Multiple Sclerosis

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Objectives

- Identify risk factors for MS
- Describe pathophysiology of MS
- Distinguish between forms of MS
- Compare disease modifying therapies and develop a suitable therapeutic plan
- Determine appropriate symptomatic management

What does MS look like?

- Julia – a 35yo white married mother of 3 who is exhausted all the time and can't drive because of vision problems and numbness in her feet
- Jackson – a 25yo African-American man who stopped working because he can't control his bladder or remember what he read in the morning paper
- Maria – a 10yo Hispanic girl who falls down a lot and whose parents just told her she has MS
- Loretta – a 47yo white single woman who moved into a nursing home because she can no longer care for herself

National Multiple Sclerosis Society "Multiple Sclerosis: What you need to know about the disease"

What is Multiple Sclerosis (MS)?

- Chronic progressive immune-mediated disease of the central nervous system (CNS)
- Classic definition: lesions of the central nervous system with dissemination in space and time
- Immune system attacks the myelin and the nerve fibers
- Often leads to significant disability
- Disability is associated with focal areas of lesions

Epidemiology of MS

Overview

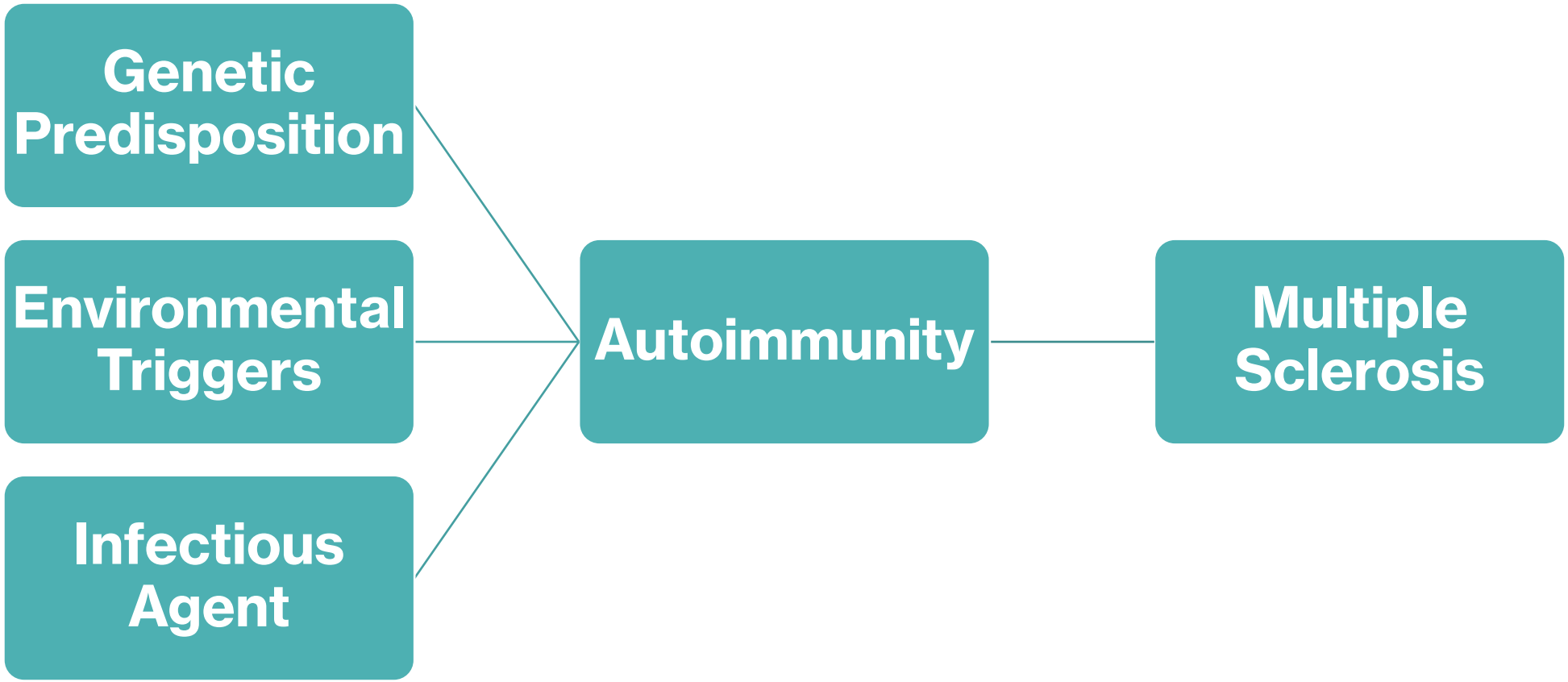
- > 2.8 million people with MS worldwide
- Nearly 1 million people affected in the United States
- ~12,000 new cases per year in the United States

Epidemiology of MS

Distribution

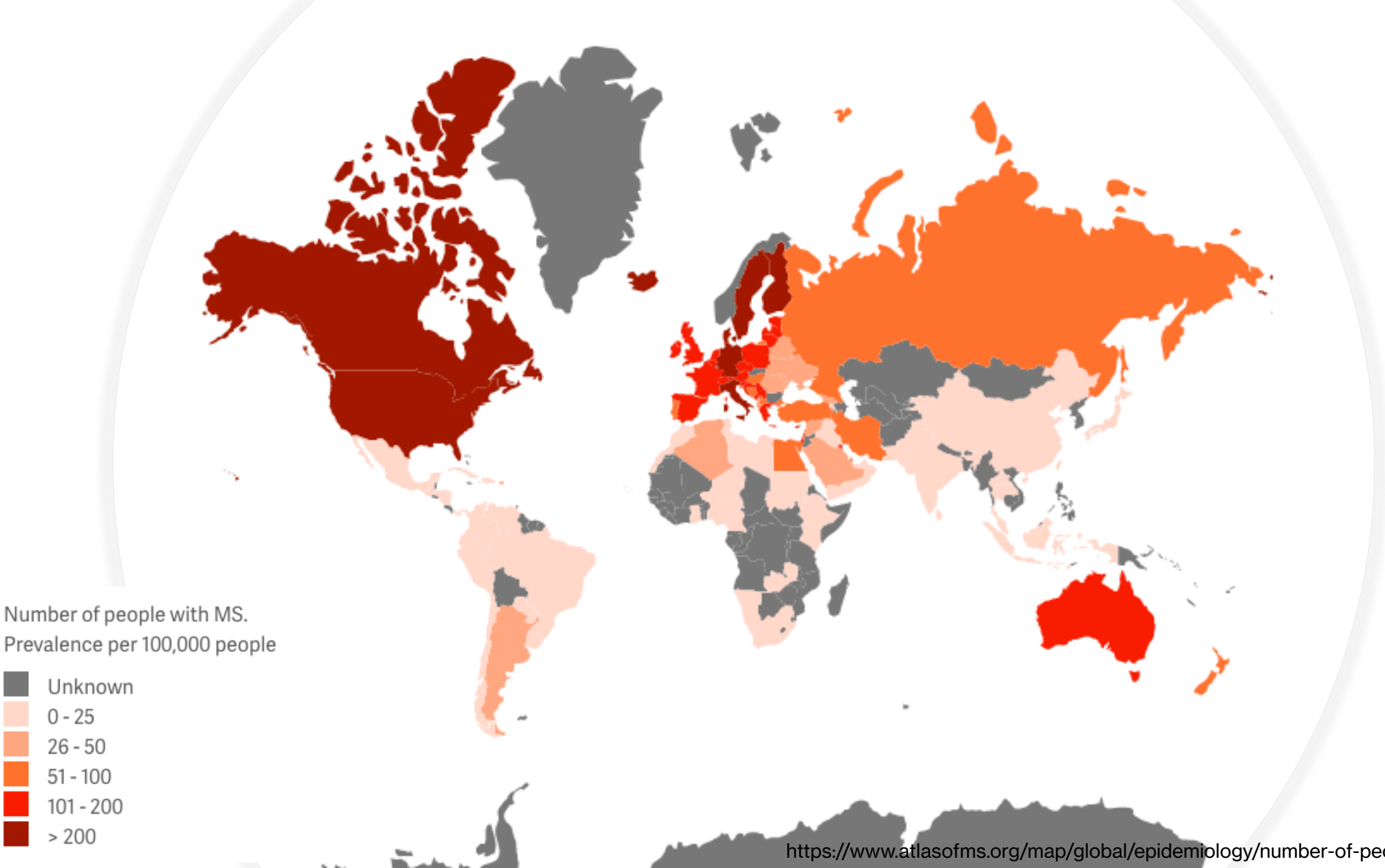
- Age
  - Onset usually between 20 and 50 years of age
- Geography (latitude)
  - 5-10/100,000 in tropical zones
  - 50-100/100,000 in temperate zones
- Gender
  - MS is 3x more common in women than in men
- Ethnic Background
  - Highest prevalence is thought to be in Caucasians of northern Europeans ancestry
  - Historically, it was thought that MS was less common in African Americans, however, that may not be the case
  - Hispanics and Asians are significantly less likely to develop MS

What Causes MS?



Environment

- Tobacco
  - Smokers have a 2-fold increased risk of developing MS
  - Smokers have a more aggressive disease course and are more likely to enter progressive pattern sooner
- Obesity
  - Obesity in childhood and adolescence can increase the risk of developing MS
- Vitamin D
  - Higher levels of serum 25-hydroxyvitamin D are associated with lower incidence of developing MS and a lower risk of relapse in those that have a diagnosis of MS
  - Goal level for vitamin D is 60–80 ng/dL
- Geographic gradient
  - MS is known to occur more frequently in areas further from the equator



https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms#

Infectious Agents

- Epstein-barr virus (EBV)
  - Very common in the general population
  - Risk of MS is 2-3x greater in those with infectious mononucleosis
- Other infectious agents proposed
  - Human herpes virus 6
  - Chlamydia pneumoniae
  - Canine distemper
  - Measles

Kateryna Kon / shutterstock.com

Jeffrey Epstein shown in a 2006 mug shot. (Photo: Palm Beach Sheriff's Office)

