Multiple Sclerosis: Background Information

Includes content created by: Whitney Huryta SDPT, Liz Waddell, PT, DPT, MSCS, Melissa Cummings, PT, DPT, MSCS; Jen Tooher PT, DPT; and Karen McCulloch, PT, PhD, NCS and information from Herb Karpatkin (Medbridge) and the National MS Society.

Objectives

1. Describe the pathophysiology, etiology, epidemiology, and diagnostic criteria of MS.

2. Distinguish between the clinical progression of various types of MS, including: relapsing-remitting, secondary progressive, primary progressive, and primary relapsing.

3. Differentiate between positive and negative prognostic factors in MS.

4. Describe disease-modifying drugs as well as common drugs used for symptom management in MS, including common side-effects and adjust PT sessions accordingly when necessary.

5. Distinguish the difference between exacerbations and pseudoexacerbations.

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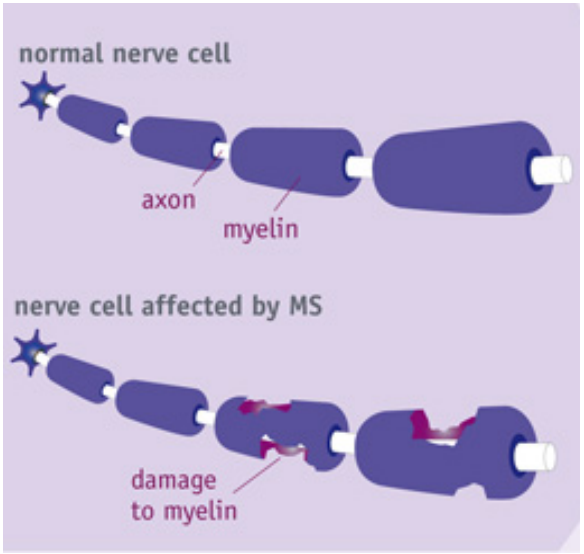
What is MS?

- Immune-mediated disease
- Affects CNS
- Characterized by inflammation, demyelination, and degenerative changes



What is an exacerbation?

- Exacerbations (aka relapse, flare-up, attack)
  - When symptoms return or worsen
  - Must last 24 hours to differentiate from a pseduoexacerbation
  - An exacerbation can last days to weeks
  - Symptoms occurring within 30 days are considered the same exacerbation

Cost of MS

- 50-80% can't continue working >10 years after diagnosis
- High cost burden (2nd only to CHF for chronic disease cost)
- Lifetime financial cost $1.2 million
- Factors: medication costs, missed work/early retirement, outpatient care, inpatient care, long-term care, mobility devices, etc.

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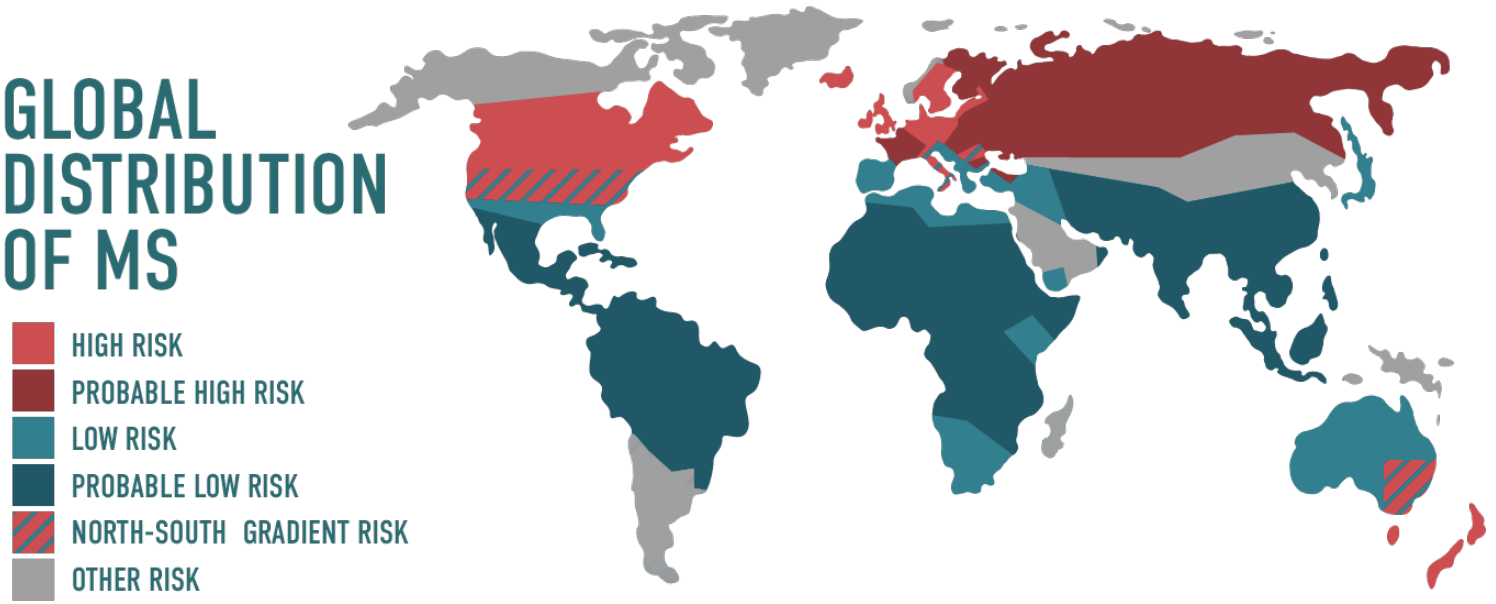
Epidemiology: Who gets MS?

- Population of people with MS:
  - US: 450,000
  - World: >2.3 million
- ~3 female: 1 male
- Caucasians most affected
  - Recent increase in report of female African American
- Age at diagnosis:
  - 20-50 (most common mid-20s to early 30s)
  - Can be diagnosed at any age

Geographic Distribution



It used to be thought that there was a higher density of people with MS further from equator (Vitamin D); however recent studies question this latitudinal gradient

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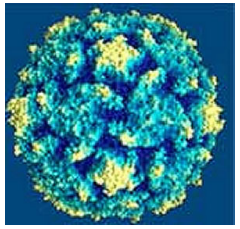
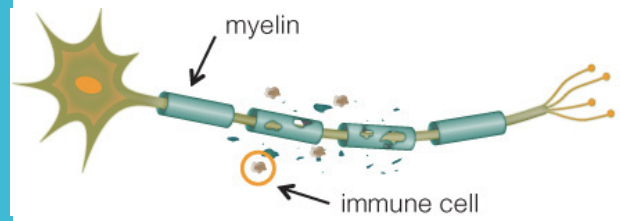
Etiology: What causes MS?



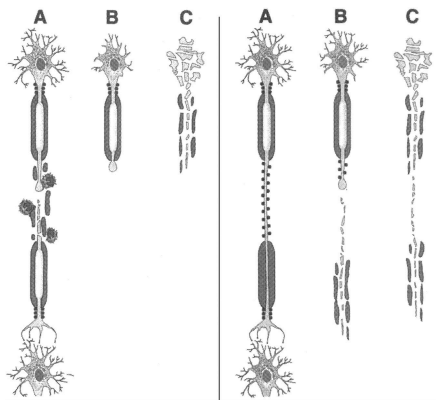
Genetic Predisposition

Environmental Trigger



Immune Attack

Loss of myelin & nerve fiber



Etiology: What causes MS?

