Evolving Treatment Options and Care Management Strategies:

A Multiple Sclerosis Update for Pharmacists

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MS Update: Examining a Rapidly Evolving Treatment Landscape

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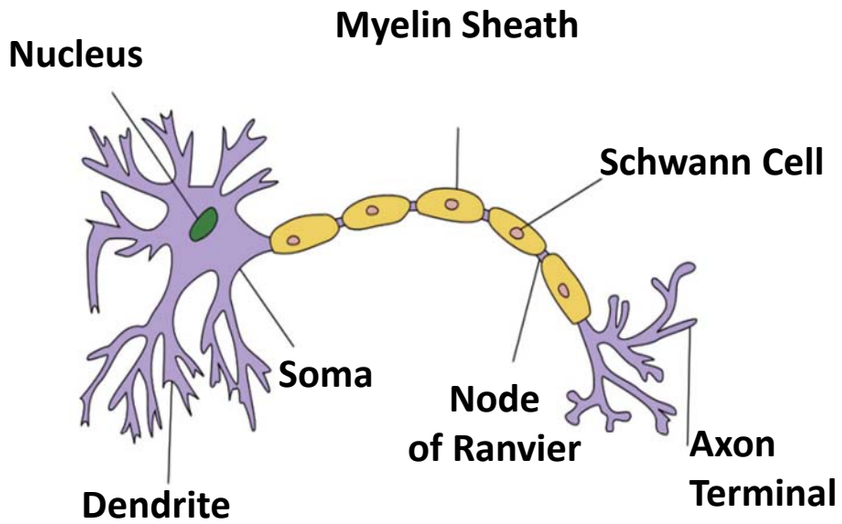
Learning Objective

- Apply current evidence-based treatment data to optimize clinical outcomes for patients with multiple sclerosis (MS)

What Is Multiple Sclerosis?

- Chronic progressive autoimmune disease of the central nervous system (CNS)
- Associated with focal areas of damage, axon injury, axon transection, neurodegeneration, and subsequent scar or plaque formation
- Often leads to significant disability
  - Median survival in MS population is less than observed in the general population
- Primary etiology unknown, but likely multifactorial



Calabresi PA, Newsome SD. Multiple sclerosis. In: Weiner WJ, Goetz CG, Shin RK, eds. *Neurology for the Non-Neurologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:192-221.
Ascherio A. *Expert Rev Neurother*. 2013;13(12 Suppl):3-9.

Epidemiology

- United States: ~1 million affected (northeast greatest prevalence)
- Most common cause of nontraumatic disability in 18- to 60-year-old population
- Female predominance with peak incidence between 20 and 40 years old
- National annual cost of MS: $6.8 to $11.9 billion

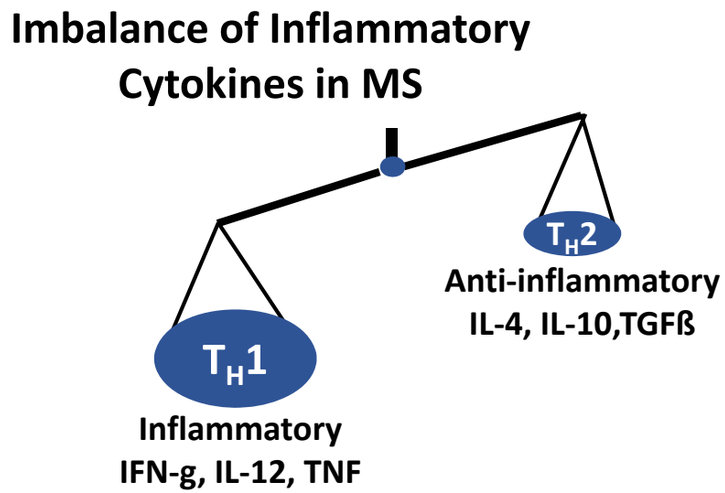
Calabresi PA, Newsome SD. Multiple sclerosis. In: Weiner WJ, Goetz CG, Shin RK, eds. *Neurology for the Non-Neurologist*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:192-221.

Ascherio A. *Expert Rev Neurother*. 2013;13(12 Suppl):3-9.

Whetten-goldstein K, Sloan FA, Goldstein LB, Kulas ED. *Mult Scler*. 1998;4(5):419-25.

Wallin MT. The prevalence of multiple sclerosis in the United States: a population-based healthcare database approach. Poster presented at: ECTRIMS 2017; October 25-28; Paris, France.

Inflammation and Neuronal Degeneration



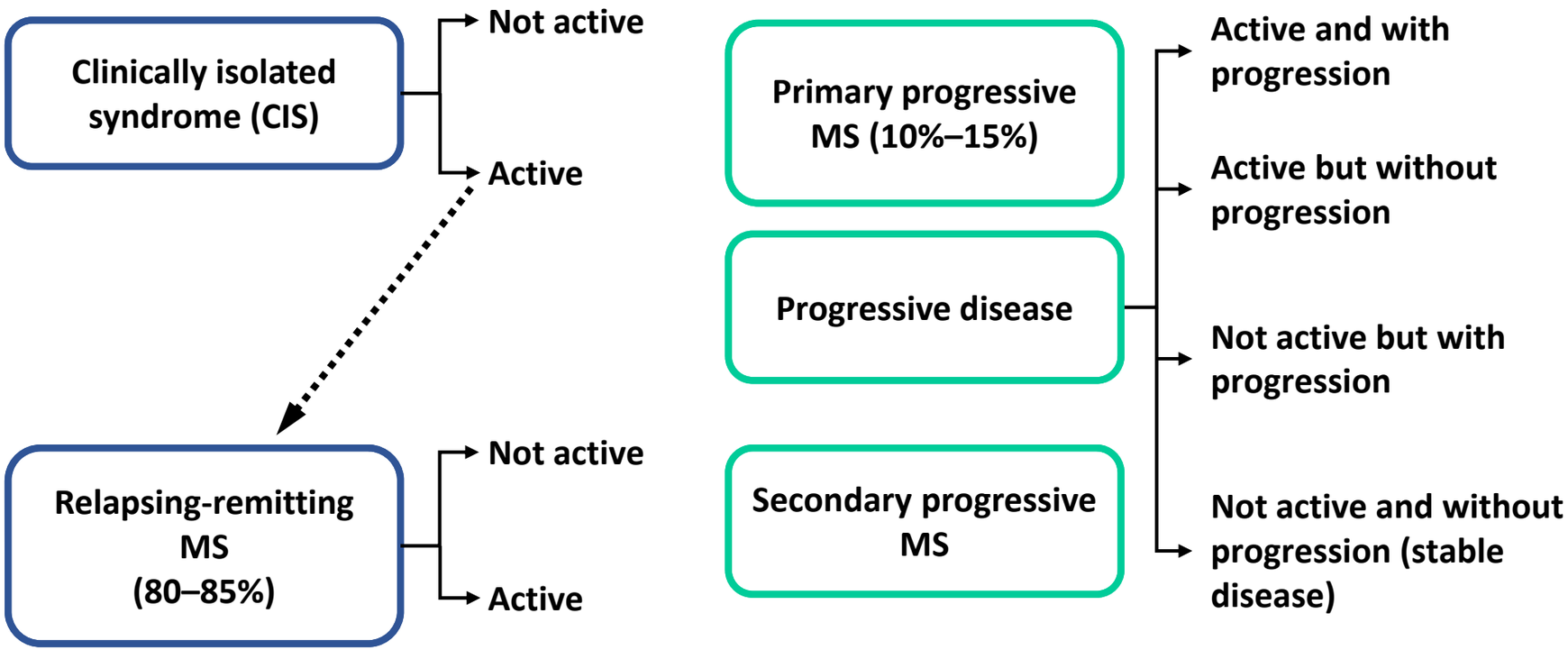
Acute Inflammation → **Relapse**

Neuronal Degeneration → **Disability**

- Loss of axons is the main cause of permanent disability in MS
- Axonal damage has been shown to occur in acute inflammatory plaques[1]
- Axonal damage could be the result of cumulative inflammatory damage over time or a parallel degenerative process related to loss of trophic support or an independent axonal degeneration[2]

1. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. *N Engl J Med*. 1998;338(5):278-85.
2. Trapp BD, Ransohoff RM, Fisher E, Rudick RA. *The Neuroscientist.* 1999;5(1):48-57.

