stable MRI	1 relapse in the previous year and/or new T2 gadolinium-enhancing lesions on MRI	1 relapse and new gadolinium-enhancing lesions and/or significant increase in T2 lesions while on DMTs 2 or more relapses in the previous year and MRI activity in patients not on DMT	**Steady increase in neurological disability independent of relapses following an initial relapse course**	Steady increase in neurological disability independent of relapses from disease onset
Treatment	DMT	• Glatiramer acetate • Interferon beta	Active monitoring with clinical assessment and MRI	• Dimethyl fumarate • Fingolimod • Teriflunomide • Interferon beta • Mitoxantrone • Natalizumab • Pegylated interferon (IFN) • Cladribine	• Alemtuzumab • Fingolimod • Natalizumab	**No licensed treatments**	• Ocrelizumab • Mitoxantrone
	Standard	• Offer high-dose corticosteroids for management of acute disabling relapses after ruling out infections • Offer treatment for ongoing symptoms such as bladder disturbances, constipation, spasticity, and pain • Promote brain health including smoking cessation, regular exercise, healthy diet and weight loss if appropriate • Treat comorbidities including depression, hypertension, diabetes and osteoporosis					

Angelis DF, et al. BMJ. 2018 Nov 27;363:k4674.

Mitoxantrone (Novantrone©)

- MOA: Induces DNA cross-links and strand breaks leading to apoptosis

Souorce: Mitoxantrone [Package Insert]. Lake Forest, IL: Hospira, Inc; May 2018.

Mitoxantrone (Novantrone©)

- Dosing
  - 12 mg/m² IV every 3 months
  - Lifetime cumulative dose limit of approximately 8–12 doses over 2–3 years (140 mg/m²)
- FDA indication
  - Reducing neurological disability and frequency of clinical relapses in adult patients with MS:
    - Progressive relapsing, secondary chronic relapsing, worsening relapsing-remitting MS
  - Approval 2000
- Monitoring
  - Baseline: CBC, heart function and LFTs
  - Follow-up: CBC, LFTs and annual monitoring of heart function indefinitely
    - Contraindicated in chronic heart failure (LVEF <50%)

Source: Mitoxantrone [Package Insert]. Lake Forest, IL: Hospira, Inc; May 2018.

Mitoxantrone (Novantrone©)

- Adverse effects:
  - Nausea, hair loss, menstrual change, URI, UTI, mouth sores, irregular heartbeat, back pain, blue-green urine
- Warnings:
  - Administered under physician with experience w/cytotoxic chemotherapy
  - Secondary acute myeloid leukemia
  - Cardiotoxicity
- Pregnancy category D

Source: Mitoxantrone [Package Insert]. Lake Forest, IL: Hospira, Inc; May 2018.

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

- Study design
  - Phase III, multi-centered, randomized, placebo controlled, double blinded
- Purpose
  - Evaluate the safety and efficacy of Ocrelizumab in adults with PPMS
- Patient population (n=732)
  - According to the McDonald criteria with an EDSS screening from 3 to 6.5 points in a 2:1 ratio between March 2011-July 2015
- Assigned in a 2:1 ratio to received treatment every 24 weeks for 120 weeks
  - Two infusions of ocrelizumab 300 mg IV for cycle 1 and 1 infusion of ocrelizumab 600 mg IV for each subsequent cycle
  - Matching placebo

Source: Montalban X, Hauser SL, Kappos L, et al. N Engl J Med. 2017 Jan 19;376(3):209-220.