- Cause is unknown
- Combination of immunologic, genetic, environmental, and potentially infectious agents
- Specific considerations:
  - Epstein-Barr Virus- History of past EBV infection associated with first demyelinating event
  - Vitamin D- Deficiency may increase susceptibility
  - Smoking- Increased risk with smoking and secondhand smoke exposure
  - Obesity- Some studies have suggested a link between obesity in teenage & young adult years and an increased risk of MS. (Mokry et al, 2016)

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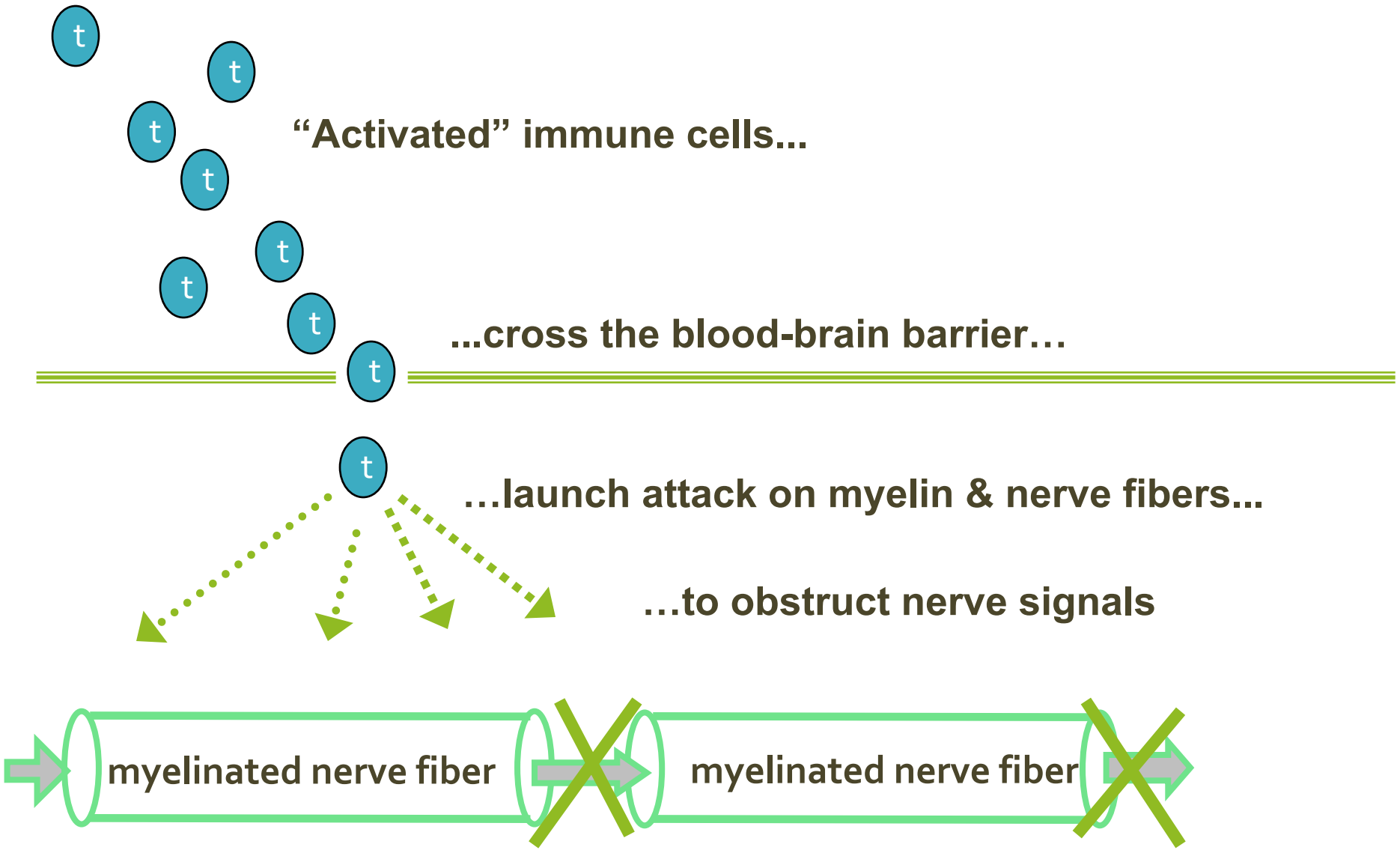
What is the pathophysiology of MS?

- **Immune-mediated** disease
- Characterized by
  - Episodes of **inflammation**
  - The blood brain barrier (BBB) becomes permeable. Allows immune cells (T cells, B cells, macrophages…) access to the CNS (brain, spinal cord, optic nerves)
  - Antibodies and immune cells wrongly identify myelin as a foreign substance
  - The immune system attacks myelin resulting in **demyelination**
  - Results in neural **degeneration**: focal areas of damage, axon injury, axon transection, axon degeneration, neurodegeneration, and scarring/plaque formation

Click here for a 2 minute introduction to MS courtesy of YouTube!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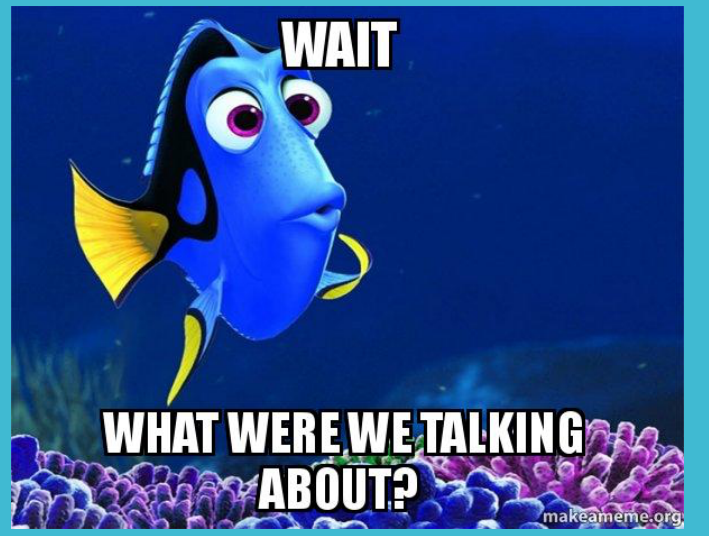
“Activated” immune cells...
...cross the blood-brain barrier…
…launch attack on myelin & nerve fibers...
…to obstruct nerve signals
myelinated nerve fiber
myelinated nerve fiber

Navigator



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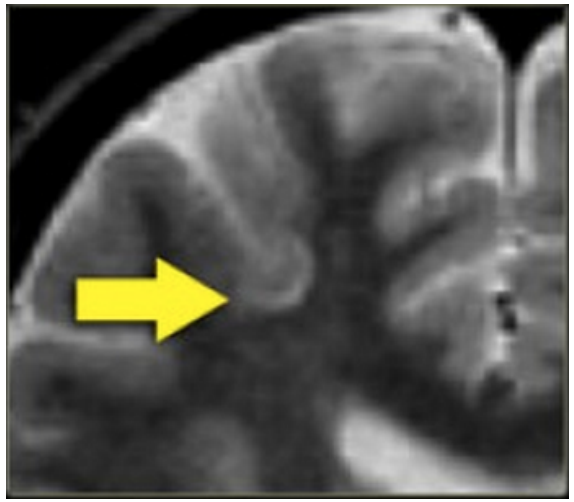
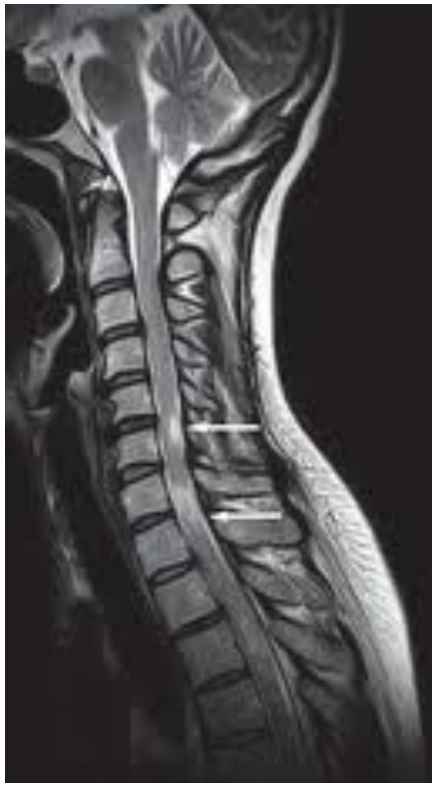
Common Lesion Areas