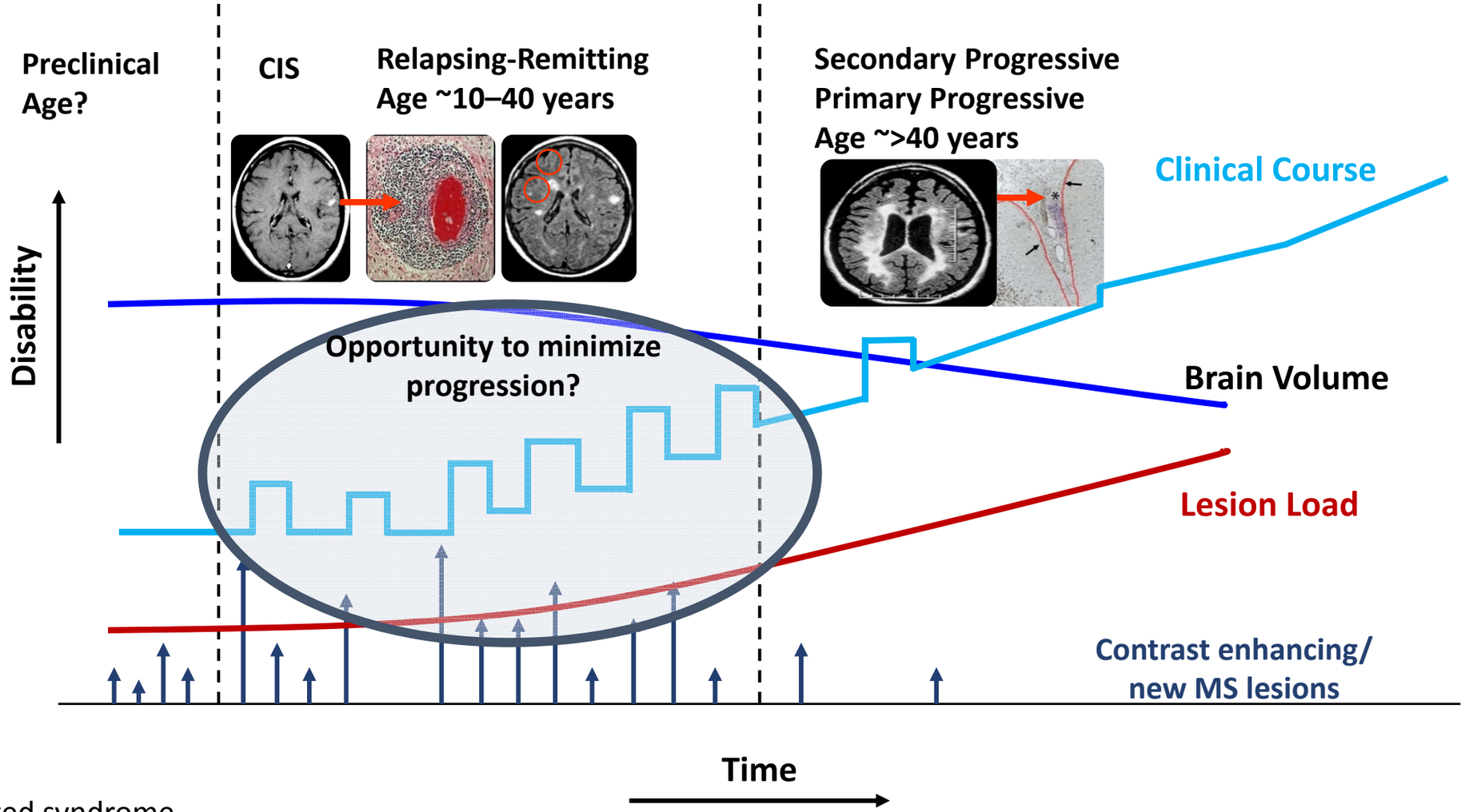
Multiple Sclerosis Disease Subtypes



- Active: Inflammatory activity measured by clinical relapses and/or MRI activity
- Progression: Measured by clinical evaluation
- Radiologically isolated syndrome not included

Lublin FD, Reingold SC Cohen JA, et al. *Neurology.* 2014;83(3):278-86.

Multiple Sclerosis Disease Course



CIS: clinically isolated syndrome

Slide courtesy of P. Calabresi, MD.

Factors Associated With More Aggressive Disease

Clinical Factors
• Male gender
• Older age at onset
• African-American
• Motor, cerebellar, and sphincter involvement
• Frequent relapses followed by poor recovery from the relapse
• Multifocal involvement at onset

Paraclinical Factors
• MRI high lesion burden at presentation
• 2 gadolinium-enhancing/new T2 lesions or >2 T1-hypointense lesions
• 2 spinal cord lesions
• Brain atrophy
• Low vitamin D

Freedman MS, Selchen D, Arnold DL, Prat A, et al. *Can J Neurol Sci.* 2013;40(3):307-23.

Common Symptoms

Primary

- Fatigue
- Weakness
- Numbness/tingling
- Dizziness/vertigo
- Gait difficulties
- Spasticity
- Diplopia (binocular)
- Visual loss
- Cognitive decline
- Mood disorder
- Pain
- Bladder and bowel problems
- Sexual dysfunction

Secondary

- Falls
- Injury
- Bladder infections from urinary retention
- Physical deconditioning

Tertiary

- Vocational changes
- Social isolation
- Change in relationships

MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Diagnosis

- Based on clinical history, neurologic exam, paraclinical tests (ie, MRI), and exclusion of other possible causes
- Objective evidence of CNS white matter lesions disseminated in time and space
  - Disseminated CNS lesions in time and space can be demonstrated clinically (exacerbations with objective signs on examination, eg, optic neuritis) or by MRI with/without gadolinium
  - Can diagnose MS after a single attack with McDonald criteria
- CSF in selected patients: cell count, IgG index, and oligoclonal bands
- Blood work obtained to rule out mimics

CSF: cerebrospinal fluid

Polman CH, Reingold SC, Banwell B, et al. *Ann Neurol*. 2011;69(2):292-302.
Polman CH, Reingold SC, Edan G, et al. *Ann Neurol.* 2005;58(6):840-6.