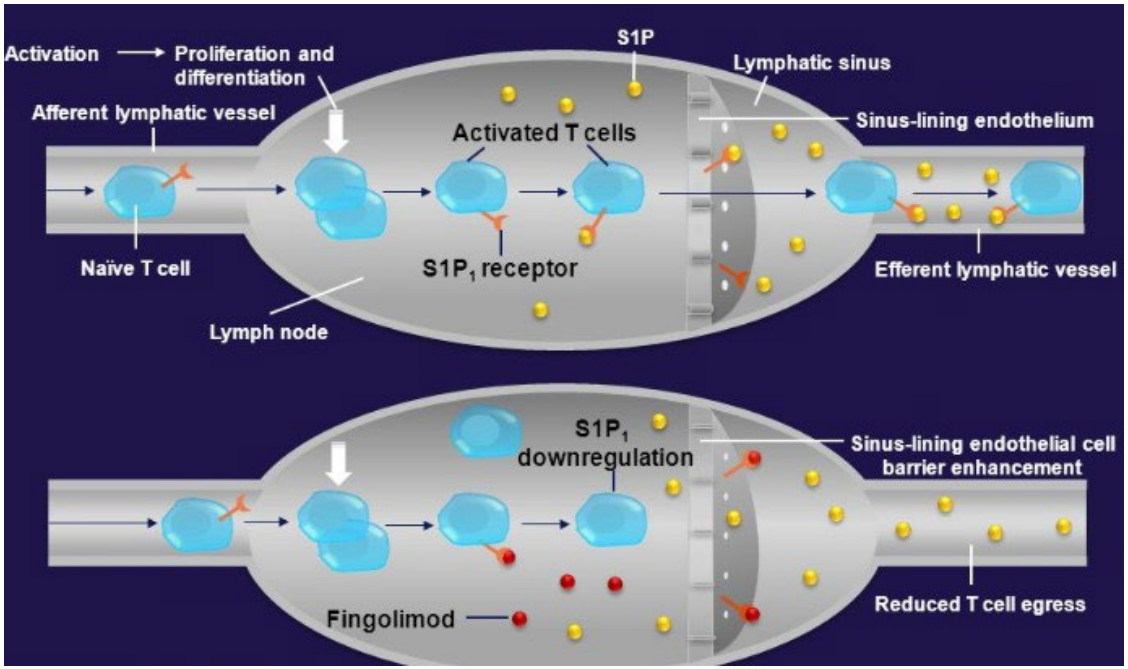
Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

- Endpoints
  - Confirmed disability progression
    - Week 12:
      - Ocrelizumab 32.9%, placebo 39.3% (HR 0.76, 95% CI 0.59-0.98, p=0.03)
    - Week 24:
      - Ocrelizumab 29.6%, placebo 35.7% (HR 0.75, 95% CI 0.58-0.98, p=0.04)
  - Total volume of MRI brain lesions:
    - Ocrelizumab 3.4%, placebo 7.4% (p=0.02)
  - Side effect:
    - Increased incidences of infusion related reactions, upper respiratory symptoms, and oral herpes
- Conclusion
  - Ocrelizumb had lower rates of clinical and MRI progression than placebo for PPMS

Source: Montalban X, Hauser SL, Kappos L, et al. N Engl J Med. 2017 Jan 19;376(3):209-220.

Siponimod (Mayzent©)

- MOA: blocks the lymphocytes' ability to emerge from lymph nodes; reducing the amount of lymphocytes available to the CNS



Sources: Horga A, et al. Expert Rev Neurotherp. 2008;8:699-714.
Mayzent (siponimod) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2019.

Siponimod (Mayzent©)

- Dosing
  - Initial: 0.25 mg capsule once daily for 1-2 days, increasing to 1 mg or 2 mg capsule once daily over 4-5 days (maintenance)
- FDA indication
  - For the treatment of adults with RRMS in adults
    - Isolated syndrome (CIS), RRMS and SPMS
  - Approval 2019
- Monitoring
  - CBC and LFTs at baseline and every 6 months
  - EKG and blood pressure at baseline and every initiation
  - Ophthalmologic and respiratory function annually

Source: Mayzent (siponimod) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2019.

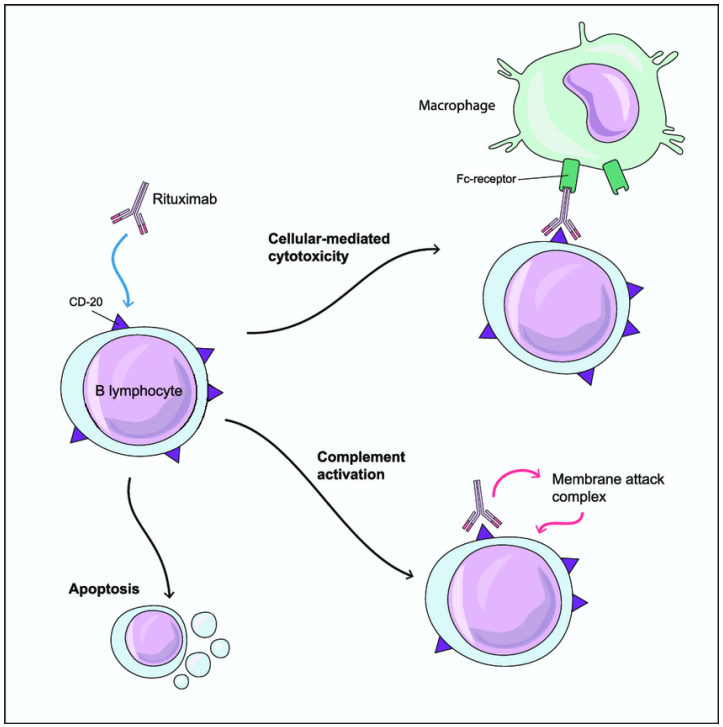
Siponimod (Mayzent©)

- Adverse effects:
  - Headache, high blood pressure, abnormal liver tests
- Warnings:
  - Bradycardia
  - Hypertension
  - Infection
  - Liver damage
  - Macular edema
  - PML
  - Posterior Reversible Encephalopathy Syndrome (PRES)
- Pregnancy category **X**

Source: Mayzent (siponimod) [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2019.