Genetic Factors

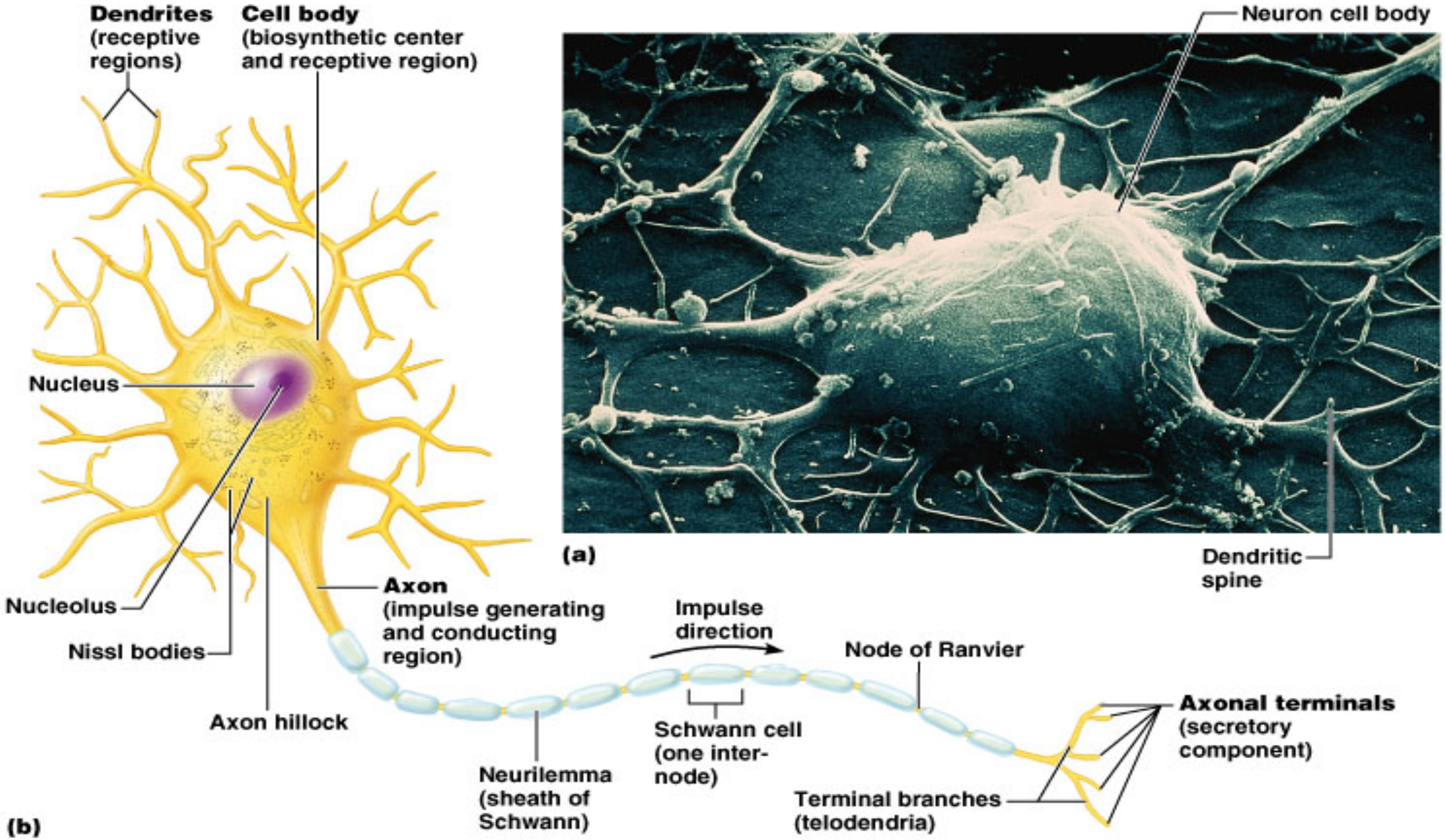
- MS is not an inherited disease
- There is a genetic risk that may be inherited
  - General population (0.1%)
  - Person with a close relative (1-4%)
  - Identical twin (25%)
- ~ 200 genes have been identified that contribute to the overall risk of developing MS
  - HLA-DRB1*15*01
  - IL2RA
  - IL7RA

Other Theories

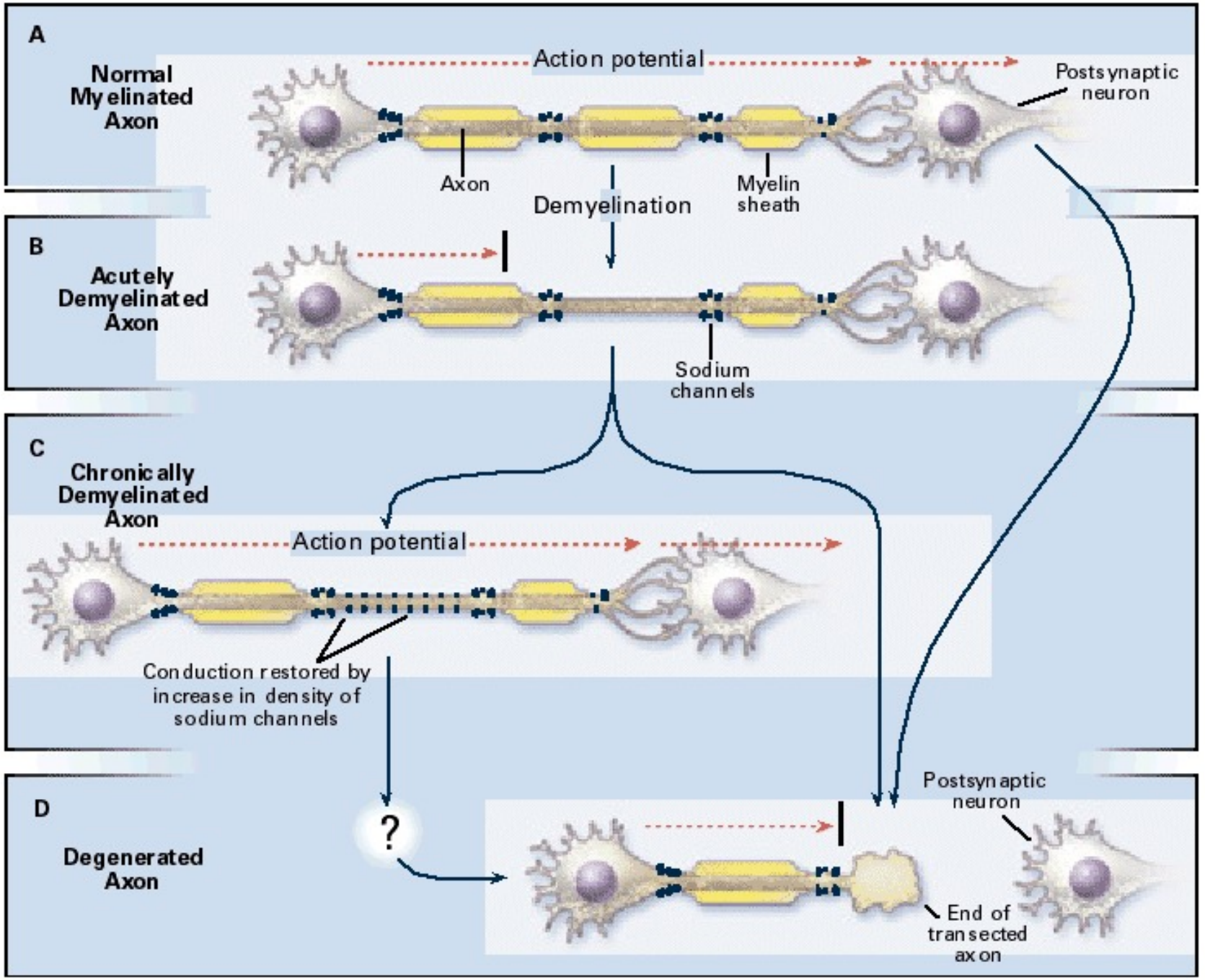
- Environmental allergies
- Exposure to household pets
- Exposure to heavy metals
- Organic solvents

What happens in MS?

- MS is an abnormal immune response that causes inflammation and damage in the CNS, specifically the myelin sheath in the brain and spinal cord
- Demyelination occurs as well-demarcated, focal, scattered lesions (plaques) in the brain, optic nerves and spinal cord
- Lesions can disrupt the messages traveling along the nerves
- Inflammation and demyelination are followed by focal gliosis (scar tissue formation)
- Remyelination may occur but tends to be abnormal and incomplete

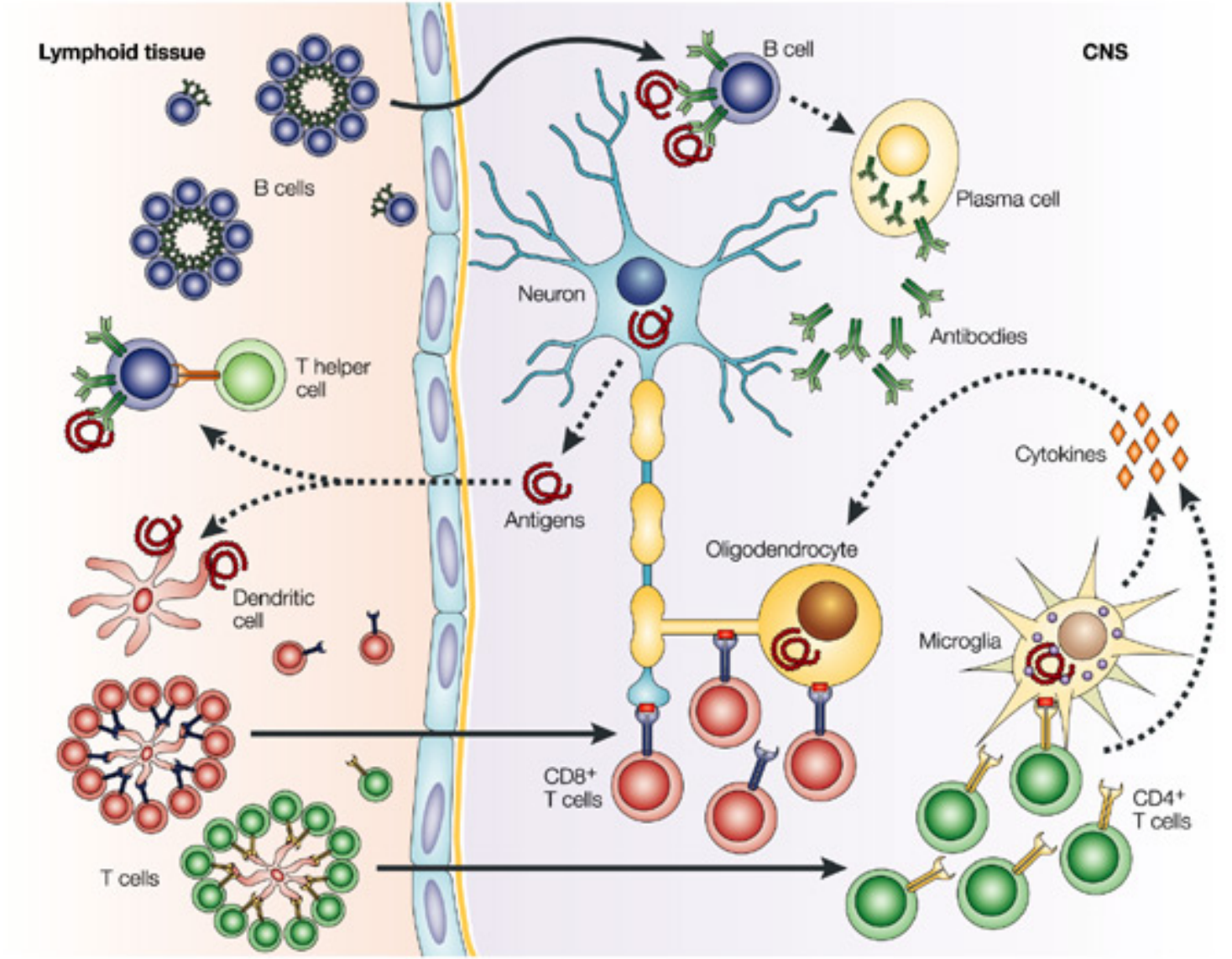

Dendrites
(receptive
regions)
Cell body
(biosynthetic center
and receptive region)
Nucleus
Nucleolus
Nissl bodies
Axon hillock
Axon
(impulse generating
and conducting
region)
Neurilemma
(sheath of
Schwann)
Impulse
direction
Schwann cell
(one inter-
node)
Node of Ranvier
Terminal branches
(telodendria)
Axonal terminals
(secretory
component)
(b)
Neuron cell body
Dendritic
spine
(a)