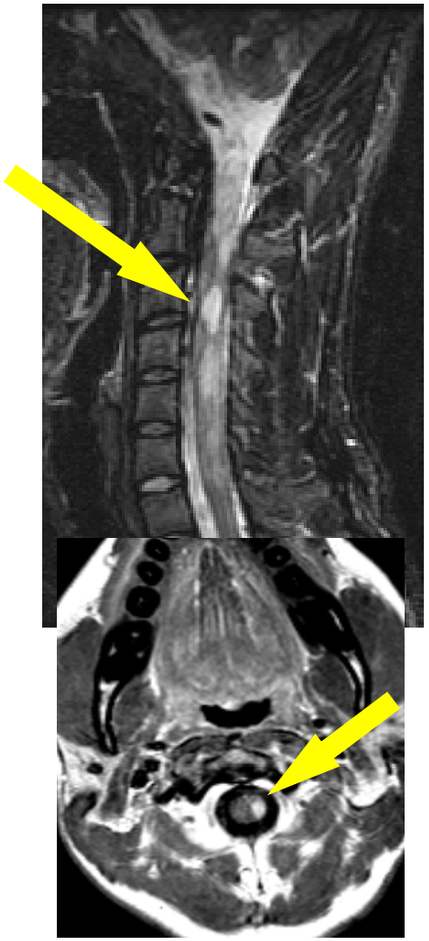
Typical MRI Features

Periventricular

Corpus callosum and juxtacortical/cortical

Infratentorial

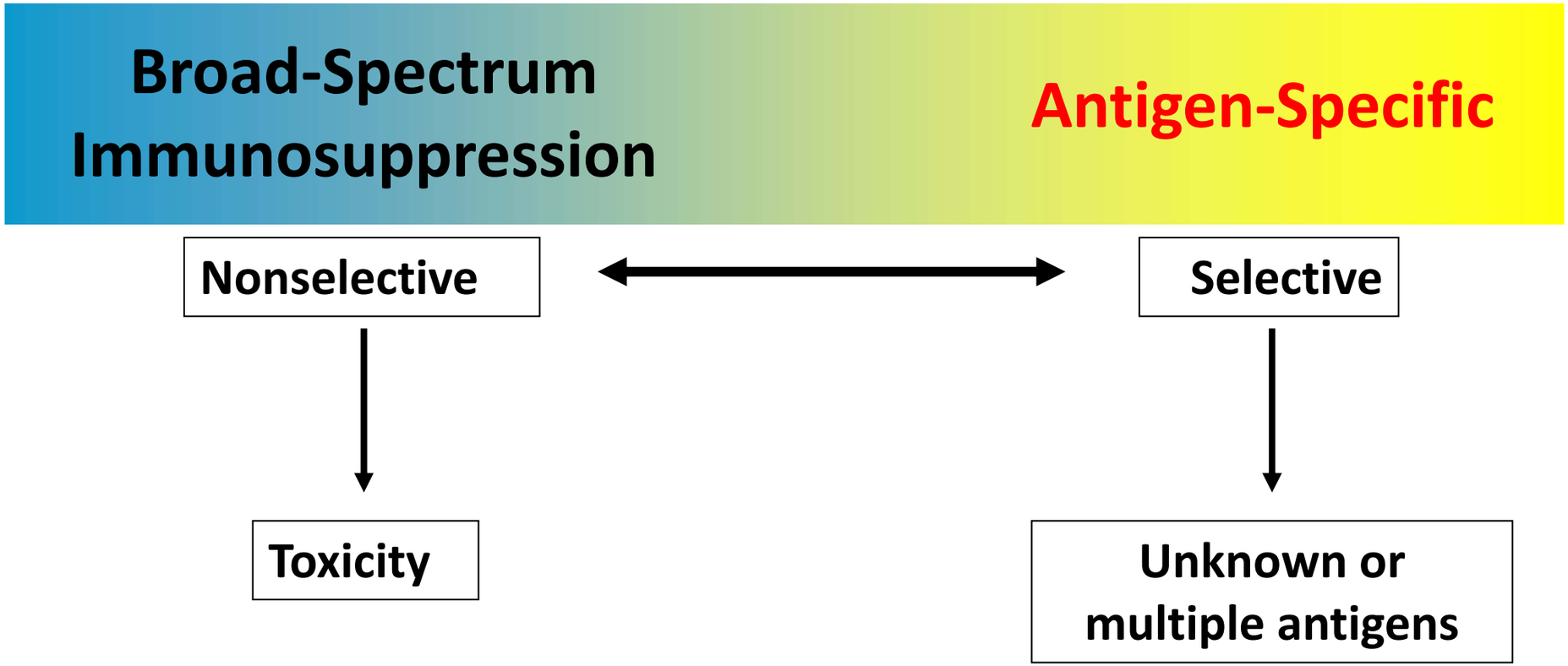
Spine lesions



Therapeutic Goals

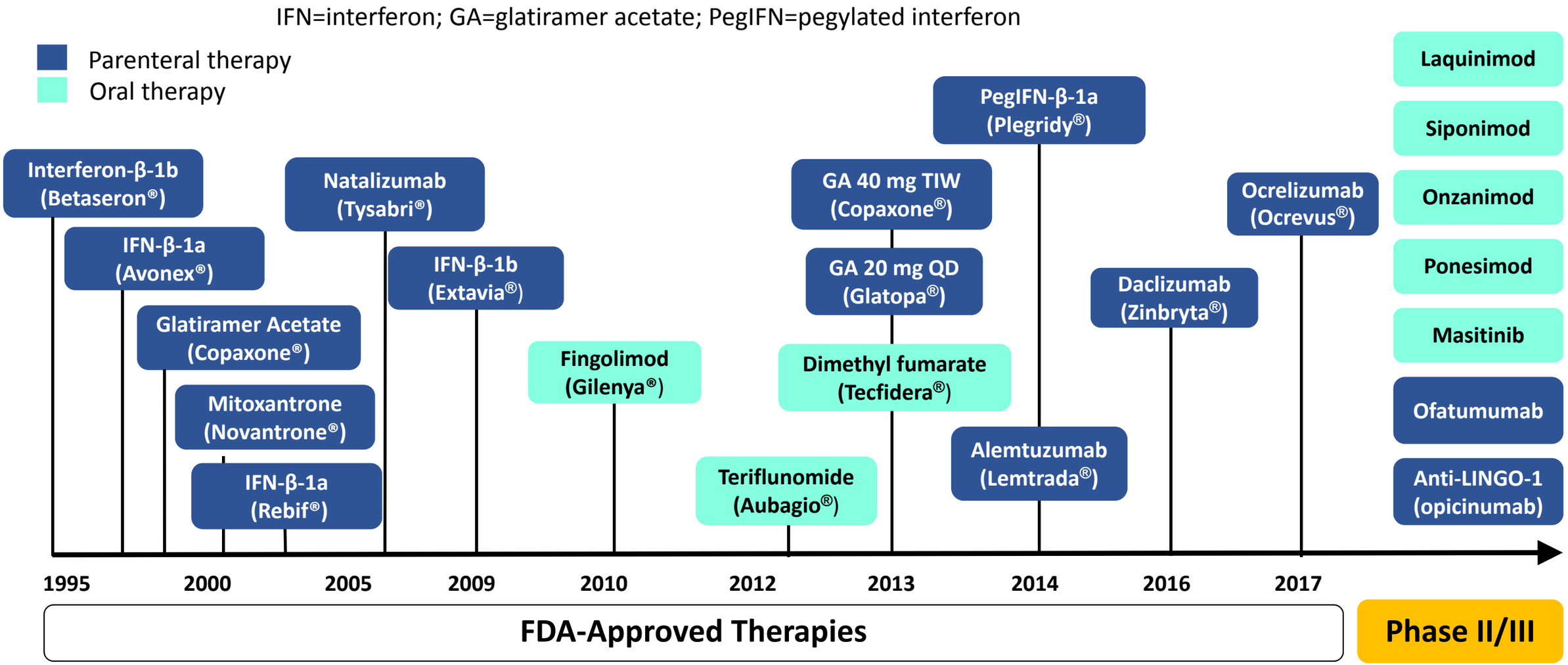
- In the absence of a cure for MS, current goals of disease-modifying therapy (DMT) are to
  - Prevent relapses
  - Prevent development of new or enhancing lesions on MRI
  - Prevent disability
- Additional goals in the management of MS are to
  - Relieve symptoms
  - Maintain well-being
  - Optimize quality of life

Strategies to Attenuate an Immunologically-Mediated Attack



Slide courtesy of P. Calabresi, MD.

Evolving Treatment Landscape



Timeline of Progress in MS Research. National Multiple Sclerosis Society. https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Timeline-of-Research.pdf. Accessed November 5 2017.
Timeline of approved compounds in MS. Multiple Sclerosis Discovery Forum. http://www.msdiscovery.org/MSLine. Accessed November 5, 2017.

FDA Indications for MS Disease Modifying Therapies

Disease Modifying Therapy	Year Approved	FDA Indication			
		CIS	RRMS	PPMS	SPMS
Interferon β-1b (Betaseron)	1993	✓	✓		
Interferon β-1b (Extavia)	1993	✓	✓		
Interferon β1-a (Avonex)	1996	✓	✓		
Glateramer acetate (Copaxone)	1996	✓	✓		
Interferon β-1a (Rebif)	1996		✓		
Mitoxantrone (Novantrone)	2000		✓		✓
Natalizumab (Tysabri)	2004		✓		
Fingolimod (Gilenya)	2010		✓		
Teriflunomide (Aubagio)	2012		✓		
Dimethyl fumarate (Tecfidera)	2013		✓		
Peginterferon β-1a (Plegridy)	2014		✓		
Alemtuzumab (Lemtrada)	2014		✓		
Daclizumab (Zinbryta)	2016		✓		
Ocrelizumab (Ocrevus)	2017		✓	✓	

Injectable DMTs: Efficacy

Pivotal Clinical Trials	Agent	Relapses	MRI Activity	12-Week Disability Progression – EDSS
Multiple Sclerosis Collaborative Research Group[1-3]	**IFN β-1a** (Low dose)	ARR: ↓ 18%	Gd+ lesions: ↓50% T2 lesions: no effect	↓ 37%
PRISMS[4,5]	**IFN β-1a** (High dose)	ARR: ↓ 33%	Gd+ lesions: ↓84% T2 lesions: ↓78%	↓ 30%
ADVANCE[6,7]	**Peg IFN β-1a**	ARR: ↓ 36%	Gd+ lesions: ↓86% T2 lesions: ↓67%	↓ 38%
IFNB Multiple Sclerosis Study Group[2,8,9]	**IFN β-1b**	ARR: ↓ 34%	Gd+ lesions: ↓83% T2 lesions: ↓75%	↓ 29% (insignificant Δ from baseline)
Copolymer 1 MS Study Group[10]	**Glatiramer acetate**	ARR: ↓ 29%	Not adequately assessed	Not significant
DECIDE[11, 12]	**Daclizumab vs IFN β-1a**	ARR: ↓ 45%	Gd+ lesions: ↓65% T2 lesions: ↓54%	Not significant

ADVANCE: Efficacy and Safety Study of Peg IFN β-1a in Participants with RMS; ARR: annual relapse rate; DECIDE: Efficacy and Safety of Daclizumab vs Interferon β1a in RRMS; DMTs: disease-modifying therapies; EDSS: Expanded Disability Status Scale; Gd: gadolinium; PRISMS: Prevention of Relapses and Disability by IFN β-1a Subcutaneously in MS

1. Jacobs LD, Cookfair DL, Rudick RA, et al. *Ann Neurol*. 1996;39(3):285-94. 2. Klawiter EC, Cross AH, Naismith RT. *Neurology*. 2009;73:984-90. 3. Simon JH, Jacobs LD, Campion M, et al. *Ann Neurol*. 1998;43(1):79-87. 4. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet*. 1998;352(9139):1498-504. 5. 3 ways Rebif was proven effective. EMD Serono Web site. http://www.rebif.com/why-rebif/rebif-efficacy. Accessed November 2017. 6. Calabresi PA, Kieseier BC, Arnold DL, et al. *Lancet Neurol*. 2014;13(7):657-65. 7. Plegridy [prescribing information]. Cambridge, MA: Biogen Idec Inc; 2015.8. The IFNB Multiple Sclerosis Study Group. *Neurology*. 1993;43(4):655-61. 9. Paty DW, Li DK. *Neurology*. 1993;43(4):662-7. 10. Johnson KP, Brooks BR, Cohen JA, et al. *Neurology*. 1995;45(7):1268-76. 11. Kappos L, Wiendl H, Selmaj K, et al. *N Engl J Med*. 2015;373(15):1418-28. 12. *Neurology Reviews*. 2015 June;23(6):24.

Oral DMTs: Efficacy

Pivotal Clinical Trials	Agent	Relapses	MRI Activity	12-Week Disability Progression-EDSS
FREEDOMS[1]	**Fingolimod**	ARR: ↓ 54%	Gd+ lesions: ↓82% T2 lesions: ↓74%	↓ 32%
TEMSO[2]	**Teriflunomide** (14 mg)	ARR: ↓ 32%	Gd+ lesions: ↓80% Lesion volume: ↓67%	↓ 30%
DEFINE[3]	**Dimethyl fumarate**	ARR: ↓ 53%	Gd+ lesions: ↓90% T2 lesions: ↓85%	↓ 38%

FREEDOMS: Efficacy and Safety of Fingolimod in Patients with RRMS; TEMSO: Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients with MS; DEFINE: Efficacy and Safety of Oral BG00012 in RRMS.

1. Kappos L, Radue EW, O'connor P, et al. *N Engl J Med*. 2010;362(5):387-401.
2. O'connor P, Wolinsky JS, Confavreux C, et al. *N Engl J Med*. 2011;365(14):1293-303.
3. Gold R, Kappos L, Arnold DL, et al. *N Engl J Med*. 2012;367(12):1098-107.