Juxtacortical

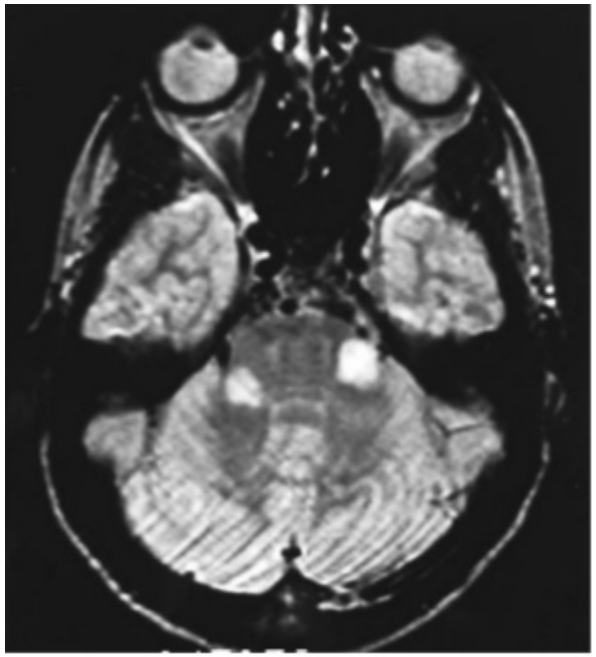


Periventricular

Spinal Cord



Infratentorial



Click here to visit website and learn more

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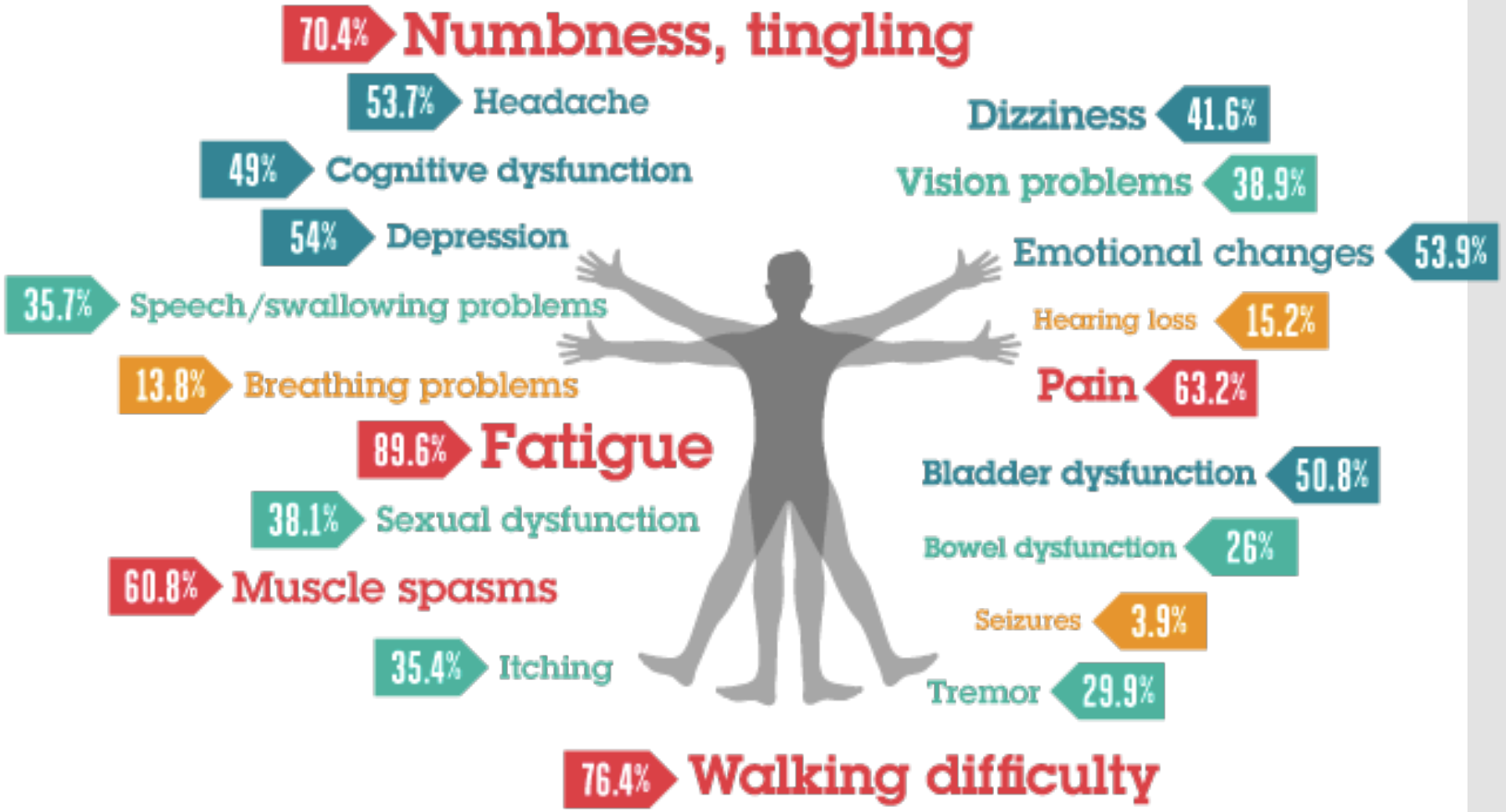
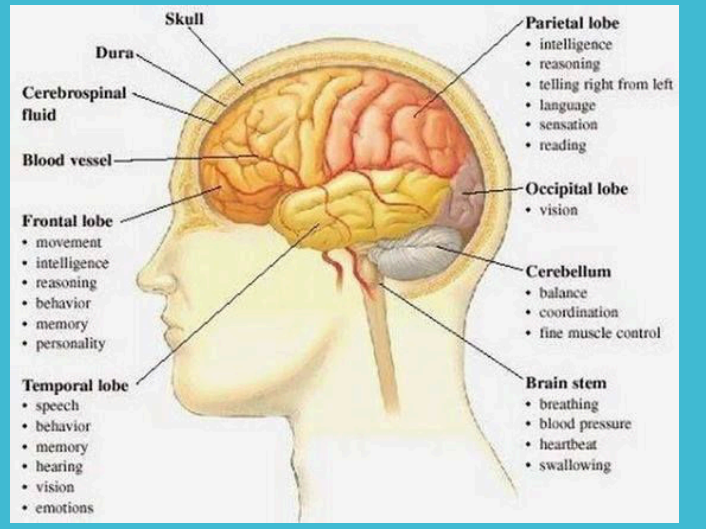
What are the symptoms of MS?