Demyelination in MS



Pathophysiology of MS

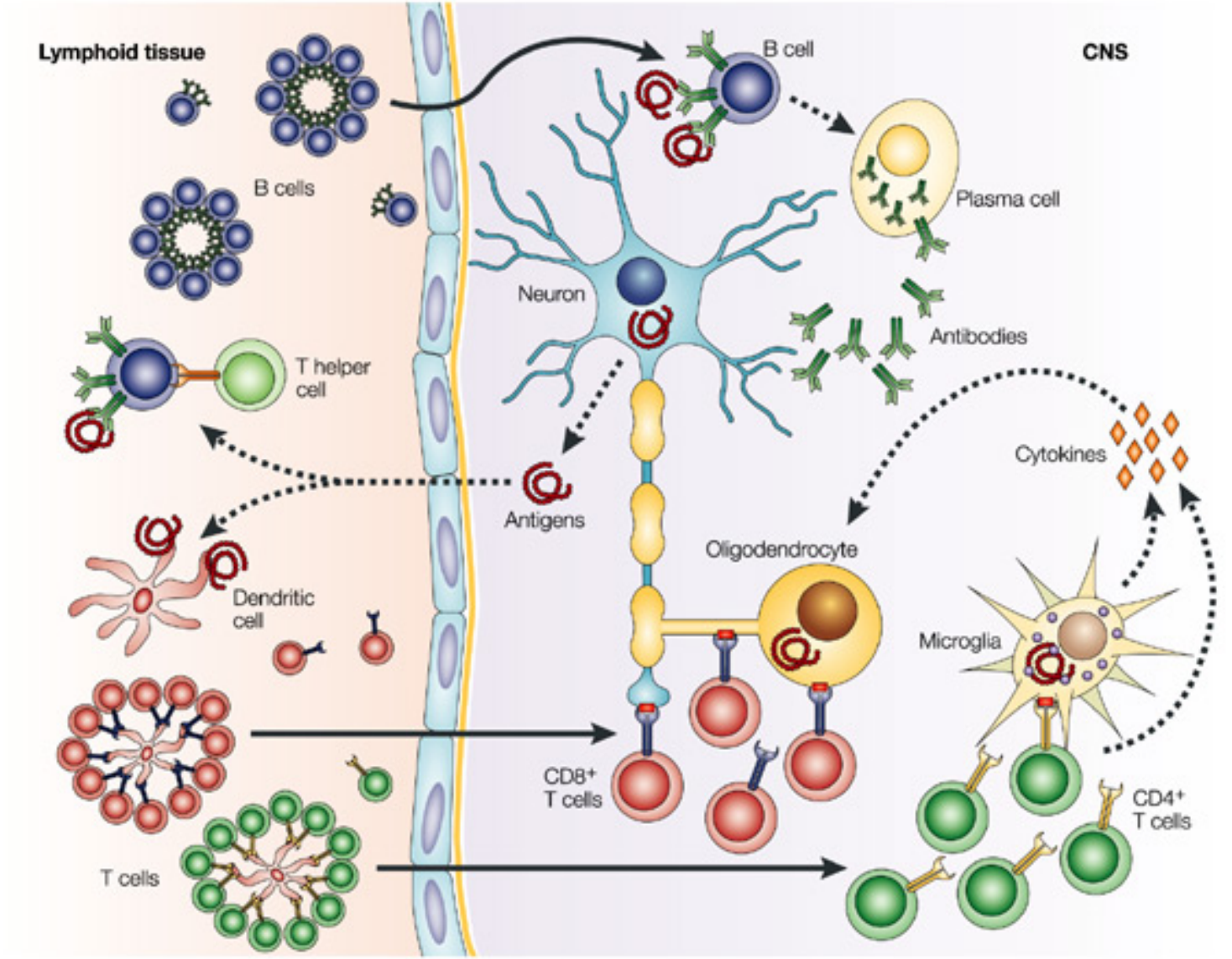
- Autoreactive lymphocytes are activated in the periphery
- Lymphocytes enter the CNS through the BBB
- Exposure of autoantigens in the CNS reactivate the lymphocytes



Nature Reviews | Neuroscience

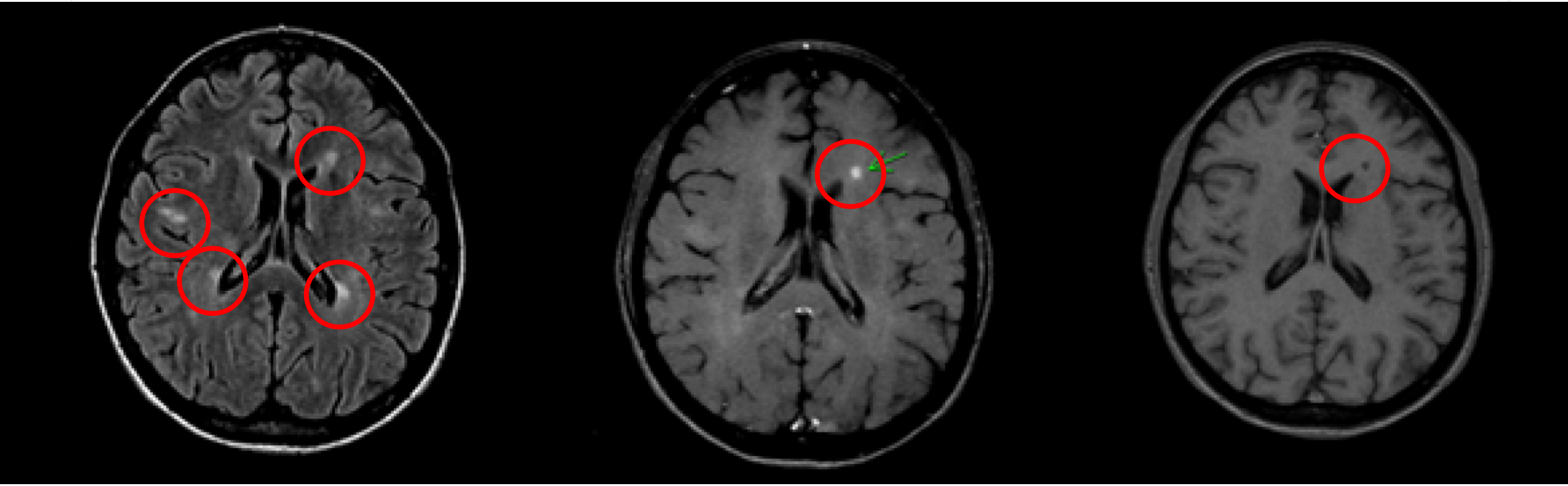
Pathophysiology of MS

- T cells recognize myelin as foreign and attack it
- B cells make antibodies that mark myelin
- Initiates inflammatory response releasing cytokines and antibodies that interact with macrophages
- Macrophages use antibodies to engulf oligodendrocytes and myelin



Nature Reviews | Neuroscience

MS Lesions on Brain MRI



Fluid-attenuated inversion recovery (FLAIR) image

T1 post-gadolinium (contrast)

T1-weighted MRI

Common Presenting Symptoms

- Fatigue
- Sensory disturbances
  - Numbness, tingling, burning, tightness
- Optic neuritis
  - Progressive monocular vision loss, impaired color vision, pain with eye movement, centrocecal scotoma
- Motor disturbance
- Brain stem / cerebellar involvement
  - Vertigo, diplopia

Symptoms of MS

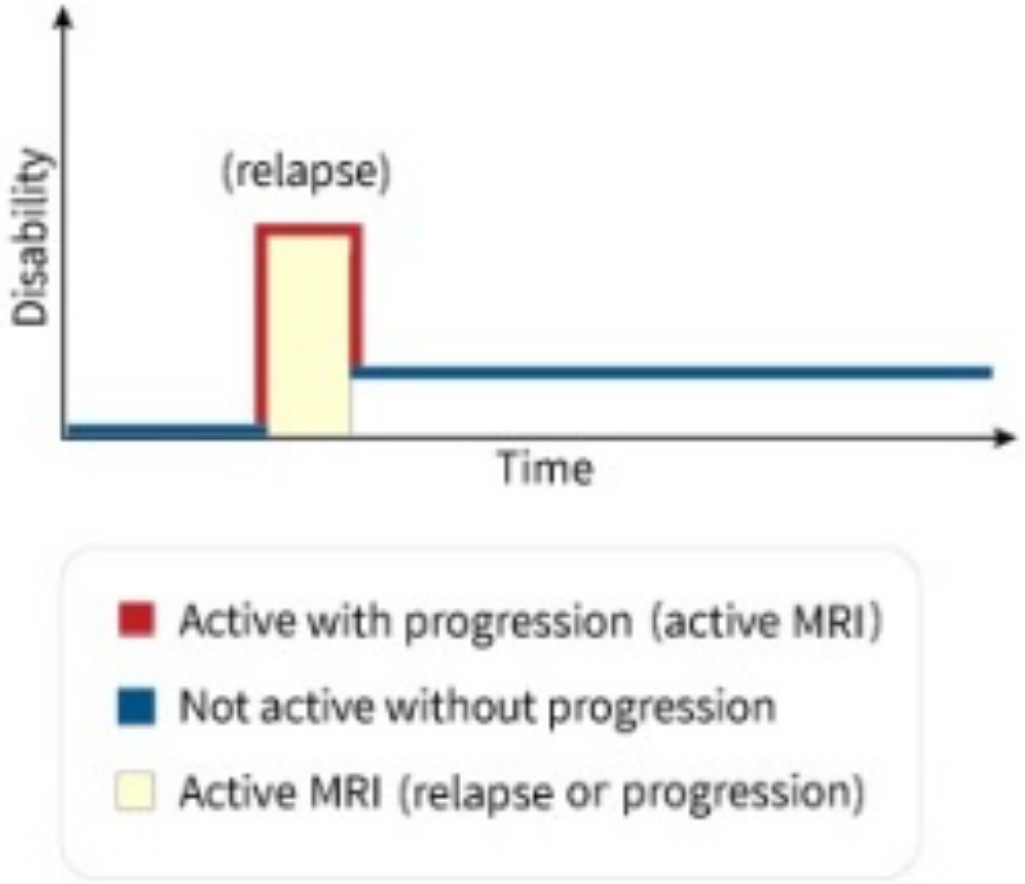
Primary	Secondary	Tertiary
• Fatigue • Weakness • Numbness/tingling • Dizziness/vertigo • Diplopia • Vision loss • Cognitive decline • Mood disorder • Pain • Bladder and bowel problems • Sexual dysfunction • **Gait difficulties** • **Spasticity** • **Speech/swallowing problems** • **Tremor**	• Falls • Injury • Bladder infections from urinary retention • Physical deconditioning	• Vocational changes • Social isolation • Change in relationships