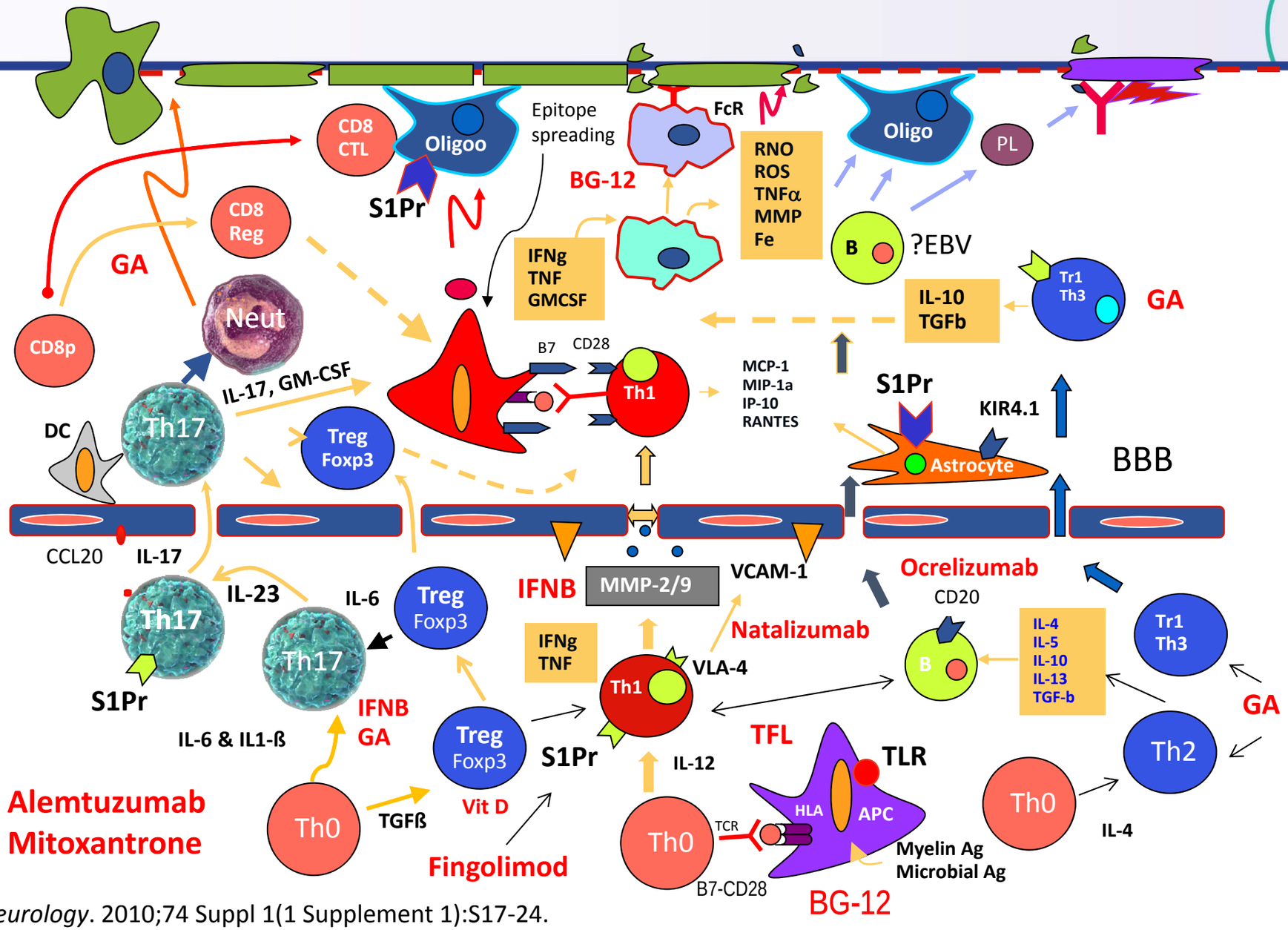
IV DMTs: Efficacy

Pivotal Clinical Trials	Intervention	Relapses	MRI Activity	12-Week Disability Progression- EDSS
AFFIRM[1]	**Natalizumab**	ARR: ↓ 68%	Gd+ lesions: ↓92% T2 lesions: ↓83%	↓ 42%
CARE-MS I[2]	**Alemtuzumab vs IFNβ-1a**	ARR: ↓ 55%	Gd+ lesions: 7% vs 19% T2 lesions: 48% vs 58%	Not significant
CARE-MS II[3]	**Alemtuzumab vs IFNβ-1a**	ARR: ↓ 49%	Gd+ lesions: 9% vs 23% T2 lesions: 46% vs 68%	↓ 42%
OPERA I[4]	**Ocrelizumab vs IFNβ-1a**	ARR: ↓ 46%	Gd+ lesions: ↓94% T2 lesions: ↓77%	Pooled result: ↓ 40%
OPERA II[4]	**Ocrelizumab vs IFNβ-1a**	ARR: ↓ 47%	Gd+ lesions: ↓95% T2 lesions: ↓83%	

AFFIRM: Safety and Efficacy of Natalizumab in the Treatment of MS; CARE-MS I and II: Safety and Efficacy of Alemtuzumab vs IFNβ-1a in RRMS; ARR: annualized rate of relapse.

1. Polman CH, et al. *N Engl J Med*. 2006;354:899-910. 2. Cohen JA, et al. *Lancet.* 2012;380:1819-1828. 3. Coles AJ, et al. *Lancet*. 2012;380:1829-1839; 4. Ocrelizumab [prescribing information]. Genentech, Inc. 2017.

DMT Immunological Targets



Dhib-jalbut S, Marks S. *Neurology*. 2010;74 Suppl 1(1 Supplement 1):S17-24.

Injectable DMTs: Safety and Monitoring

Agent	Minor Side Effects	Serious Side Effects	Monitoring
IFNβ-1a (low dose)[1]	Flu-like symptoms, headache, transaminitis, depression	Suicidal ideation, anaphylaxis, hepatic injury, provoke rheumatic conditions, congestive heart failure, blood dyscrasias, seizures, autoimmune hepatitis	CBC with differential, LFTs, TFTs, interferon neutralizing antibodies (if clinically warranted), skin surveillance
IFNβ-1a (high dose)[2]	Same as above; injection-site reactions	Same as above; skin necrosis	Same as above
Peg IFNβ-1a[3]	Same as above	Same as above	Same as above
IFNβ-1b[4,5]	Same as above	Same as above	Same as above
Glatiramer acetate[6]	Injection-site reactions; post-injection vasodilatory reaction	Lipoatrophy, skin necrosis, anaphylaxis	No specific labs, skin surveillance
Daclizumab[7]	Flu-like symptoms; transaminitis; rash and itching; dry flaky skin; depressed mood	Hepatic injury including autoimmune hepatitis; other immune-mediated disorders; cutaneous events including severe skin reactions	LFTs including total bilirubin levels, CBC with differential

CBC: complete blood count; LFTs: liver function tests; TFTs: thyroid function tests; ALT: alanine amino-transferase; AST: aspartate-aminotransferase

1. IFNβ-1a [prescribing information]. Cambridge, MA: Biogen Idec Inc; 2016. 2. IFNβ-1a [prescribing information]. Rockland, MA: EMD Serono, Inc; November 2015. 3. Pegylated IFNβ-1a [prescribing information]. Cambridge, MA: Biogen Idec Inc; October 2015. 4. IFNβ-1b [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2016. 5. IFNβ-1b [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2015. 6. Glatiramer acetate [prescribing information]. Overland Park, KS: TEVA Neuroscience, Inc; 2015. O'Connor PW, et al. *Handb Clin Neurol*. 2014;122:465-501. 7. Daclizumab [prescribing information]. Cambridge, MA: Biogen Inc. May 2016.

Oral DMTs: Safety and Monitoring

Agent	Minor Side Effects	Serious Side Effects	Monitoring
Fingolimod[1]	Lymphopenia (absolute lymphocyte count >200), transaminitis	Bradycardia, heart block, hypertension, risk of infections (herpetic, cryptococcal), lymphopenia (absolute lymphocyte count <200), transaminitis, macular edema, skin cancer, reactive airway, PRES, PML	First-dose cardiac monitoring, eye and skin examinations, CBC with differential, LFTs, varicella-zoster virus IgG prior to starting medication, PFTs (if clinically indicated)
Teriflunomide[2]	Diarrhea, nausea, hair thinning	Transaminitis, lymphopenia, teratogenic (men and women), latent tuberculosis, neuropathy, hypertension	CBC with differential, LFTs (monthly for first 6 months), PPD or Tb spot/Quantiferon prior to starting, wash out (if needed)
Dimethyl fumarate[3]	Flushing, gastrointestinal distress	Transaminitis, leukopenia, PML	CBC with differential, LFTs

CBC: complete blood count; LFT: liver function tests; PFT: pulmonary function tests; PPD: purified protein derivative; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome.

1. Fingolimod [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2016. 2. Teriflunomide [package insert]. Cambridge, MA: Genzyme Corporation; June 2016. 3. Dimethyl fumarate [prescribing information]. Cambridge, MA: Biogen Idec Inc; February 2016.

Oral DMTs: Important Treatment Effects

Fingolimod[1]

- 70% to 80% reduction in peripheral lymphocyte counts (ALC 200–600/mm^3 is typical) and 20% neutrophil count; nadir in 2 weeks
- Peripheral counts return to normal 1–2 months after discontinuation
- FDO bradycardia (1:200); mean decrease in heart rate of 13 beats/min
- Higher-risk cardiac patients: cardiology evaluation and admit
- Treatment interruption >12–14 days needs repeat FDO
- Monitor blood pressure over time

Teriflunomide[2]

- Long half-life (18–19 days)
- Slow drug clearance (up to 2 years); use cholestyramine/activated charcoal to quickly eliminate
- Uncommon hepatotoxicity

Dimethyl Fumurate[3]

- 30% reduction in lymphocytes; incidence of infections similar to placebo
- 30% to 40% experience flushing and gastrointestinal distress (symptomatic treatment)
- Chronic lymphopenia and progressive multifocal leukoencephalopathy risk

ALC = absolute lymphocyte count; FDO= first dose observation.

1. Fingolimod [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2016. 2. Teriflunomide [package insert]. Cambridge, MA: Genzyme Corporation; June 2016. 3. Dimethyl fumarate [prescribing information]. Cambridge, MA: Biogen Idec Inc; February 2016.

IV DMTs: Safety and Monitoring

Agent	Minor Side Effects	Serious Side Effects	Monitoring
Natalizumab[1]	Headaches, joint pain, fatigue, wearing-off phenomenon	Progressive multifocal leukoencephalopathy, infusion reaction, herpes zoster, other infections, liver failure	CBC with differential, LFTs, serum JCV antibody (every 6 months), MRI, natalizumab antibodies (if clinically warranted)
Alemtuzumab[2]	Infusion reactions	Autoimmune thyroid disease, ITP, Goodpasture syndrome, infections (HSV, VZV)	Monthly CBC with differential, LFTs, urinalysis with urine cell counts, TFTs every 3 months
Ocrelizumab[3]	Upper respiratory tract infections and infusion reactions	Severe infusion reactions, reactivation hepatitis, opportunistic infections, malignancies	Hepatitis panel, CBC with differential, LFTs, PPD or Tb spot/Quantiferon prior to starting

ITP: immune thrombocytopenic purpura

1. Natalizumab [prescribing information]. Cambridge, MA: Biogen Idec Inc; May 2016. 2. Alemtuzumab [package insert]. Cambridge, MA: Genzyme Corporation; May 2016. 3. Ocrelizumab [prescribing information]. San Francisco, CA: Genentech, Inc. 2017.

Treatment of Primary Progressive MS

- Ocrelizumab is the first DMT approved for treatment of PPMS
  - Phase 3 data demonstrated a clinically significant change in 12-week disability progression vs placebo (32.9% vs 39.3%, HR 0.76; CI 0.59 to 0.98, $P = .03$)[1]
  - The beneficial effect on disability persisted through 24-weeks (29.6% vs placebo 35.7%, $P = .04$)[1]
- To date, trials for fingolimod and glatiramer acetate have not been able to show a statistically significant progression delay in PPMS[2,3]

1. Montalban X, Hauser SL, Kappos L, et al. *N Engl J Med*. 2016. 2. Lublin F, Miller DH, Freedman MS, et al. *Lancet*. 2016;387(10023):1075-1084. 3. Wolinsky JS, Narayana PA, O'connor P, et al. *Ann Neurol*. 2007;61(1):14-24.

Ocrelizumab: Efficacy in PPMS

Pivotal Clinical Trials	Intervention	12-Week Disability Progression-EDSS	24-Week Disability Progression-EDSS	MRI Activity	Timed 25 Foot Walk
ORATORIO	Ocrelizumab vs. Placebo	↓ 24%	↓ 25%	Mean change volume of T2 lesions at Week 120 (cm^3): Ocrelizumab: -0.39 Placebo: 0.79 $P<0.0001$	↓ 29%

Ocrelizumab [prescribing information]. San Francisco, CA: Genentech, Inc. 2017.