Symptoms depend on area of CNS impacted



- **Cortical** – intellect, memory
- **Optic nerve-** blurry/gray vision, blindness in one eye
- **Brainstem**– diplopia, trigeminal neuralgia, Bell's palsy, vertigo, nystagmus
- **Cerebellar** – ataxia, dysmetria, dysdiadochokinesis
- **Spinal cord** – paraparesis, dysesthesias, bowel & bladder function, spasms

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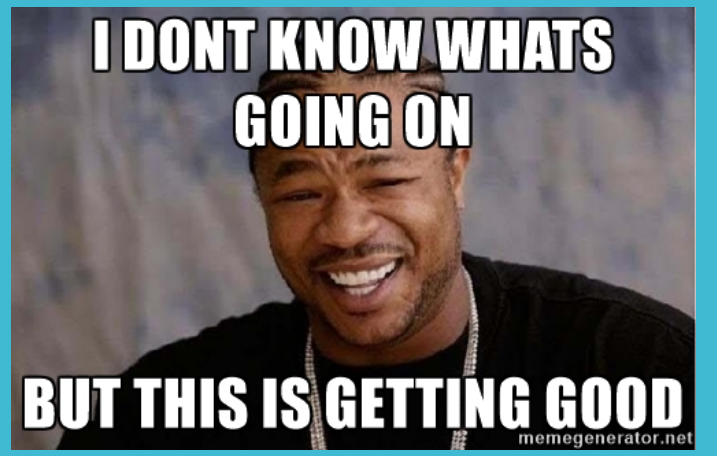

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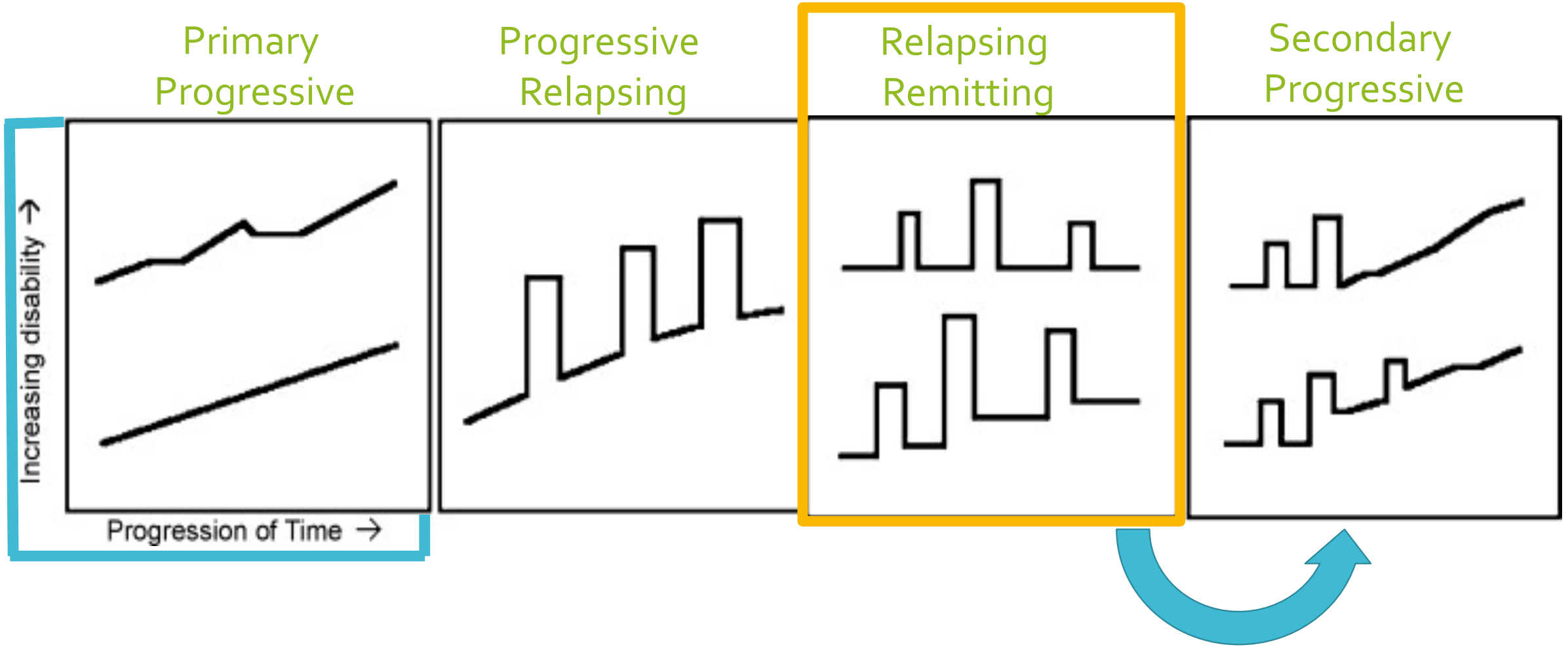
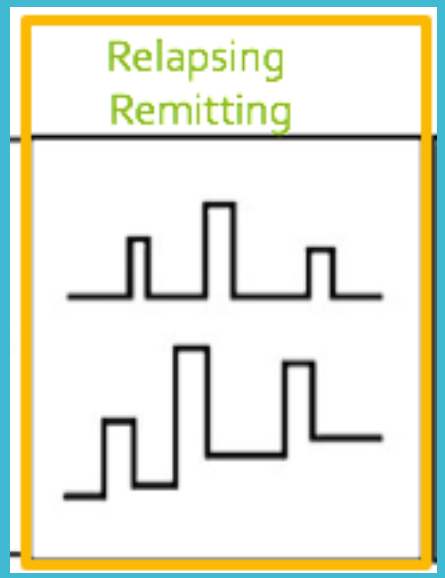
Clinically Isolated syndrome (CIS)

- A single episode of neurologic symptoms lasting at least 24 hours
- Occurs in one or more sites in the CNS
- May or may not develop into multiple sclerosis
- May begin an MS medication to minimize future disability

What are the types of MS?