Diagnosis of MS

- History
  - Duration of symptoms
- Physical exam
  - Objective neurological signs
- Laboratory
  - MRI, CSF, evoke potentials, serologies
- Requires dissemination in time and space
  - Space: Evidence of scarring in 2 or more separate areas of CNS
  - Time: Evidence that the plaques occurred at different time points
- Critical thinking
  - No better explanation

Clinical Patterns of MS: Clinically Isolated Syndrome (CIS)

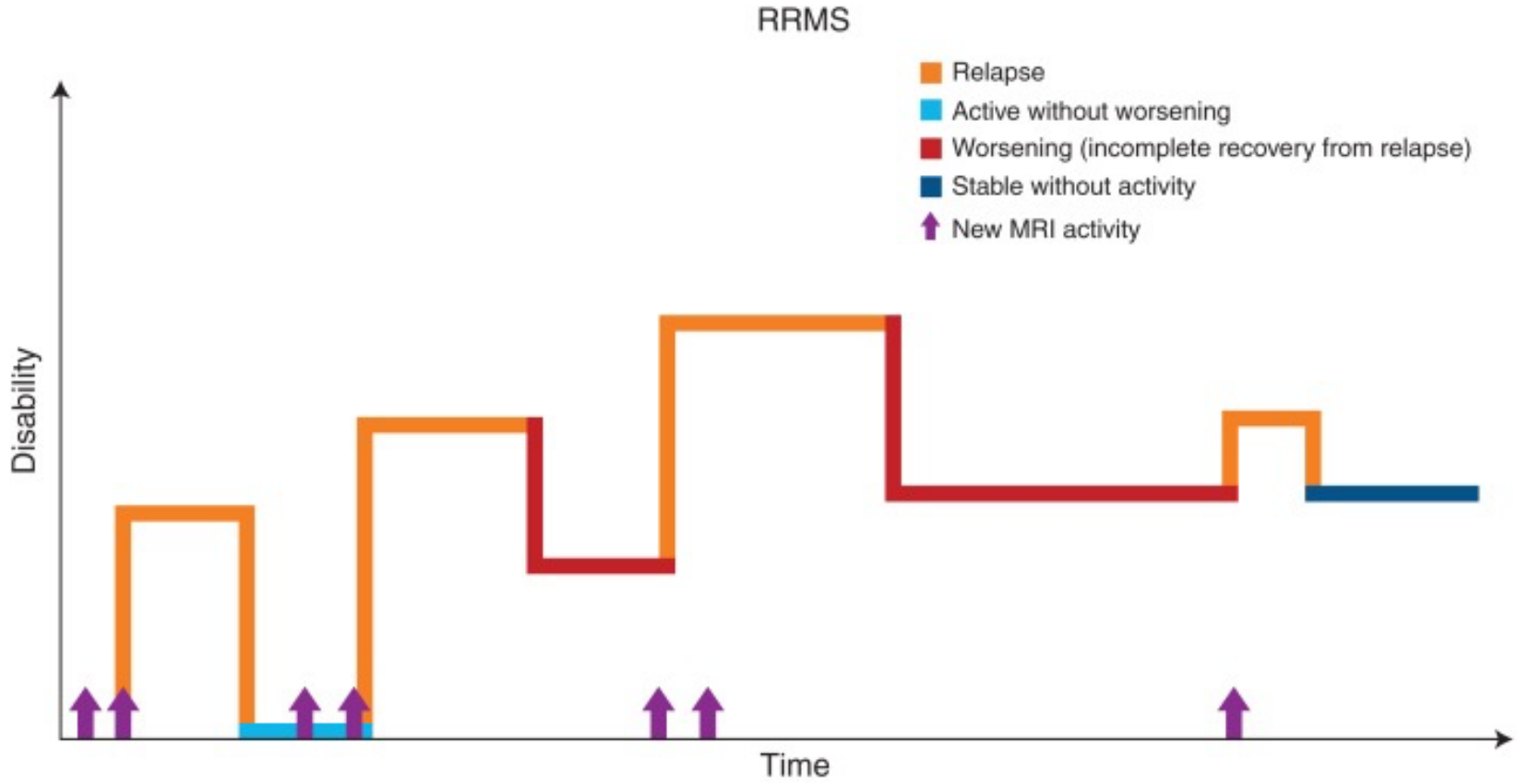
- First episode of neurologic symptom
- Lasts at least 24 hours
- Monofocal or multifocal episode
- Individual may or may not go on to develop MS



https://my-ms.org/ms_types.htm

Clinical Patterns of MS: Relapsing Remitting MS (RRMS)

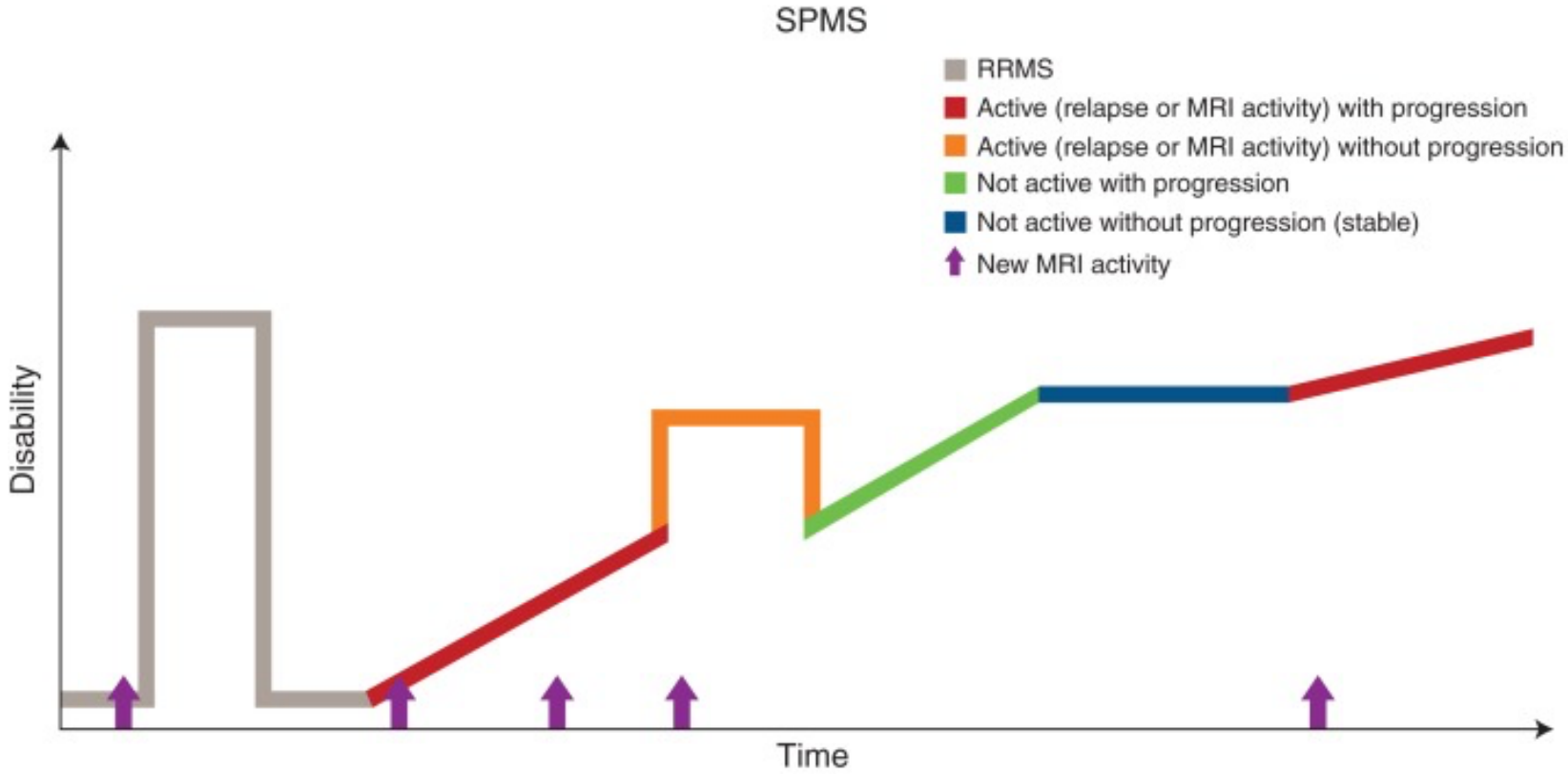
- Irregular occurrences of attacks, followed by full or partial neurological recovery between attacks
- 85% of all MS cases



Lubin et al. 2014

Clinical Patterns of MS: Secondary Progressive MS (SPMS)

- Progressive accumulation of disability after initial relapsing course
- Without treatment, approximately 50% of patients with RRMS transition to SPMS within 10 years



