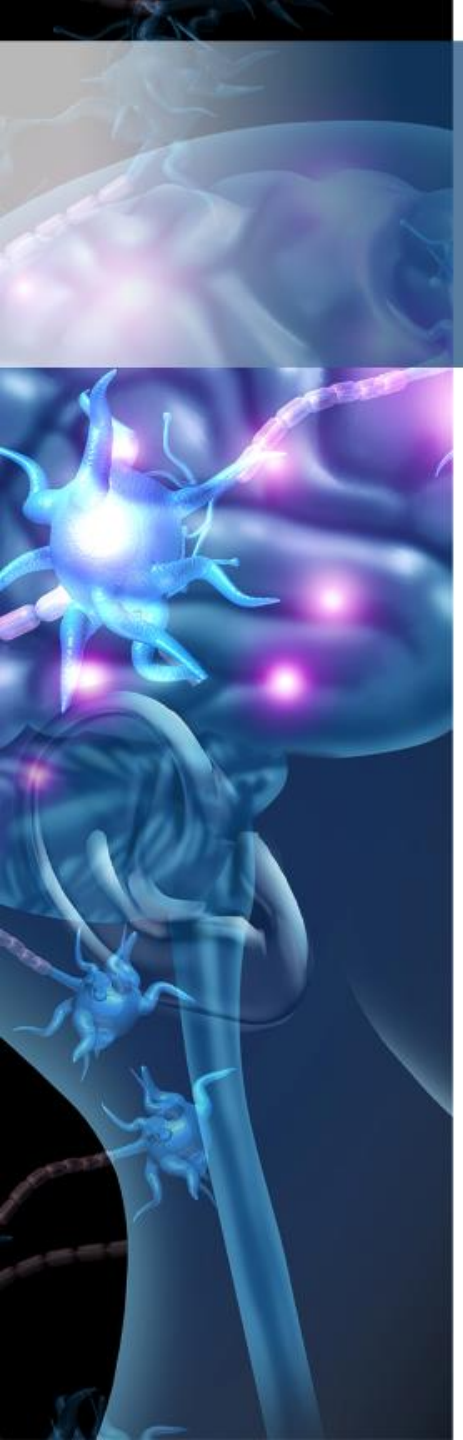
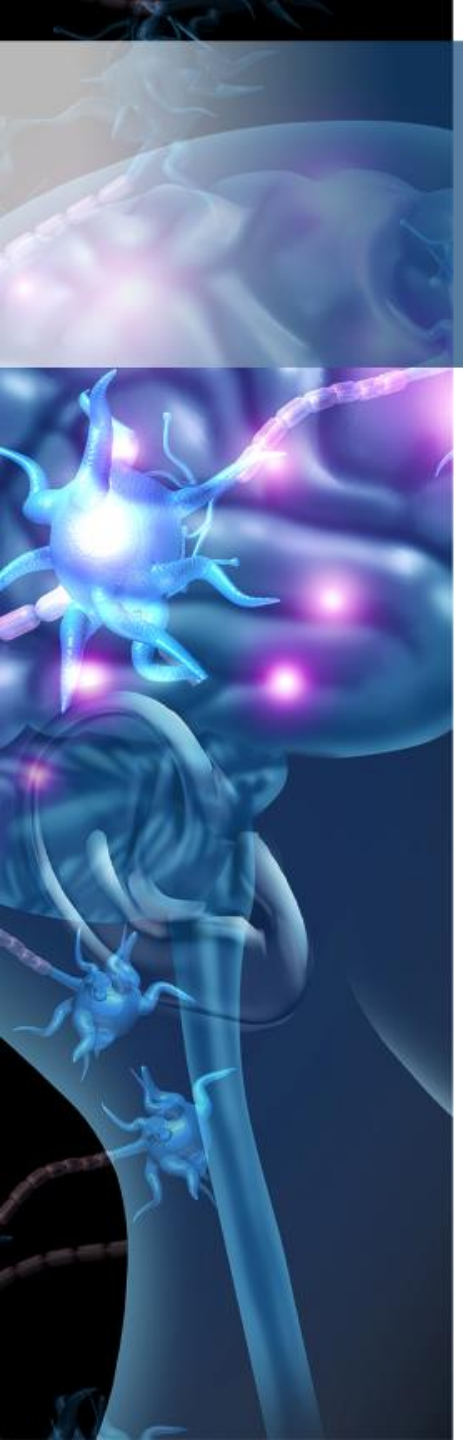
Contemporary Specialty Pharmacy Issues and Challenges in the Therapeutic Management of Multiple Sclerosis



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by educational grants from Biogen and Novartis.

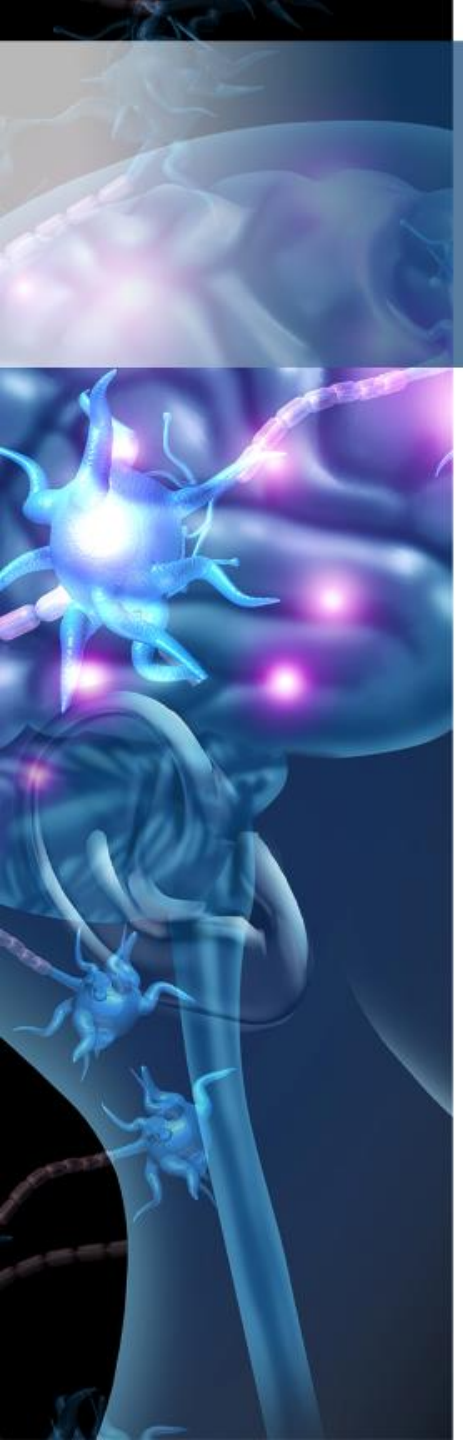


Faculty

Jacquelyn L. Bainbridge, PharmD, FCCP

Professor, Clinical Pharmacy & Department of Neurology
University of Colorado Anschutz Medical Campus
Skaggs School of Pharmacy
Aurora, CO

Dr. Jacci Bainbridge received her Doctor of Pharmacy degree from the University of Colorado, where she subsequently completed a specialty residency in neurology. She currently serves as a professor at the University of Colorado Anschutz Medical Campus in the Skaggs School of Pharmacy and Pharmaceutical Sciences and the Department of Clinical Pharmacy and the Department of Neurology in the School of Medicine. She is a frequent lecturer on topics of neurological and pharmacological interest in the areas of restless legs syndrome, multiple sclerosis, epilepsy, migraine, neuroprotection, chronic pain disorders, cannabis, and movement disorders.



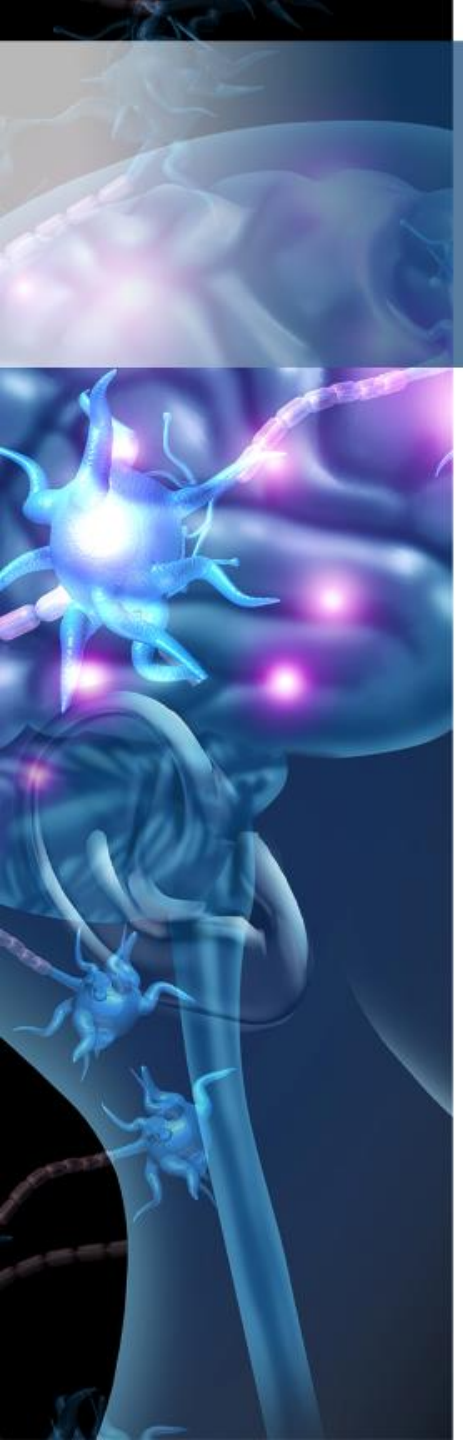
Faculty

Augusto A. Miravalle, MD, FAAN

Neurologist–Multiple Sclerosis
Advanced Neurology of Colorado, MS Center of the Rockies

Associate Clinical Professor of Neurology
Department of Neurology, University of Colorado
Aurora, CO

Dr. Miravalle is a board-certified neurologist who sub-specializes in multiple sclerosis and related neuro-immunological disorders of the brain and spinal cord.
He has been involved in both clinical and science-based research, has published numerous scientific articles, and has served as a consultant to various scientific organizations.
Dr. Miravalle received his medical degree at the University of La Plata, Buenos Aires, Argentina. He completed his neurology residency training at Loyola University, where he served as chief resident of education. He subsequently completed a clinical neuro-immunology fellowship at Harvard University.



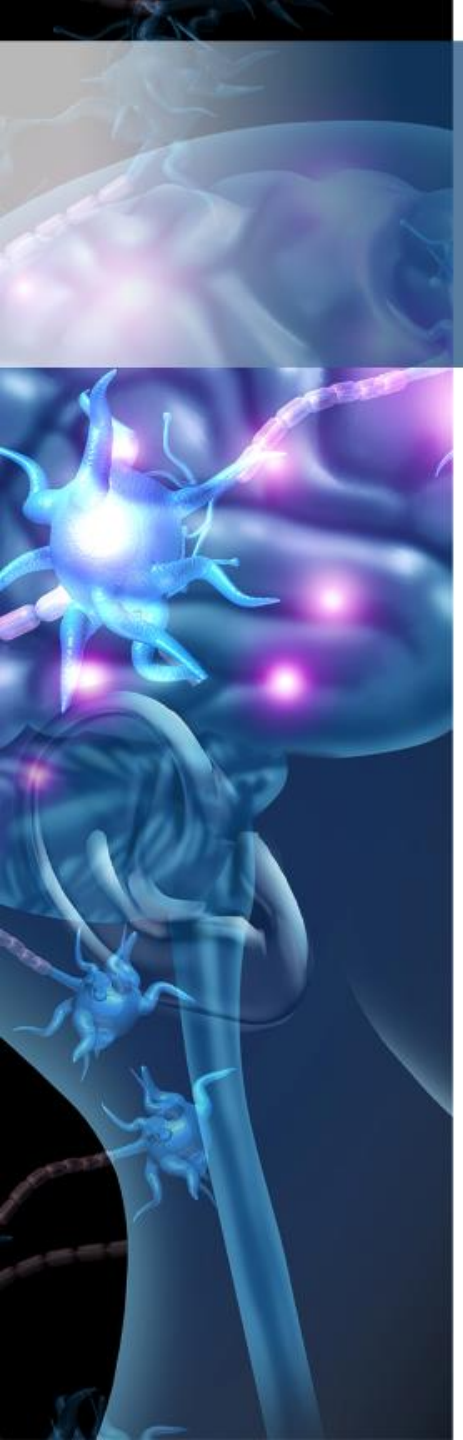
Faculty

Barbara Curiel, MD

MS Patient

Barbara is a family physician and a patient with multiple sclerosis (MS) diagnosed in 2009. She has relapsing-remitting MS. Initially upon her diagnosis, she continued to work in clinical, educational, and administrative work within the Department of Family Medicine at the University of Colorado Anschutz Medical Campus. She served as Medical Director of the A. F. Williams Family Medicine Clinic and Vice Chair of Clinical Affairs for the Department of Family Medicine, as well as a family physician for her patients.

After several years, the illness became more debilitating and she took a medical retirement in late 2012. As both a physician and a patient with MS, she provides a unique perspective about living with the daily challenges of a chronic disease and therapeutic options for treatment and support.



Disclosures

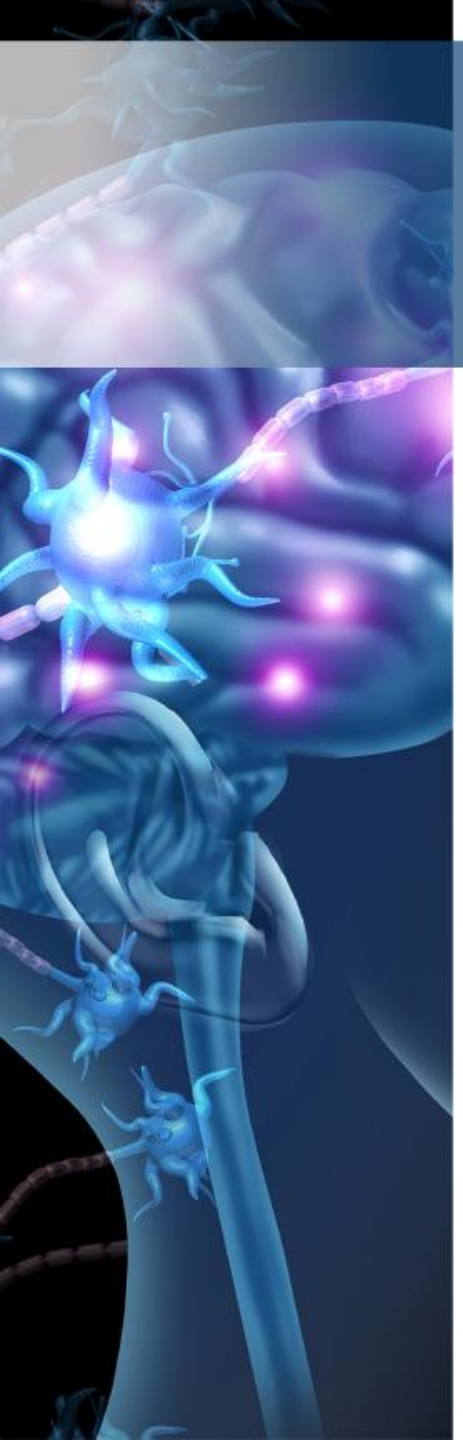
Dr. Bainbridge has disclosed that she has been on a Genentech advisory board.

Dr. Miravalle has disclosed that he has received grant/research support, served as a consultant or clinical investigator, and served on the speaker's bureau for Alexion, EMD, Genzyme, Novartis, and Serono; and he has served on the speaker's bureau for Genentech.

Dr. Curiel has disclosed that she has no actual or potential conflicts of interest in relation to this program.

The clinical/legal reviewer, Michele Faulkner, PharmD, has no actual or potential conflicts of interest in relation to this program.

Susanne Batesko, BSN, RN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.



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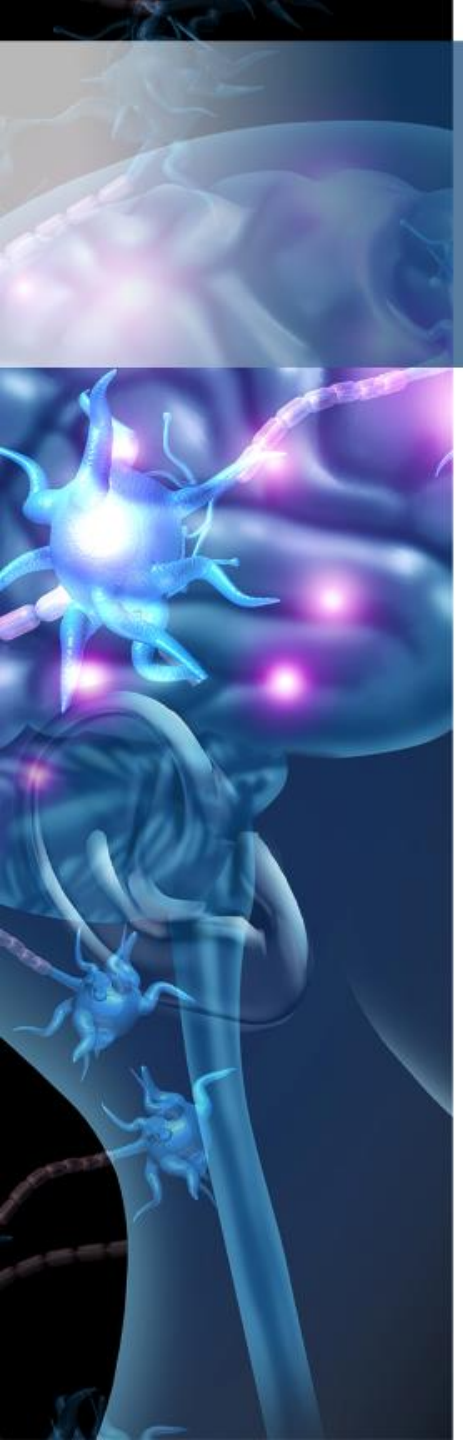
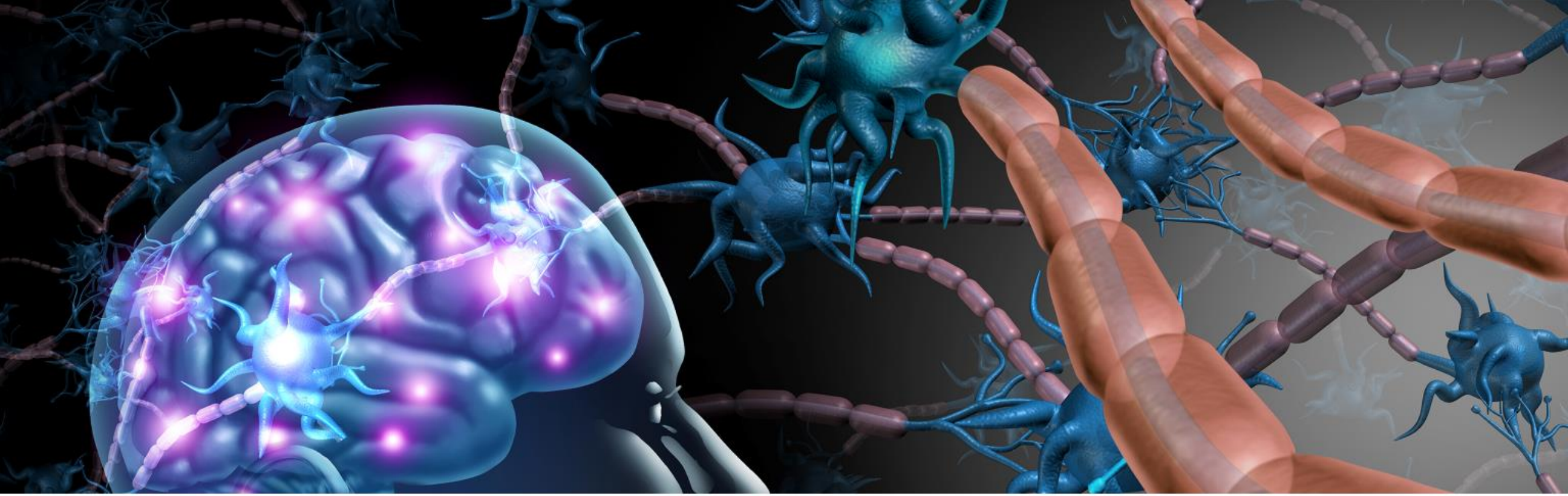
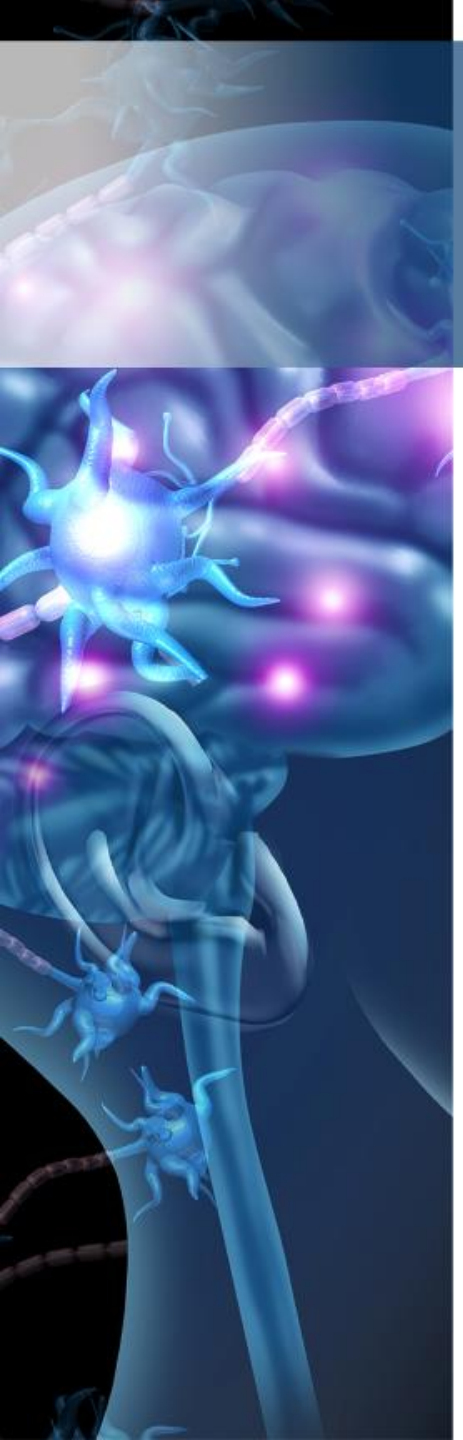


Learning Objectives

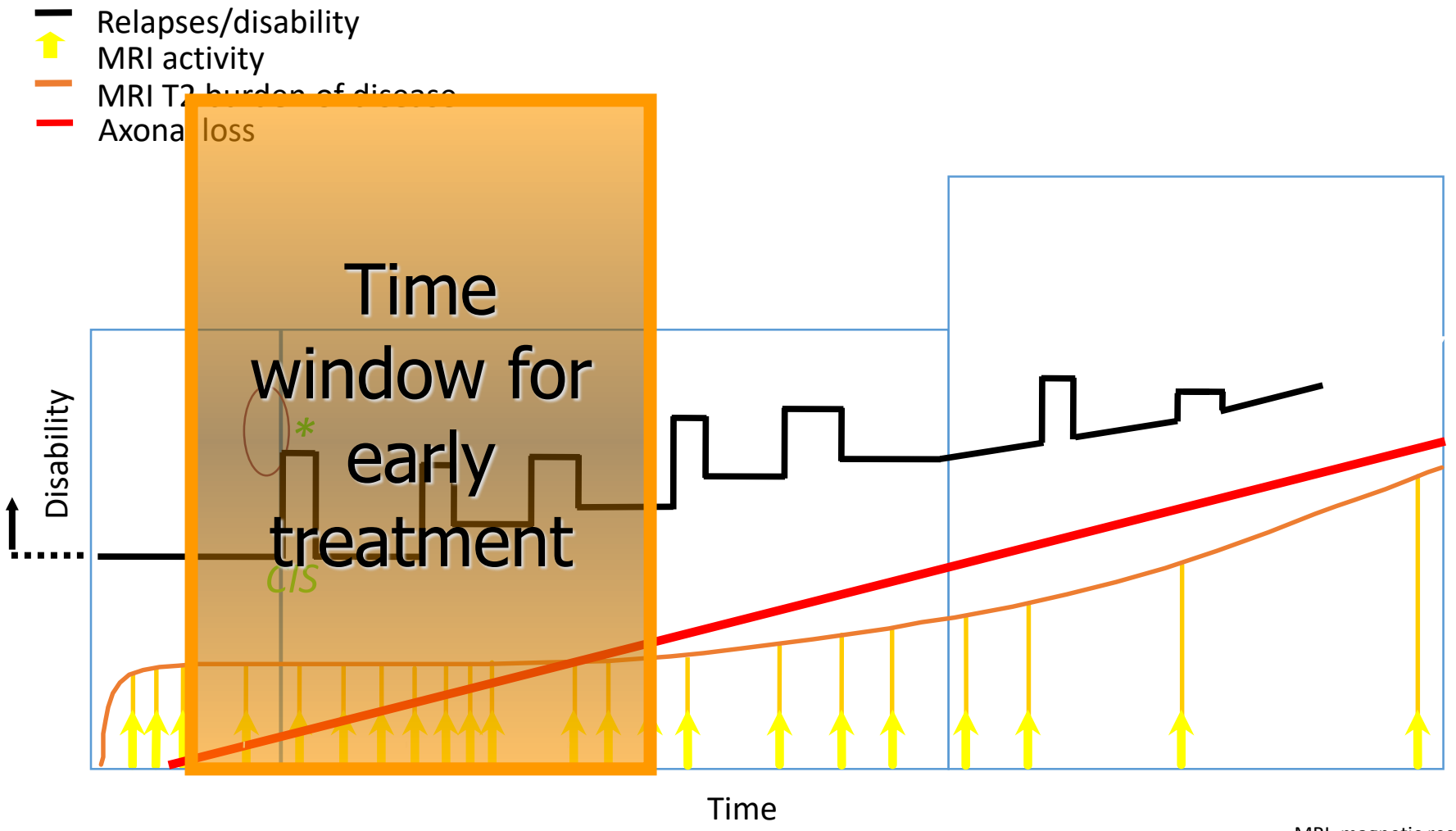
- **Identify** and **develop** strategies to overcome potential barriers that affect timely distribution of multiple sclerosis (MS) disease-modifying therapies (DMTs) to the patient through specialty pharmacies
- **Discuss** clinical practice guidelines, newer therapies, and other issues that guide therapeutic decision-making in MS
- **Plan** approaches to optimally manage key financial procedures in the administration of MS DMTs
- **Formulate** effective strategies for counseling patients on MS specialty therapies in the atmosphere of shared decision-making