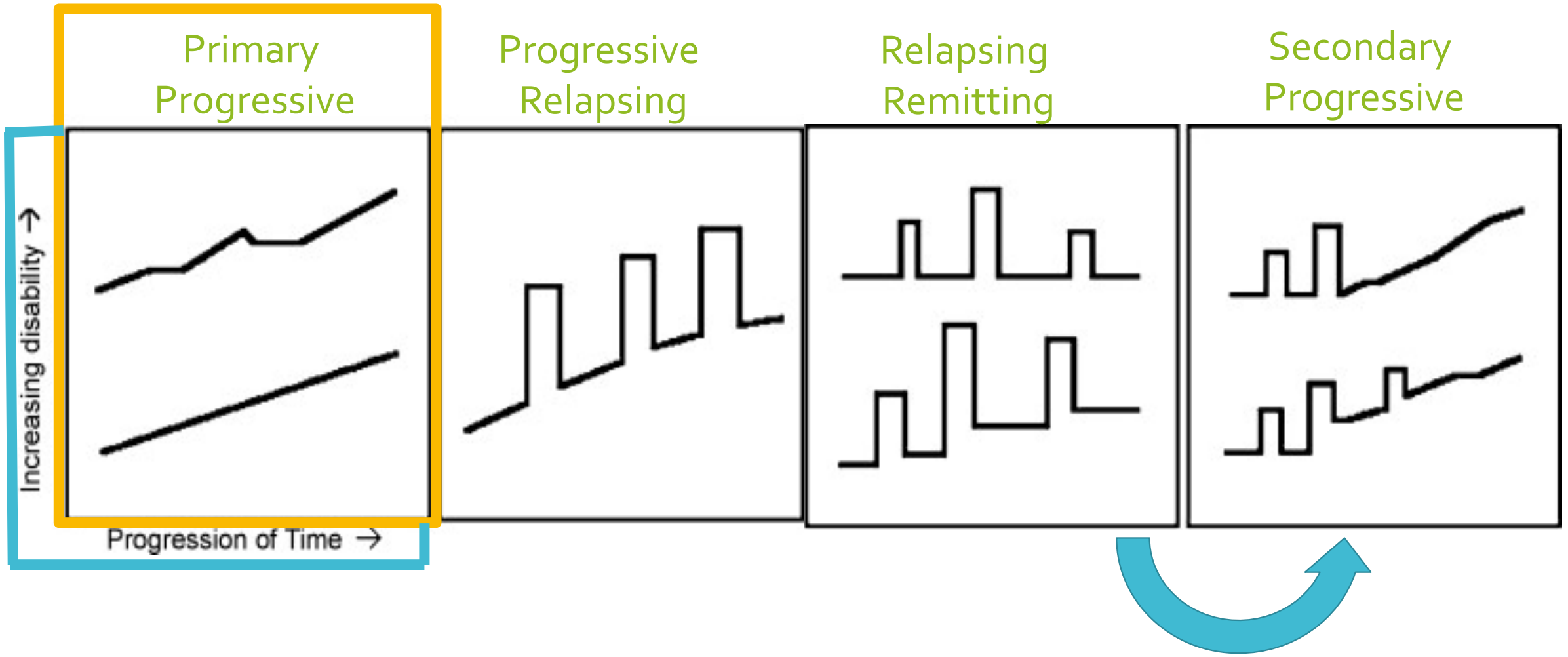


RRMS

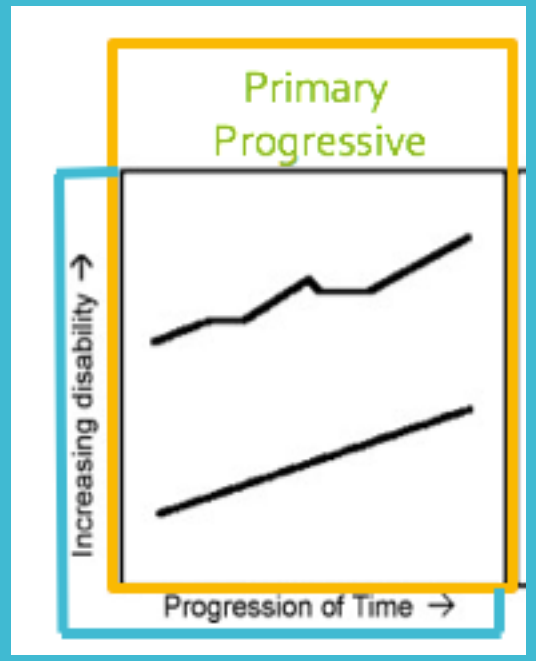


- Relapsing-remitting (RRMS):
  - 85-90% of initial diagnoses
  - Relapse aka: flare-up, attack, exacerbation
  - Symptoms of relapses have full or partial recovery in weeks to months
  - Between relapses, may have inflammatory activity that is subclinical
  - No gradual progression of symptoms

What are the types of MS?

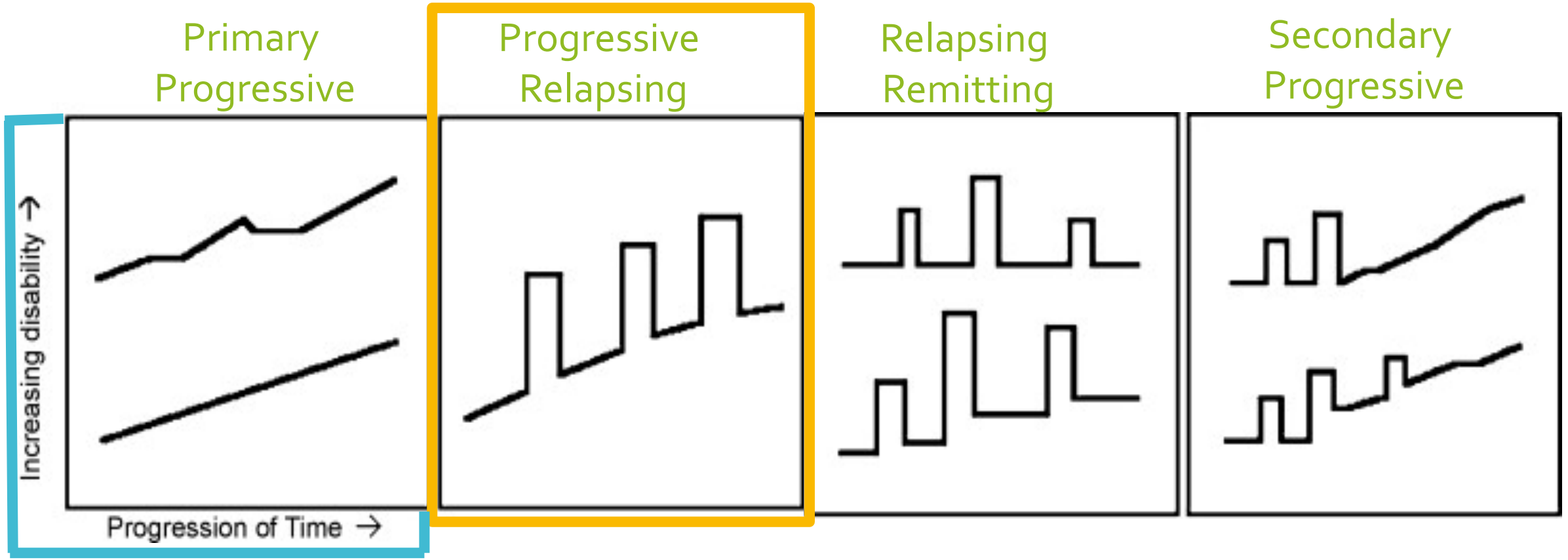


PPMS

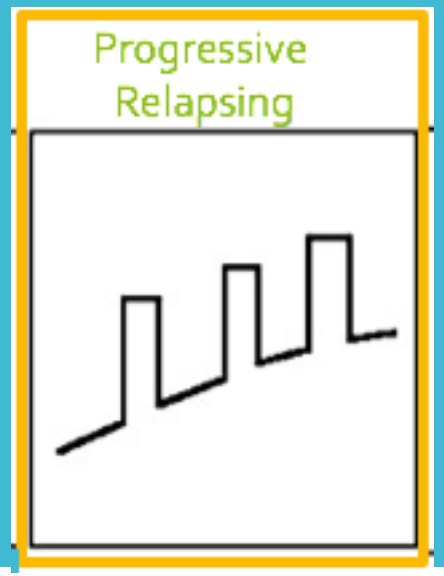


- Primary Progressive (PPMS):
  - 10% of initial diagnoses
  - Later onset than RRMS and with more equal gender distribution
  - Less inflammation and fewer brain lesions
  - Ongoing neurodegeneration and demyelination without relapses
  - More challenging to diagnose and treat (Most medications for RRMS)

What are the types of MS?