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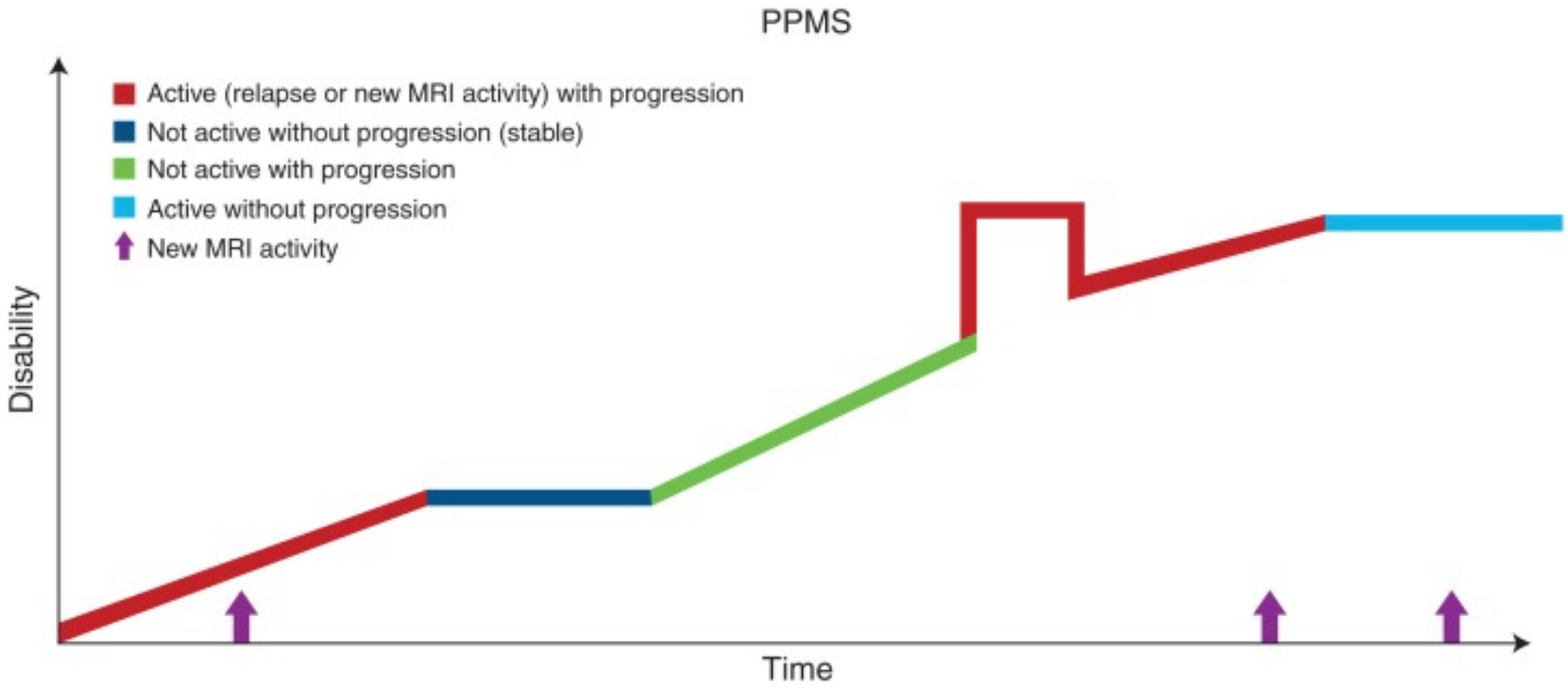
Clinical Patterns of MS: Primary Progressive MS (PPMS)

- Progressive accumulation of disability from the beginning of disease without periods of relapse
- 10-15% of all initial MS diagnosis



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Expanded Disability Status Scale (EDSS)

The EDSS: Assessing the course of disease[1]

NOTE:

The EDSS scale is weighted toward measuring ambulation and is not especially sensitive to cognitive change.

Adapted from Kurtzke JF. *Neurology*. 1983;33:1444-1452. For educational purposes only.

Prognosis

Characteristics that predict a better outcome:

- Female
- Onset before age 35
- Sensory symptoms
- Monofocal rather than multifocal episodes
- Complete recovery following a relapse

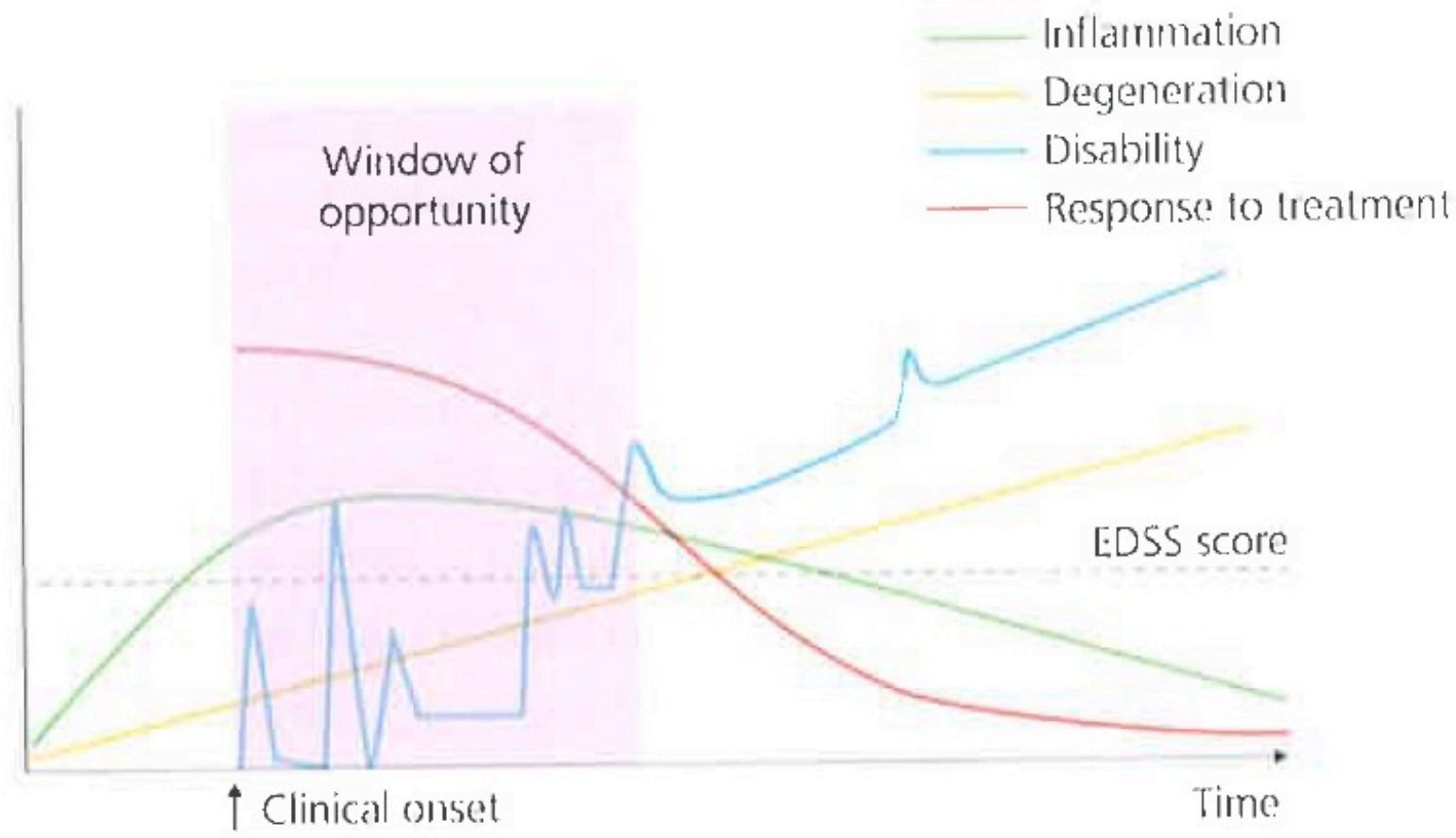
Risk factors for poor prognosis:

- Age 40+ at onset
- Male gender
- African American
- Motor, sphincter, cerebellar, or spinal cord symptoms
- Brain stem or spinal cord lesions at onset
- 2+ attacks in the first 2 years of onset
- Incomplete recovery from relapse

Therapeutic Goals

- Disease-modifying therapy
  - Prevent relapses
  - Prevent development of new or enhancing lesions on MRI
  - Prevent disability
- Treatment of relapse
- Symptomatic management
  - Relieve symptoms
  - Maintain well-being
  - Optimize quality of life
- Rehabilitation
  - Improve or maintain function
- Psychosocial management

When to Treat?



Treatment Adherence Issues

- Patient readiness
- Factors that impact adherence:
  - Lack of knowledge about MS
  - Unrealistic expectations
  - Denial of illness
  - Side effects
  - Cultural factors
  - Lack of support (medical team, personal support system)
  - Distrust of medical community

MS Disease-Modifying Therapies (DMTs)

"Platform" Therapies

- Interferons
  - IFN β-1b (Betaseron)
  - IFN β-1b (Extavia)
  - IFN β-1a IM (Avonex)
  - IFN β-1a SubQ (Rebif)
  - PegIFN-β-1a (Plegridy)
- Glatiramer acetate (Copaxone and Glatopa)
- Ofatumumab (Kesimpta)

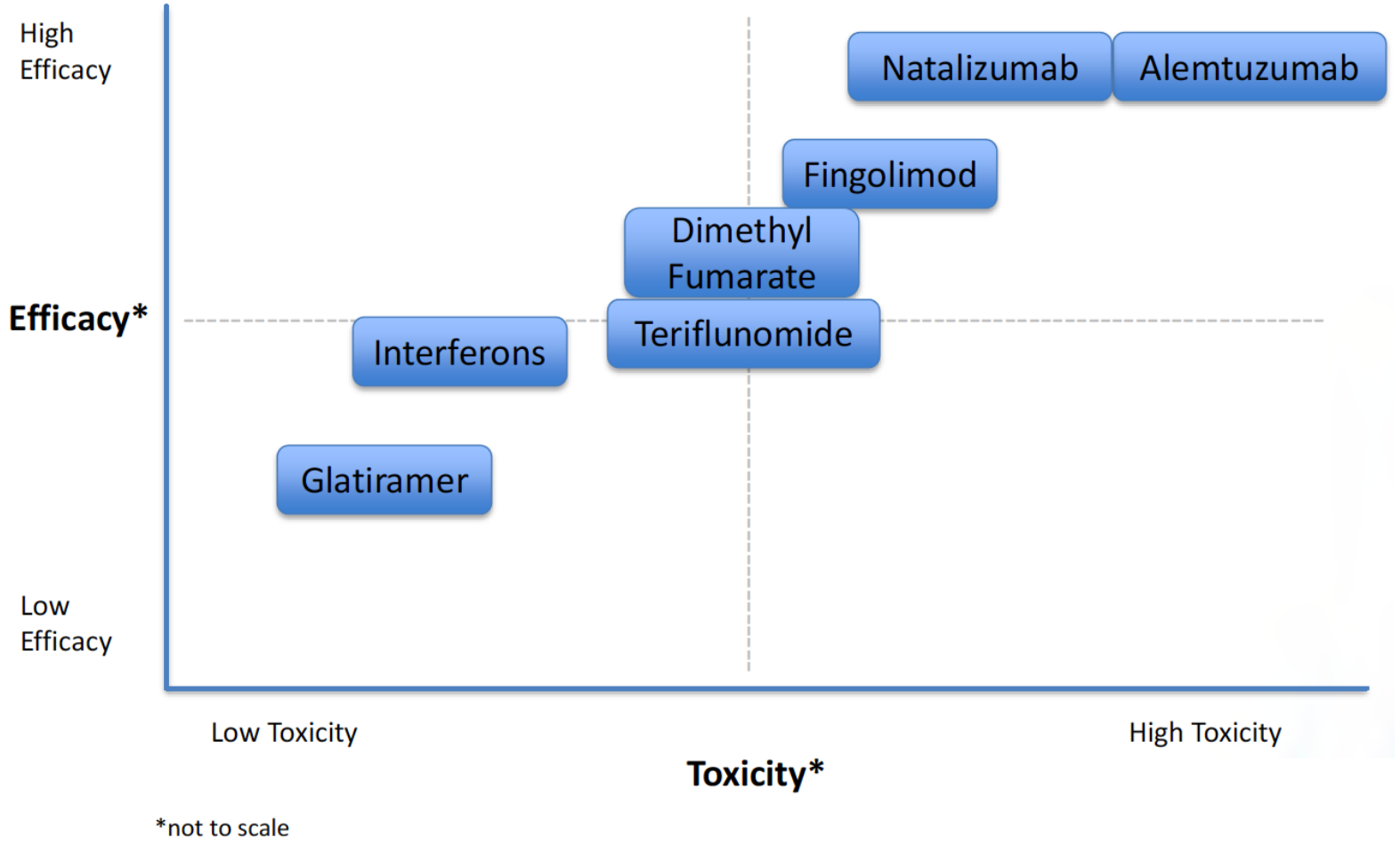
Oral Therapies

- Fingolimod (Gilenya)
- Terifluomide (Aubagio)
- Monomethyl fumarate (Bafiertam)
- Dimethyl fumarate (Tecfidera)
- Siponimod (Mayzent)
- Cladribine (Mavenclad)
- Diroximel fumarate (Vumerity)
- Ozanimod (Zeposia)