Expectations of Therapies: Setting Up Goals

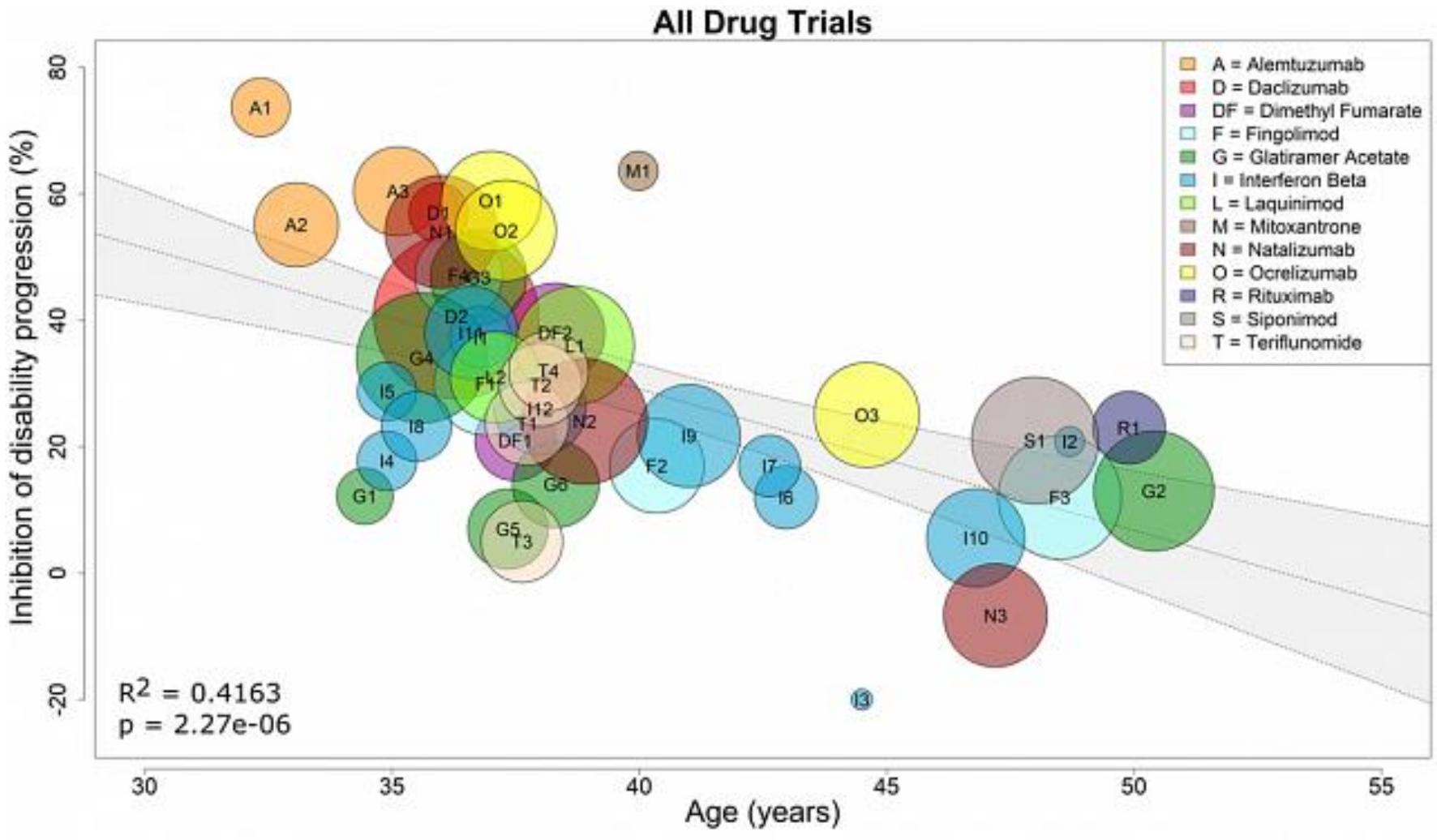


Natural History of MS
Clinical and MRI Measures



MRI, magnetic resonance imaging.

Efficacy of MS Drugs is Linked to Age

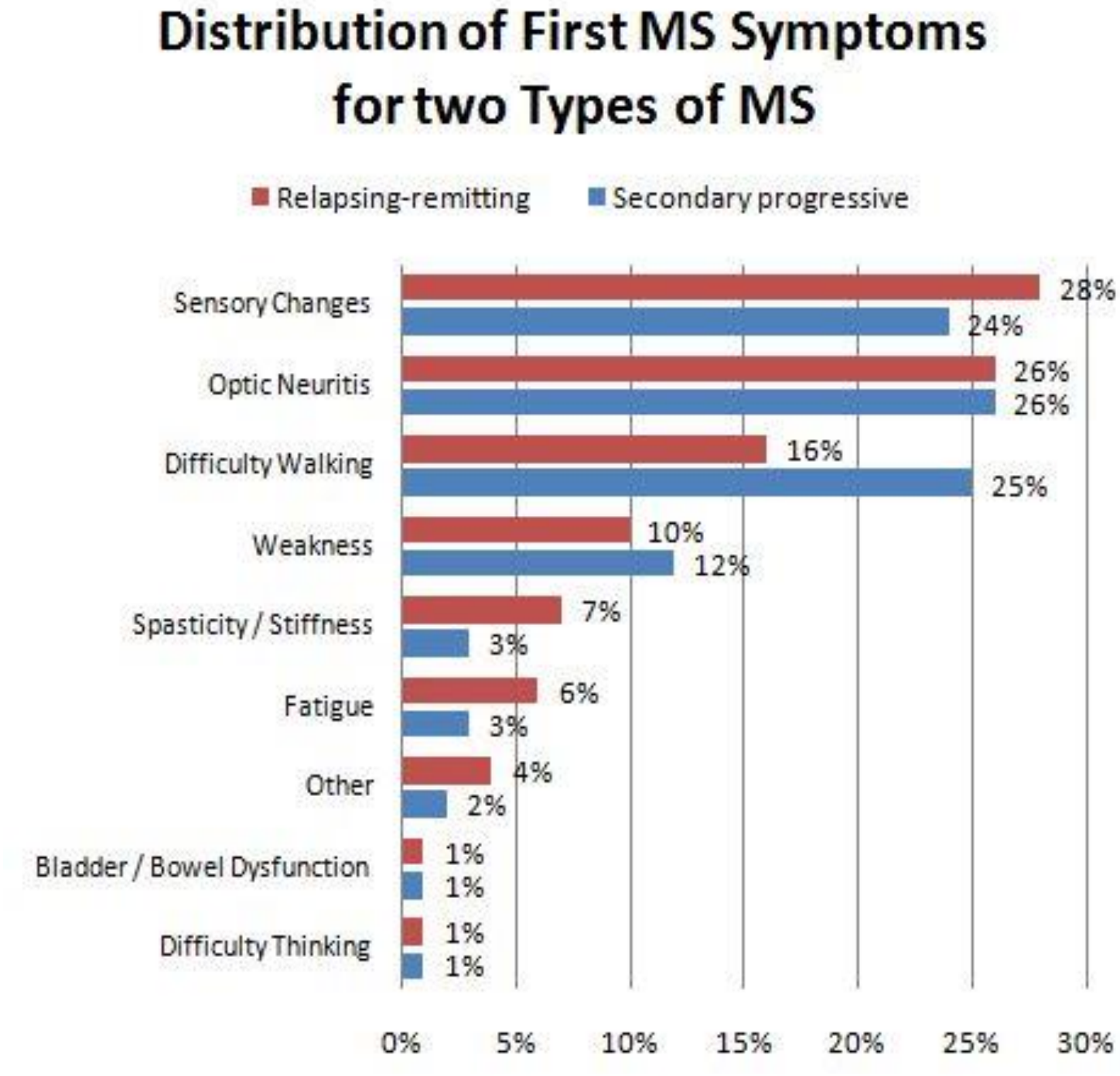


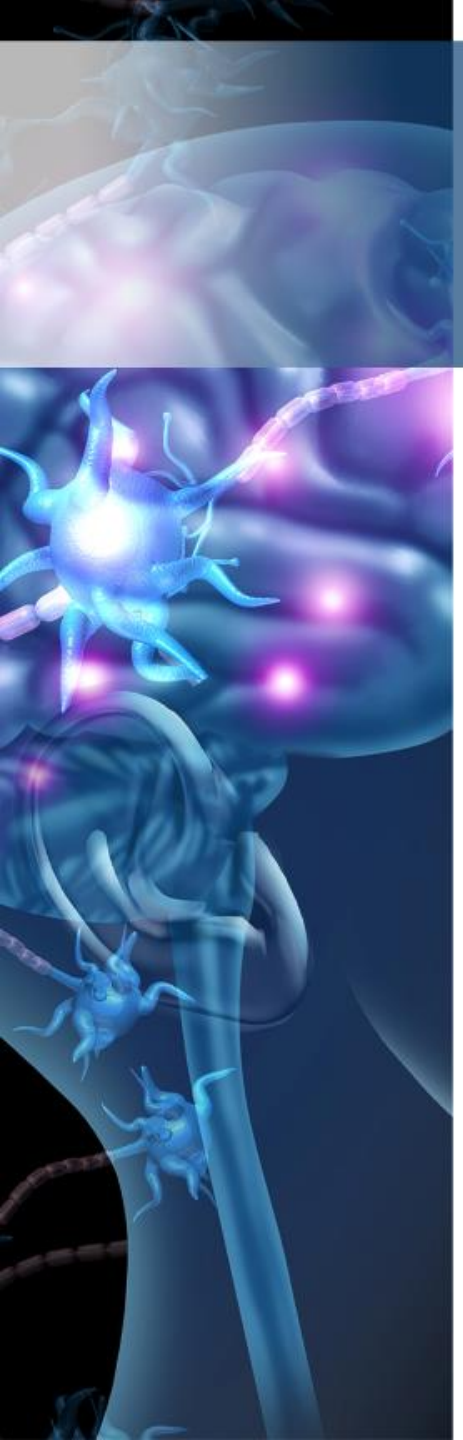
Relapses

- Symptoms + signs
- More than 24 hours
- Deficits
- Absence of infection

Progression

- Fatigue
- Decline > 6 months
- Cognitive decline
- Absence of deconditioning

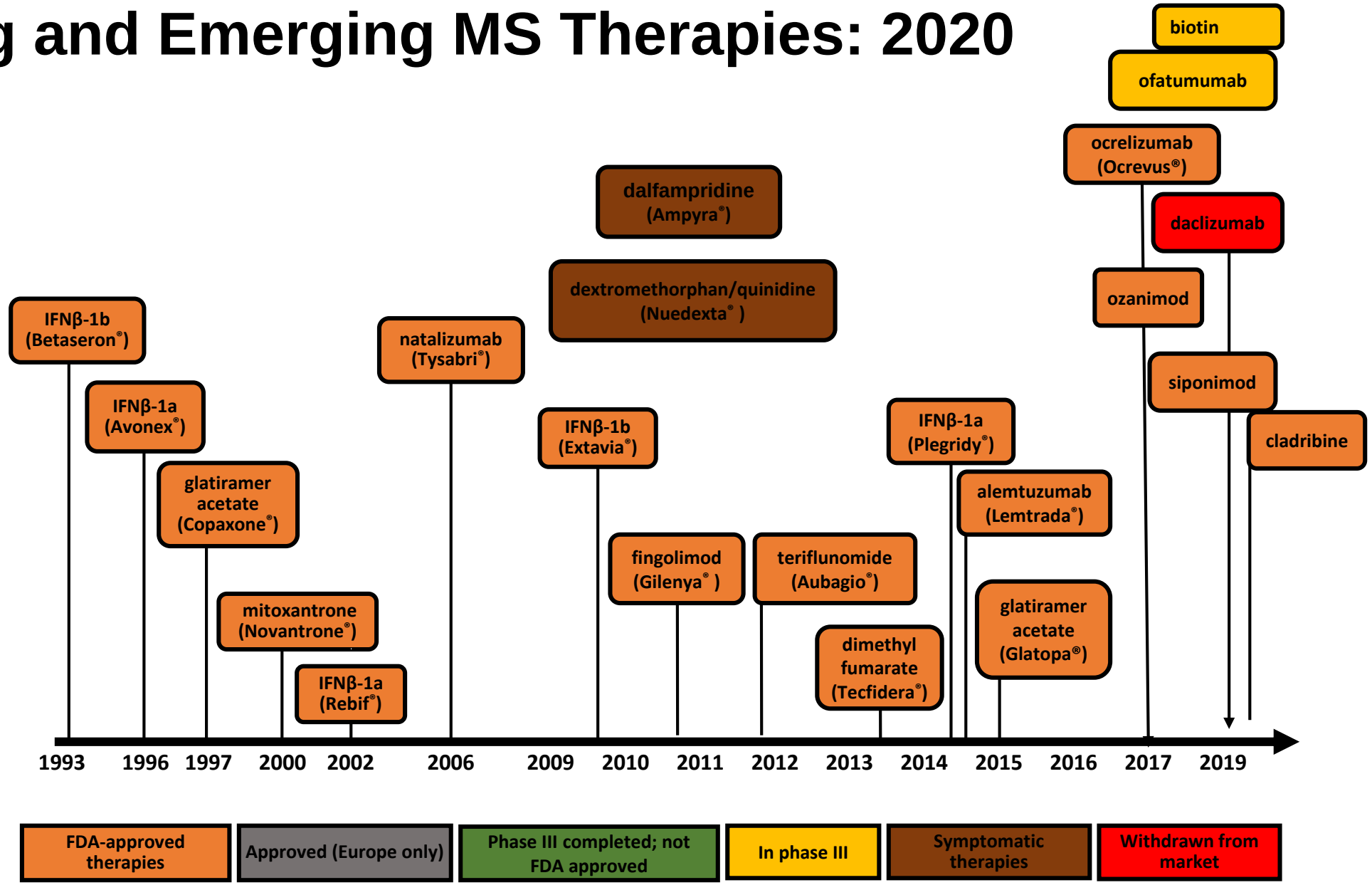




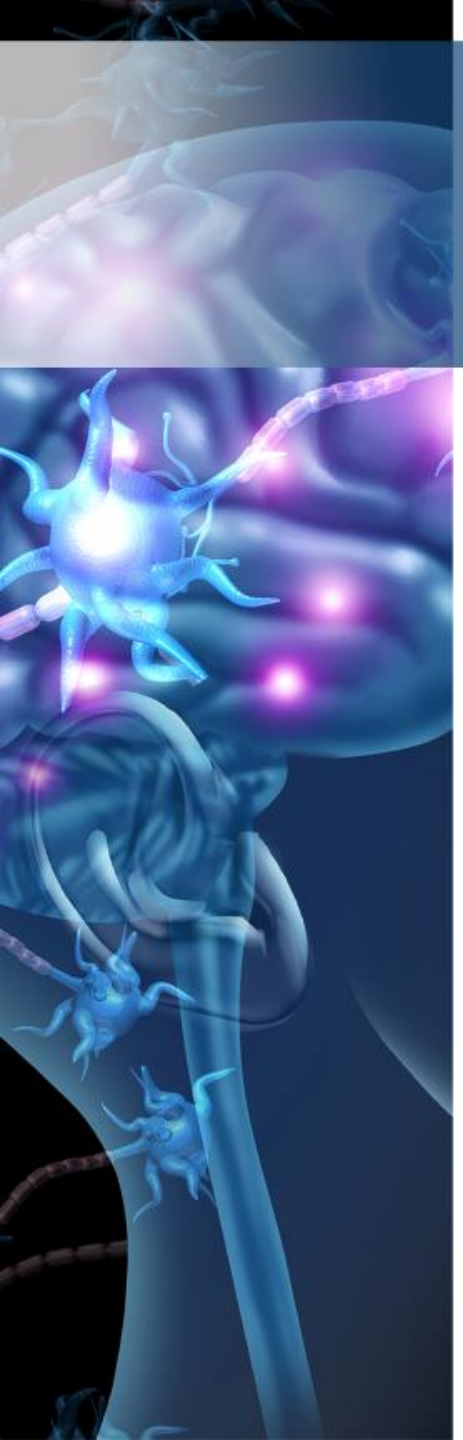
Prognostic Factors

	Good	Poor
Race	Caucasian	Black
Age at onset	young (< 35 years)	older (≥ 35 years)
Gender	female	male
Smoker	no	yes
Subtype	relapsing	progressive
First attack	optic neuritis, sensory, unifocal	motor, cerebellar, sphincter, multifocal
Recovery	complete	incomplete
Attack rate	low	high (≥ 2 in 1 year)
Disability at 5 years	no	yes
MRI lesions	cerebral	brainstem, cord
Lesion load	low	high
Enhancement	absent	present

Existing and Emerging MS Therapies: 2020



FDA, United States Food and Drug Administration.

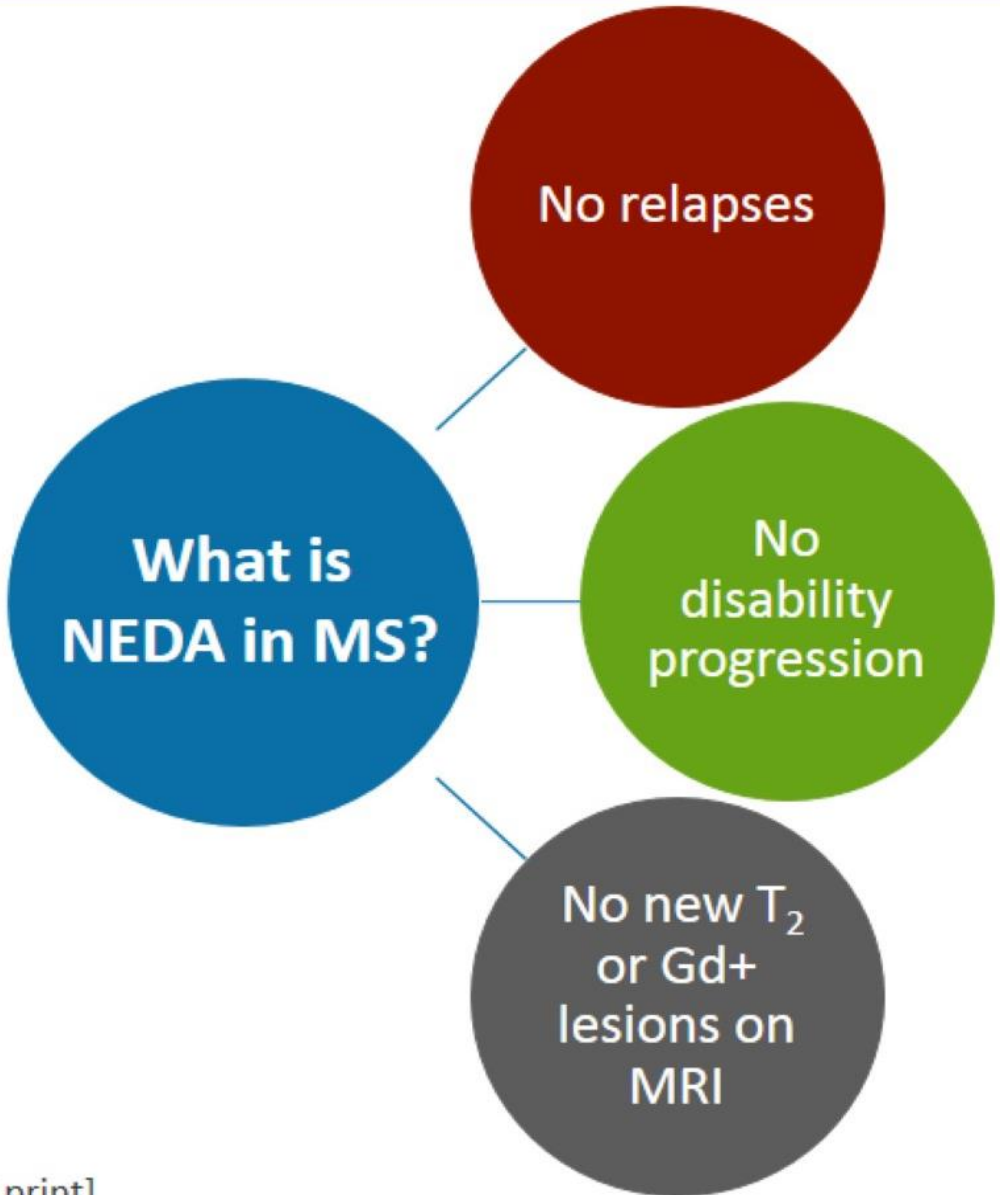


Disease-Modifying Therapy: Selection Factors

Determinant	Factors
Patient related	Comorbidity, lifestyle, personal preferences, pregnancy issues
Disease related	Phenotype, clinical/MRI disease activity, prognostic profile
Drug related	Efficacy, tolerability, convenience, side effects, availability/cost

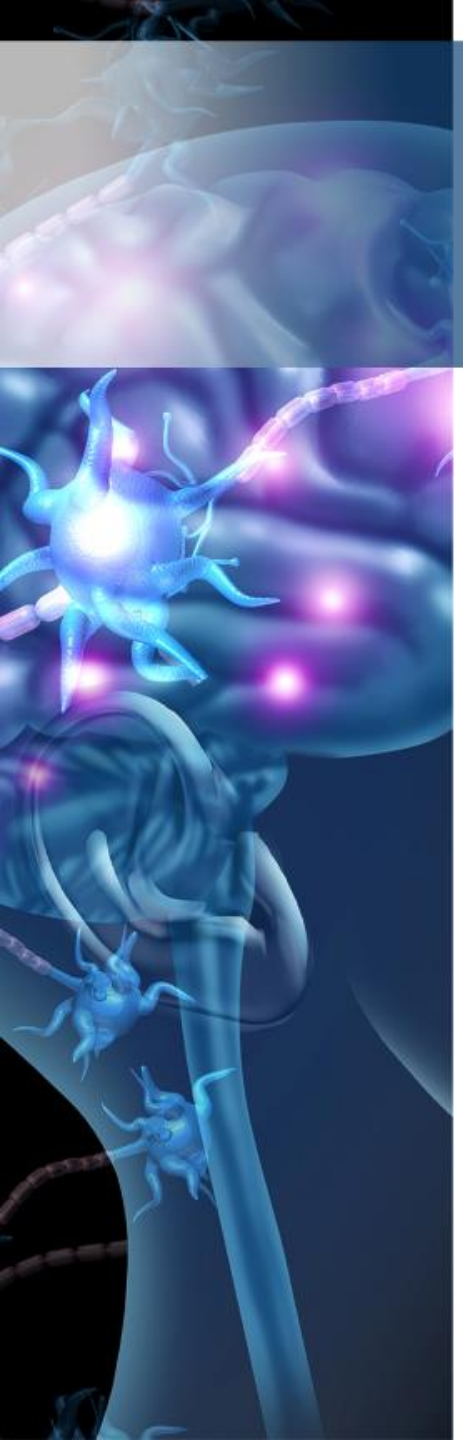
NEDA

- NEDA is a treatment goal in many chronic diseases treated with DMTs
- Using NEDA as a treatment target in MS emphasizes protection of the brain
- May need to update NEDA definition to include
  - Slowing of brain and spinal cord atrophy
  - Neurofilament levels in peripheral blood
  - Patient-reported outcomes



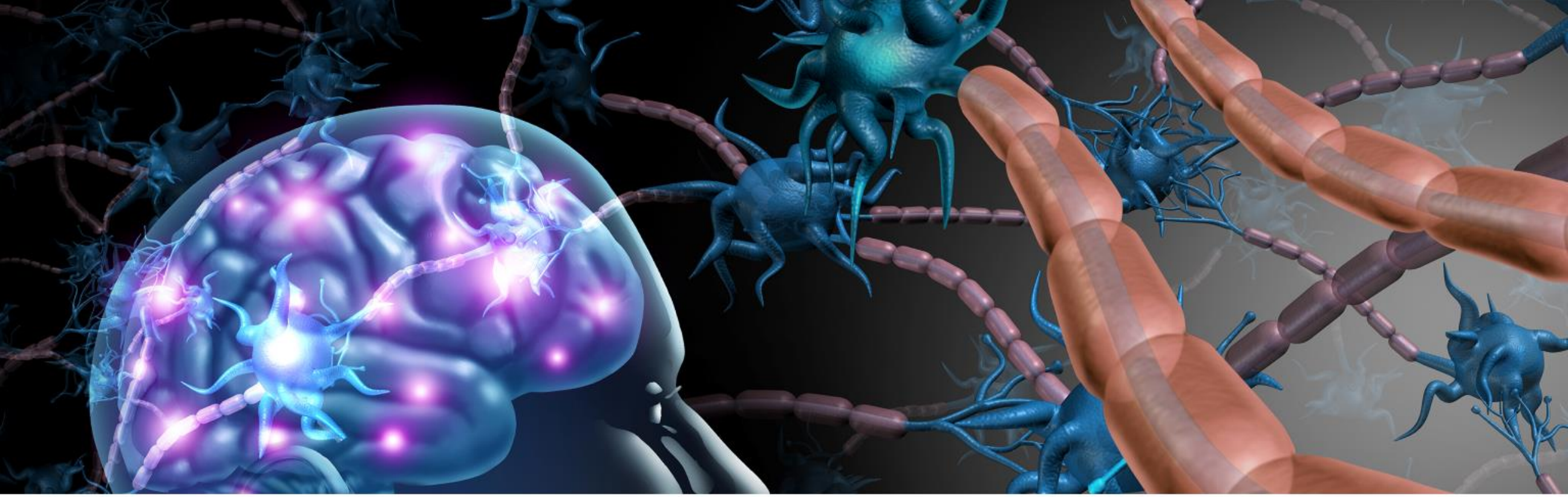
Giovannoni G, et al. *Mult Scler*. 2017. [Epub ahead of print]

NEDA, no evidence of disease activity.