PRMS

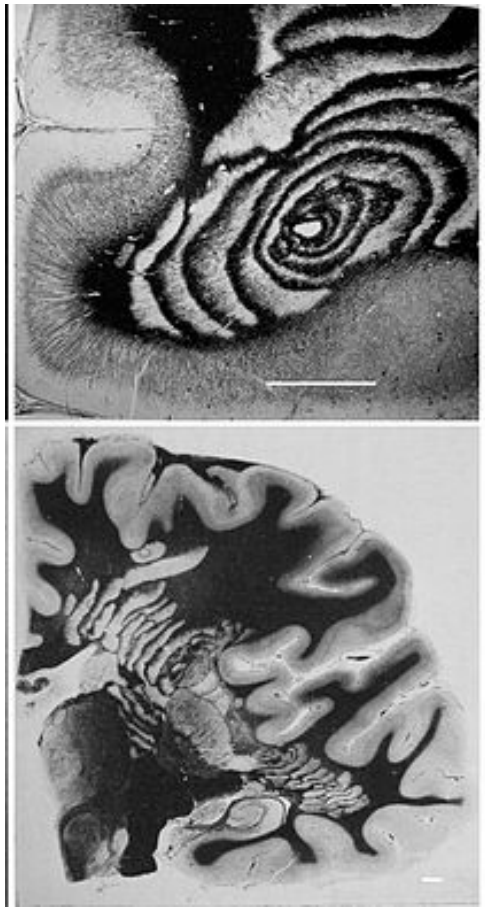


- Progressive Relapsing (PRMS):
  - Typically diagnosed following initial diagnosis of PPMS
  - Very little research due to small patient population (5%)
  - Steady progression of disease with occasional exacerbations along the way
  - Disease progresses without remission

https://www.youtube.com/watch?v=1BlufiE46Ps

Pediatric MS & Rare MS Variants

- Pediatric MS
  - 8,000-10,000 cases in the US
  - 2-5% of adults with MS have a history of symptoms before age 18
- Tumefactive aka fulminant MS or Marburg's variant – aggressive lesion of at least 2cm. May lead to death in 1-2 years
- Balo concentric – concentric rings of deymelination



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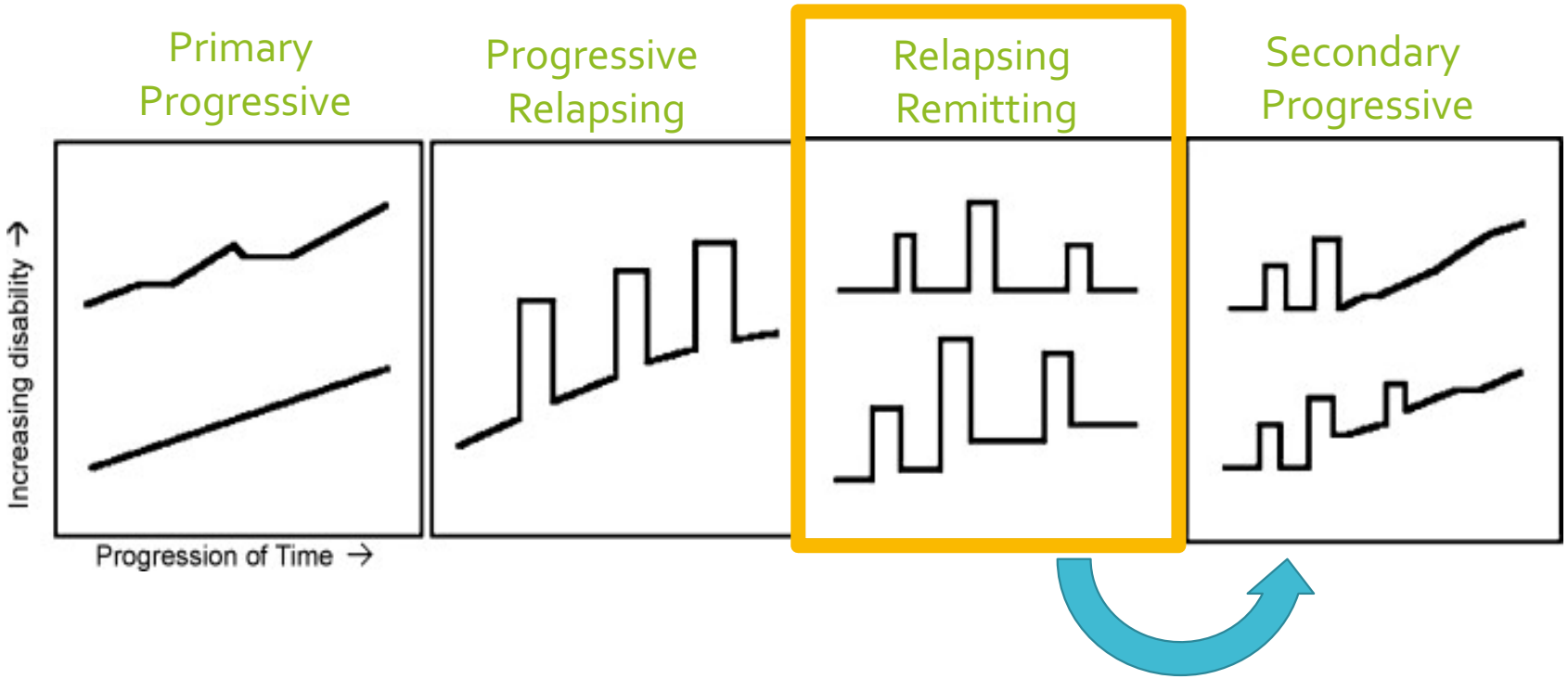
Disease progression: SPMS

- Secondary Progressive (SPMS)
  - About 50% with RRMS eventually develop SPMS with steady and irreversible neurologic decline with or without exacerbations
  - Progressive axonal loss in areas of pre-existing plagues



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How is MS diagnosed?

Evidence of:

- **Dissemination in space:** Lesions in 2 separate areas of the CNS (juxtacortical, periventricular, infratentorial, spinal cord)
- **Dissemination in time:** Evidence that damage occurred at least 30 days apart.