Monoclonal Antibodies

- Natalizumab (Tysabri)
- Alemtuzumab (Lemtrada)
- Ocrelizumab (Ocrevus)
- Mitoxantrone (Novantrone)

DMT Efficacy vs. Toxicity



*not to scale

Defining Efficacy

Reduction of clinical response

- Annual Relapse Rate (ARR)

Delay of disability progression

- Confirmed Disability Progression (CDP)
- Expanded Disability Status Scale (EDSS)

Reduction of new lesions

- MRI outcomes

Defining “Suboptimal” Response

- Progression of EDSS > 1.5 points in 6-12 months
- > 2 clinically relevant attacks within 6 months
- Persistence of active disease on MRI
  - Gadolinium enhancing lesions
  - Increased lesion load
  - Development of general or focal atrophy (black holes)

MS Disease-Modifying Therapies

“Platform” Therapies or Self-Injected DMTs

Drug	Indication	Route	Dose	Frequency
IFN β-1b	Relapsing	SubQ	0.25 mg	Every other day
IFN β-1a	Relapsing	IM	30 mg	Every 7 days
IFN β-1a	Relapsing	SubQ	44 mcg	3x per week
PegIFN β-1a	Relapsing	SubQ	125 mcg	Every 14 days
Glatiramer	Relapsing	SubQ	20 mg	Once daily
Glatiramer	Relapsing	SubQ	40 mg	3x per week
Ofatumumab	Relapsing	SubQ	20 mg	Monthly

Interferons (IFNs)

- Mechanism of action
  - Stabilizes the BBB: ↓ matrix metalloproteinases
  - Reduce CNS inflammation by inhibiting T-cell activation, proliferation, and migration into CNS
- IFN beta 1-b
  - First DMT
  - Subcutaneous injection administered every other day
- IFN beta 1-a
  - Several formulations (intramuscular, subcutaneous, pegylated preparations)

INFs: Monitoring/Managing/Patient Education

- **Injection site reactions**
  - Pain, erythema, swelling/bruising
  - SubQ > IM
  - Incidence ↓ after 3 months
- **Flu like symptoms**
  - 2-8 hours post-dose and resolves after ~24 hours
  - Improves with continued dosing
  - Greatest frequency with IFN β-1a IM

INFs: Monitoring/Managing/Patient Education

- LFT abnormalities
  - Greatest risk during 1st year
  - Monitor LFTs at 1, 3, and 6 months, then periodically
- Leukopenia/lymphopenia
  - ↓ WBC and lymphocytes with all IFNs
  - Monitor CBC w/ differential at 1, 3, and 6 months then periodically
- Depression
  - Risk with all IFNs
  - Screen for depression at baseline and on-going counseling should be provided

Impact of Neutralizing Antibodies to Beta Interferon

- Exposure to interferon products can lead to the development of neutralizing antibodies
- Interferon beta-1a less antigenic than interferon beta 1-b
- Average interferon bioavailability lower for Nab (+) vs Nab (-) patients
  - Risk for becoming Nab (+): Betaseron > Rebif > Avonex
- Clinical significance: response lower for Nab (+) patients
- This may require larger interferon doses or changing therapies

Glatiramer Acetate (GA)

- Mixture of random polymers of four amino acids and is similar to myelin basic protein (component of myelin sheath of nerves)
- Mechanism of action
  - Synthetic protein that mimics myelin basic protein (MBP) and blocks T-cell mediated damage to myelin
  - Produces T-cells that suppress the immune attack on myelin
  - Exerts effect within the BBB

GA: Monitoring/Managing/Patient Education

- **Injection site reactions**
  - Pain, erythema, swelling and pruritis
  - No difference between doses
- **Immediate post-injection reaction (IPIR)**
  - Systemic reaction following injection
  - Flushing, chest tightness, palpitations, dyspnea, anxiety
  - Self-limiting with spontaneous recovery
- Lipoatrophy
  - Most prevalent with glatiramer acetate 20mg
  - Permanent and often disfiguring

Ofatumumab

- Mechanism of action
  - Binds to CD20 on immune B cells and depletes them
- Most common adverse effects
  - **Respiratory tract infection**
  - **Headache**
  - **Injection-related reaction**
- Live or live-attenuated vaccines are not recommended during treatment
- Levels of immunoglobulins should be monitored before, during and after treatment
- PML

Oral DMTs

Drug	Indication	Route	Dose	Frequency
Fingolimod	Relapsing	Oral	0.5 mg	Once daily
Siponimod	Relapsing	Oral	1 - 2 mg	Once daily
Teriflunomide	Relapsing	Oral	7 - 14 mg	Once daily
Dimethyl fumarate	Relapsing	Oral	240 mg	Twice daily
Cladribine	Relapsing	Oral	3.5mg/kg	2-year trt course
Monomethyl fumarate	Relapsing	Oral	190 mg	Twice daily
Diroximel fumarate	Relapsing	Oral	462 mg	Twice daily
Ozanimod	Relapsing	Oral	0.92	Once daily

Fingolimod

- Mechanism of action:
  - Prevents lymphocytes from exiting lymph nodes by blocking sphingosine 1-phosphate (S1P) receptor, which is important in cell transport and other biological processes
- Drug Interactions
  - Ketoconazole
    - Ketoconazole inhibits CYP 3A4, therefore it increases fingolimod by 70% with concomitant use
  - Class 1a & Class III antiarrhythmics
    - Concomitant use contraindicated
    - 1a = quinidine, procainamide, disopyramide
    - III = amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, dronedarone

Fingolimod: Managing/Monitoring/Patient Education

- First-dose effects – bradycardia
  - Observe patients for signs and symptoms of bradycardia for ≥6 hours after first dose with hourly pulse and BP measurement
  - Obtain ECG prior to dosing and at the end of the observation period
- Lymphopenia
- Opportunistic infections
- Malignancies – skin examination prior to treatment initiation
- Macular edema – changes in vision
- Pulmonary function tests – if positive patient history
- PML

Fingolimod: Managing/Monitoring/Patient Education

- **Headache**: most prominent and severe the first 2 weeks of therapy
- **LFT abnormalities**
- Infection
  - Recent CBC should be available before treatment initiation.
  - Patients should be vaccinated for varicella virus if antibody negative.
  - Consider stopping therapy if serious infection develops.
  - Avoid live attenuated vaccines during treatment and for at least 2 months after stopping therapy (FluMist, yellow fever, varicella).

Siponimod

- Mechanism of action: sphingosine 1-phosphate (S1P) receptor inhibitor
  - Binds to 2 receptors on the surface of the cells (S1P1 and S1P5)
    - Blocks lymphocytes from leaving the lymph nodes and entering peripheral blood
    - Also binds to S1P1 AND S1P5 on oligodendrocytes and astrocytes which are thought to promote remyelination and prevent inflammation
- CYP2C9 *1/*1 maintenance dose of 2 mg daily
- CYP2C9 *1/*3 or *2/*3 genotype maintenance dose of 1 mg daily
- Contraindicated in patients with CYP2C9 *3/*3

Simponimod: Managing/Monitoring/Patient Education

- Most common side effects: **headache, hypertension, changes in LFTs**
- Serious adverse events: decrease in white blood cells, bradycardia, rhythm abnormalities, decreased pulmonary function, infections, and liver toxicity
- Contraindicated in patients who have had recent myocardial infarction, unstable angina, stroke, transient ischemic attack, advanced heart failure, or have 2nd or 3rd degree AV block
  - Electrocardiogram (ECG) before first dose of siponimod

Ozanimod

- Mechanism of action: sphingosine 1-phosphate receptor modulator
  - Binds to 2 receptors on the surface of the cells (S1P1 and S1P5)
    - Blocks lymphocytes from leaving the lymph nodes and entering peripheral blood
    - Also binds to S1P1 AND S1P5 on oligodendrocytes and astrocytes which are thought to promote remyelination and prevent inflammation

Ozanimod: Managing/Monitoring/Patient Education

- Most common side effects:
  - **Upper respiratory tract infection**
  - **Elevated LFTs**
  - **Orthostatic hypotension**
  - **Back pain**
  - **Hypertension**
- Pre-dose tests and evaluations:
  - CBC and LFTs
  - Eye exam in those with a history of certain eye disorders or diabetes

Teriflunomide

- Mechanism of action
  - Active metabolite of leflunomide
  - Inhibits pyrimidine synthesis
  - Disrupts the interaction of T cells with antigen presenting cells
  - May decrease activated lymphocytes in CNS

Teriflunomide: Drug Interactions

Teriflunomide induces CYP1A2:

- Warfarin (Major)
- Clozapine (Major)
- Olanzapine (Moderate)
- Tizanidine (Moderate)
- Fluvoxamine (Moderate)
- Tacrine (Moderate)
- Haloperidol (Moderate)
- Imipramine (Moderate)
- Naproxen (Moderate)
- Duloxetine (Moderate)
- Cyclobenzaprine (Moderate)

Teriflunomide inhibits CYP2C8:

- Pioglitazone (Moderate)

Teriflunomide: Managing/Monitoring/Patient Education

Most common side effects

- **Diarrhea**
- **Nausea**
- **Thinning hair**

Serious adverse events

- Hepatotoxicity (black box warning)
- Infection
- Peripheral neuropathy
- Acute renal failure
- Hyperkalemia
- Skin rash
- Increased blood pressure
- Cardiovascular deaths
- Teratogenic (black box warning)