Panel Discussion

- Involving the patient in treatment decision-making

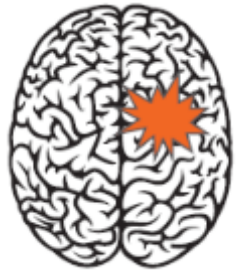


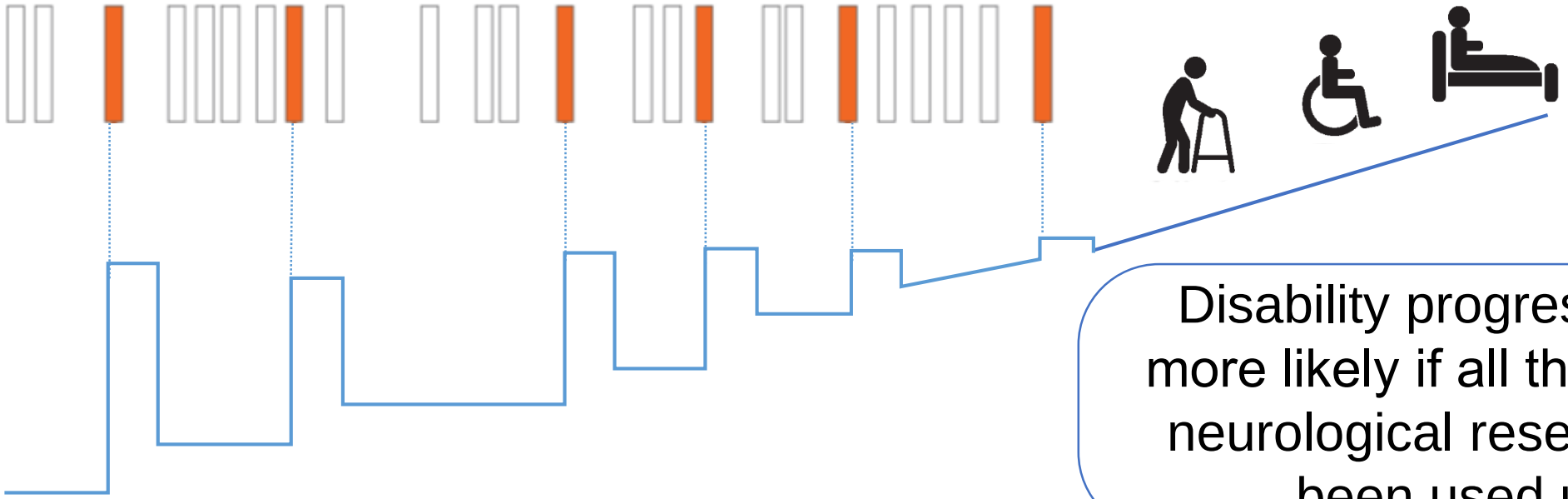
Progression Versus Worsening: How Can You Differentiate between Them in Clinical Practice?

The Importance of Brain Health

Neurological reserve declines

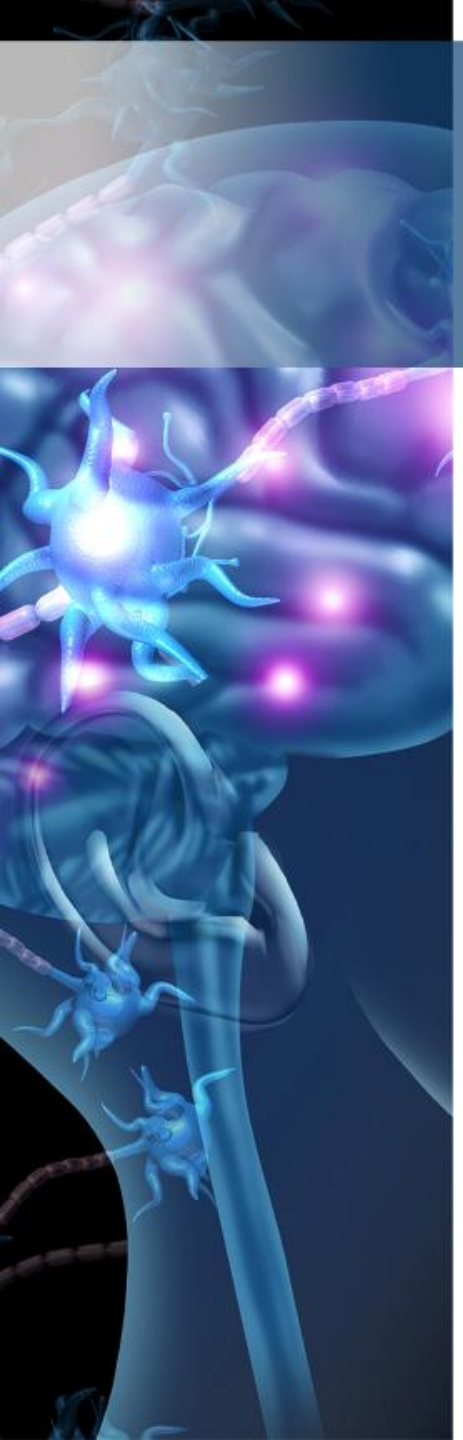
The finite capacity of the brain to adapt to damage – **neurological reserve** – is slowly used up





Disability progression is more likely if all the brain's neurological reserve has been used up

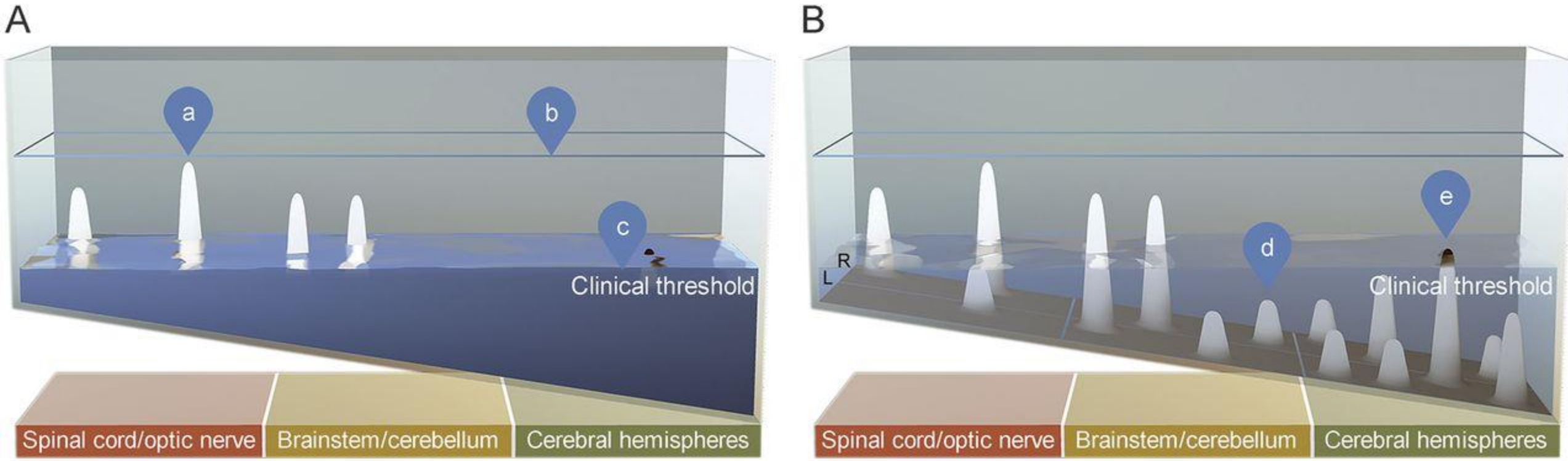
Adapted with permission from Giovannoni G, et al. *Brain health: time matters in multiple sclerosis.* Oxford PharmaGenesis Ltd.; 2015.



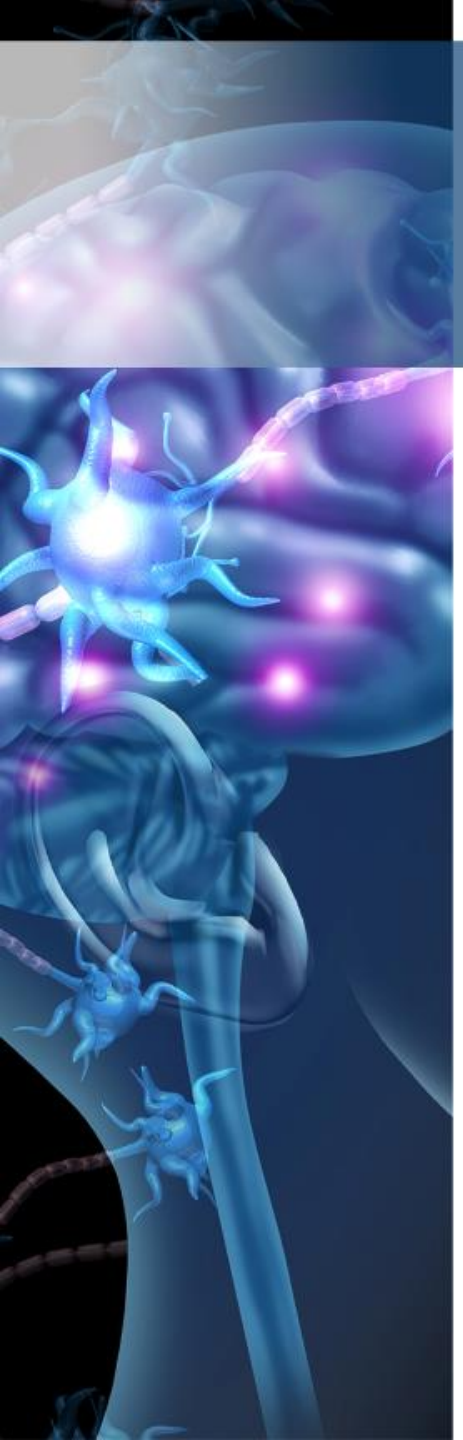
What is Brain Reserve?

- Brain reserve is the ability to tolerate age-related changes and disease-related pathology in the brain without developing clear clinical symptoms or signs
- The brain is a remarkably flexible organ
- Neuronal plasticity is the ever-changing adaptation of the brain to new conditions
  - If MS disease activity damages tissue in one area, other areas can work harder to compensate

Topographical Model of MS

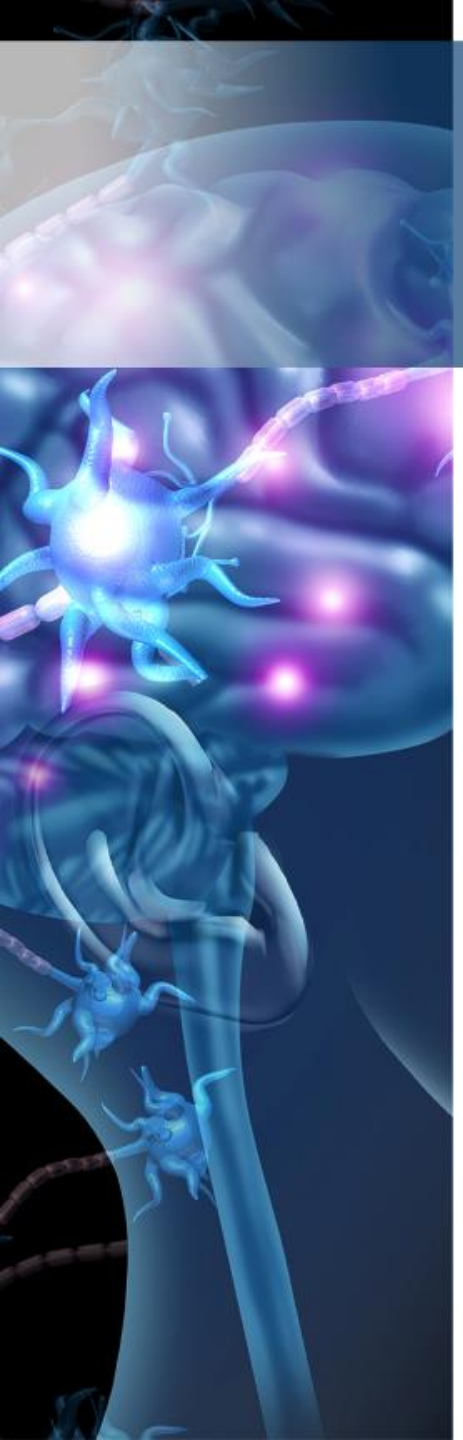


Krieger SC, et al. *Neurol Neuroimmunol Neuroinflamm.* 2016;3(5):e279.



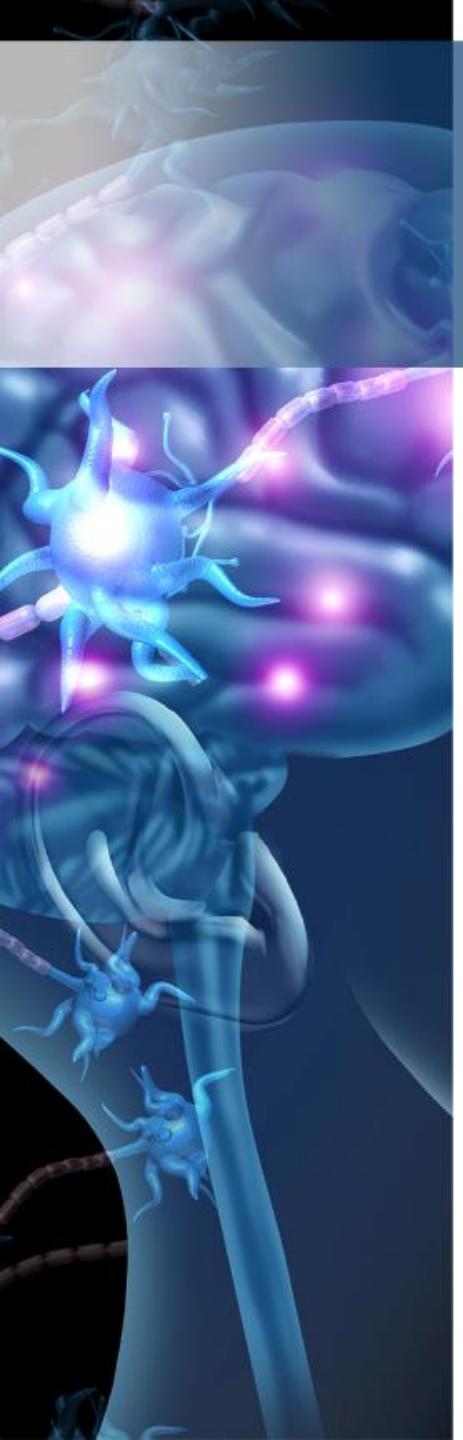
General Principles

- Advanced neuroimaging shows that functional changes occur in the brain of MS patients during and in between relapses
- This functional reorganization is present early during the course of the disease and even in the presence of preserved or fully recovered function
- Functional reorganization differs from those of healthy volunteers, even when recovery interventions drive performance improvements



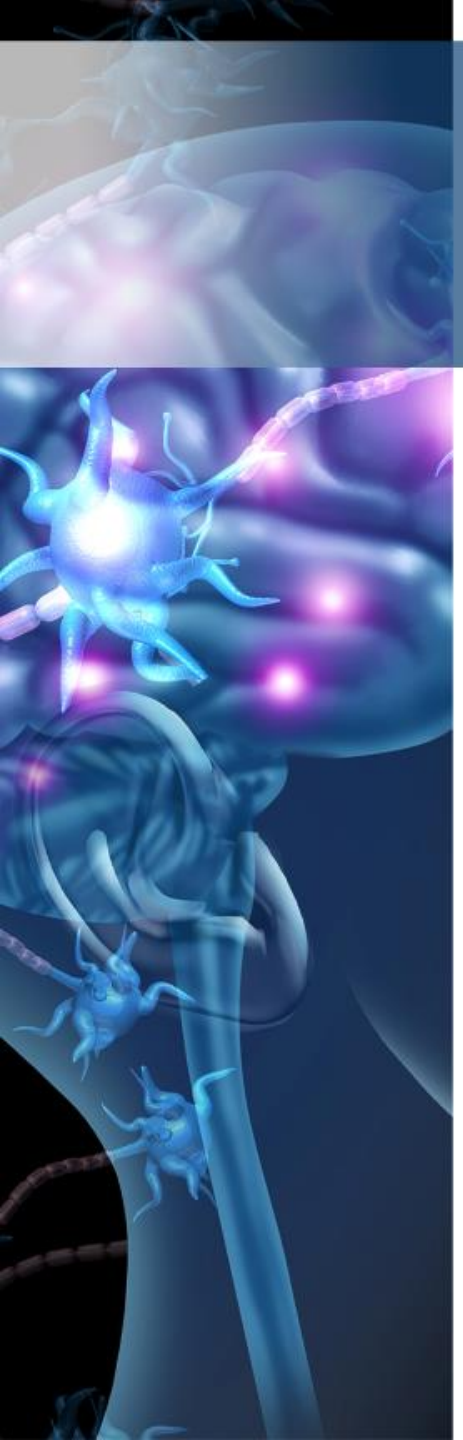
Inflammation and Neuronal Plasticity

- Inflammation can influence synaptic transmission, impairing the ability to compensate for loss of function
- Inflammation can damage connections between brain regions, hindering plasticity to effectively drive recovery
- Inflammation can alter neurovascular coupling – a fundamental function of the brain that ensures a balance between energy demand imposed by neural activity and substrate delivery through blood flow

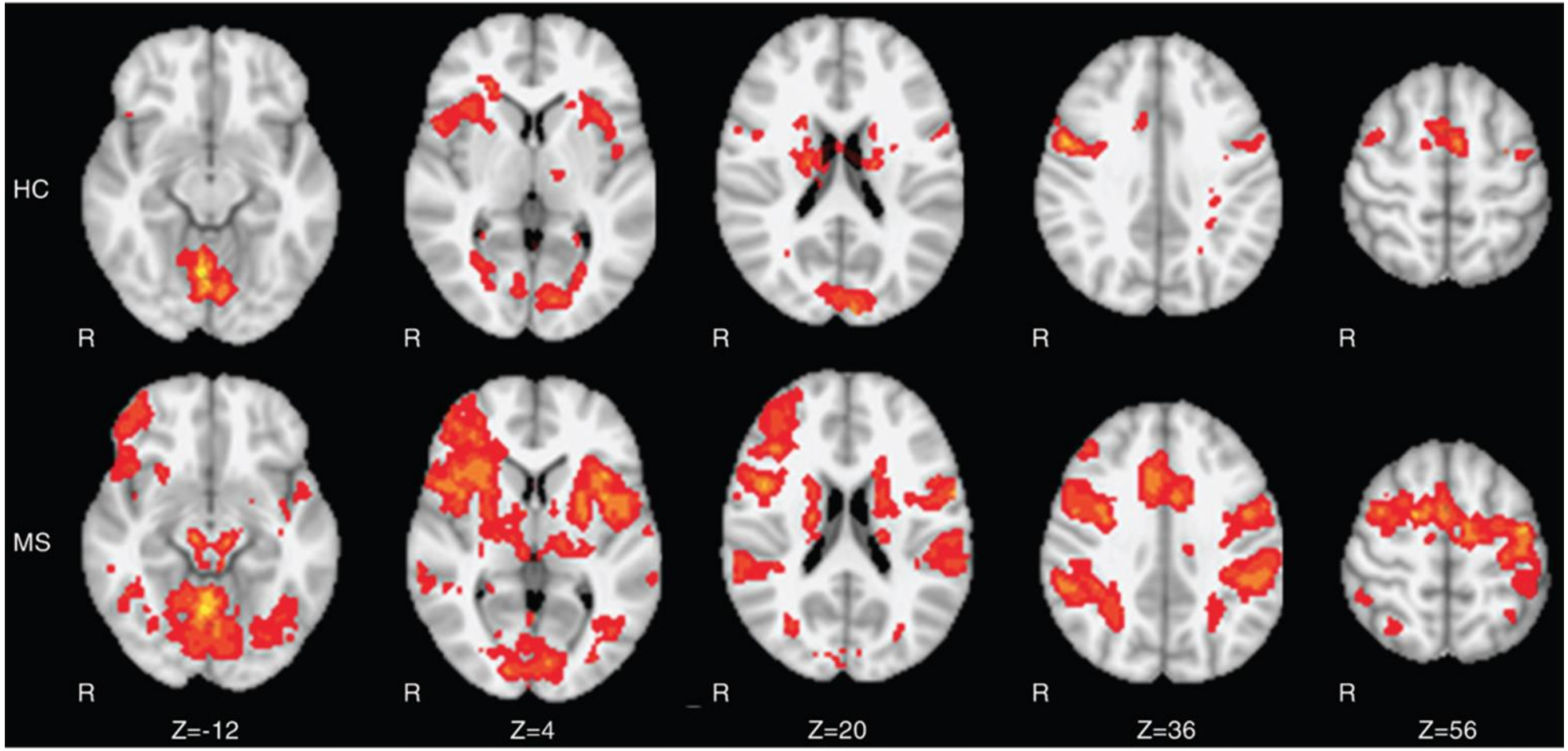


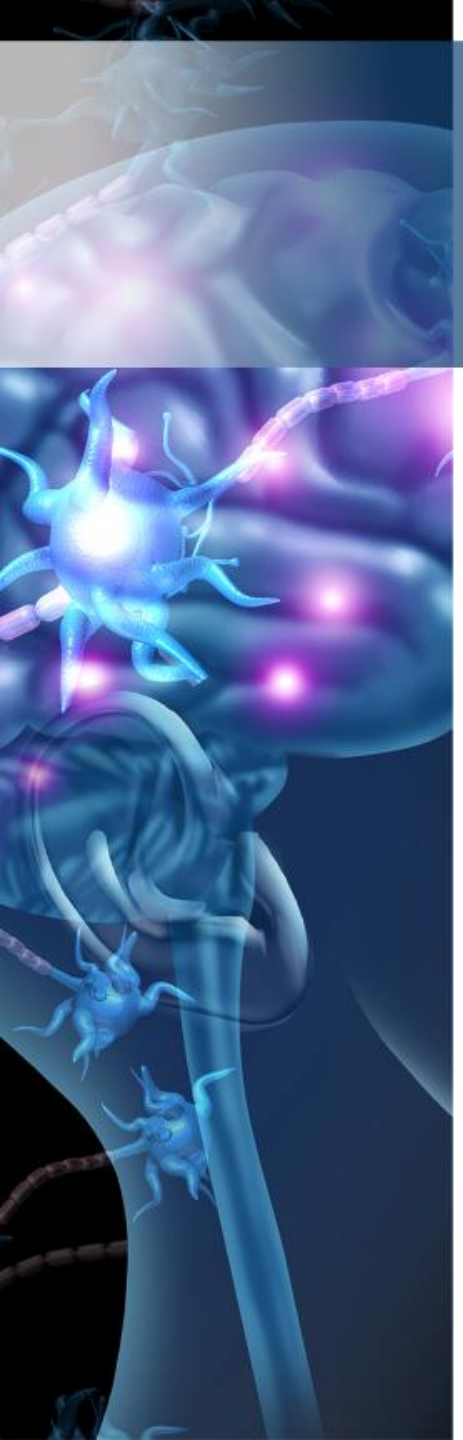
Motor Tasks

- MS patients have greater cortical activation than healthy subjects, often involving motor areas in both cerebral hemispheres, in all disease forms
- The comparison of different MS phenotypes suggests a more extended activation with disease duration
- Increased cortical activation was found to correlate with the severity of tissue damage (lesions)