Rituximab (Rituxan©)

- MOA: monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes, activating complement-dependent B-cell cytotoxicity



Sources: D'Rozario J, et al. *Ther Adv Hematol*. 2019 May 10;10:2040620719844697.
Rituxan (rituximab) [Package Insert]. South San Francisco, CA: Genentech Inc; January 2020.

Rituximab (Rituxan©)

- Dosing
  - Initial: 1000 mg IV on days 1 and 15
- Off label-FDA indication
  - ANN for reducing risk of relapse and reducing T2 lesion size in patients with RRMS
- Monitoring
  - Baseline: CBC, peripheral CD20 cells, renal function, HBV and LFTs
  - Baseline: CBC, peripheral CD20 cells, renal function, and LFTs (at weekly and monthly intervals)
  - Ophthalmologic and respiratory function annually

Sources: Rituxan (rituximab) [Package Insert]. South San Francisco, CA: Genentech Inc; January 2020.
Hauser SL, et al. N Engl J Med. 2008 Feb 14;358(7):676-88.

Rituximab (Rituxan©)

- Adverse effects:
  - Abdominal pain, edema, flushing, hypertension, nausea, electrolyte abnormalities, fever, infusion reactions
- Warnings:
  - Cytopenias
  - Infection
  - Renal toxicity
  - Tumor lysis syndrome
  - HBV infection
  - Infusion related reactions
  - PML
  - Mucocutaneous reactions
  - Posterior Reversible Encephalopathy Syndrome (PRES)
- Pregnancy category **X**

Source: Rituxan (rituximab) [Package Insert]. South San Francisco, CA: Genentech Inc; January 2020.

POLLING QUESTION 5:

Terry is 36 y/o female with CIS for 10 years. She is recently married and now with insurance coverage is hoping to start on an oral DMT. She tells you she wants to start a family. Which of the following options would you recommend?

A. Glatiramer
B. Lemtrada
C. Aubagio
D. Tecfidera

QUESTION 5 RESPONSE:

Terry is 36 y/o female with CIS for 10 years. She is recently married and now with insurance coverage is hoping to start on an oral DMT. She tells you she wants to start a family. Which of the following options would you recommend?

A. Glatiramer
B. Lemtrada
C. Aubagio
D. **Tecfidera**

POLLING QUESTION 6:

Which of the following therapies used in MS does NOT require a REMS program?

A. Gilenya (fingolimod)
B. Tysabri
C. Lemtrada
D. Avonex

QUESTION 6 RESPONSE:

Which of the following therapies used in MS does NOT require a REMS program?

A. Gilenya (fingolimod)
B. Tysabri
C. Lemtrada
D. **Avonex**

ADJUNCTIVE THERAPY

Adjunctive Therapy

Symptom	Management	Comments
Sensory symptoms	Carbamazepine Phenytoin Amitriptyline Nortriptyline Gabapentin Pregabalin	• Consider NSAIDS for resulting joint pain
Spasticity	Baclofen Tizanidine Diazepam Cyclobenzaprine Dantrolene Gabapentin Botulinum toxin A	• Titrate to effect • Dantrolene and intrathecal baclofen used in severe cases
Bladder symptoms	Oxybutynin Imipramine/amitriptyline Prazosin Hyoscyamine Botulinum toxin A Solifenacin	

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

Adjunctive Therapy

Symptom	Management	Comments
Pathologic Laughing or Crying	Amitriptyline Fluvoxamine Dextromethorphan/Quinidine	• Mixed data for the use of TCAs
Insomnia	Chloral Hydrate Diphenhydramine Flurazepam	• Use with caution
Fatigue	Amantadine Antidepressants Modafinil Methylphenidate Dextroamphetamine	
Other Considerations	Flu Shot Pneumovax Risk of DVT	• Yearly • Assess mobility

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

Going Forward

- Biomarkers to assist in defining treatment failure
- Ideal time for initiation of therapy
- No studies comparing all drugs
- No role for combination disease modifying therapy

Source: Bhise V, et al. *Expert Rev Clin Immunol*. June 2016:1-21.

Take Home Points

- MS is a progressive disease with no cure
  - Goals of therapy are to slow disease progression, treat exacerbations & manage symptoms
- The majority of treatments are injections or infusions & education on proper administration & expected side effects is important
- Pharmacists can play an important role in terms of patient education & recommendations on managing specific symptoms

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Thank You!

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