- Accelerated Elimination Procedure:
  - Cholestyramine: 8 grams Q8H x 11 days (if not tolerated, 4 grams Q8H x 11 days)
  - Activated charcoal: 50 grams Q12H X 11 days
  - Will decrease serum concentration of teriflunomide by 98%

Teriflunomide: Managing/Monitoring/Patient Education

- Pregnancy: counsel/confirm use of reliable contraception in women of child-bearing potential and men
- Counsel patients about potential treatment adverse effects such as headache and hair thinning
- Obtain serum transaminase and bilirubin levels and CBC within 6 months before initiating therapy
- Patients should be brought up to date with all immunizations before initiating therapy – Live vaccines should not be administered concurrently
- Monitor renal function; however, in clinical trials ~10 patients had acute renal failure; upon retesting, patients had normal creatinine; the cause may be uric acid nephropathy

Teriflunomide: Managing/Monitoring/Patient Education

- Screen for latent tuberculosis with tuberculin skin test; if positive, manage with standard medical practice prior to starting therapy
- Check blood pressure before commencing therapy and periodically thereafter
- Monitor LFTs at least monthly for first 6 months after initiation and at regular intervals thereafter
- Consider suspending/discontinuing treatment and using accelerated elimination procedure if serious infection develops or liver injury
- Discontinue therapy and use accelerated elimination procedure in patients who wish to become pregnant or become pregnant

Cladribine

- Mechanism of action:
  - Selectively targets and depletes immune system's B and T cells
- Dosing: 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg
  - 2 courses separated by at least 43 weeks (~ 10 months)
  - After completing 2-course regimen, medication is not given again

Cladribine: Managing/Monitoring/Patient Education

- **Upper respiratory tract infections**
- **Headaches**
- **Decreased lymphocyte counts**
- Increased risk for herpes zoster infection and cancers
- Contraindicated in pregnant women and men and women of reproductive potential who do not plan to use effective contraception
- Due to severe adverse event profile, generally only recommended for patients who have inadequate response or are unable to tolerate an alternative drug
- Prior to drug administration:
  - Screened to exclude infections, malignancy, and pregnancy
  - Baseline MRI
  - Lymphocyte monitoring (before, during, and after treatment)

Dimethyl fumarate

- Mechanism of action
  - Anti-inflammatory properties
  - Activates nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which is involved in the cellular response to oxidative stress

Dimethyl fumarate: Managing/Monitoring/Patient Education

- **Flushing**
- **Abdominal pain**
- **Diarrhea**
- **Nausea**
- Elevated LFTs
- Decreased lymphocyte counts
- Respiratory infections
- Chronic itching
- PML

Dimethyl fumarate: Managing/Monitoring/Patient Education

- CBC should be performed within 6 months before initiating treatment; recommended annually and as clinically indicated thereafter
- Administration of medication with food may reduce the incidence of flushing and GI upset
- Consider symptomatic therapies to manage GI events during initial treatment period
- Consider withholding treatment in patients with serious infections until resolved

Monomethyl fumarate

- Mechanism of action
  - Modulate the immune response to be less inflammatory
  - Possibly antioxidant properties that could protect against damage to the brain and spinal cord

Monomethyl fumarate: Managing/Monitoring/Patient Education

- Most common side effects
  - **Flushing, redness, itching, or rash**
  - **Nausea, vomiting, diarrhea, or stomach pain**
    - Take without food to reduce incidence of GI upset
- Possible serious adverse effects
  - PML
  - Decreased lymphocyte count
  - Elevated LFTs

Diroximel fumarate

- Mechanism of action
  - Modulate the immune response to be less inflammatory’
  - Possibly antioxidant properties that could protect against damage to the brain and spinal cord
- Similar to dimethyl fumarate with less GI side effects

Infused DMTs

Drug	Indication	Route	Dose	Frequency
Natalizumab	Relapsing	IV	300 mg	Every 28 days
Alemtuzumab	Relapsing	IV	12 mg	Every 12 months
Ocrelizumab	Relapsing and PP	IV	600 mg	Every 6 months
Mitoxantrone	Relapsing	IV	12 mg/m^2	Every 3 months

Natalizumab

- Mechanism of action
  - Monoclonal antibody: Inhibits the cellular adhesion molecule α-4 integrin and prevents immune cells from crossing the BBB and entering the CNS
- Black Box Warning - Progressive multifocal leukoencephalopathy (PML):
  - Potentially disabling and fatal viral disease characterized by progressive damage of the white matter of the brain in multiple locations
  - Risk factors:
    - ↑ treatment duration (> 2 years)
    - Prior infection to anti-JC virus
    - Prior immunosuppressant therapy
  - Test for anti-JC virus every 6 months

Natalizumab and PML

Estimated US Incidence of PML Stratified by Risk Factor[b]

ANTI-JCV ANTIBODY-NEGATIVE PATIENTS		
1/10,000		

ANTI-JCV ANTIBODY-POSITIVE PATIENTS		
TYSABRI Exposure	**No Prior Immunosuppressant Use**	**Prior Immunosuppressant Use**
1-24 months	<1/1000	1/1000
25-48 months	2/1000	6/1000
49-72 months	4/1000	7/1000
73-96 months	2/1000	6/1000

https://www.tysabrihcp.com/en_us/home/efficacy-safety/pml-risk.html

REMS

- All patients must be enrolled in TOUCH program
- Determine anti-JC virus antibody serostatus; check every 6 months if seronegative

JC virus = John Cunningham virus
IS = immunosuppressant

Natalizumab: Monitoring/Management/Patient Education

- **Headache**
- **Fatigue**
- Hypersensitivity reactions – use diphenhydramine and methylprednisolone
- Neutralizing antibodies
- Melanomas/other cancers
- Liver injury
- Reactivation of latent viruses
- Immune reconstitution inflammatory syndrome (IRIS)

Almetuzumab

- Mechanism of action:
  - Recombinant monoclonal antibody
  - Causes antibody-dependent cellular cytolysis, complement-mediated lysis, and depletes circulating T and B lymphocytes by binding to CD52, on the surface of B and T lymphocytes, monocytes, macrophages, and natural killer cells
- Reserved for patients with highly active disease who have had inadequate response to 2 or more DMTs or where other DMTs cannot be used

Almetuzumab: Dosing

- Dosing
  - First treatment course: 12 mg/day IV for 5 consecutive days (60 mg total dose)
  - Second treatment course (1 year later): 12 mg/day IV for 3 consecutive days (36 mg total dose)
- Premedication/prophylaxis
  - Methylprednisolone 1000 mg (or equivalent) immediately prior to infusion for the first 3 days
  - Herpes viral prophylaxis – oral acyclovir 200 mg twice daily (from first day of treatment until at least 2 months after completion of treatment OR CD4+ count $\geq$ 200 cells/mcL)

Almetuzumab: Safety

- Black Box Warnings:
  - Infusion reactions: Serious and life-threatening infusion reactions, can occur after the 2-hour monitoring period.
  - Autoimmune disorders: Serious, sometimes fatal autoimmune conditions including immune thrombocytopenia and antiglomerular basement membrane disease
  - Malignancy: Increase the risk of malignancies (thyroid cancer, melanoma, and lymphoproliferative disorders)
  - Only available through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) program

Almetuzumab: Managing/Monitoring/Patient Education

- Infusion reactions, during and minimum of 2 hours
- Varicella zoster virus (VZV) antibodies
- CBC with differential, prior to treatment and monthly until 48 months post-treatment
- Serum creatinine levels, and urinalysis with urine cell counts monthly until 48 months after discontinuing therapy
- Thyroid function, prior to treatment and every 3 months thereafter until at least 48 months post-treatment
- Signs and symptoms of thyroid cancer
- Baseline and yearly skin exams

Ocrelizumab

- Indicated: Relapsing remitting and primary progressive
- Mechanism of action:
  - Recombinant humanized anti-CD20 monoclonal antibody
  - Binds to CD20 on B lymphocytes to promote cytolysis
- Dosing:
  - Starting dose: 300 mg IV infusion followed by 300 mg infusion 2 weeks later
  - Subsequent doses: 600 mg IV infusion every 6 months
- Starting ocrelizumab therapy sooner rather than later may slow disability progression in PPMS

Ocrelizumab: Managing/Monitoring/Patient Education

- Pre-medicate with steroids, antihistamines and an antipyretic
- Contraindicated in patients with active hepatitis B
- Patients should receive all necessary immunizations at least 6 weeks before starting medication
  - Live-attenuated and live vaccines are not recommended during treatment or until B-cell repletion occurs
- Common adverse events

Infusion reaction
Respiratory tract infection
Skin infection
Depression
Back pain
Cough
Diarrhea
Peripheral edema

Mitoxantrone

- Limited use due potential for heart damage and leukemia
- Common side effects
  - Nausea
  - Thinning hair
  - Loss of menstrual periods
  - Bladder infections
  - Mouth sores

Treatment of MS Relapse and Symptom Management

Relapse vs. Symptoms

- MS relapses are sudden flare-ups of disease activity
- MS symptoms are chronic or ongoing indicators of MS lesion damage in the CNS