How to Measure Neuronal Plasticity



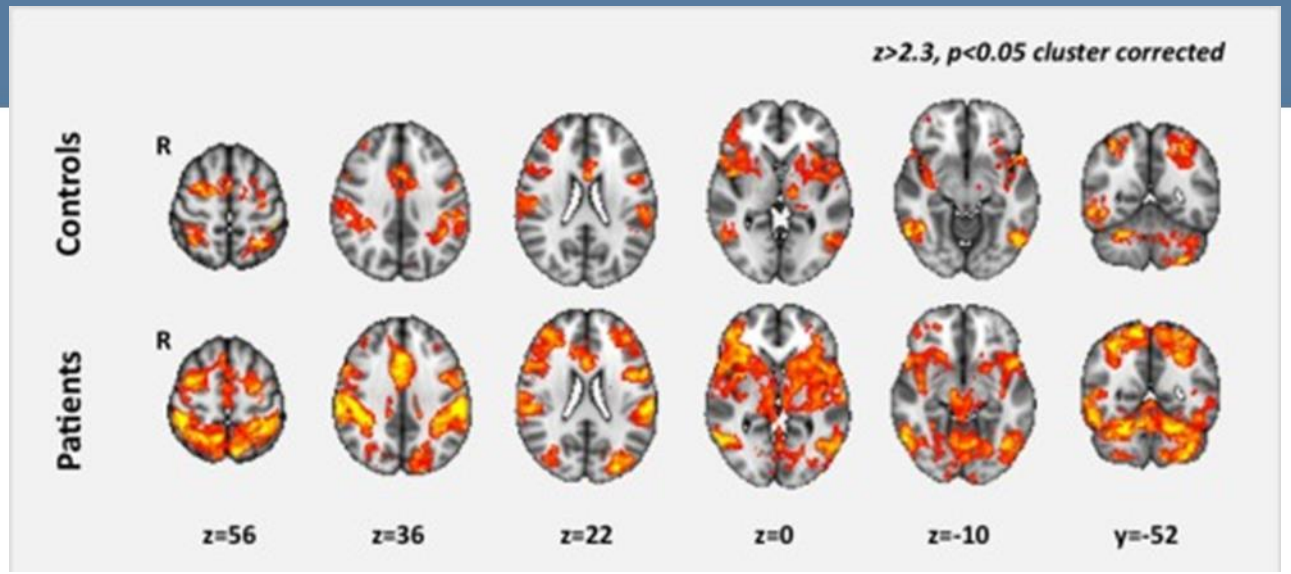


Cognitive Tasks

- Greater cortical activation during the performance of cognitive tasks in patients with no or minimal cognitive impairment compared with healthy subjects

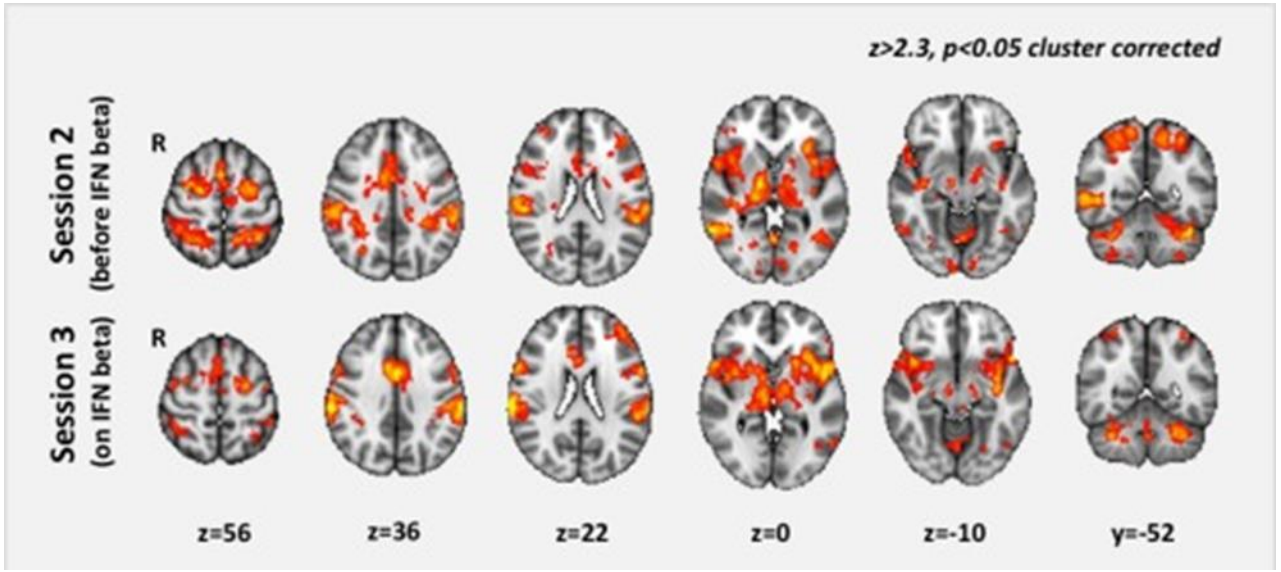
- Severe MS patients did not display any additional activation, suggesting that the compensatory mechanisms had become exhausted

Training Improves Reserve



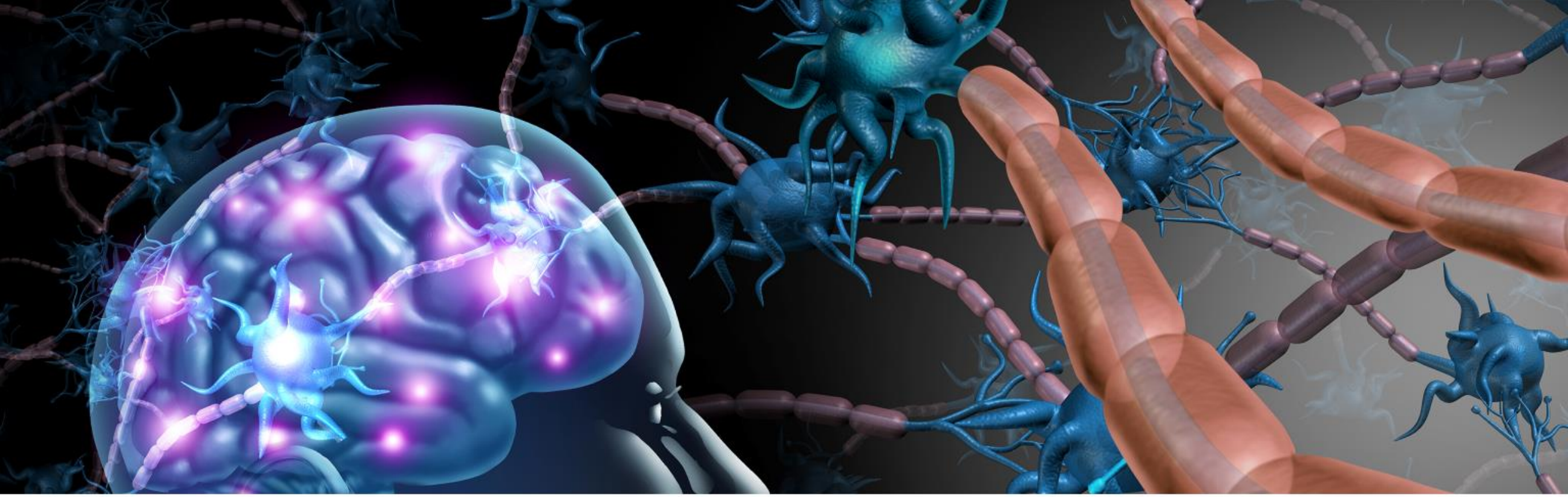
Controls

Baseline

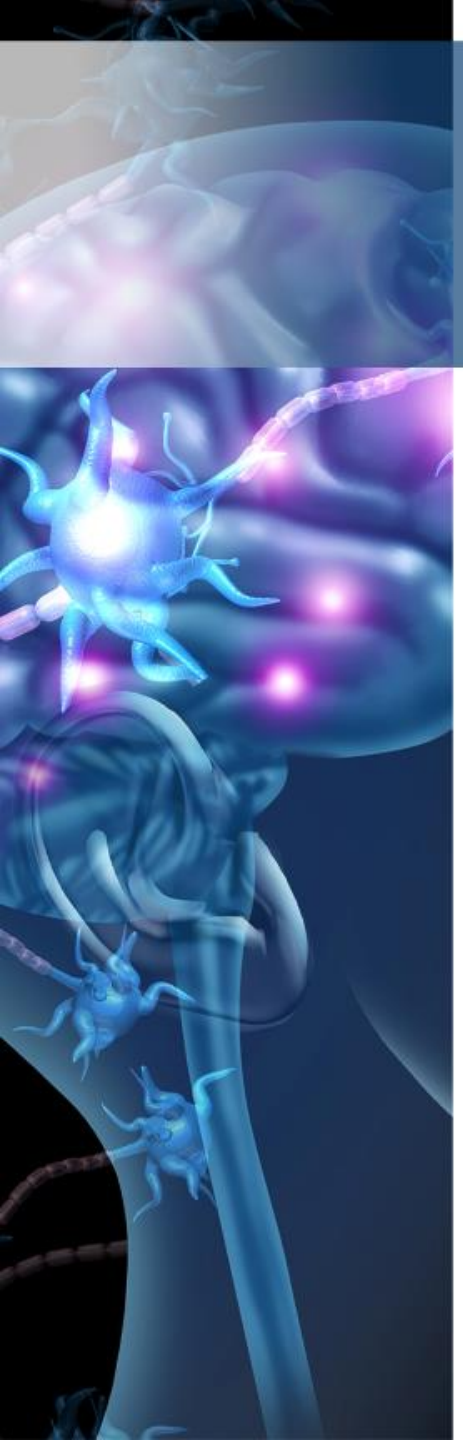


After 1 session

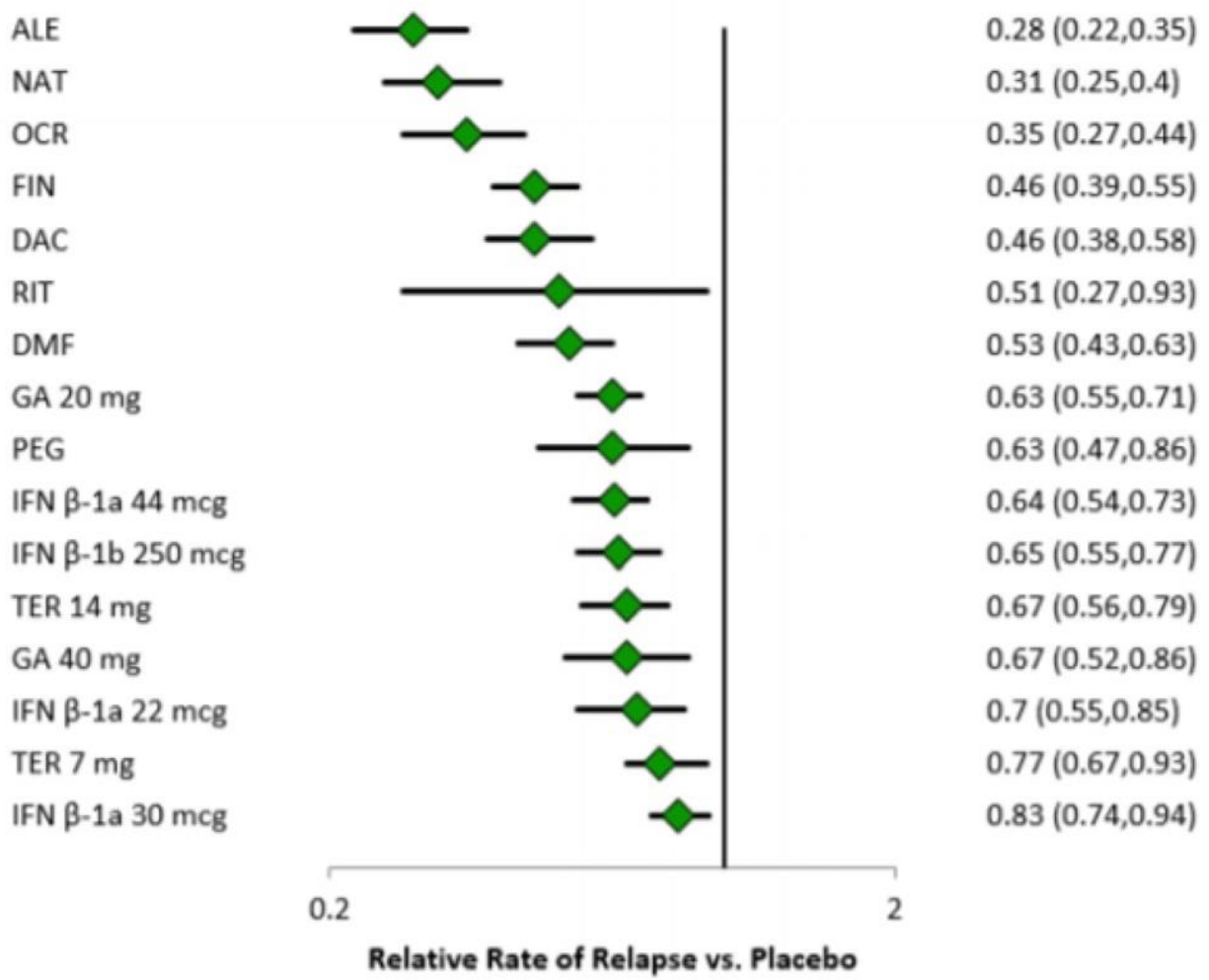
After 2 sessions



Disease-Modifying Therapies

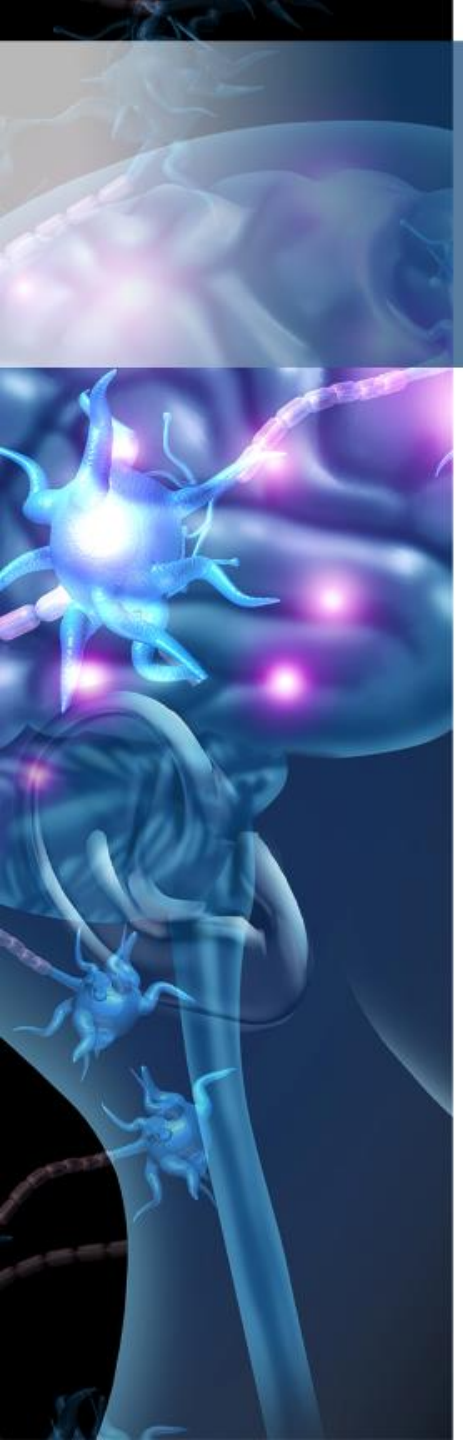


Comparative Effectiveness of DMTs on ARR

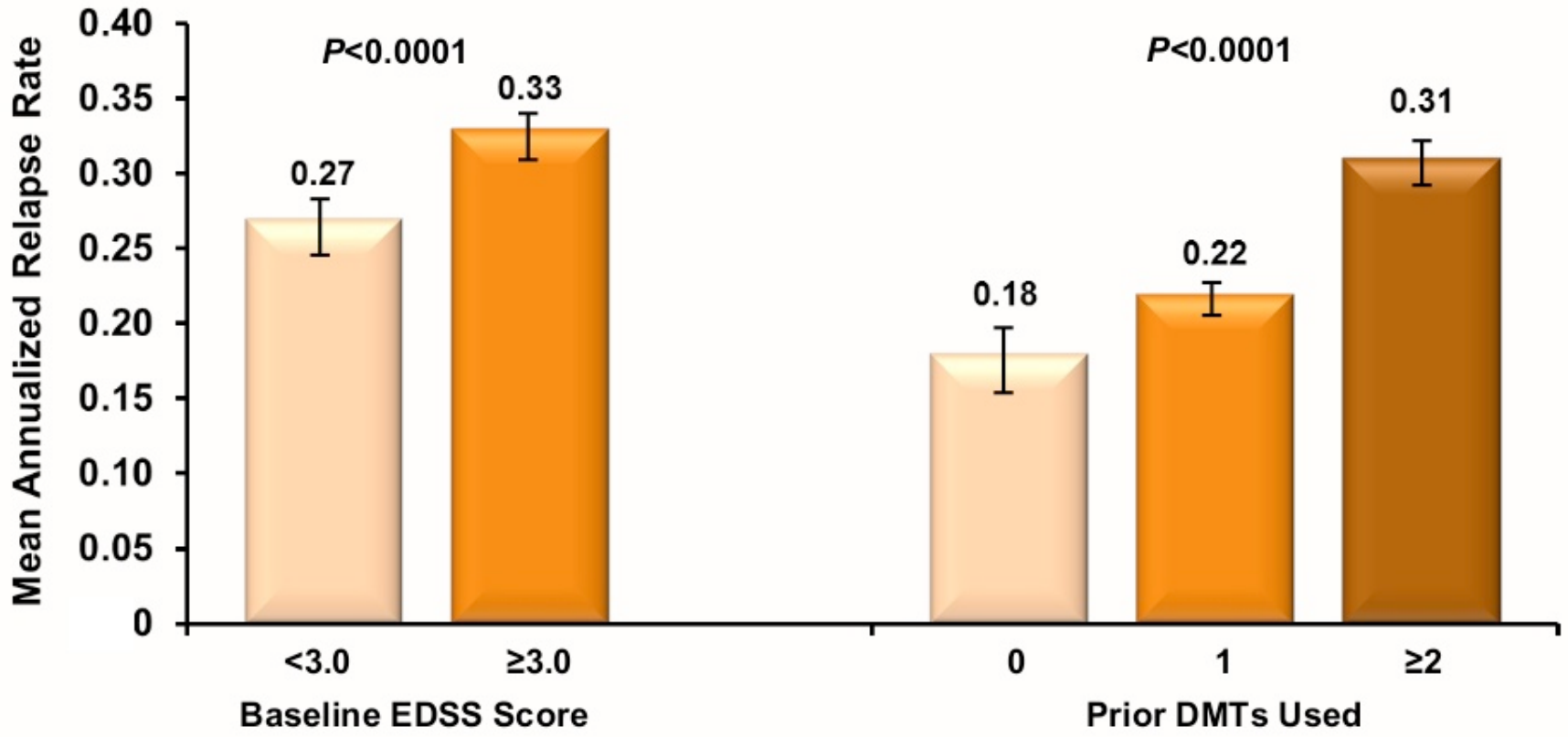


The diamonds represent the point estimate from the NMA for the RR of relapse rate for each DMT vs placebo; the horizontal bars represent the 95% CI. Numbers <1 indicate a reduction in the relapse rate for each DMT vs placebo. ICER Final Evidence Report 2017 website. Reproduced with permission from ICER.

ARR, annualized relapse rate.



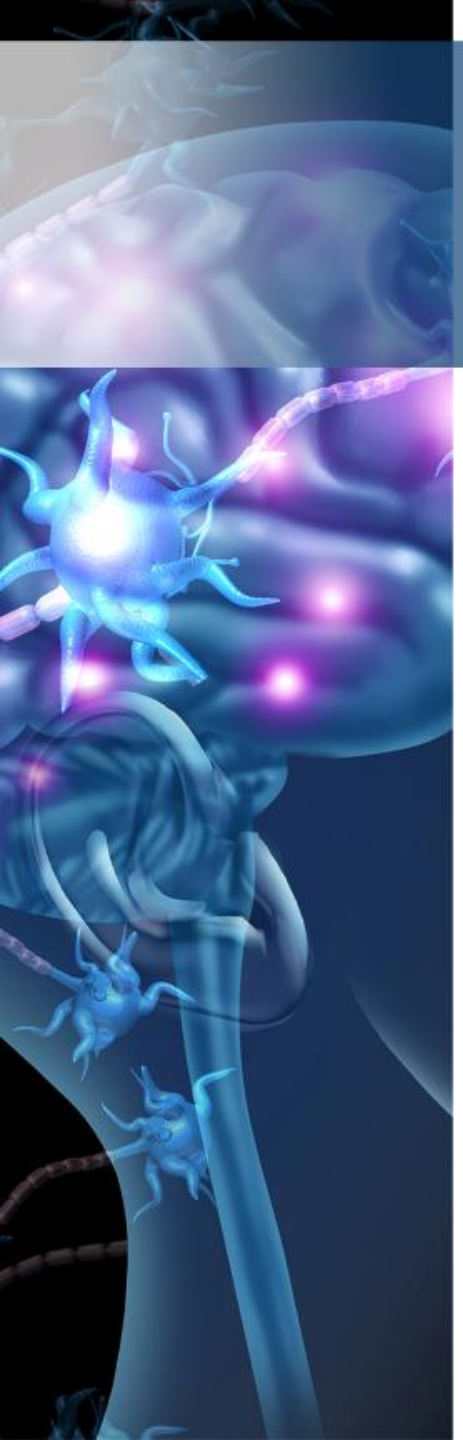
TOP: Earlier Natalizumab Treatment Favors Annualized Relapse Rate Outcomes



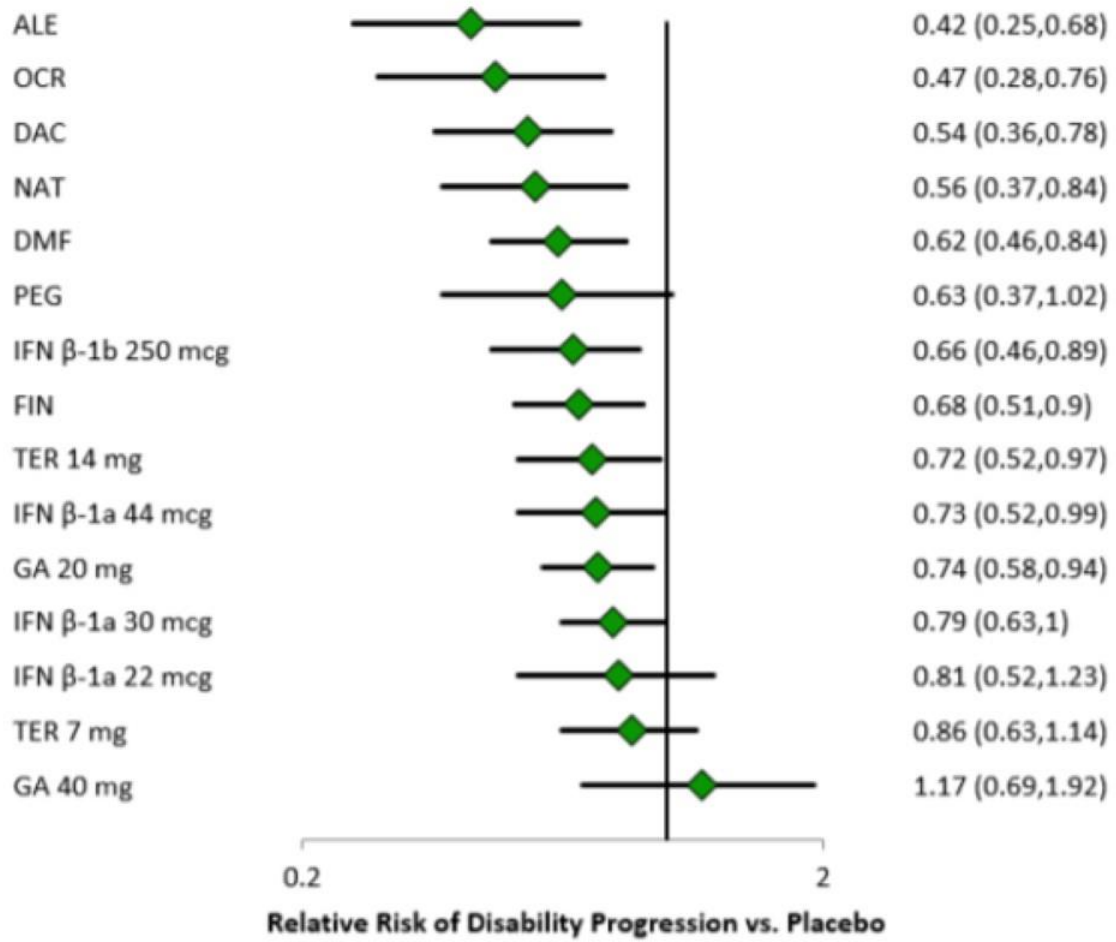
P values from a negative binomial regression model adjusted for gender, baseline EDSS score (<3.0 vs ≥3.0l), relapse status in the prior year (≤1 vs >1), prior DMT use (<3 vs ≥3), disease duration (<8 vs ≥8 years), and treatment duration (≥3 vs <3 years), except for the factor of interest. Error bars represent 95% CIs.