Treatment of MS in Pediatric Patients

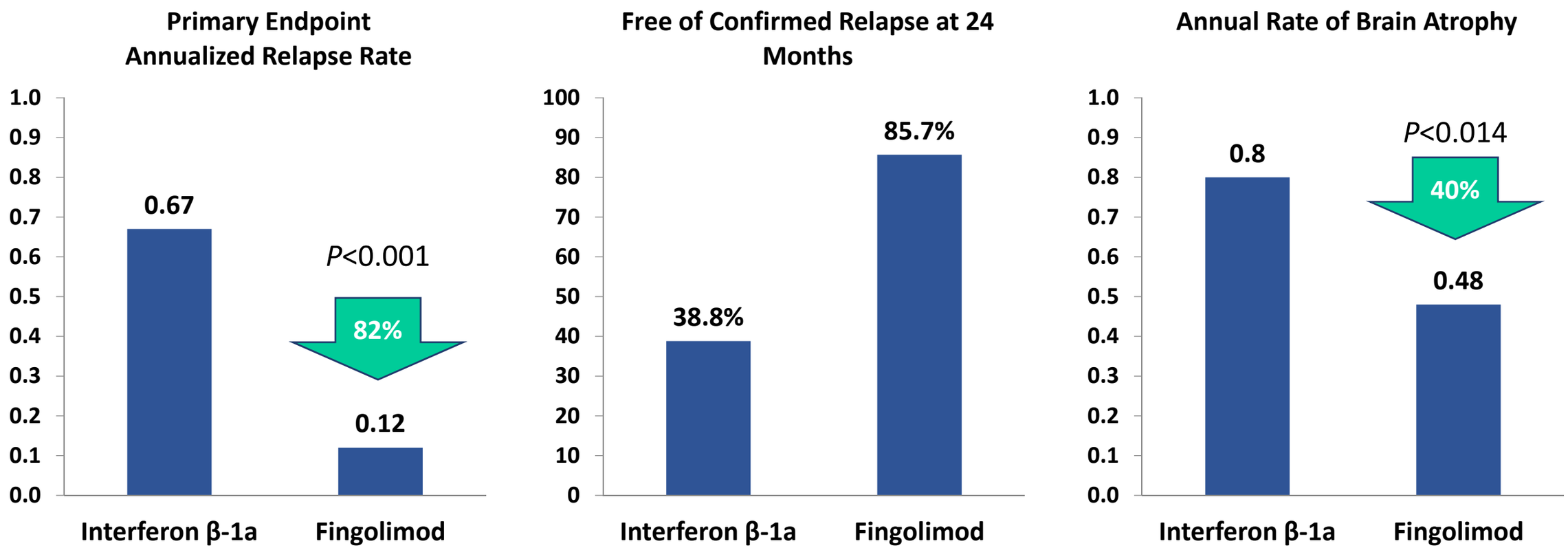
- Approximately 3–5% of patients with MS experience disease onset before 18 years of age with 2–3 times more frequent relapses than adults
- There are no disease-modifying therapies specifically approved for the treatment of MS in children and adolescents
- PARADIGMS study (NCT01892722)
  - 24-month Phase 3 trial in pediatric MS patients (10 to < 18 years) randomized to either daily oral fingolimod or weekly intramuscular interferon β-1a
- The study met its primary endpoint, showing a significant reduction in relapses in patients treated with fingolimod vs β-1a

Safety and Efficacy of Fingolimod in Pediatric Patients With Multiple Sclerosis. (2017) Retrieved from https://clinicaltrials.gov/ct2/show/NCT01892722 (Identification No. NCT01892722). Accessed October 2017.

Novartis landmark Phase III trial shows fingolimod significantly reduces relapses in children and adolescents with MS [press release]. Basel, Switzerland: Novartis Media Relations; September 5, 2017. https://www.novartis.com/news/media-releases/novartis-landmark-phase-iii-trial-shows-fingolimod-significantly-reduces. Accessed October 2017.

PARADIGMS Trial: Treatment of Pediatric Patients

- 24-month Phase 3 trial (NCT01892722)
- n=215 pediatric MS patients (10 to < 18 years) randomized to either daily oral fingolimod or weekly intramuscular interferon β-1a



- Serious adverse events occurred in 17.8% of fingolimod recipients vs 9.3% of interferon recipients

Chitnis T, et al. Presented October 28, 2017 at ECTRIMS-ACTRIMS. Abstract 276.

Emerging Multiple Sclerosis Therapies

Agent	Target/ Mechanism of Action	Possible Indication	Route of Administration	Status
Laquinimod	Immunomodulation of immune cells	RRMS, Progressive MS	Oral	Phase 3
Ofatumumab	Anti-CD20 MAb	RRMS	IV/SC	Phase 3
Ponesimod	Sphingosine-1-phosphate receptor 1 (S1P1) receptor modulator; receptor subtypes (1>5>3)	RRMS	Oral	Phase 3
Ozanimod	S1P modulator; receptor subtypes 1 and 5	Relapsing MS	Oral	Phase 3
Siponimod	S1P modulator; receptor subtypes 1 and 5	SPMS	Oral	Phase 3
Masitinib	Tyrosine kinase inhibitor	PPMS SPMS	Oral	Phase 3
Anti-LINGO-1	Neuroprotection/remyelination	Relapsing MS	IV	Phase 2

Fabian M, Krieger S. MS Research Update 2017. Multiple Sclerosis Association of America Web site. https://mymsaa.org/publications/msresearch-update-2017/. Published May 2017. Accessed October 2017.

Laquinimod

- Phase 3 CONCERTO trial (n=1800)
  - 24-month trial designed to compare two doses of laquinimod with placebo (NCT01707992)
  - Primary outcome: confirmed disease progression in patients with RRMS
  - Laquinimod failed to slow disease progression in RRMS patients; development in RRMS has been discontinued[1]
- Phase 2 ARPEGGIO trial in patients with PPMS (n=375)[2]
  - 48 week trial to evaluate the effect of laquinimod (0.6 and 1.5 mg/day) vs placebo on brain atrophy and clinical outcomes (NCT02284568)
  - Higher dose discontinued due to CV side effects
  - Results expected in 4Q 2017

1. Teva and Active Biotech Announce CONCERTO trial of Laquinimod in RRMS Did Not Meet Primary Endpoint [press release]. Petach Tikva Israel: Teva Pharmaceutical Industries Ltd; May 5, 2017. http://www.tevapharm.com/news/teva_and_active_biotech_announce_concerto_trial_of_laquinimod_in_rrms_did_not_meet_primary_endpoint_05_17.aspx. Accessed October 2017; 2. Thöne J, Linker RA. *Drug Des Devel Ther*. 2016;10:1111-8.

Ofatumumab

- Phase 2 MIRROR trial (n=232) evaluated 3, 30, and 60 mg Q12W and 60 mg Q4W ofatumumab SC vs placebo
  - Week 0-12 showed 65% contrast lesion reduction
  - Week 4-12 showed ≥90% ↓ (for cumulative doses ≥30 mg)
  - Linear B cell suppression: 32-64 cells/mcL associated with 1 new lesion/year (vs 16 new lesions with placebo)
- Phase 3 trials (ASCLEPIOS I and II) in Relapsing MS began enrolling in September 2016 (NCT02792218, NCT02792231)
  - Primary endpoint: annualized relapse rate

Sorensen PS, Lisby S, Grove R, et al. *Neurology*. 2014;82(7):573-81.
Sorensen PS, Tolson J, Lewis E, et al. *Neurology.* 2014;82(S10): I7-1.007.