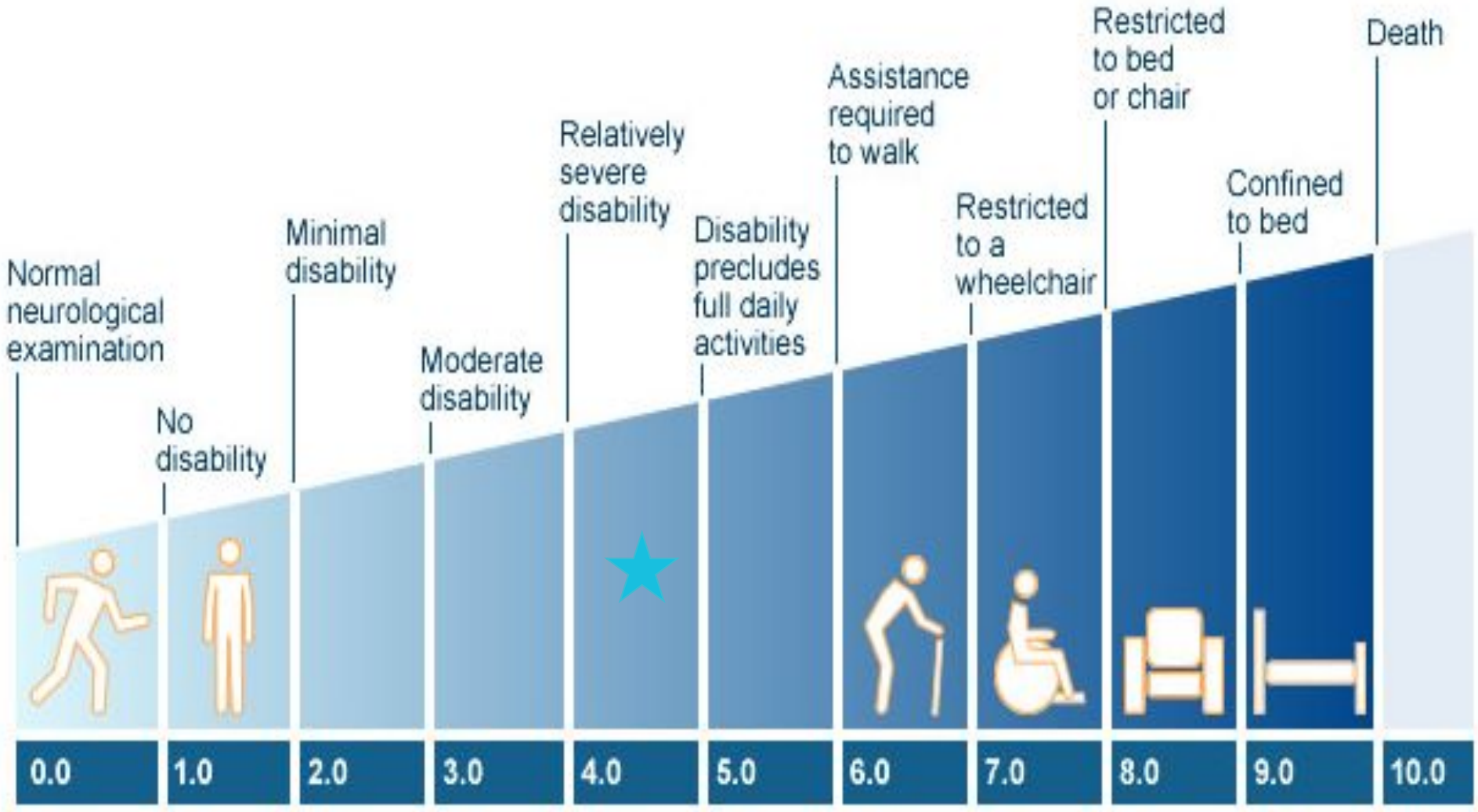
- **Other Considerations:**
  - Clinical symptoms – at least 24 hours duration
  - Tests – MRI, lumbar puncture, visual evoked potential
  - Rule out all other causes

Diagnosis - McDonald Criteria

ATTACKS	LESIONS	CRITERIA TO MAKE DIAGNOSIS
2+	2 or more	None
2+	1	Dissemination in space demonstrated by MRI or further attack
1	2	Dissemination in time demonstrated by MRI or further attack
1	1	Dissemination in space and time demonstrated by MRI or further attack
0 (progression from onset)		1 year of progression and 2 of the following: • Positive brain MRI • Positive spinal cord MRI • Positive cerebrospinal fluid

EDSS –

Kurtzke Expanded Disability Status Scale



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How do we determine prognosis for people with MS?

Unfavorable Indicators	Favorable Indicators
• Male gender • Onset of symptoms at age >40 • Initial symptoms involving cerebellum, cognition, or bladder control • Initial symptoms that affect multiple regions of the body • Incomplete remission • Rapid progression • Smoker • Greater symptoms at onset	• Female gender • Onset of symptoms at age <40 • Initial sensory symptoms only • Involvement of only one CNS system at onset • Full recovery between flare ups • Absence or late onset of cerebellar symptoms • Use of DMT • Fewer MRI lesions

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Treatment Options

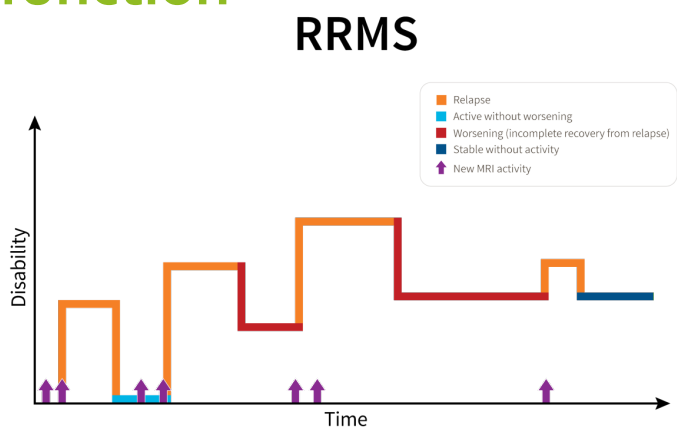
5 Categories:

1. Treatment of relapses (exacerbations, flare-ups, attacks- last at least 24 hours)
2. Symptom management
3. Disease Modification
4. **Rehabilitation (to maintain/improve function)**
5. Psychosocial Support

How are relapses treated?

- Not all relapses require treatment
  - Mild, sensory sx are allowed to resolve on their own.
  - Sx that interfere with function (e.g., visual or walking problems) are usually treated
- 3-5 day course of IV methylprednisolone—with/without an oral taper of prednisone
  - High-dose oral steroids used by some neurologists
- **Rehabilitation to restore lost function**
- Psychosocial support

Mild intensity exercise during periods of relapse



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How are MS symptoms managed?

- Symptom management continues throughout the disease course
- Effective symptom management involves a combination of medication, **rehabilitation** strategies, emotional support—and *good coordination of care*
- Virtually every medication used to treat MS symptoms is used off-label

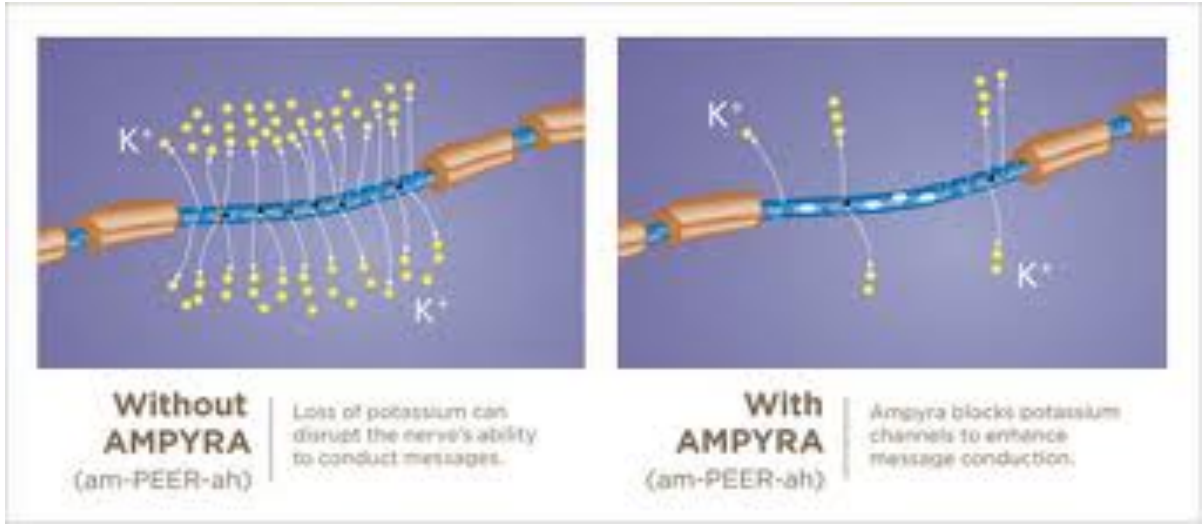
Managing Symptoms: Medications

- *Walking difficulties (ampyra)
- *Fatigue (amantadine)
- *Pain (gabapentin)
- *Spasticity (baclofen, botox)
- *Dizziness and vertigo (meclizine)
- Bladder dysfunction & infection, bowel dysfunction
- Depression/emotional changes
- Tremors
- Sexual problems