DMT=disease-modifying therapy; CI=confidence interval.

Wiendl et al. Presented at ENS; June 8–11, 2013; Barcelona, Spain,. P372.

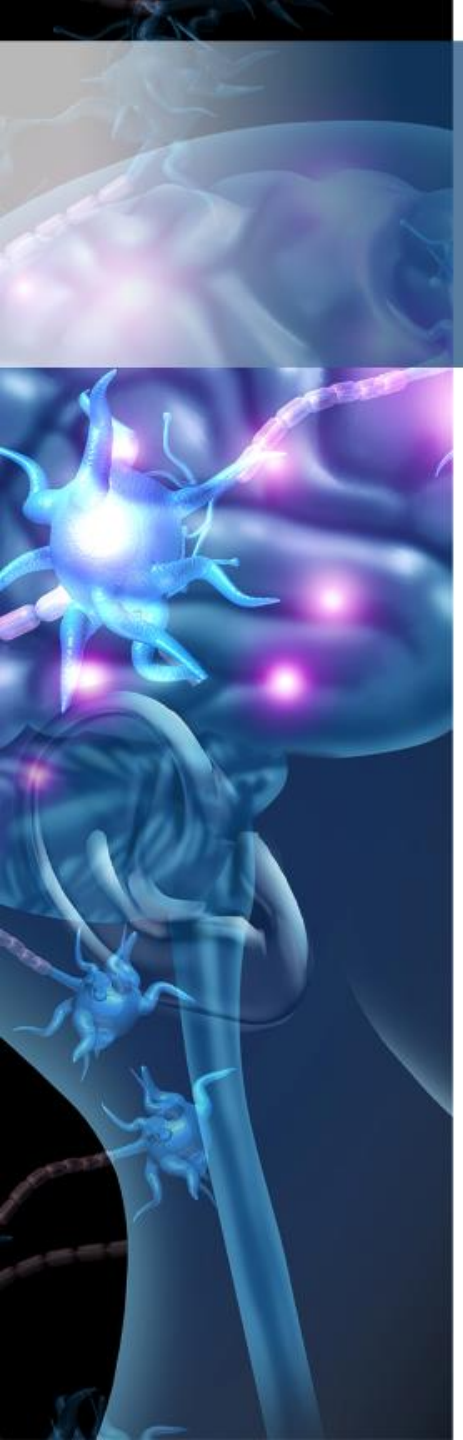


Ability of DMTs to Prevent Sustained Accumulation of Disability



The diamonds represent the point estimate from the NMA for the RR of disability progression for each DMT vs placebo; the horizontal bars represent the 95% CI. Numbers < 1 indicate a reduction in disability progression for each DMT vs placebo.

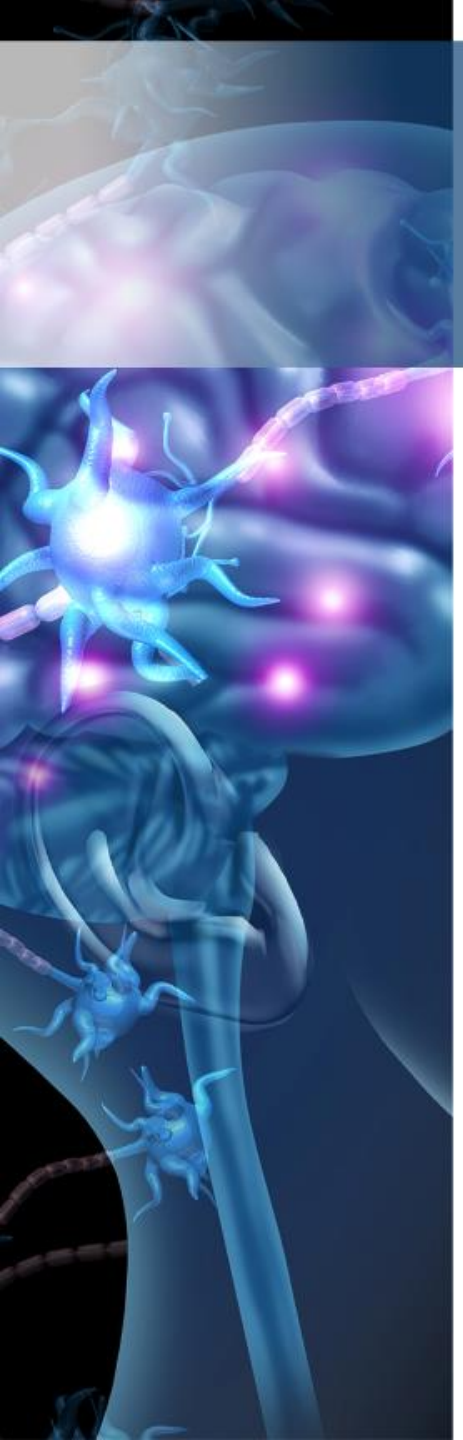
ICER Final Evidence Report 2017 website. Reproduced with permission from ICER.



Comparative Effectiveness of DMTs on Rate of Brain Volume Loss

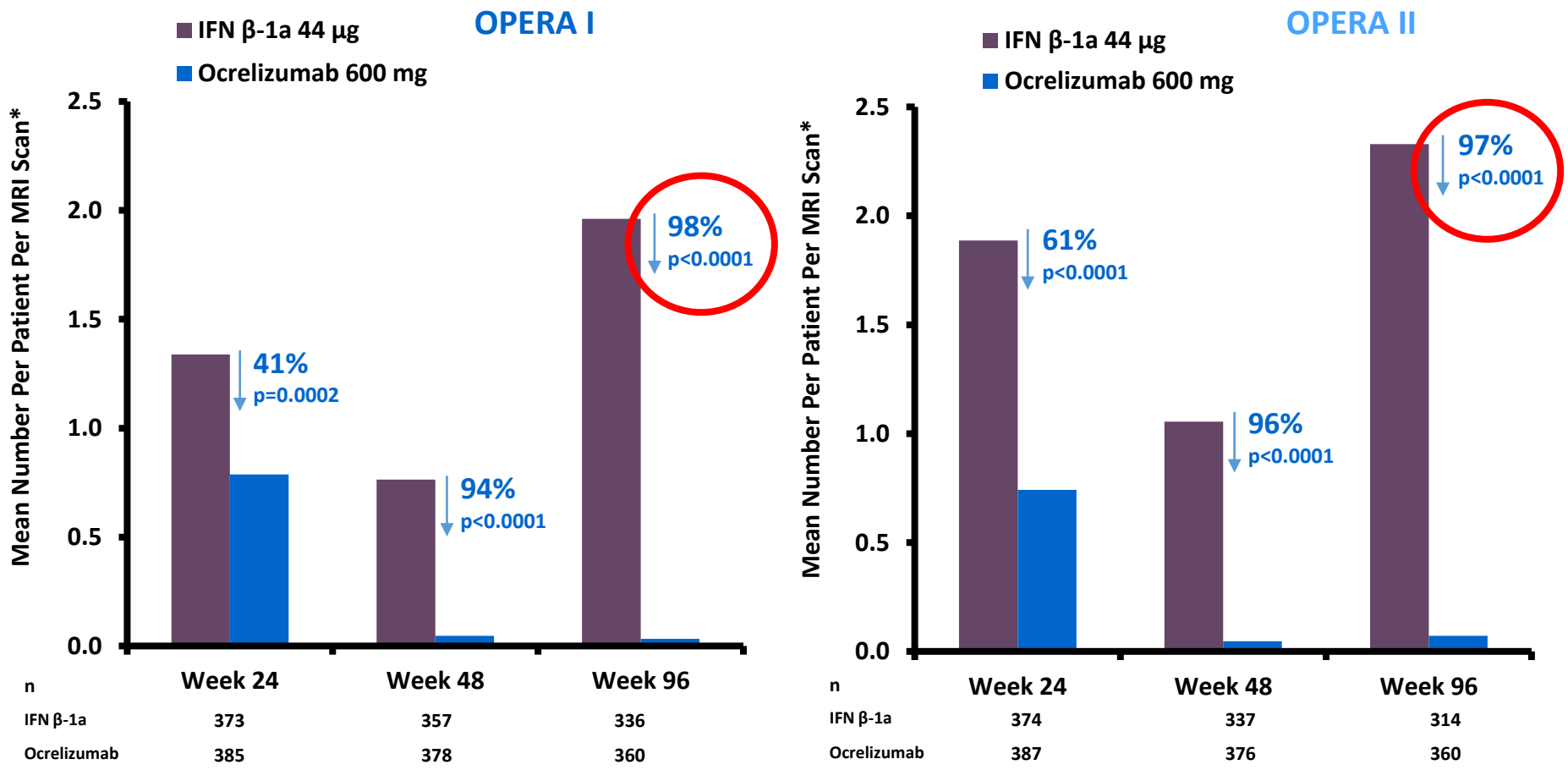
Agent (Comparator)	Decrease in Brain Atrophy, %
Natalizumab (placebo)*[a]	45
Alemtuzumab (IFN β-1a SC)[b]	40
Fingolimod (placebo)†[c]	30
Dimethyl fumarate (placebo)‡[d]	30 (bid), 17 (tid)
Laquinimod (placebo)[e]	28
Teriflunomide (placebo)[f]	25 (NS)
IFN β-1a IM (placebo)[e]	0
Glatiramer (placebo)[g]	25

*Year 2 results; brain atrophy was greater in year 1 and less in year 2 in patients treated with natalizumab in the AFFIRM trial.
†Average reduction in brain atrophy from baseline to 6 mo, baseline to 12 mo, and 12 to 24 mo.
‡ Average reduction in brain atrophy from 6 mo to 2 y.
a. Miller DH, et al. 2007;68:1390-1401; b. Cohen JA, et al. *Lancet.* 2012;380:1819-1828; c. Kappos L, et al. *N Engl J Med.* 2010;362:387-401; d. Arnold DL, et al. *J Neurol.* 2014;261:1794-1802; e. Vollmer TL, et al. *J Neurol.* 2014;261:773-783; f. O'Connor P, et al. *N Engl J Med.* 2011;365:1293-1303; g. Sormani MP, et al. *Neurology*. 2004;62:1432-1434.



Exploratory Endpoint:

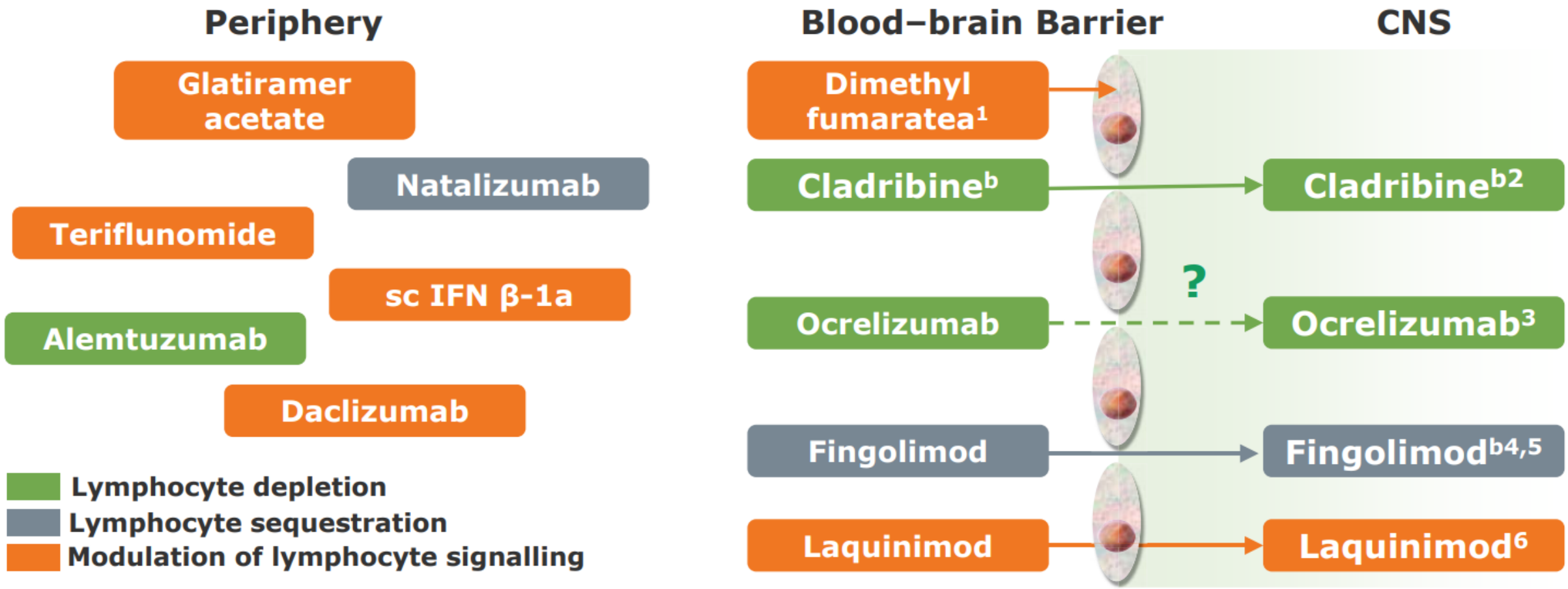
Significant reduction in total new and/or enlarging T2 hyperintense lesions compared with IFN β-1a



*Adjusted by baseline T2 lesion count, baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW).
EDSS, Expanded Disability Status Scale; IFN, interferon; ROW, rest of the world.

Hauser SL, et al. *N Engl J Med*. 2017;376(3):221-34.

Is there a need for a MS therapy with evidence of direct action on the inflammatory activity in the CNS compartment?



[a]Preclinical evidence suggests that dimethyl fumarate stabilises the blood-brain barrier. [b]These agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. CNS, central nervous system; IFN, interferon; PI, Prescribing Information; sc, subcutaneous; SmPC, Summary of Product Characteristics. Rebif® EU SmPC; Copaxone® SPC; Aubagio® EU SmPC; Tecfidera® EU SmPC; Tysabri® EU SmPC; Gilenya® EU SmPC; Lemtrada® EU SmPC; Zinbryta® EU SmPC.

1. Kunze R et al. *Exp Neurol*. 2015;266:99–111; **2.** Liliemark J. *Clin Pharmacokinet*. 1997;32:120–31; **3.** Ruhstaller TW et al. *Ann Oncol*. 2000;11:374–375; **4.** Hunter SF et al. *CNS Drugs*. 2016;30:135–147; **5.** Groves A et al. *J Neurol Sci*. 2013;328:9–18; **6.** Brück W, Wegner C. *Neurol Sci*. 2011;306:173–179. Website links available on request.

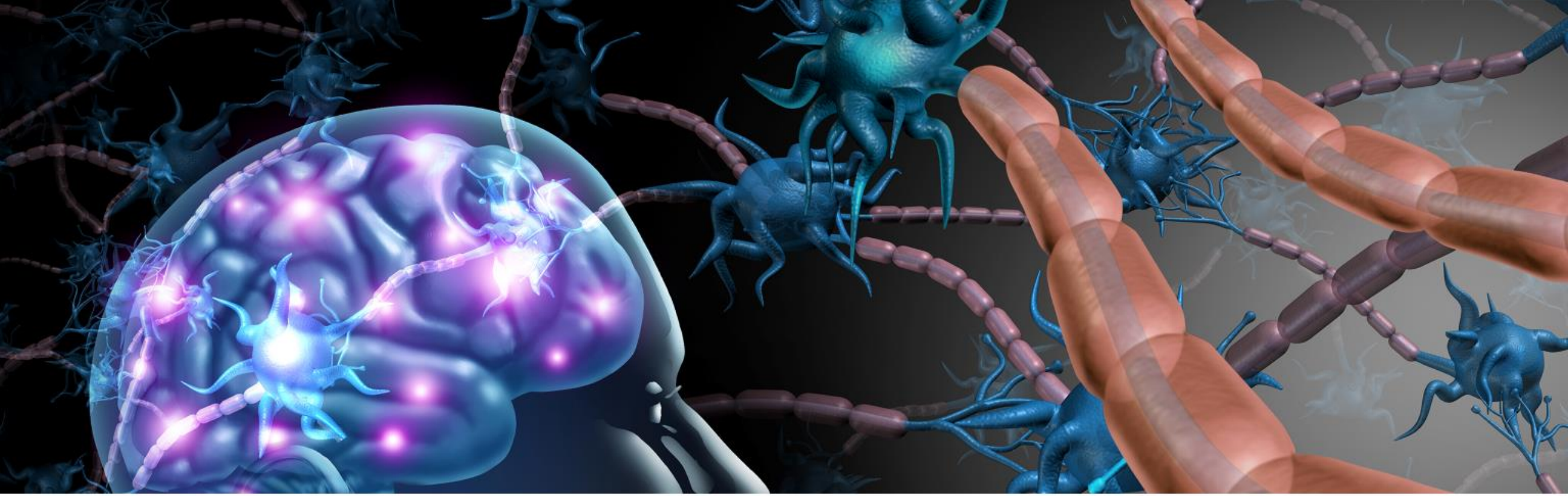
Phase 3 Trials of DMDs in Progressive MS

When inflammation is compartmentalized in the CNS, drugs that cannot cross the blood–brain barrier have no significant effect on the disease course[1]

Agent[a]	Type of MS	Duration (years)	Primary outcome	*P* value
Glatiramer acetate[2]	PPMS	3[b]	Time to sustained progression of accumulated disability HR 0.87 (95% CI, 0.71–1.07)	0.1753
Fingolimod[3]	PPMS	3–5	3-month CDP[c] RR 5.05%; HR 0.95 (95% CI, 0.80–1.12)	0.544
Ocrelizumab[4]	PPMS	~3	3-month CDP HR 0.76 (95% CI, 0.59–0.98)	0.0321
Rituximab[5]	PPMS	2	Time to CDP 30.2% (rituximab) vs 38.5% (placebo)	0.1442
Natalizumab[6]	SPMS	2	Patients with CDP on ≥1 of EDSS, T25FW or 9HPT 44% vs 48%; OR 0.86 (95% CI, 0.66–1.13)	0.287
Siponimod	SPMS	Max 3	delay in time to confirmed disability progression as measured by EDSS	0.013

No data are available for teriflunomide, dimethyl fumarate, alemtuzumab, daclizumab or cladribine tablets in PMS. [a]Agents not approved anywhere in the world for use in progressive MS; [b]Terminated early for non-efficacy reasons. [c]Composite endpoint including change in EDSS, 9HPT and T25WT. 9HPT, 9-hole peg test; CDP, confirmed disability progression; CI, confidence interval; CNS, central nervous system; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OR, odds ratio; PPMS, primary progressive MS; RR, risk reduction; SPMS, secondary progressive MS; T25FW, timed 25-foot walk test.

1. Perez-Cerda F et al. *Multi Scl Demylin Dis*. 2016;2016:1–9; **2.** Wolinsky JS et al. *Ann Neurol*. 2007;61:14–24; **3.** Lublin F et al. *Lancet*. 2016; 387:1075-1084; **4.** Montalban X et al. *Neurology*. 2016;86(Suppl 16):S49.001; **5.** Hawker K et al. *Ann Neurol*. 2009;66:460–471; **6.** Steiner D et al. Presented at AAN 2016 [P009] Kappos L et al. Efficacy and safety of siponimod in secondary progressive multiple sclerosis – Results of the placebo controlled, double-blind, Phase III EXPAND study. Oral presentation presented at: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis; September 14-17, 2016; London, UK.



When To Switch Therapies?

Common reasons for discontinuation of MS therapies

Intolerable side-effects	Adverse reaction: injection site reaction, infusion reaction, infection Flu-like symptoms, headache, fatigue Laboratory abnormalities: increased liver enzymes, sever autoimmune hypothyroidism
Neutralizing antibodies	Anti-IFNβ, anti-natalizumab
Risk of life threatening infection	JCV causing PML
Unacceptable disease activity	Clinical activity: relapse rate, Cognitive decline, increased EDSS MRI activity: Appearance of two or more T2 lesions, persistence of active lesion A mix of clinical MRI parameters
Pregnancy	Attempt at conception Actual pregnancy

Recommendations for determining the level of concern when considering treatment modification based on relapse

	Low	Medium	High
Rate	1 relapse in the 2nd year of treatment	1 relapse in the 1st year of treatment	>1 relapse in the 1st year of treatment
	Mild	Moderate	Severe
Steroid	Not required	Required	Hospitalization required
Effect on ADL	Minimal	Moderate	Severe
Affected functional domain	1	>1	>1
Motor/cerebellar involvement	No or mild	Moderate	Severe
Recovery	Prompt	Incomplete recovery at 3 months	Incomplete recovery at 6 months
Functional defect	No	Some functional impairment	Functional impairment

ADL, activities of daily living.

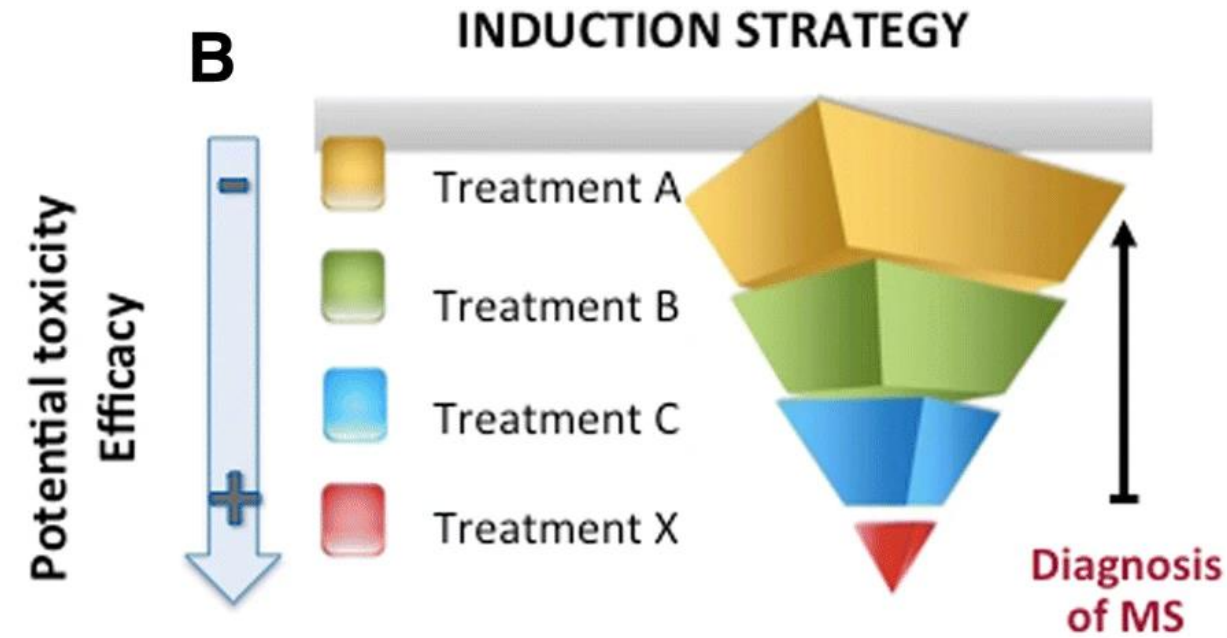
Rio and Modified Rio scores

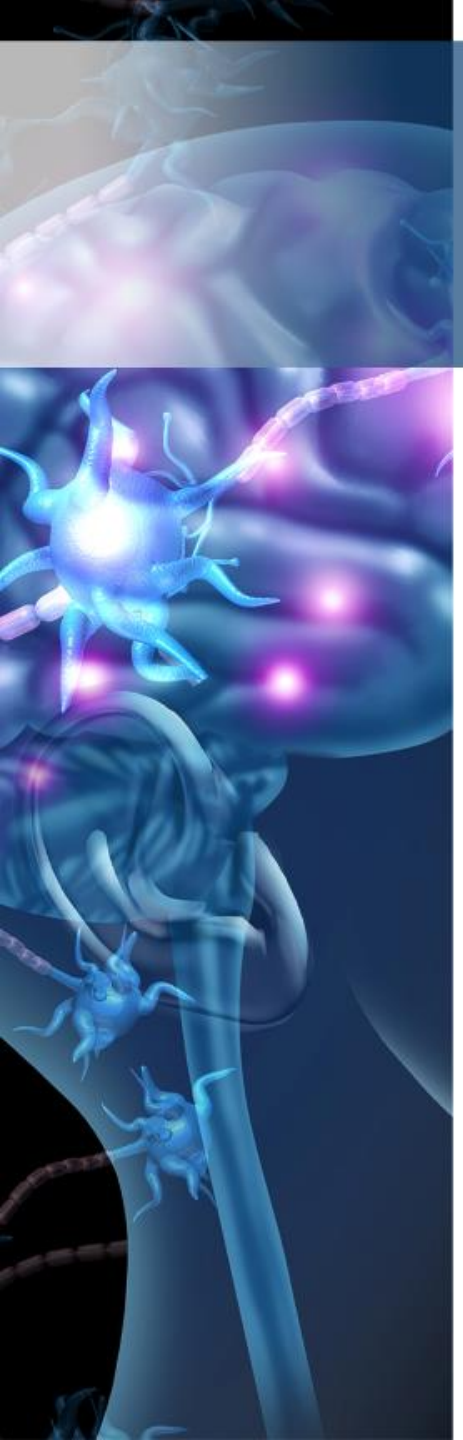
Rio score		Modified Rio score	
Criterion	Change over the first year	Criterion	Change over the first year
MRI 0	≤2 active † T2 lesions	MRI 0	≤4(5)‡ new T2 lesions
MRI 1	>2 active T2 lesions	MRI 1	>4(5)‡ new T2 lesions
Relapse 0	No relapses	Relapse 0	No relapses
Relapse 1	≥1 relapse	Relapse 1	1 relapse
		Relapse 2	≥2 relapses
EDSS 0	Increased in EDSS of <1 point	Not included	
EDSS 1	Increased in EDSS of ≥1 point Sustained over at least 6 month		

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging. Adapted from Sormani et al.[12] with permission.