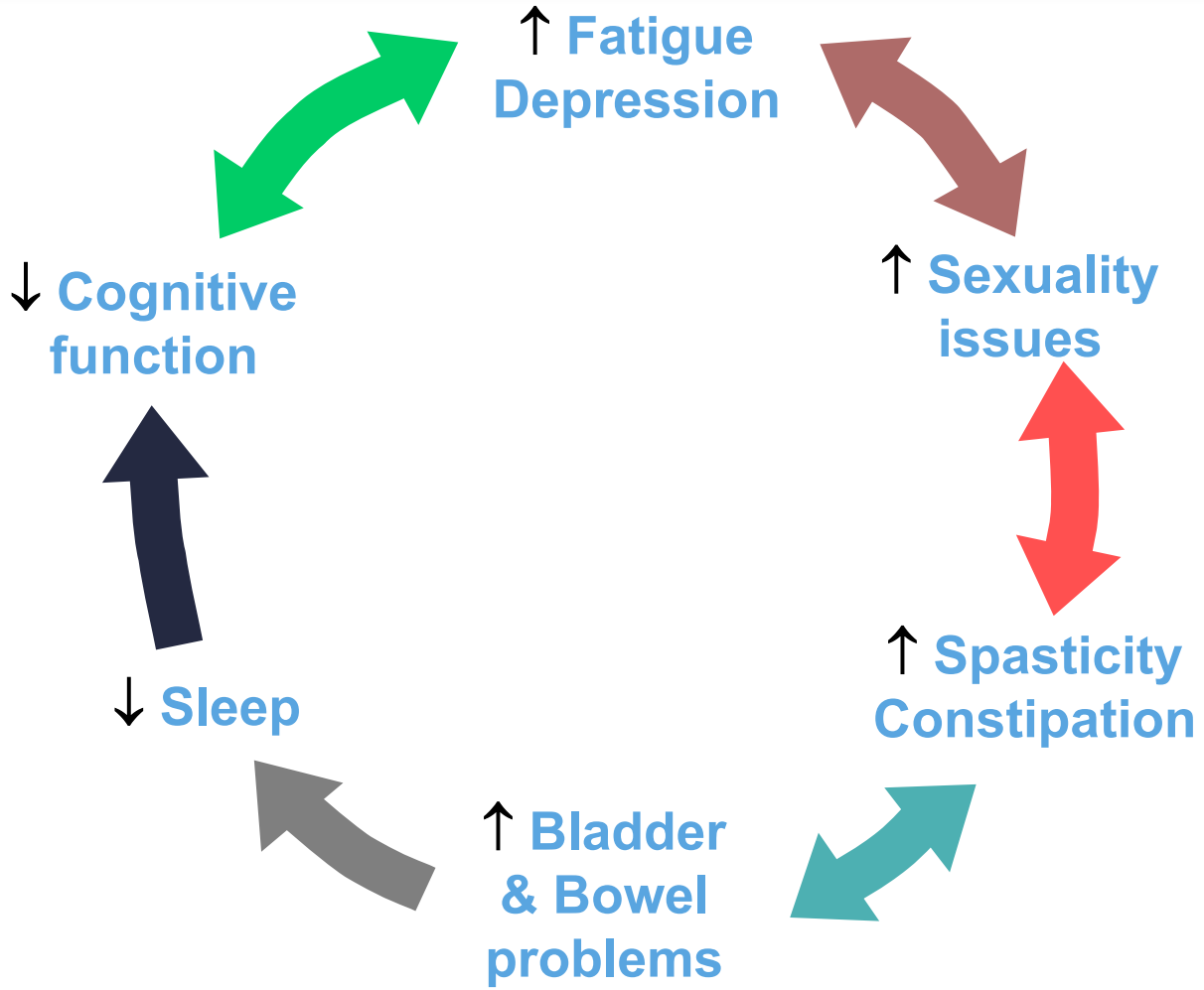
Acute Attacks

- Attack/Relapse/Exacerbation/Flare
  - Episode of focal neurological disturbance lasting longer than 24 hours
  - Preceded by a period of clinical stability of at least 30 days
  - No alternate explanation (infection or fever)
- When to treat
  - Not all relapses require treatment
  - Functionally disabling symptoms
    - Vision loss, diplopia, weakness
    - Mild sensory attacks are often not treated
- Treatment with glucocorticoids
  - Methylprednisolone IV: 500 – 1000 mg daily for 3-7 days (with or without prednisone taper)
  - Oral prednisone: 625 – 1250 mg daily for 3-7 days (with or without taper)

MS Symptoms

Treatment Plan

- Prioritize
- Rule out other causes
- Symptoms related to medication side effect
- Interdependence of symptoms



Common MS Symptoms

- Paresthesia (numbness, tingling, burning)
- Neuropathic pain
- Fatigue
- Mood disturbance (depression)
- Weakness
- Gait changes and balance problems
- Dizziness and vertigo
- Spasticity
- Cognitive dysfunction
- Bowel/bladder dysfunction
- Sexual dysfunction

Sensory and Pain Symptoms

- Sensory symptoms
  - Trigeminal neuralgia (one of the more common symptoms)
  - Burning, itching, L'Hermitte's sign, face twitching
  - Carbamazepine 200 mg PO BID or TID
  - Alternatives: gabapentin, topiramate, tiagabine, TCAs
- Neuropathic pain (50%)
  - Difficult to treat
  - Carbamazepine, TCAs, gabapentin, pregabalin, duloxetine, topiramate, tiagabine, capsaicin cream, etc

Fatigue

- Address factors that could exacerbate fatigue (depression or medication side effects)
- Non-pharmacologic strategies (ie. exercise)
- Modafinil 100–400 mg once daily in the AM
- Armodafinil 150-250 mg once daily in the AM
- 4-aminopyridine 5–20 mg twice daily (AM and in the early afternoon)
- Selective serotonin reuptake inhibitors (SSRI)
  - Fluoxetine 10–40 mg once daily in the AM
- Amantadine 100 mg twice daily (AM and in the early afternoon)

Spasticity

- Can cause functional disability impairing ambulation, interfering with activities of daily living
- First line: Oral baclofen 5-25 mg three times daily
- Second-line agents; frequently used in combination with oral baclofen
  - Tizanidine
  - Diazepam
  - Clonazepam
  - Dantrolene
  - Clonidine
  - Gabapentin
- Refractory spasticity
  - Botulinum toxin
  - Intrathecal baclofen

Depression

- Frequency of death by suicide has been found to be 7.5 times greater in MS patients than in controls (suicide not correlated with disability)
- Treatment similar to major depressive disorder (SSRIs, SNRIs, bupropion, TCAs, mirtazapine, psychotherapy)
- Consider comorbidities when selecting agent:
  - Insomnia → Mirtazapine, TCAs
  - Neuropathy → Duloxetine, TCAs
  - Sexual dysfunction → Bupropion
  - Fatigue → SNRIs (venlafaxine, duloxetine, desvenlafaxine), fluoxetine, stimulants
  - Cognition/balance → Avoid TCAs
  - Incontinence → SNRIs, TCAs

Bladder Dysfunction

- Failure to store (hyperreflexive bladder, overactive bladder)
  - Anticholinergic medications: oxybutynin, tolterodine
    - With or without low-dose imipramine (synergistic effect)
  - Remove cholinesterase inhibitor if incontinence started soon after its initiation
  - β3 agonist
- Sphincter dyssynergia
  - Alpha-1 blockers: terazosin, tamsulosin
- Failure to empty
  - Cholinergic agents (bethanechol)
- Nocturia
  - Desmopressin acetate (DDAVP)

Gait Impairment

- Gait impairment can result from spasticity, weakness, fatigue, sensory loss, and visual loss
- Some eventually require a cane or wheelchair
- Treatment with dalfampridine (Ampyra) can improve walking in some patients
- Chemical name: 4-aminopyridine
- Mechanism of action:
  - Broad spectrum K^+ channel blocker
  - Increases conduction in demyelinated axons

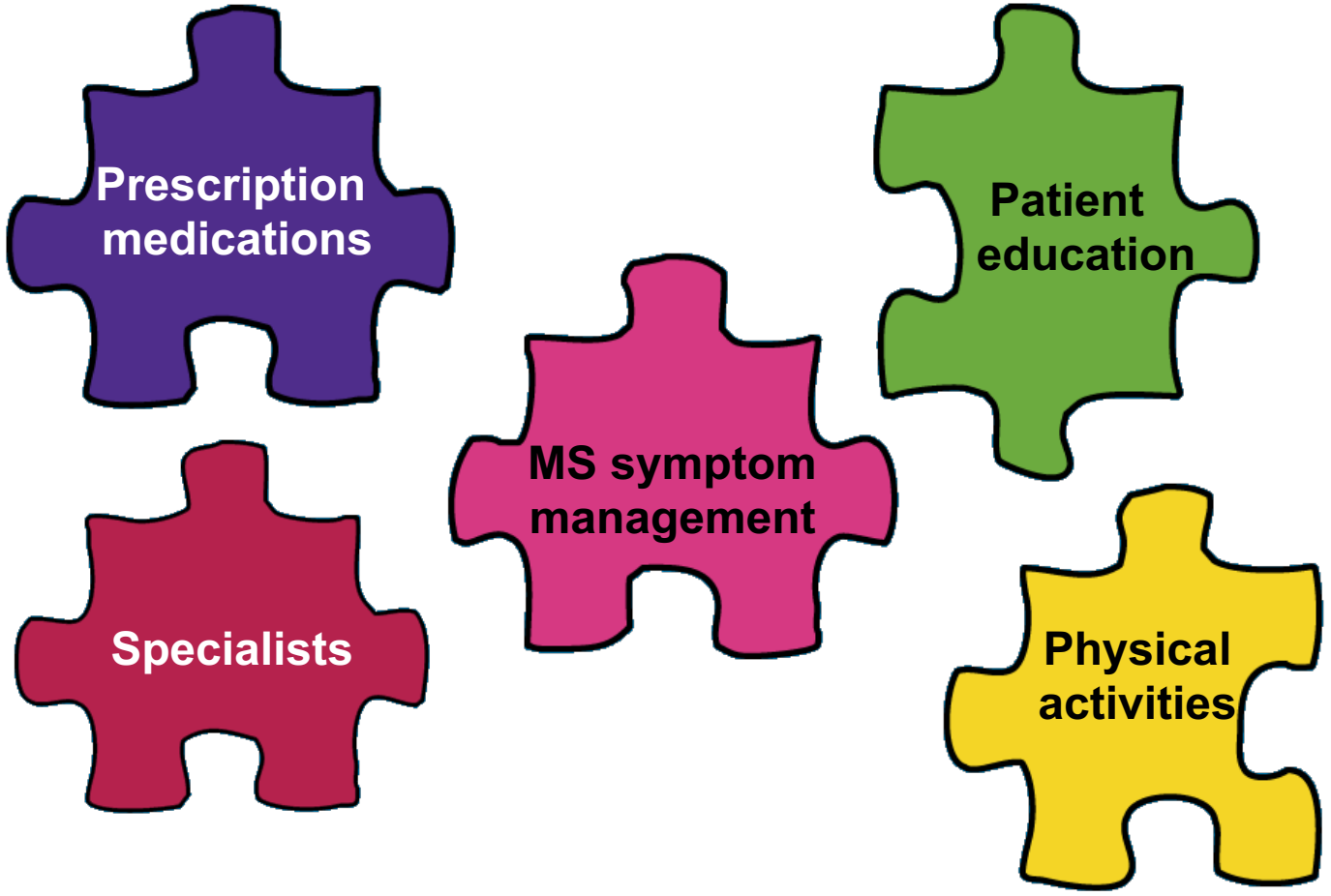
Dalfampridine (Ampyra)

- Indicated to improve walking speed in patients with MS
- Walking speed increased by 25% vs 5-7% with placebo
- 90% renally eliminated unchanged
- Substrate of CYP2E1
- Adverse effects: dizziness, insomnia, UTI, seizures
- No apparent changes in QTc noted
- Dose: 10 mg po BID
- DO NOT USE WITH CrCl< 50ml/min because of increased seizure risk

Cannabis for MS

- Effect on spasticity
  - Improves muscle stiffness almost 2-fold
  - Improvements were also seen in patient reported body pain, spasms, sleep quality, and overall quality of life
- Negatively impact cognition
- Sativex
  - Oral spray derived from cannabis
  - Dose per spray: 2.7mg THC / 2.5mg CBD
  - Significantly improves spasticity
  - Available in 15 countries

Managing MS



National Multiple Sclerosis Society

Questions?

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