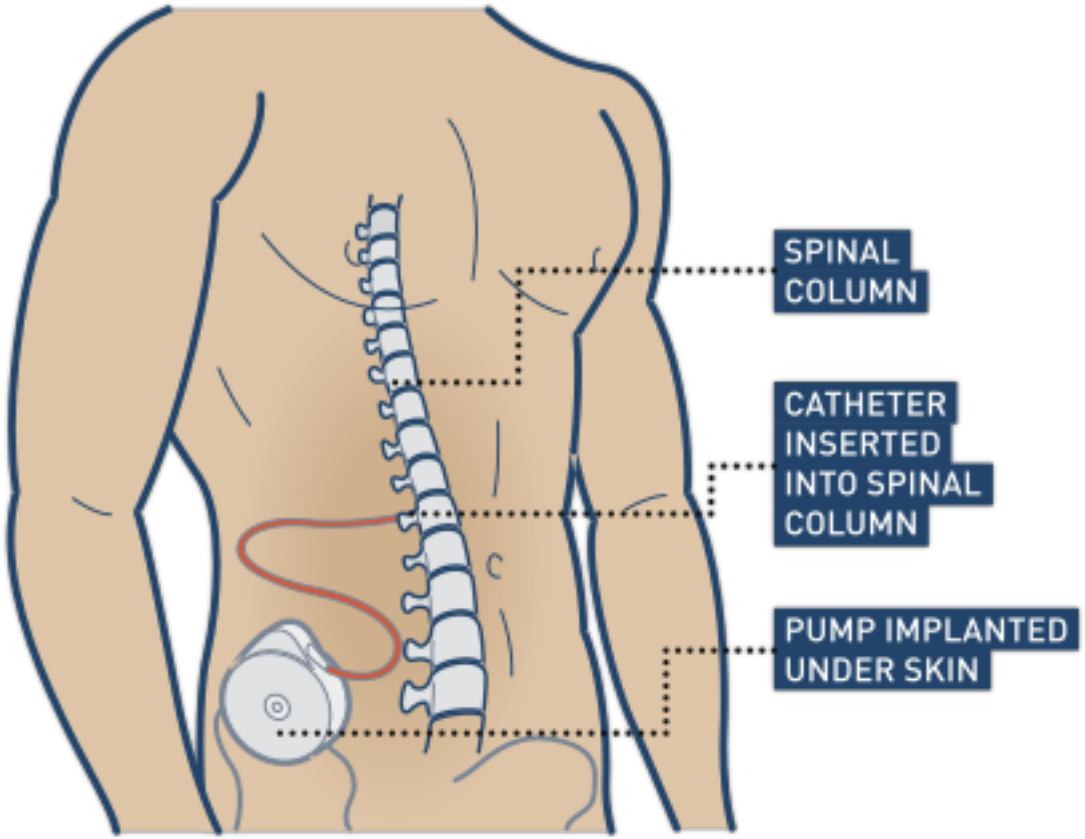
* =Particular importance for PT management

"The Walking Drug"

- Ampyra (Fampridine)
  - Increased lower extremity muscle strength
  - Blocks potassium channels along the nerve to improve nerve conduction
  - Not effective for everyone – 20% decreased time on T25FWT indicates responder
  - Improved T25FWT, 2MWT, BBS (Fjeldstad C et al 2015, IJMSC)



Baclofen pump



Treatment Options

5 Categories:

1. Treatment of relapses (exacerbations, flare-ups, attacks- last at least 24 hours)
2. Symptom management
3. Disease Modification

Coming up after the break!

Disease Modifying Therapies (DMTs)

The goal is to reduce:

- Frequency and severity of relapses
- MRI lesions
- Accumulation of disability

Mechanism:

- Limit ability of immune cells to cross the BBB and limit inflammatory properties of cells crossing the BBB

Treatment:

- Start Early
- Manage side effects
- Assess responsiveness to treatment
  - Switch therapies: suboptimal treatment response, adverse effects, inadequate adherence
  - Change to a drug with a different mechanism of action (MOA)

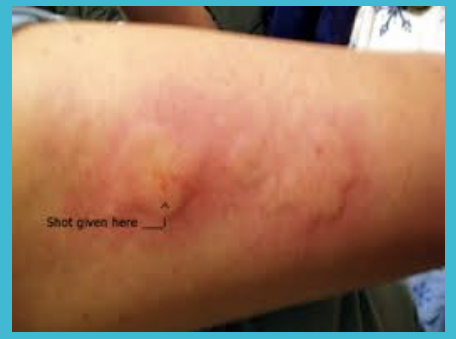
How is the disease course treated[1]?

- Thirteen disease-modifying therapies are FDA-approved for relapsing forms of MS:

INJECTIONS!

  - dimethyl fumarate (Tecfidera®) [oral]
  - fingolimod (Gileny®) [oral]
  - teriflunomide (Aubagio®) [oral]
  - alemtuzumab (Lemtrada®) [inf]
  - mitoxantrone [inf]
  - natalizumab (Tysabri®) [inf]

DMT -Injections



MAIN POINTS:

- Multiple types (Interferons & Copaxone)
- *Intramuscular or subcutaneous
- *Side effects: injection site reactions (rash), pain in abdomen or chest, SOB, depression and flu-like symptoms

How is the disease course treated[1]?

- Thirteen disease-modifying therapies are FDA-approved for relapsing forms of MS:
  - glatiramer acetate (Copaxone®; Glatopa™ - generic equivalent) [inj.]
  - interferon beta-1a (Avonex®, Plegridy™, Rebif®) [inj.]
  - interferon beta-1b (Betaseron® and Extavia®) [inj.]

ORAL Meds!

  - alemtuzumab (Lemtrada®) [inf]
  - mitoxantrone [inf]
  - natalizumab (Tysabri®) [inf]

DMT- Oral

MAIN POINTS:

- 3 types (Aubagio, Gilenya, Tecfidera)
- *Side effects: flu-like symptoms, flushing, headaches, coughing, abdominal pain, back pain

How is the disease course treated?

- Thirteen disease-modifying therapies are FDA-approved for relapsing forms of MS:
  - glatiramer acetate (Copaxone®; Glatopa™ - generic equivalent) [inj.]
  - interferon beta-1a (Avonex®, Plegridy™, Rebif®) [inj.]
  - interferon beta-1b (Betaseron® and Extavia®) [inj.]
  - dimethyl fumarate (Tecfidera®) [oral]
  - fingolimod (Gileny®) [oral]
  - teriflunomide (Aubagio®) [oral]

INFUSIONS!

DMT- Infusion

MAIN POINTS:

- 3 types: Lemtrada, Novatrone, Tysabri
- *Typically not first choice
- *Side effects: rash, fever, headache, muscle aches, fatigue (flu-like symptoms), insomnia, temporary recurrence of neurological symptoms, nausea, infection, depression

Recap: What do the disease-modifying drugs do?

Encourage pt's to communicate with their doctors about DMTs!

Treatment Options

5 Categories:

1. Treatment of relapses (exacerbations, flare-ups, attacks- last at least 24 hours)
2. Symptom management
3. Disease Modification
4. **Rehabilitation (to maintain/improve function)**
5. Psychosocial Support