	Level of concern		
Activity on MRI	Low	Medium	High
New Gd-enhancing or accumulation of new T2 lesion per year	1 lesion	2 lesions	≥3 lesions


ESCALATION STRATEGY
A
Potential toxicity
Efficacy
+
-
Treatment X
Treatment C
Treatment B
Treatment A
Diagnosis
of MS


INDUCTION STRATEGY
B
Potential toxicity
Efficacy
-
+
Treatment A
Treatment B
Treatment C
Treatment X
Diagnosis
of MS



Shared Decision-Making

- A process in which clinicians, including pharmacists, and patients work together to decide about interventions on the basis of clinical evidence and the patient's informed preferences

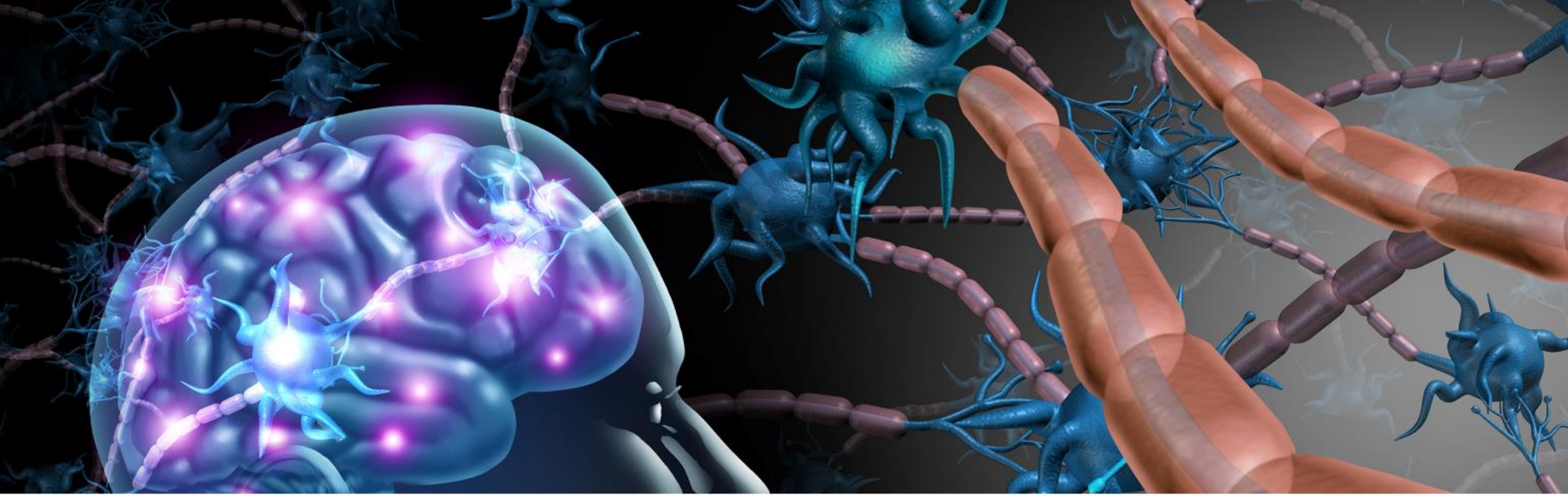
- The Affordable Health Care Act (HR3950F) includes Sec. 3506, which mandates and funds establishment of
  - Decision aids
  - Shared decision-making (SDM) resource centers
  - Preference-sensitive care

Dr. Heesen, who has worked on the topic of MS and SDM for decades, says that "SDM is a bioethical must and a quality-of-care indicator"

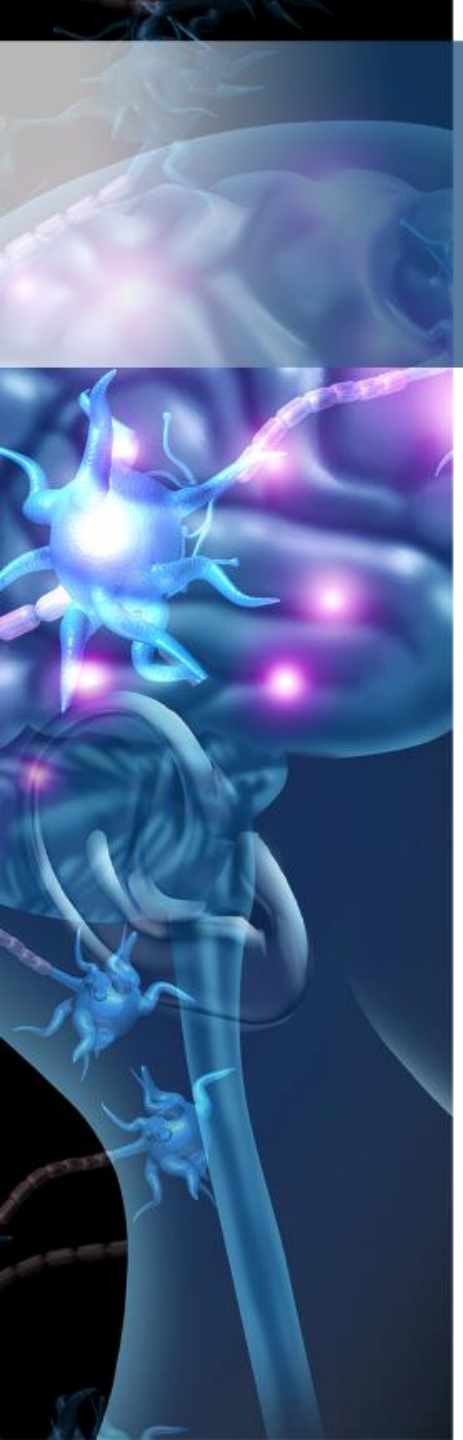
TABLE. SELECTED CLINICAL TRIALS FOR MULTIPLE SCLEROSIS

Drug	Type[a]	Major outcome measures (study duration)	Drug class/mechanism of action	Phase	Trial status	N	NCT number
Evobrutinib	RMS	Active lesions (12-24 wks)	Bruton TKI	2	ANR	267	NCT02975349
Evobrutinib	RMS	Annualized relapse rate (96 wks)	Bruton TKI	3	Recruiting	950	NCT04032158
SAR442168	RMS	New active lesions (12 wks)	Bruton TKI	2	Recruiting	127	NCT03889639
SAR442168	RMS	New active lesions (12 wks)	Bruton TKI	2	Recruiting	105	NCT03996291
Masitinib	PMS	Disability progression (96 wks)	TKI	3	ANR	656	NCT01433497
Imatinib	RRMS	Functional system score (28 d)	TKI	2	Recruiting	200	NCT03674099
Ibudilast	PMS	Brain atrophy and safety (96 wks)	Anti-inflammatory	2	Completed	255	NCT01982942
BIIB033	RMS	Disability and safety (72/96 wks)	antiLINGO-1 MAb	2	ANR	263	NCT03222973
Elezanumab	RMS	Disability progression (52 wks)	antiRGMa MAb	2	Recruiting	165	NCT03737851
AHSCT	RRMS	Disease activity and disability (5 yrs)	Immune reset	3	Recruiting	100	NCT03477500
AHSCT	RRMS	Disease activity and disability (5 yrs)	Immune reset	3	Recruiting	200	NCT03342638
AHSCT	MS	Disease disability change (5 yrs)	Immune reset	2	ANR	110	NCT00273364
Simvastatin	SPMS	Disability progression (3 yrs)	Statin	3	Recruiting	1180	NCT03387670
Vitamin D_3	CIS	Conversion of clinically isolated syndrome to multiple sclerosis (2 yrs)	Vitamin D_3	3	Recruiting	316	NCT01817166
Vitamin D_3	RRMS	Annualized relapse rate (2 yrs)	Vitamin D_3	3	ANR	172	NCT01490502
MD1003	PMS	Disability progression (15-27 mos)	High dose biotin	3	ANR	642	NCT02936037
Lipoic acid	PMS	Brain atrophy progression (2 yrs)	Multiple	2	Recruiting	118	NCT03161028
Nanocrystalline gold	RRMS	VEP and MS disability (48 wks)	Under investigation	2	Recruiting	150	NCT03536559
Laquinimod	PPMS	Brain volume change (24 mos)	Anti-inflammatory	2	Completed	374	NCT02284568
GNbAC1 mAb	RRMS	Active lesions (12 and 24 wks)	To target HERV	2	Completed	270	NCT02782858
IMU-838	RRMS	Number of active lesions (24 wks)	DHODH inhibitor	2	Recruiting	195	NCT03846219
Erythropoietin alfa	ON	Visual acuity and RNFLT-G (6 mos)	Neurotrophic agent	3	ANR	100	NCT01962571
Pioglitazone, montelukast, hydroxychloroquine, losartan	MS	Disability progression (1.5 yrs)	Under investigation	2	Recruiting	250	NCT03109288
Balloon venoplasty	RRMS SPMS	Clinical and safety outcomes (48 wks)	To improve CCSVI	2	Completed	104	NCT01864941
SPARC1103	MS	Muscle spasticity (24 d)	$GABA_B$ receptor agonist	2	Completed	142	NCT02027025
VSN16R	MS	Spasticity (26 days)	BKCa calcium activated K^+ channel modulator	2	Completed	160	NCT02542787
Amantadine, modafinil, methylphenidate	MS	Fatigue (5 wks)	Stimulants	3	Completed[a]	140	NCT03185065
BX-1 (dronabinol)	MS	Spasticity (16 wks)	Cannabis	3	Recruiting	384	NCT03756974
ADS-5102	MS	Walking speed (12 wks)	Amantadine ER	3	Recruiting	540	NCT03436199
ADS-5102		Walking speed (52 wks)	Amantadine ER				NCT03567057
Arbaclofen ER	RRMS SPMS	Muscle spasticity and disability (1 yr)	R enantiomer of baclofen	3	ANR	323	NCT03319732
Arbaclofen ER	MS	Muscle spasticity and global function (84 d)	R enantiomer of baclofen	3	Completed[a]	536	NCT03290131
Intranasal insulin	MS	Cognitive function (24 wks)	Insulin	2	Recruiting	105	NCT02988401
Adderall XR	MS	Cognitive function (12 wks)	Stimulant	3	Recruiting	180	NCT02676739

[a] Study population as reported by study authors at clinicaltrials.gov; [b] Results not posted. Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; ANR, active nonrecruiting; CCSV, hronic cerebrospinal venous insufficiency; CIS, clinically isolated syndrome; DHODH, dihydroorotate dehydrogenase; ER, extended release; HERV, human endogenous multiple sclerosis-associated retrovirus; LINGO-1, leucine rich repeat and immunoglobin-like domain-containing protein 1; MS, multiple sclerosis, PMS, progresive MS; PPMS, primary progressive MS; ON, optic neuritis; RMS, relapsing MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; RGMa, repulsive guidance molecule A; RNFLT-G, retinal ganglion nerve fiber layer thickness; TKI, tyrosine kinase inhibitor; VEP, visual evoked potentials.



MS Therapies and Specialty Pharmacy Considerations

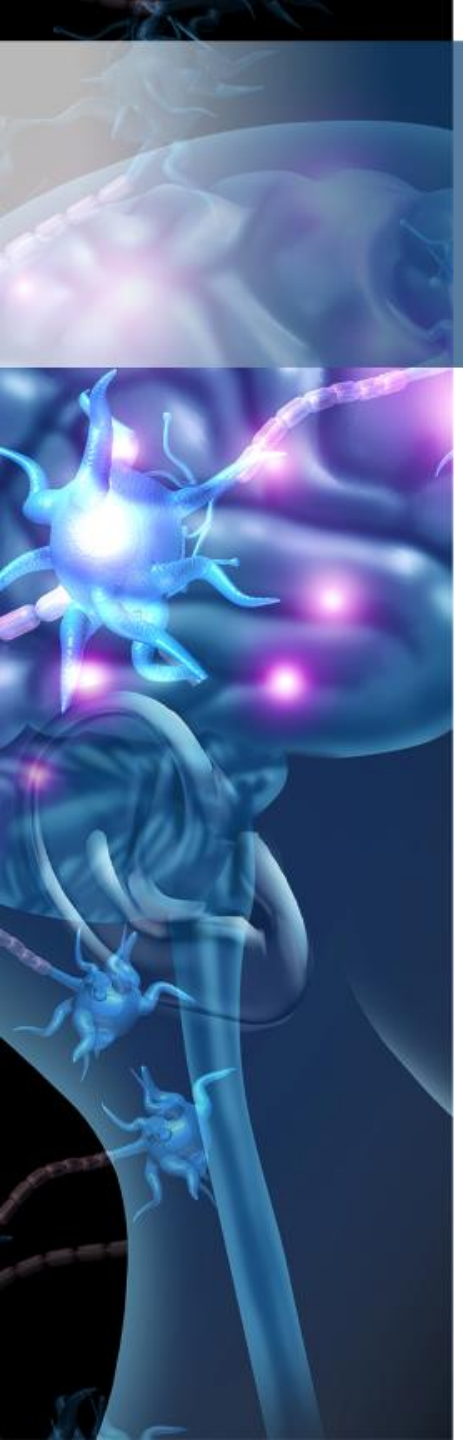


MS Medications

First-generation self-injectables	Second-generation orals	Second-generation infusions/injectables
Glatiramer acetate (Copaxone; Glatopa)	Dimethyl fumarate (Tecfidera)	Alemtuzumab (Lemtrada)
Interferon β-1a IM (Avonex)	Diroximel fumarate (Vumerity)	Natalizumab (Tysabri)
Interferon β-1a SQ (Rebif)	Monomethyl fumarate (Bafiertam)	Ocrelizumab (Ocrevus)
PEG INF β-1a SQ (Plegridy)	Fingolimod (Gilenya)	Ofatumumab* (Arzerra) SQ
Interferon β-1b (Beaseron; Extavia)	Siponimod (Mayzent)	Mitoxantrone (Novantrone)
	Ozanimod (Zeposia)	
	Teriflunomide (Aubagio)	
	Cladribine (Mavenclad)	

*Only FDA approved for CCL.

IM, intramuscular; PEG, pegylated; SQ, subcutaneously.

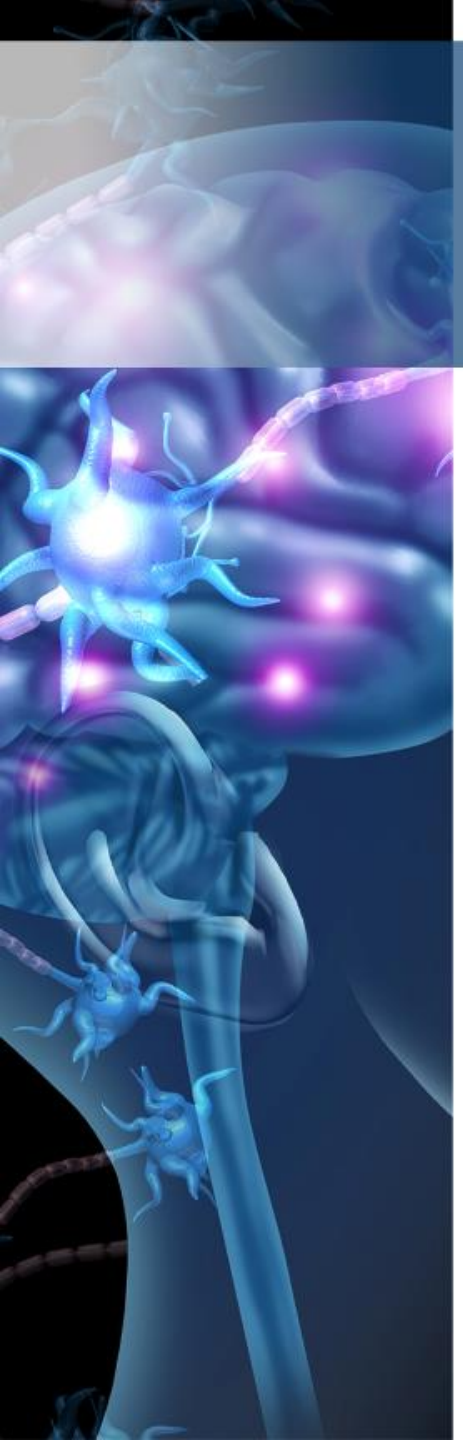


MS Specialty Medications: Unique Considerations – Pre-administration

- Require blood work for all DMTs
- Live attenuated virus vaccines may result in an increased risk of secondary transmission of infection by the live vaccine and reduced effectiveness of immunization
  - Smallpox, rubella, mumps, poliovirus, measles, influenza – flu mist, varicella, zoster, yellow fever, adenovirus, dengue tetravalent, rotavirus, typhoid*, cholera*, BCG*

*Whole-cell vaccines, bacterial: not available in the U.S.

MicroMedex Solutions. http://micromedex.com/.; https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/prinvac.pdf. Accessed July 13, 2020.

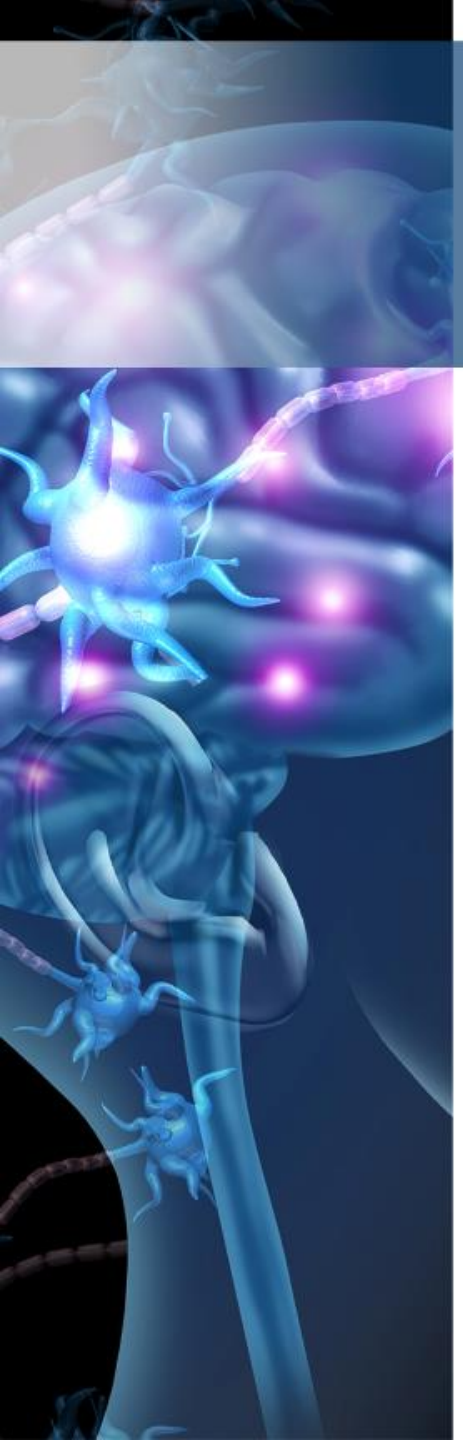


MS Specialty Medications: Unique Considerations – Pre-medications

- Alemtuzumab – methylprednisolone 1000 mg for 3 days prior to infusion of each infusion course; consider antihistamines and/or antipyretics
  - Initiate herpes viral prophylaxis on the first day of each treatment course; continue for a least 2 months after completion or until CD4+ count is at least 200 cells/µL
  - Determine history of varicella or varicella zoster virus vaccination
  - Perform TB screening, baseline skin exam
- Ocrelizumab – antihistamine 30 to 60 minutes prior to infusion and methylprednisolone 100 mg IV 30 minutes prior to infusion; consider an antipyretic
  - Perform hepatitis B virus screening prior to initiation
- Ofatumumab – acetaminophen and cetirizine (or equivalent antihistamine) orally up to 2 hours before each injection, SQ
  - Perform hepatitis B virus prior to initiation
- Diroximel fumarate (DRF) (not recommended in moderate or severe renal failure), Dimethyl fumarate (DMF), monomethyl fumarate (active metabolite of DRF and DMF) – non-enteric coated aspirin up to 325 mg administered 30 minutes prior to dosing
  - Do not use DRF with DMF
  - Counsel on herpes zoster

IV, intravenously; TB, tuberculosis.

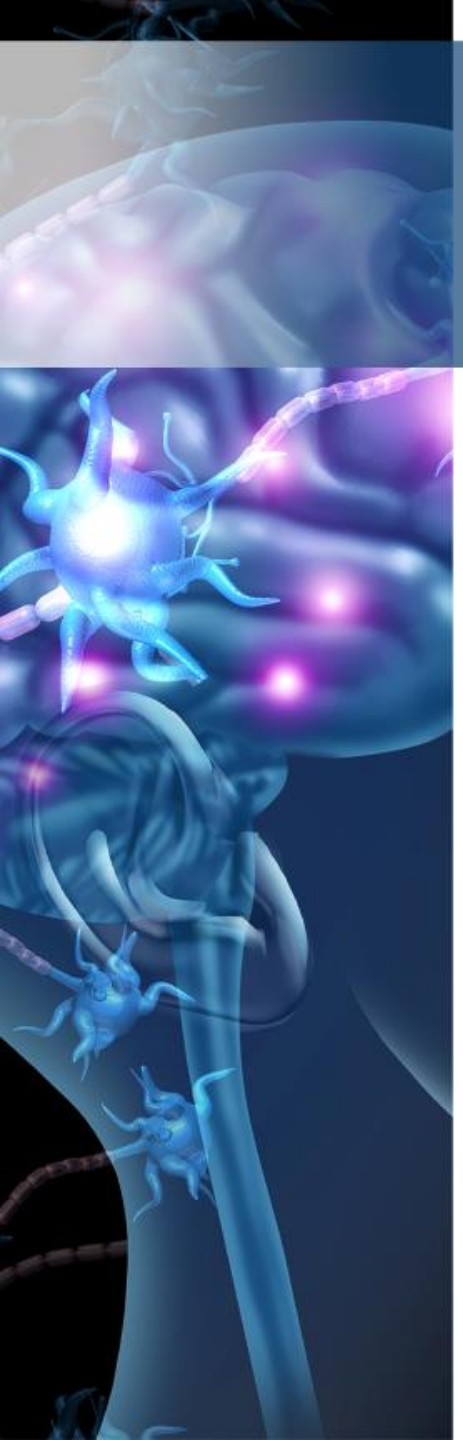
MicroMedex Solutions. http://micromedex.com/.; https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/prinvac.pdf. Accessed July 13, 2020.