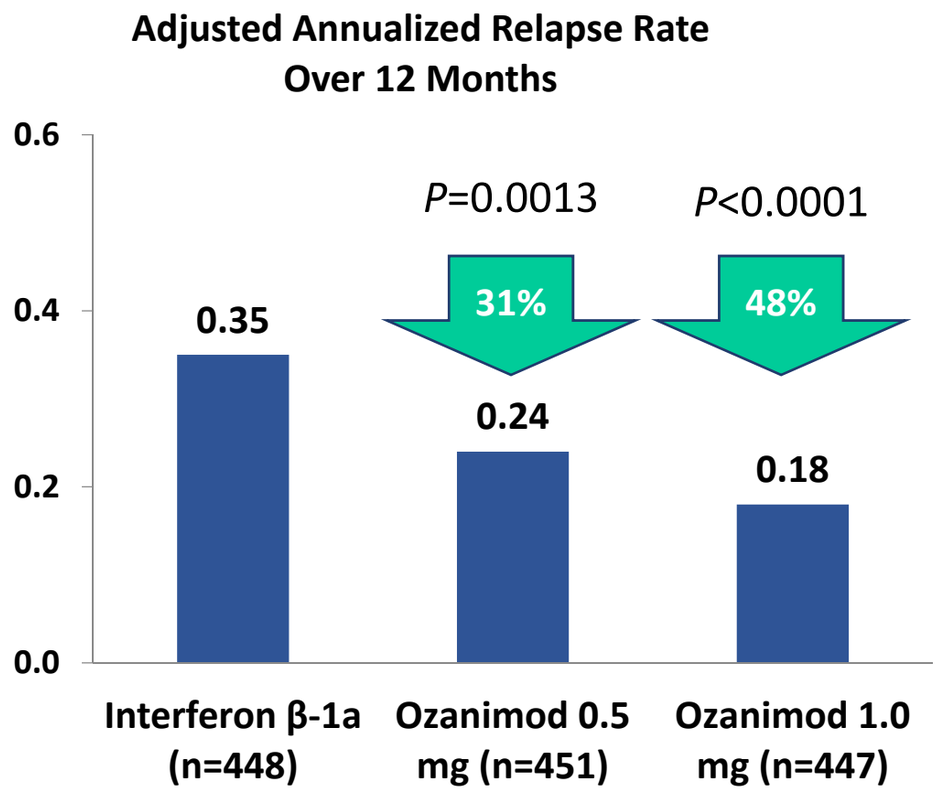
Ponesimod: Phase 2 and 3 Trials

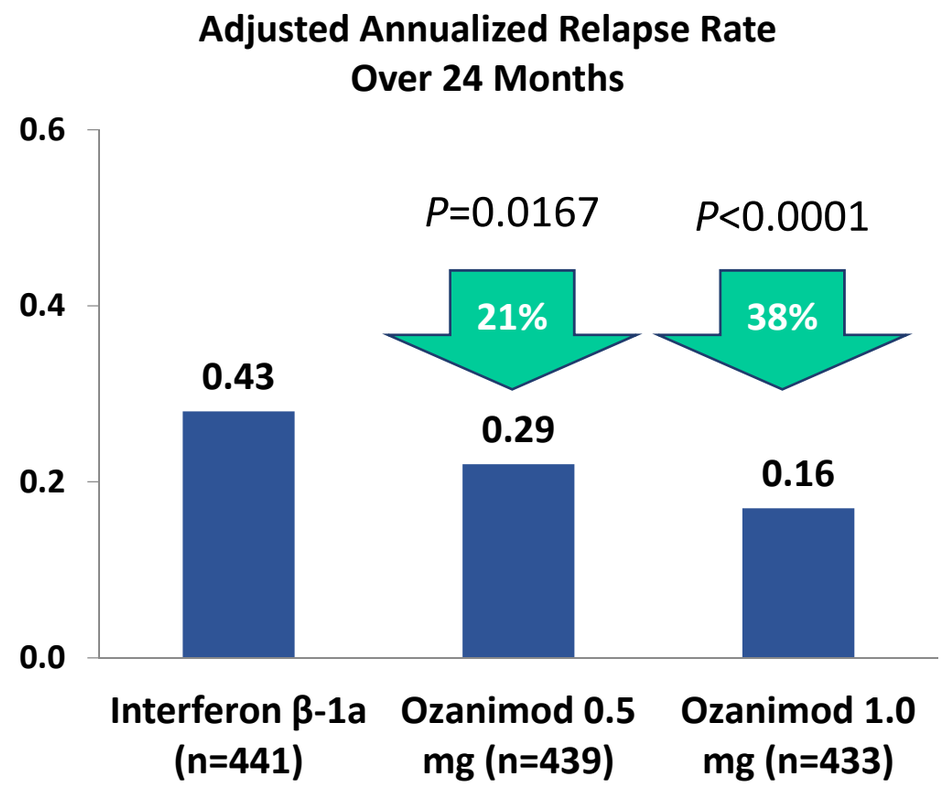
- Phase 2b study of 464 patients with relapsing remitting MS investigated orally administered ponesimod (10, 20 and 40 mg) or placebo for 24 weeks
  - The cumulative number of new gadolinium-enhancing (Gd+) lesions detected on MRI scans at Weeks 12 and 24 were significantly reduced in a dose-dependent manner by 43%, 83% and 77% with ponesimod 10, 20 and 40 mg, respectively
  - Annualized relapse rate (ARR) up to week 24 was approximately 0.33, 0.42 and 0.25 in the 10, 20 and 40 mg ponesimod groups, respectively, vs 0.525 in the placebo group
- Phase 3 OPTIMUM Trial to determine whether ponesimod is more efficacious than teriflunomide in reducing relapses (NCT02425644)
  - Multi-center, randomized, double-blind, parallel-group, active-controlled, 3-year superiority study (n=1100 RMS patients)
  - Results expected in 2018

D'Ambrosio D, et al. *Ther Adv Chronic Dis*. 2016;7:18-33.
Baghouz M. Specialty Pharmacy Times. February 3, 2017. https://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2017/january-2017/late-stage-pipeline-review-for-multiple-sclerosis-treatments. Accessed October 2017.

Ozanimod: Phase 3 SUNBEAM/RADIANCE Trials

- Comparison of the safety, effectiveness and tolerability of two oral doses of ozanimod (0.5 mg and 1 mg) vs IM injection of interferon beta-1a once a week for 12 months (SUNBEAM) and 24 months (RADIANCE)
- N=1346 patients with relapsing MS





- There was no distinct serious adverse event pattern observed

Comi GT, et al. Presented October 27, 2017 at ECTRIMS-ACTRIMS. Abstract 232.

Siponimod Phase 3 EXPAND Study

- Patients with SPMS (n=1,651) randomized to 2 mg siponimod or placebo
  - Primary endpoint: Delay in time to 3-month disability progression as measured by EDSS
  - Secondary endpoints: Delay in time to 6-month confirmed disability progression, time to confirmed worsening of at least 20% from baseline in the timed 25-foot walk test, T2 lesion volume, annualized relapse rate (ARR), safety and tolerability
- EXPAND (NCT01665144) met its primary endpoint; patients receiving siponimod had a 21% reduced risk of disability progression vs placebo (p=0.013)
  - Secondary endpoints: siponimod-treated patient had 23.4% lower average change in brain volume and reduced lesion volume
  - Siponimod was generally well tolerated; adverse events were similar to those reported with other SP1 receptor modulators

Kappos L, Bar-Or A, Cree B, et al. Efficacy and safety of siponimod in secondary progressive multiple sclerosis: results of the placebo controlled, double-blind, phase III EXPAND study. Abstract 250. Paper presented at ECTRIMS 2016; September 16, 2016; London.

Masitinib: Ongoing Phase 3 Trial

- Blinded, randomized, placebo-controlled, 96 week phase 3 trial to investigate the superiority of masitinib vs placebo (NCT01433497)
- N=600 patients with primary progressive or relapse-free secondary progressive MS
- Clinical endpoints:
  - Change in MS Functional Composite Score (MSFC)
  - Change in Multiple Sclerosis Quality of Life 54 items (MSQOL-54)
  - Change in Expanded Disability Status Score (EDSS)
- Study is ongoing with results anticipated in 2017

Baghouz M. Specialty Pharmacy Times. February 3, 2017. https://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2017/january-2017/late-stage-pipeline-review-for-multiple-sclerosis-treatments. Accessed October 2017.

Anti-LINGO-1: Phase II

- Phase II SYNERGY trial (n=400) in patients with either RRMS or SPMS were randomized to one of five groups for 72 weeks
  - Groups 1-4 were given anti-LINGO + IFNβ-1a (Avonex)
  - Group 5 was given IFNβ-1a + placebo
  - Primary endpoint: Improvement in disability scores vs IFNβ-1a alone
  - No statistical difference was seen between the overall anti-LINGO group and control group
  - Subgroup of patients demonstrated improvement so Phase IIb study enrolling

Biogen Reports Top-Line Results from Phase 2 Study of Opicinumab (Anti-LINGO-1) in Multiple Sclerosis [press release]. Cambridge, MA: Biogen Investor Relations; June 6, 2016. http://media.biogen.com/press-release/investor-relations/biogen-reports-top-line-results-phase-2-study-opicinumab-anti-lingo. Accessed October 2017.

Summary

- Multiple sclerosis is a common, chronic demyelinating disease of the central nervous system that usually presents in the prime of life
- Ability to treat MS is evolving rapidly and becoming more complicated as additional agents are introduced
- Introduction of effective and generally safe disease-modifying therapies has made a “one size fits all” approach to treatment of relapsing-remitting MS obsolete
- Effective treatment for progressive subtypes of MS remains a significant unmet need
- Goal of treatment is to balance efficacy, safety, and tolerability of therapeutic interventions for each patient

Care Management Strategies to Enhance Overall Outcomes for Patients with MS

Aimee Banks, PharmD, BCPS
Vanderbilt University Medical Center
Multiple Sclerosis Clinic

Learning Objectives

- Review multiple sclerosis (MS) symptom management strategies
- Employ care planning strategies to boost adherence to treatment plans and improve overall coordination of multidisciplinary MS care

Multiple Sclerosis Requires Lifelong Care

- Diagnosis typically occurs between 20 and 40 years of age
  - Majority of people who have MS will experience a relatively normal life span with many living for more than 20 years with the disease
- In addition, common chronic comorbidities (eg, hypertension, diabetes, heart disease, depression, anxiety, lung disease) are also observed in MS patients
  - These can impact MS progression, mortality, and quality of life
- MS disease and symptom control as well as treatment of comorbid conditions requires lifelong care management

Marrie RA, Cohen J, Stuve O, et al. *Mult Scler*. 2015;21(3):263-81.

Care Management

- **Care management**: A set of activities intended to improve patient care and reduce the need for medical services by enhancing *coordination of care*
- **Goal:** Improve coordination of care while providing safe, effective, non-duplicative care in the most cost-effective manner
- **Challenge:** Identifying patients most likely to benefit from care management

Adapted from: Mechanic R. Will care management improve the value of U.S. health care? Background Paper for the 11th Annual Princeton Conference. May 20 – 21, 2004. http://healthforum.brandeis.edu/research/pdfs/CareManagementPrincetonConference.pdf. Accessed October 2017.

Keys to Successful Care Management

Success Factor	Description
Communication	• Patient satisfaction increases when the health care team explains information clearly, and tries to understand the patient's experience, and provides viable treatment/management options
In-person encounters	• Face-to-face interaction is necessary for effective care management • Care management relying solely on telephone and/or electronic encounters has not been shown to be successful
Training and personnel	• Programs with specially trained care managers working as part of a multidisciplinary team are most successful
Physician involvement	• Placing care managers with physicians in primary care practices may help facilitate physician involvement
Informal caregivers	• Patients with complex health care needs, particularly those with physical or cognitive functional decline, often need the assistance of informal caregivers to actively participate in care management
Coaching	• Involves teaching patients and their caregivers how to recognize early warning signs of worsening disease

Goodell S, Bodenheimer T, Berry-Millet R. What are the keys to successful care management? In: Care management of patients with complex health care needs. Robert Wood Johnson Foundation. https://www.rwjf.org/content/dam/farm/reports/issue_briefs/2009/rwjf49853. Published December 2009. Accessed October 2017.