MS Specialty Medications: Unique Considerations – Administration

- Fingolimod – 6-hour first-dose observation period required
  - At risk for herpes viral infections; such as herpes simplex encephalitis and varicella zoster meningitis
    - Confirm varicella (chickenpox) documentation or antibody+ or vaccination prior to start
  - HPV, PML, and cryptococcal meningitis or disseminated infection has been seen with fingolimod: monitor
  - Drugs that prolong the QT interval can cause torsades de pointes in patients with bradycardia: citalopram, chlorpromazine, haloperidol, methadone, erythromycin, ziprasidone, saquinavir, bepridil, thioridazine, pimozide
    - Monitor overnight with continuous ECG in a medical facility
  - Concomitant use with class Ia or III antiarrhythmic drugs are contraindicated
    - Class Ia: quinidine, procainamide, disopyramide
    - Class III: amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, dronedarone
    - The most common antiarrhythmic drugs used are ranolazine, amiodarone, dronederone, sotalol

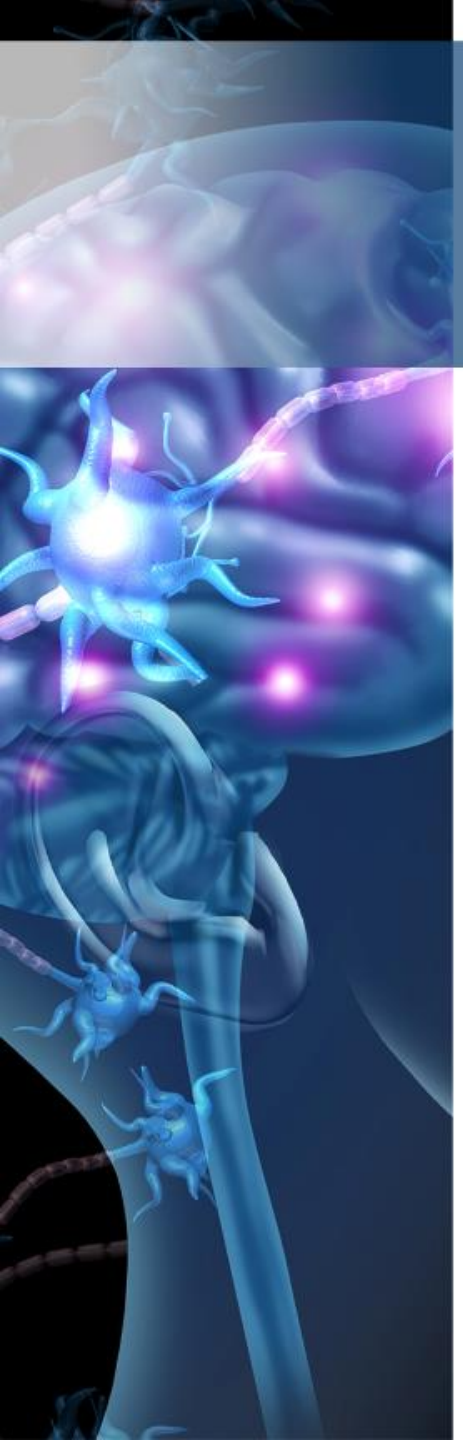
ECG, electrocardiogram, HPV, human papillomavirus; PML, progressive multifocal leukoencephalopathy.



MS Specialty Medications: Unique Considerations – Administration

- Siponimod – CYP2C9 genotyping required
  - Contraindicated with CYP2C9*3/*3 genotype
    - CYP2C9*1/*3 or *2/*3 maintenance dosage (after the initiation dose): 1 mg orally daily
    - CYP2C9*1/*1, *1/*2, or *2/*2 maintenance dosage (after the initiation dose): 2 mg orally daily
  - 6-hour first-dose monitoring in patients with sinus bradycardia (HR < 55), first or second degree Mobitz type I AV block, or history of MI or heart failure unless patient has a functional pacemaker
  - Extensively metabolized by CYP2C9 (80%) followed by CYP3A4 (18%)
  - Drugs that lower HR: use caution
    - Beta blockers, diltiazem, verapamil, ivabradine, digoxin
  - Has not been studied in patients taking QT prolongation drugs (*see fingolimod slide*): recommend cardiology consult
  - At risk for herpes viral infections
    - Herpes simplex encephalitis, varicella zoster meningitis, and varicella (chickenpox) documentation or antibody+ or vaccination prior to start
  - Cryptococcal meningitis or disseminated infection has been seen with other SP1 receptor modulators and with siponimod: monitor
  - PML has not been reported with siponimod, but it has occurred with other SP1 receptor modulators

AV, atrioventricular; CYP, cytochrome P450; HR, heart rate; MI, myocardial infarction.

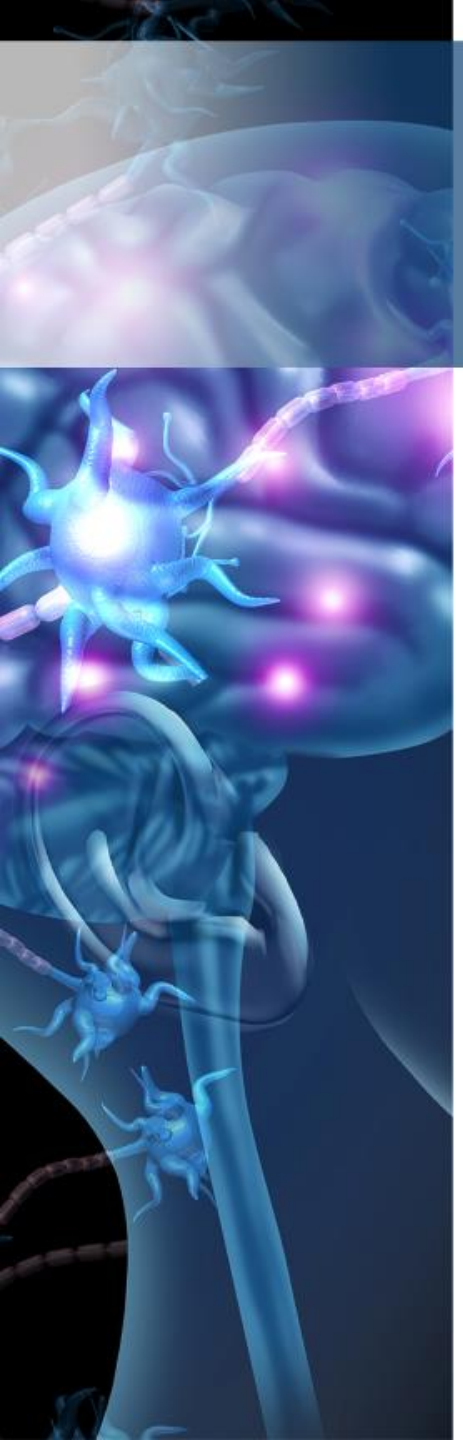


MS Specialty Medications: Unique Considerations – Administration

- Ozanimod – Major interactions
  - Tricyclic antidepressants (nortriptyline, amoxapine, amitriptyline)
  - Cyclosporine
  - MAOIs (phenelzine, rasagiline, linezolid, safinamide, selegiline)
  - BCRP inhibitors (velpatasvir)
  - SNRIs (duloxetine, milnacipran, nefazodone, desvenlafaxine, venlafaxine)
  - Strong CYP2C8 inhibitors (gemfibrozil, opioids)
  - SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram)
  - Drugs that cause QT prolongation (antiarrhythmics, first-generation antipsychotics)
  - *Essentially, ozanimod is not recommended with strong CYP2C8 inducers and inhibitors and BCRP inhibitors*
- PML not reported in the MS population

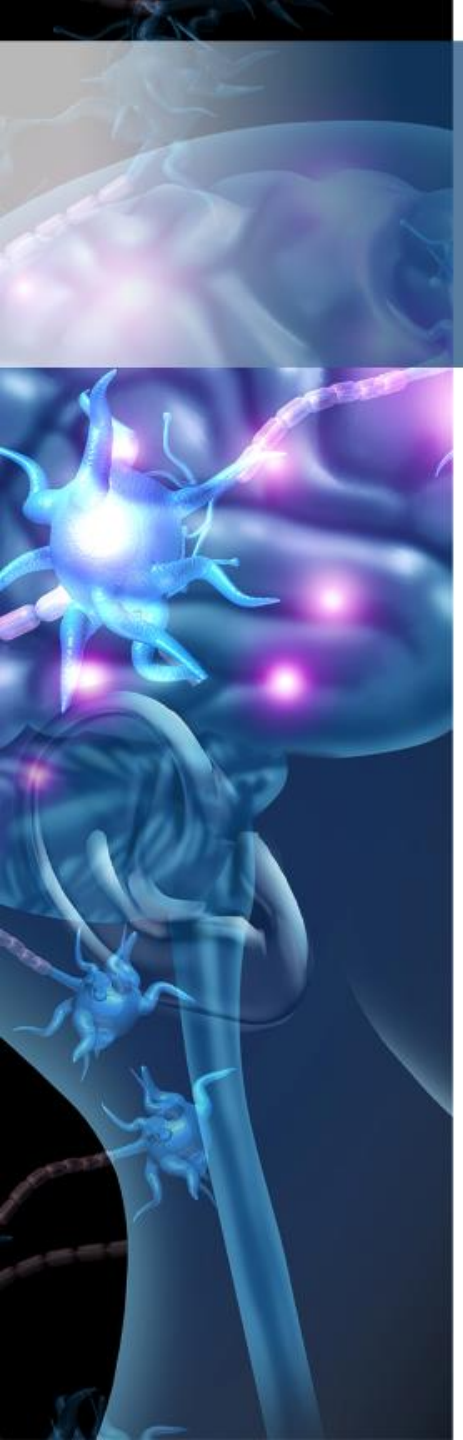
➢ Majority of drugs are immunosuppressive and have side effects requiring continued lab monitoring and should not be used with other immunosuppressive medications

BCRP; breast cancer resistance protein; MAOI; monoamine oxidase inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.



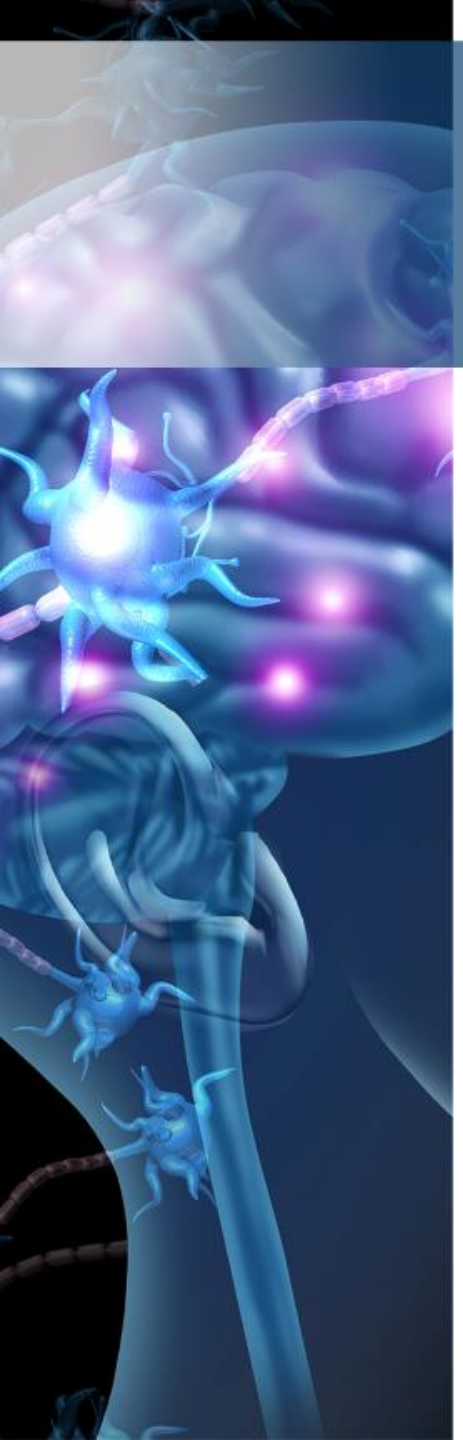
MS Specialty Medications: Unique Considerations – Administration

- Cladribine – Pro-drug
  - Give anti-herpes prophylaxis in patients with lymphocyte counts < 200 cells/µL
  - Prior to initiation, perform standard cancer screening for risk of malignancies
  - Exclude pregnancy
  - Ensure lymphocyte count is within normal limits before initiating first course and is ≥ 800 cells/µL before initiating second treatment course
  - Exclude HIV
  - Screen for TB and hepatitis B and C
  - Vaccinate with varicella zoster vaccine in antibody-negative patients
  - Not recommended for patients with moderate to severe renal or hepatic impairment
- Teriflunomide – Prior to beginning therapy, screen for TB and pregnancy
  - Black box warning for hepatotoxicity and teratogenicity
    - If this occurs, follow accelerated elimination procedure: cholestyramine 8 grams q8h x 11 days (if not tolerated, 4 grams q8h x 11 days) or activated charcoal 50 grams q12h x 11 days



MS Specialty Medications

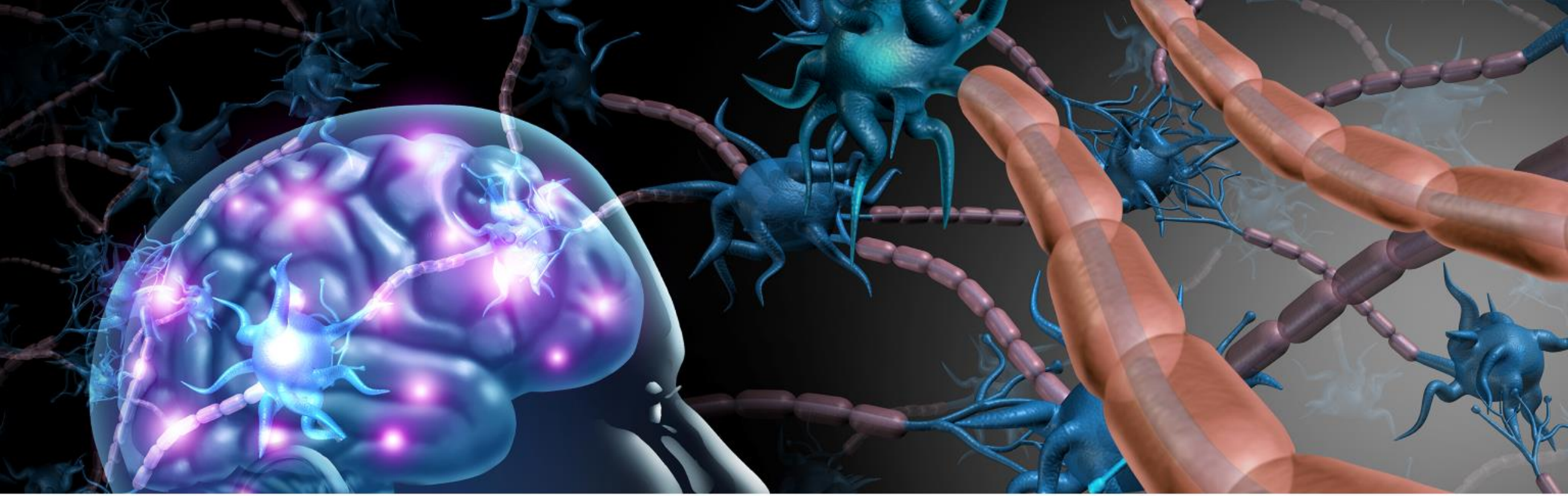
- MS DMTs are expensive and require close monitoring
- Some are harder to administer, requiring an injection or infusion
- Patients require training on how to use the self-injectable medications
- Patient counseling is important for them to understand the risks and potential side effects of the medications



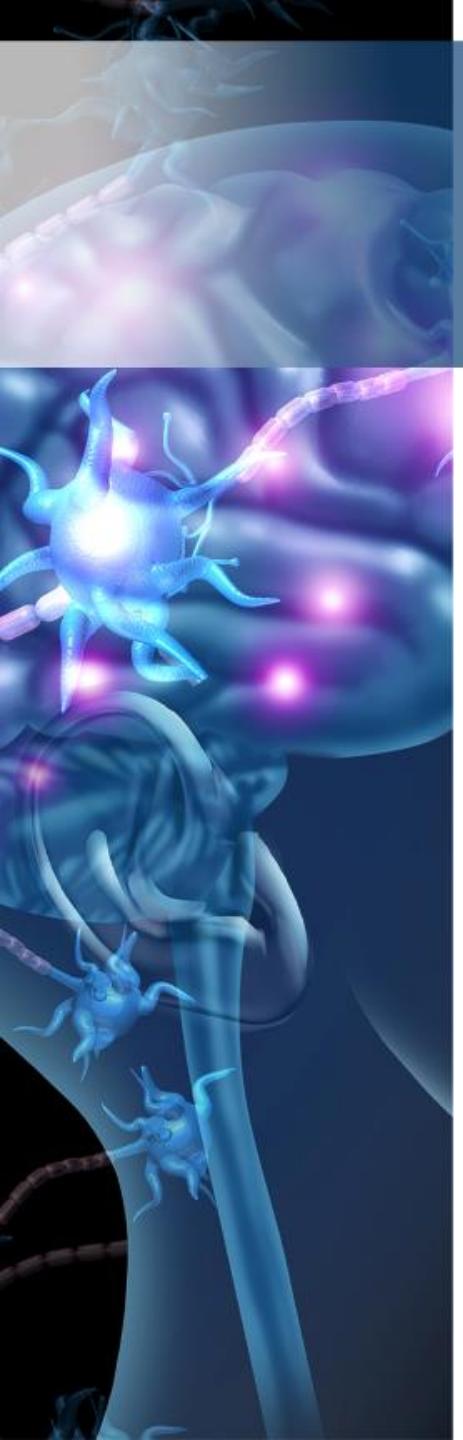
MS Specialty Medications

- DMTs are associated with higher rates of nonadherence
  - A review of 24 studies examining DMT adherence found that adherence rates varied from 41% to 88%
- Poor adherence rates may be associated with:
  - Lack of observable effect on symptoms, lack of knowledge about the disease, unrealistic expectations, lack of social support, and lifelong frequent injections
- Specialty pharmacist may be key in overcoming the barriers of nonadherence by developing long-term relationships with patients

Hanson RL, et al. *Am J Health Syst Pharm*. 2014;71(6):463-9.

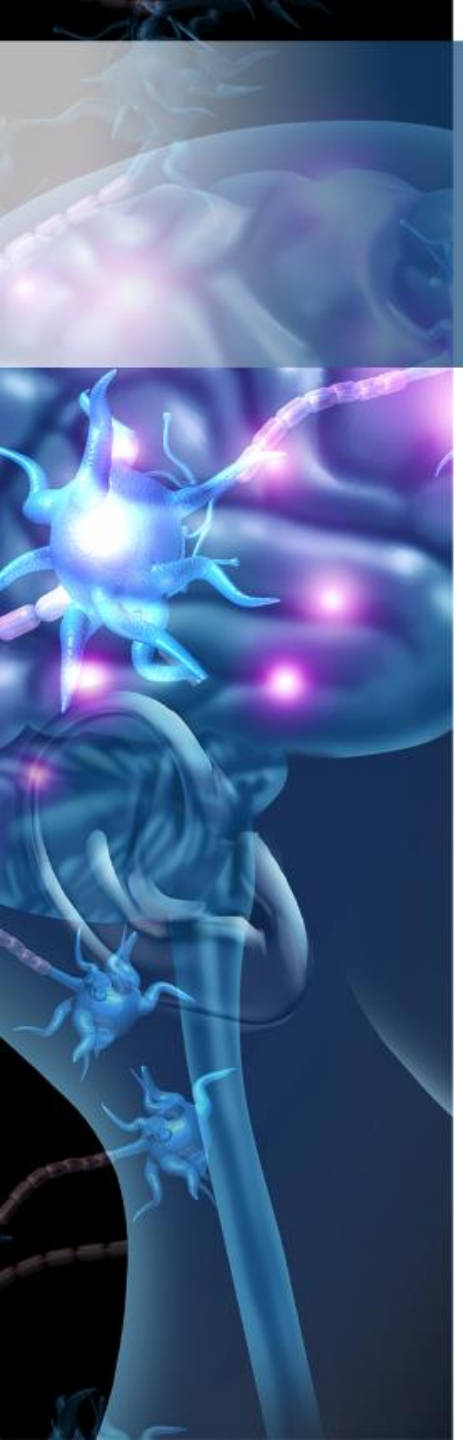


Administrative Issues



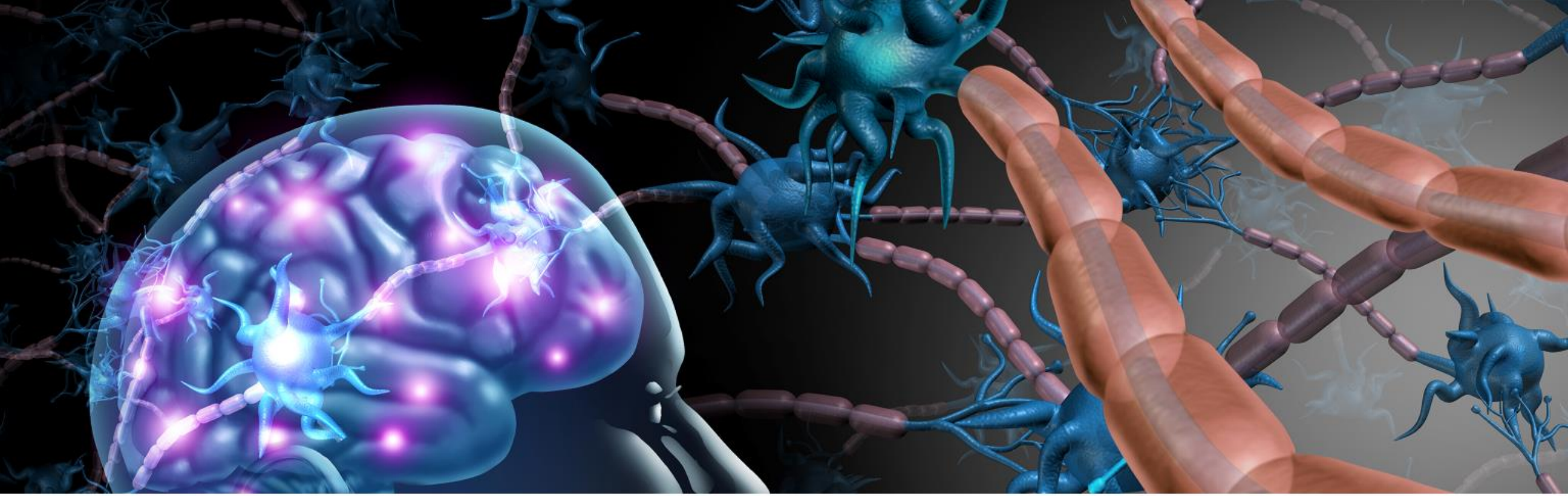
Administrative Issues

- Who is required to initially monitor labs?
- Patient not being contacted for counseling
  - Is the correct contact information being provided?
  - How many attempted outreaches before sending a formal letter?
- Allotting enough time for review of medications and patients' charts
- Allotting enough time for patient counseling

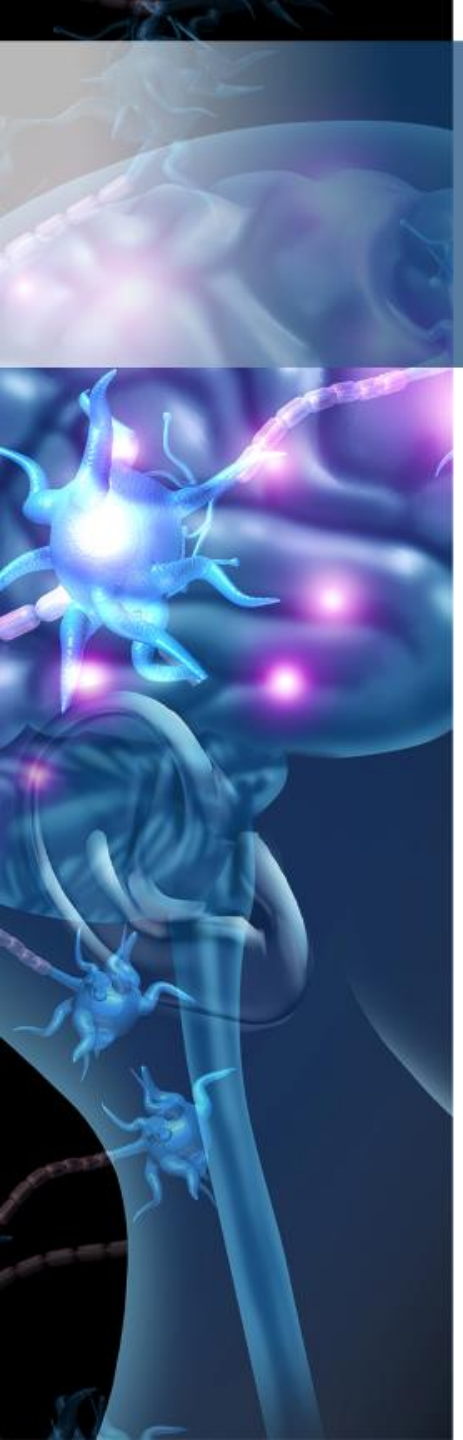


Insurance Company Hurdles

- How do you obtain payment from the insurance companies?
  - Submit a prior authorization
  - If denied, then the specialty pharmacy appeals the denial and submits a letter of medical necessity and includes reasons why formulary-preferred agents are not appropriate
  - Include reasons why we are using the specialty medications
  - Include literature to support the argument when applicable
  - If that is denied, then there is a second level of appeal or peer-to-peer (provider to insurance company agent) call needed
  - If that is denied, the specialty pharmacist relies on manufacturer programs or foundations to pay for the medication