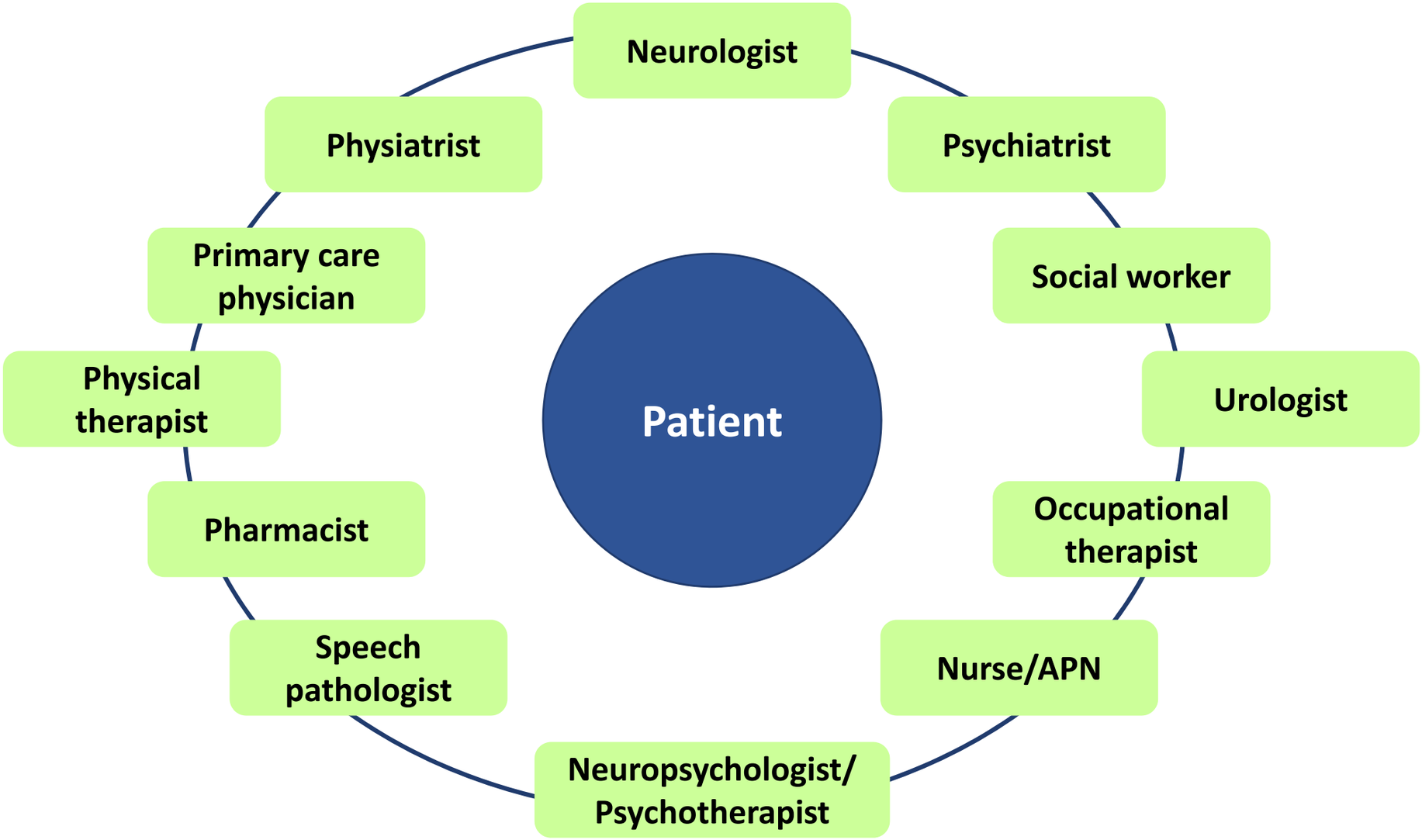
Care Coordination

- **Care Coordination:** The organization of care activities between a multidisciplinary team of providers to facilitate the appropriate delivery of health care services

Feature	Description
Clear **communication** between providers in the care network	• Essential for providing coordinated care • Includes access patient health records across the care network and tools that automate workflows and streamline communication between care providers
Assume **accountability**	• Primary care providers facilitate care coordination via inclusion of specialists, consultants, hospitals, and community service agencies in care delivery • Maintain a patient referral tracking system
Provide **patient support**	• Organize the practice team to support patients and families during referrals and care transitions
Build **relationships** and agreements	• Develop agreements to 1) standardize information, 2) set expectations, and 3) build relationships
Develop **connectivity**	• Develop and implement a standardized information transfer system including shared EMR, e-referral, structured referral forms

Adapted from McDonald KM, Sundaram V, Bravata DM, et al. Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies (Vol. 7: Care Coordination). Rockville (MD): Agency for Healthcare Research and Quality (US); 2007 Jun. (Technical Reviews, No. 9.7.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK44015/. Accessed October 2017.

Members of the MS Treatment Team



Perrin ross A. *Am J Manag Care*. 2013;19(16 Suppl):s301-6.

Primary MS Symptoms and Their Impact

Primary Symptoms *Related to direct damage of the nervous system resulting in weakness, sensory deficits, etc.*	
Site of Lesion	**Symptom(s)**
Brainstem	Diplopia; nystagmus; vertigo
Cerebellum	Ataxia; tremor
Cerebrum	Cognitive impairment; depression
Optic nerve	Optic neuritis; painful vision loss
Spinal cord	Bladder, bowel, and sexual dysfunction; weakness; spasticity
Other	Fatigue; pain; temperature sensitivity; exercise tolerance

Compston A, Coles A. *Lancet*. 2008;372(9648):1502-17.
Tullman MJ. *Am J Manag Care*. 2013;19(2 Suppl):S15-20.
MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

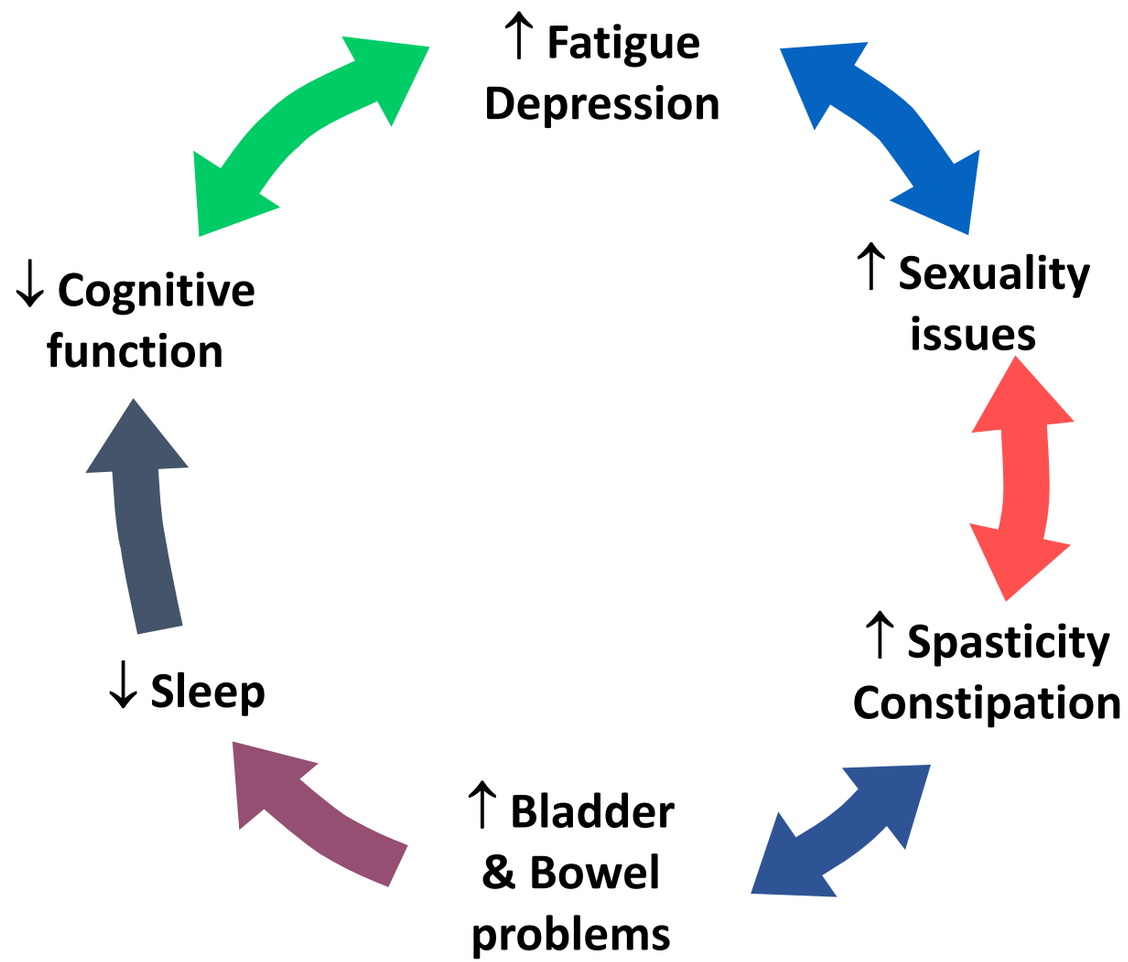
Secondary and Tertiary MS Symptoms

Secondary Symptoms *Complications of the primary symptoms*	
Symptom(s)	**Secondary to:**
Urinary tract infection	Neurogenic bladder
Loss of muscle tone, poor posture, decreased bone density	Inactivity (resulting from weakness, vertigo, ataxia)
Pressure sore	Immobility

Tertiary Symptoms *Downstream effects of the disease*	
Symptom(s)	**Tertiary to:**
Social, vocational, and psychological effects	Aloneness, isolation, loss of productivity (resulting from primary and secondary symptoms)
Depression	All of the above

Compston A, Coles A. *Lancet*. 2008;372:1502-1517.
Tullman MJ. *Am J Manag Care*. 2013;19(2 suppl.):S15-S20.
National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