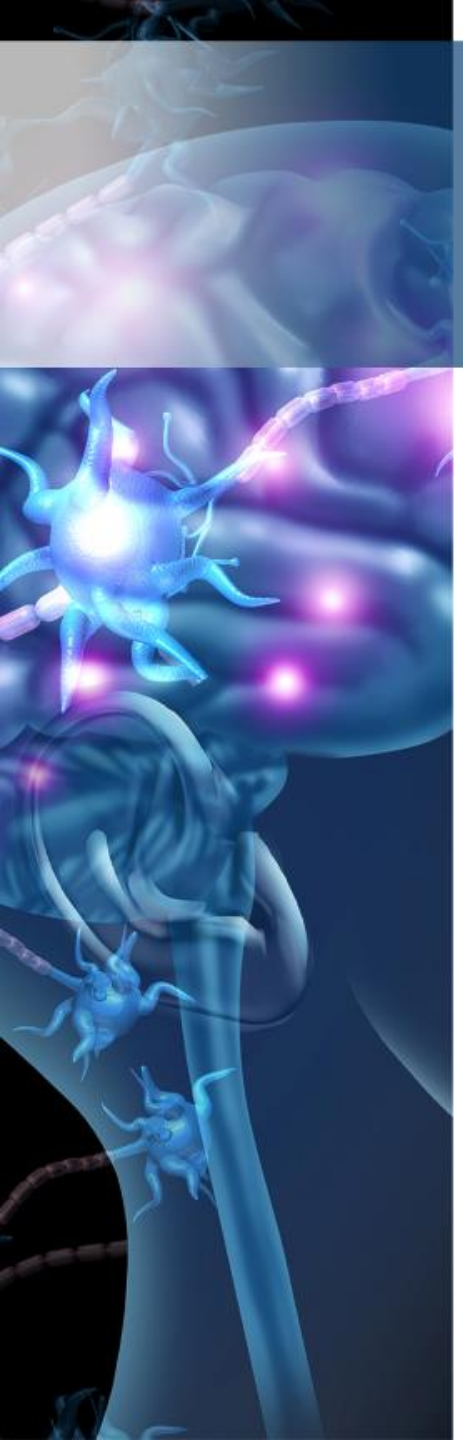


Pharmacist Communication with Healthcare Providers & Patients



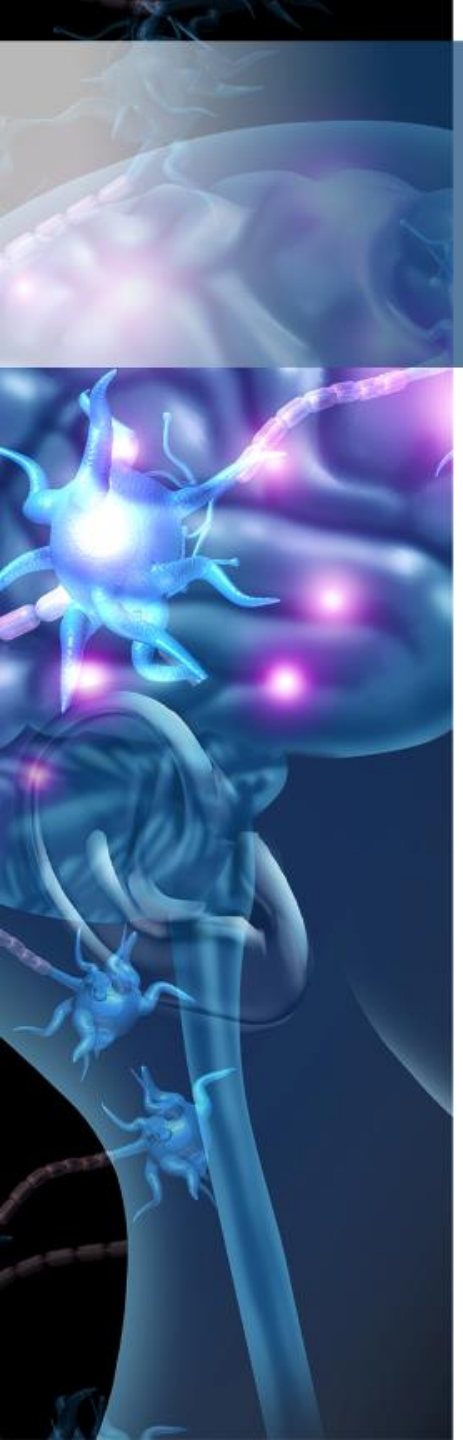
Communication with Healthcare Providers

- Pharmacists to providers
  - Make sure labs have been reviewed for administration
  - Clarify prescriptions
  - Share any concerns the patient may have after their counseling sessions
  - Interact with infusion centers



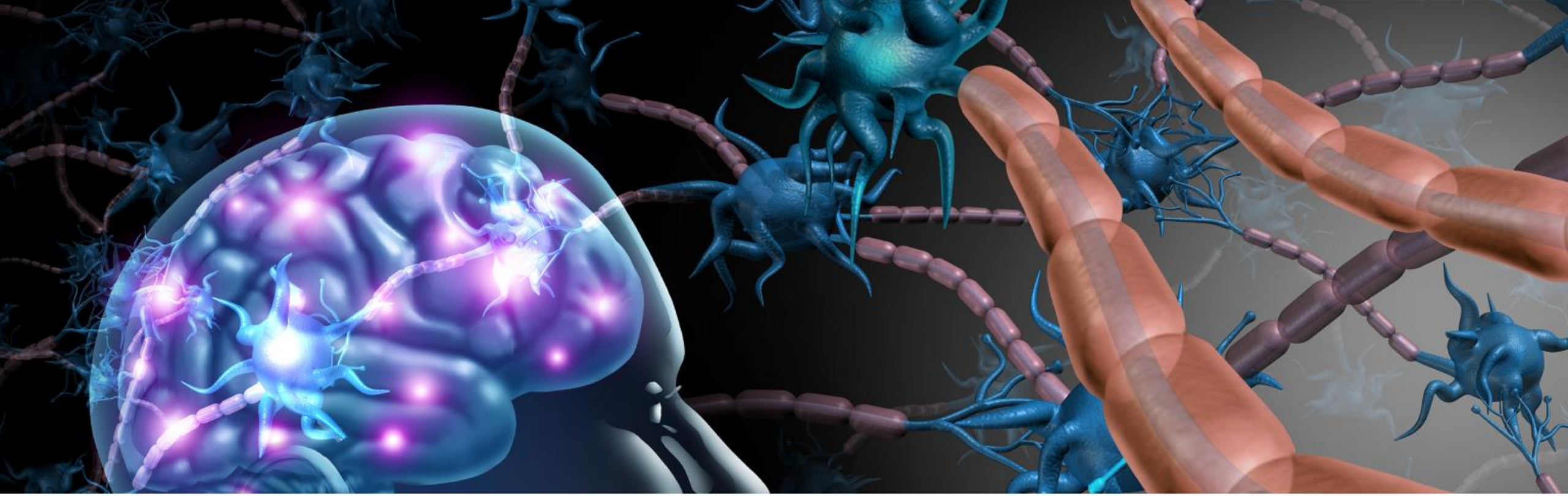
Communication with Healthcare Providers

- Providers to pharmacists
  - Notify of any disease state changes that would require medication changes or monitoring changes
  - Address any concerns related to adherence with the patient's medications
  - Order changes in therapy for the patient

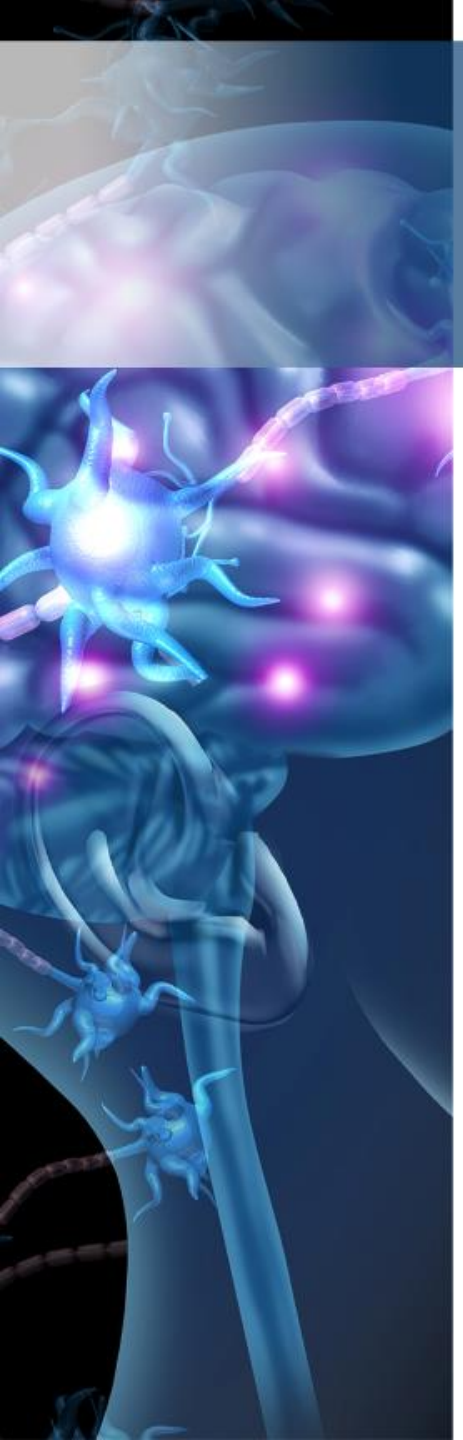


Panel Discussion

- **Financial issues**
  - Costs of MS therapies
  - Discussion of MS specialty agents, tiers, etc.
  - Assisting patients with coverage and copays
  - Navigating the forms and paperwork
- **Patient management issues**
  - Strategies for engaging with the patient, enhancing communication
  - Dosage and administration of newer MS therapies
  - Safety monitoring: how specialty pharmacists are involved
  - Adherence issues
- **What can be done better?**



Addendum



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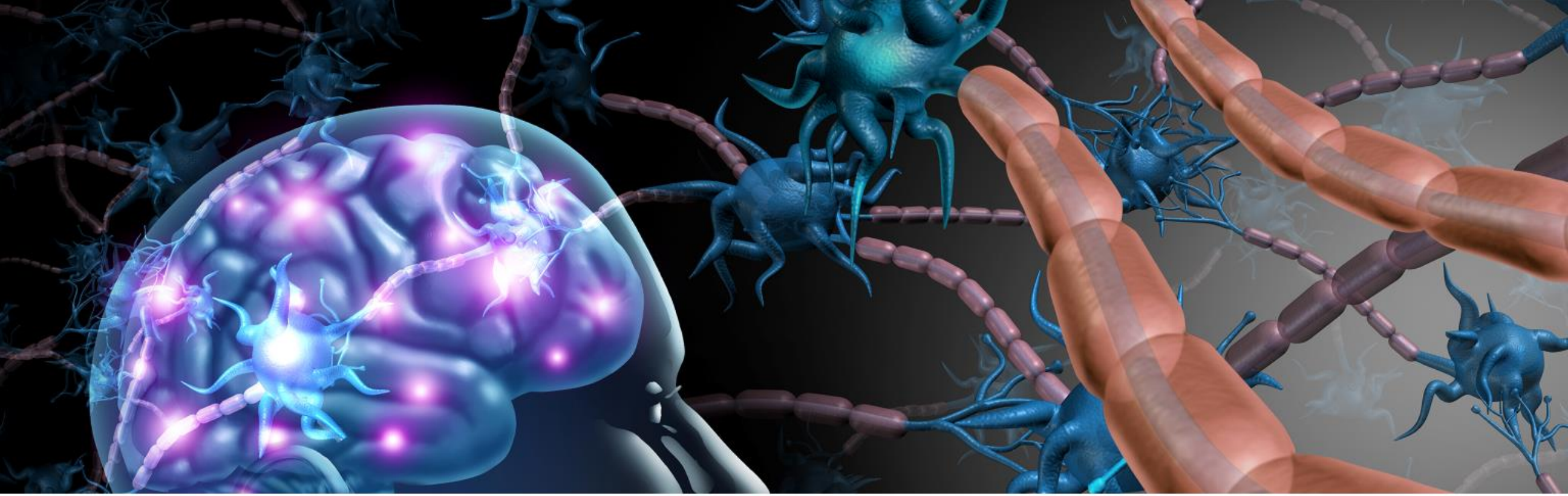
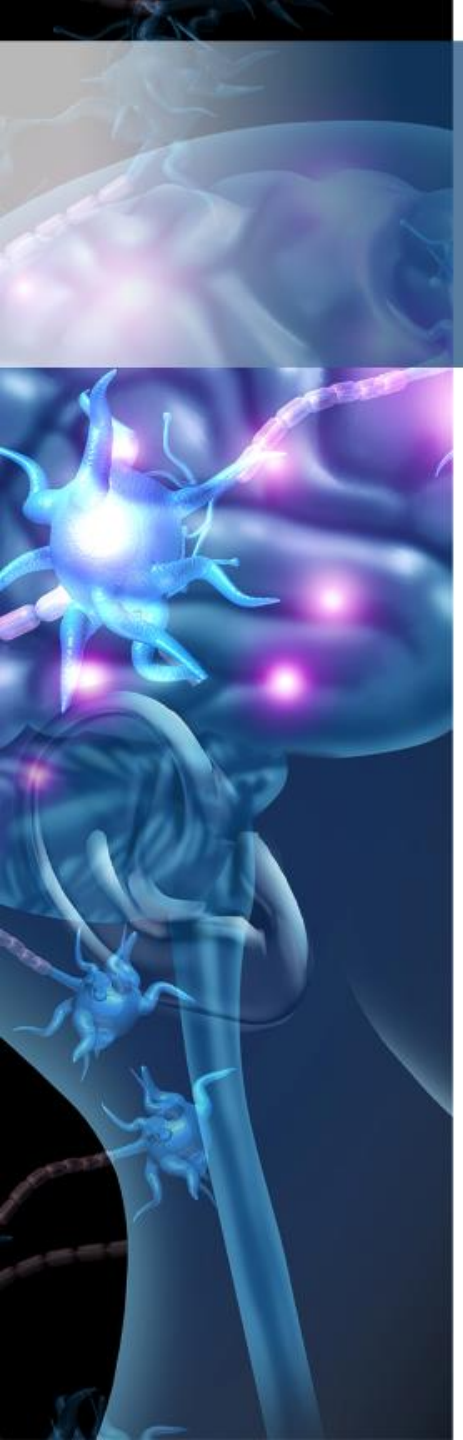


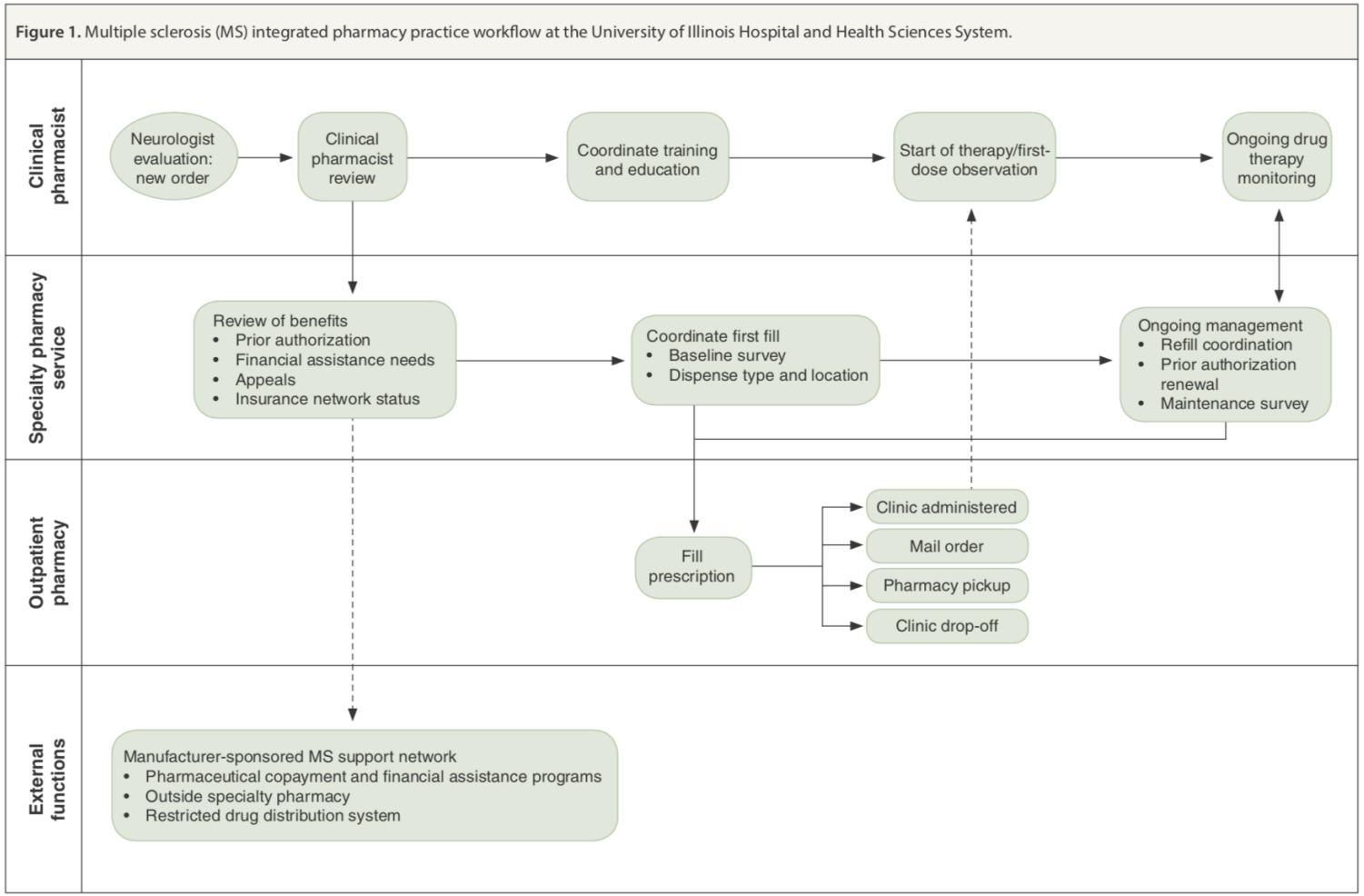
Successful MS Patient-Management Models



Integrated clinical and specialty pharmacy practice model for management of patients with multiple sclerosis

Rebekah L. Hanson, Mitra Habibi, Nehrin Khamo, Sherif Abdou, and JoAnn Stubbings

Figure 1. Multiple sclerosis (MS) integrated pharmacy practice workflow at the University of Illinois Hospital and Health Sciences System.



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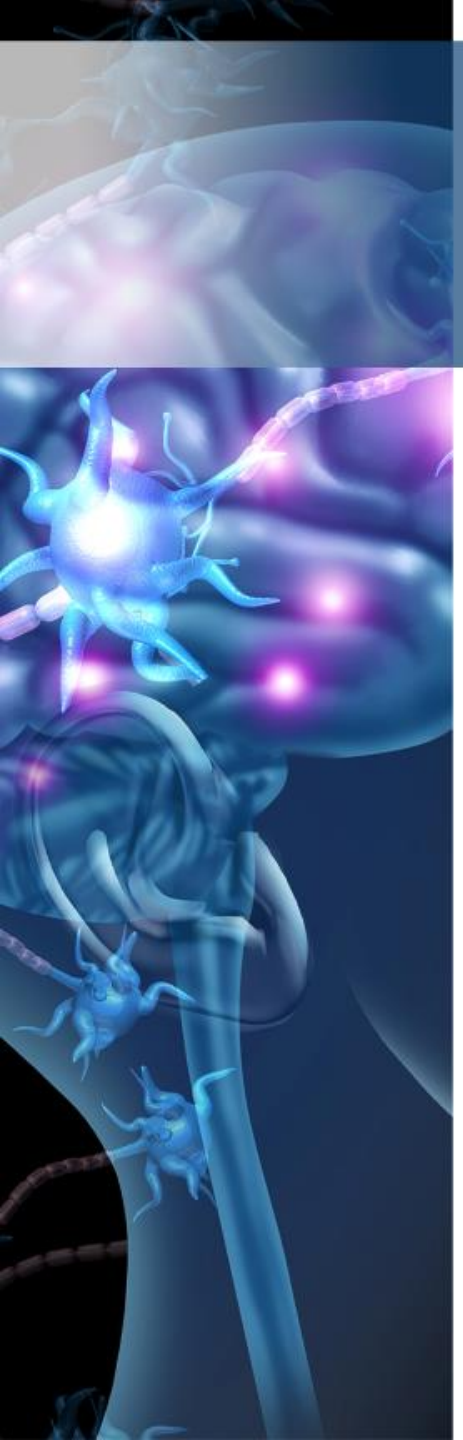


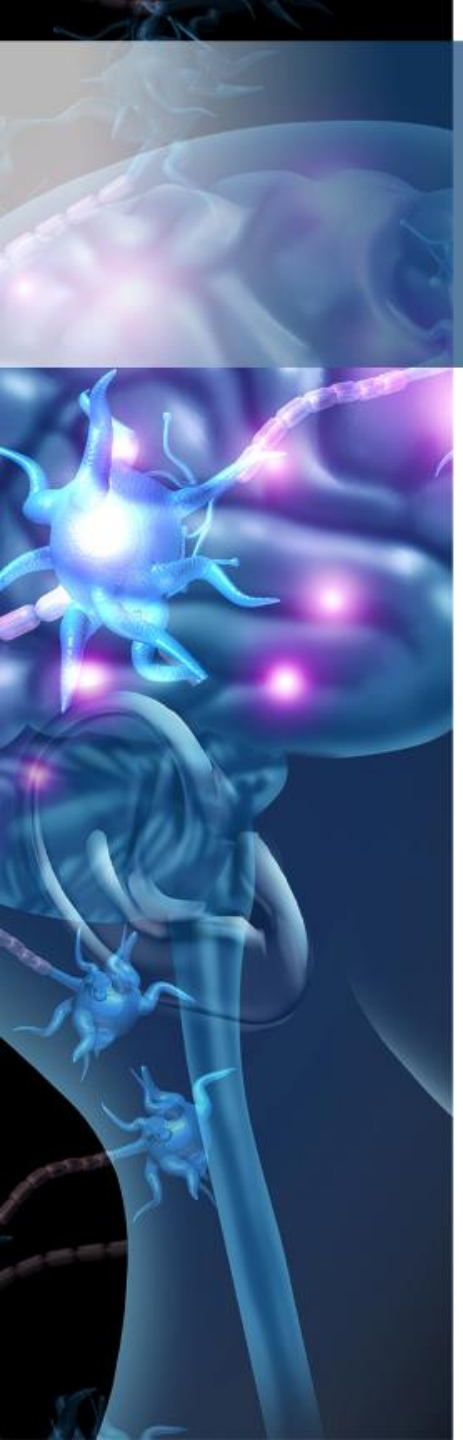
Integrated clinical and specialty pharmacy practice model for management of patients with multiple sclerosis

Rebekah L. Hanson, Mitra Habibi, Nehrin Khamo, Sherif Abdou, and JoAnn Stubbings

- University of Illinois Hospital and Health Sciences System (UI Health) implemented an MS specialty pharmacy in 2010 to help address access and adherence issues to DMTs
- Pharmacist's role:
  - Review patient profile at initial diagnosis
  - Collaborate closely with neurologist and RN
  - Face-to-face counseling services with the attending neurologist for 1 half-day per week
  - Communicate with neurologist if therapy is not working for patient and recommend new therapy
  - Review/order labs
- Model improved:
  - Was not statistically significant due to difference in number of patients between groups
    - Before specialty pharmacy (n=30) and with specialty pharmacy (n=167)
  - The calculated medication-possession ratios did improve and met their 90% service goal

RN, registered nurse.

Hanson RL, et al. *Am J Health Syst Pharm*. 2014;71(6):463-9.



Advancing Patient Care Through Specialty Pharmacy Services in an Academic Health System

Autumn Bagwell, PharmD, BCPS, AAHIVP; Tara Kelley, PharmD, CSP;
Alicia Carver, PharmD, BCPS, CSP; Jennifer B. Lee, PharmD; and Brandon Newman, PharmD, CSP

- Vanderbilt Specialty Pharmacy (VSP) model at Vanderbilt University Medical Center implemented specialty pharmacy services throughout their system, which led to patient care improvements
  - This article reviews an infectious disease clinic and MS clinic
- Pharmacist worked with other healthcare professionals to:
  - Assess appropriateness of therapy and review all baseline testing was complete
  - Educate the patient on the medication, important contact information, and expectations of obtaining the medications from the pharmacy
  - Manage PA and appeals processes
  - Ensured the patient had access to support services and programs
  - Regularly reassess the medication and the patient
- This model helped improve:
  - Time to treatment
  - Access to medication
  - Patient-centered care
  - Patient adherence
  - Financial assistance

PA, prior authorization.

TABLE 1 Vanderbilt Specialty Pharmacy Services

Basic VSP Services	Customizable Ancillary Services
Individualized initial and ongoing patient counseling	Pharmacist assistance with determining the most appropriate and cost-effective treatment regimen
Insurance benefits investigation and explanation	Pretreatment immunization and lab testing and imaging coordination
Prior authorization/appeal assistance	Ongoing lab monitoring and medication safety and efficacy follow-up
Financial counseling	Adherence information provided to prescribers
Free shipping and delivery, free ancillary supplies	Collaborative practice agreements to decrease provider burden
Refill reminder calls	REMS program management
24-hour access to on-call clinical pharmacist	Independent clinic visits with pharmacist for treatment adherence and side effects, efficacy, and drug interaction monitoring
Patient-centered individualized care	
Continued monitoring of drug interactions and recommendations for therapy modifications	

REMS = Risk Evaluation and Mitigation Strategy; VSP = Vanderbilt Specialty Pharmacy.

Bagwell A, et al. *J Manag Care Spec Pharm*. 2017;23(8):815-20.