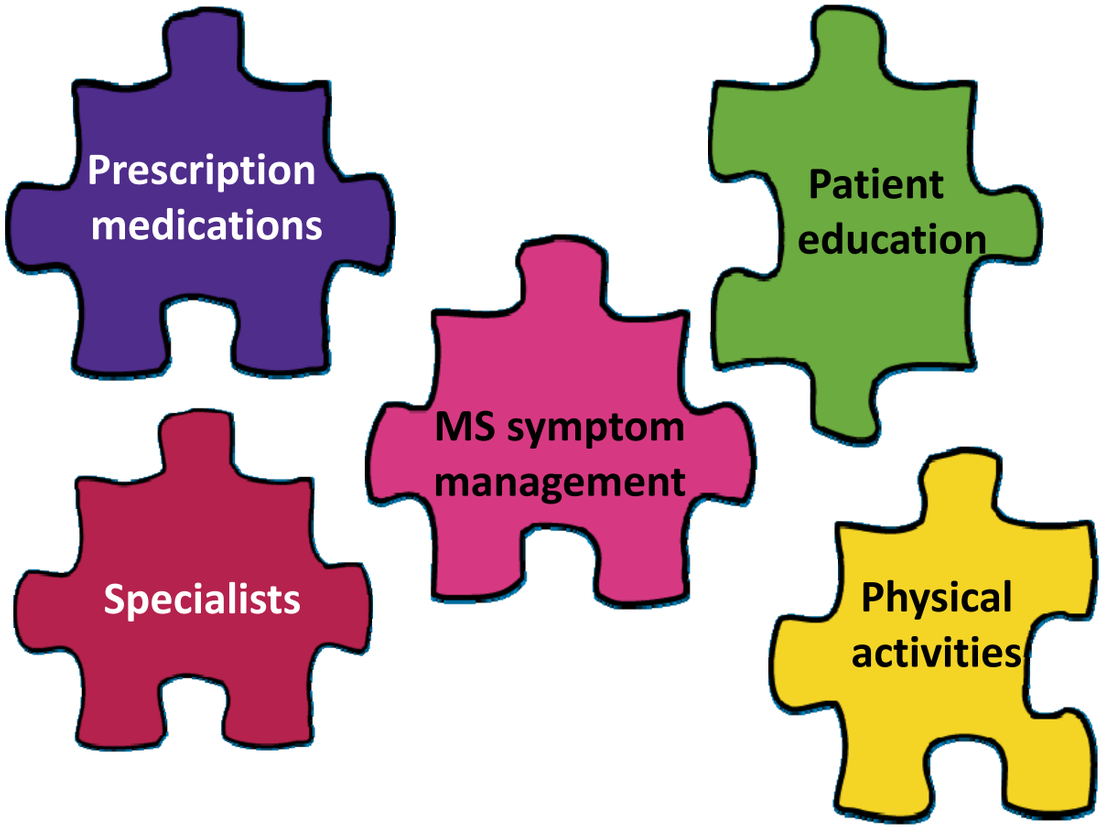
Cycle of MS Symptoms



MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Clinical Approach to Symptomatic MS Treatment

- Effective symptom management involves medication, rehabilitation strategies, emotional support—and coordinated, multidisciplinary care
- Prioritize the most bothersome/impactful symptoms
- Individualize therapy
- Initiate symptom management early and continue through the disease course
- Recognize that symptoms are often interrelated
- Treat comorbid conditions



MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing MS Fatigue

- >80% of people with MS experience fatigue
  - Often worse late in the day
  - May be exacerbated by heat or physical exertion
- Identify/address contributory factors
  - Disrupted sleep; muscle fatigue; disability-related fatigue; depression; medications
- Develop comprehensive treatment plan

Pharmacologic Treatment	Intervention
• Amantadine • Modafanil • Amphetamines • L-carnitine	• Counsel patient re: energy management (prioritizing activity, work simplification, mobility aids, etc) • Aerobic exercise • Sleep hygiene • Cooling devices (for Uhthoff's phenomenon) • Referral to occupational therapist

Bigi S, Yeh EA. *Eur Neurol Rev* 2013;8:130-135.
Henze T, et al. *Eur Neurol* 2006;56:78-105.
National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Bladder Dysfunction

- >75% of people with MS will experience bladder problems
- Storage dysfunction: small quantity of urine triggers the urge to void
  - Primary symptoms: urgency, frequency, incontinence, nocturia
- Emptying dysfunction
  - Failure to empty bladder increases risk of UTI
  - Primary symptoms: urgency, frequency, nocturia, incontinence

Pharmacologic Treatment	Intervention
• Anticholinergics (oxybutynin) • Antimuscarinics (tolterodine) • Alpha blockers (tamsulosin) • Anti-spasmodics (baclofen)	• Self-catheterization techniques • UTI symptoms recognition • Counseling re: frequent bathroom breaks; managing water intake

Bigi S, Yeh EA. *Eur Neurol Rev* 2013;8:130-135; Henze T, et al. *Eur Neurol* 2006;56:78-105.
National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Bowel Dysfunction

- Experienced by 50% of people with MS
  - Constipation—most common
    - "Diarrhea" (related to impaction)
  - Bowel incontinence—least common

- Identify/address contributory factors
  - Medications (opioids, iron, anticholinergics, diuretics)

Pharmacologic Treatment	Intervention
• OTC products as needed (stool softeners, bulk-forming agents, rectal stimulants, mild laxatives)	• Managed best with regular bowel routine • Adequate fluid/fiber intake • Exercise

National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

What Optimal Bowel/Bladder Care Looks Like

- Minimize incontinence/maximize control over when defecation/voiding occurs
- Balances risk and benefit of medications for other symptoms and their impact on the bowel/bladder
- Support as the disease progresses and adjustments are needed
- TIMELY surgical intervention when needed
- Skin integrity is maintained
- Quality of life is optimized

Managing Spasticity

- Experienced by 40-60% of people with MS (more common in the lower extremities)
- Some spasticity is useful to counteract weakness

Pharmacologic Treatment	Intervention
• GABA agonists (oral or intrathecal baclofen) • α- agonists (tizanidine) • Anticonvulsants (gabapentin, clonazepam, diazepam) • Botulinum toxin	• Time doses, titrate up • Assess for sedation, weakness • Physiotherapy

National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Sexual Dysfunction

- 60% to 80% of men and women with MS
  - Reduced libido
  - Sensory disturbances
  - Anorgasmia
- Secondary dysfunction
  - Managing MS symptoms that interfere with sexual activity/pleasure (fatigue, spasticity, etc)
  - Remove medications that may worsen sexual comfort and responsiveness (antidepressants, anticholinergics, beta blockers, etc)
- Tertiary dysfunction (feeling; attitudes)
  - Education; counseling

Pharmacologic Treatment	Intervention
• Erectile dysfunction medications (males) • Lubricants (females)	• Education and counseling • Implants (males)

Bigi S, Yeh EA. *Eur Neurol Rev* 2013;8:130-5.
Henze T, Rieckmann P, Toyka KV. *Eur Neurol*. 2006;56(2):78-105.
MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Cognitive Dysfunction

- Occurs in 50-60% of people with MS
  - Ranges from mild to severe
  - Correlates with number of lesions/lesion area on MRI, as well as brain atrophy
  - Can occur at any time, but is more common later in the disease
  - More likely in progressive MS
- Most common problems: memory; attention/concentration; information processing

Pharmacologic Treatment	Intervention
• No symptomatic medications have been shown to be beneficial • May try donepezil	• Screen for depression • Refer for neuropsychological testing, cognitive rehabilitation • Consider computer-mediated memory exercises • Encourage regular exercise and healthy sleeping habits

National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Depression

- >50% of people with MS will experience a major depressive episode
  - Results from an altered immune response, changes in neurologic function, and psychosocial factors)
- Suicide in MS is significantly higher in MS vs general population
  - Greatest risk factor for suicide in MS is depression
- Under recognized, under diagnosed, and under treated in MS

Pharmacologic Treatment	Intervention
• Antidepressants	• Screen for depression • Refer for neuropsychiatric assessment • Psychotherapy • Education and support for individuals, families, and caregivers • Effective management of mood changes • Compensatory strategies for cognitive challenges • Inclusion of support partners/family members in treatment planning

Bigi S, Yeh EA. *Eur Neurol Rev* 2013;8:130-5.
MS Symptoms. National Multiple Sclerosis Foundation Web site. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Tremor

- Incidence unknown
- Potentially severely disabling
- No specific treatments at this time

Pharmacologic Treatment	Intervention
• Commonly used therapies include propranolol, primidone, acetazolamide, buspirone, clonazepam, gabapentin, carbamazepine	• Occupational therapy • Weighting; assistive devices • Thalamic surgery for tremor (generally poor results)

National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Ataxia/Altered Gait

- Three forms of ataxia
  - Sensory
  - Vestibular
  - Cerebellar
- Ataxia is one of the most difficult MS symptoms to treat
- Evidence of therapeutic effectiveness of treatment interventions is limited

Pharmacologic Treatment	Intervention
• Dalfampridine • High dose biotin • Alpha lipoic acid	• Physical therapy including exercises or gait training such as vestibular exercises • Occupational therapy • Fall prevention training

Tourbah A, et al. *Mult Scler*. 2016;22:1719-1731.
Spain, R et al. *Neurol Neuroimmunol Neuroinflamm*. 2017 Jun 28;4(5):e374.
National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Managing Pain

- 75% of people with MS experience pain
- Neuropathic (central) pain
  - Paroxysmal pain (trigeminal neuralgia; headache)
  - Continuous pain (dysesthesias)
- Nociceptive (secondary) pain
  - Musculoskeletal pain

Pharmacologic Treatment	Intervention
• Anticonvulsants (gabapentin, topiramate) • Antidepressants (tricyclics, duloxetine) • NSAIDs • Opioids only prn • Intrathecal baclofen	• Physical therapy

National Multiple Sclerosis Foundation. Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed October 2017.

Adoption of Healthy Lifestyle Habits

- Diet and Nutrition
  - Although there's no special “MS diet,” what and how you eat can make a difference in your energy level, bladder and bowel function, and overall health
  - Vitamin D may have important effects on the immune system and may help regulate cell growth and differentiation
- Smoking cessation
  - In addition to general health and safety concerns, smoking increases a person's risk of developing MS and of disability progression

National Multiple Sclerosis Foundation. Unhealthy habits. https://www.nationalmssociety.org/smoking. Accessed November 2017.
National Multiple Sclerosis Foundation. Diet and nutrition. https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Diet-Nutrition. Accessed November 2017.

The Allure of Complementary Medicine

- MS treatments are only partially effective
- Personal testimonials are extremely powerful
- Many people believe *"Safe…natural…healthy…effective…"*

  and distrust the effects of mainstream medicine
- It feels good to "take charge" of a chronic, unpredictable disease

Bowling AC. Optimal Health with Multiple Sclerosis. New York, NY: Demos Health; 2014.

Occurrence of Common Comorbidities in MS

- Analysis of comorbidities in newly diagnosed patients with MS vs age-matched controls
- All comorbidities were more common in MS vs control (except hyperlipidemia)
- Clinicians need to be aware of any comorbidities and their treatment when prescribing MS medication due to the potential for unwanted interactions between therapies

Comorbidity	Rate Ratio	*P* value
Fibromyalgia	2.87	<0.0001
Epilepsy	2.18	<0.0001
Depression	2.04	<0.0001
Bipolar disorder	1.86	<0.0001
Inflammatory bowel disease	1.68	<0.0001
Anxiety	1.61	<0.0001
Chronic lung disease	1.34	<0.0001
Ischemic heart disease	1.30	<0.0001
Hypertension	1.17	<0.0001
Diabetes	1.17	<0.0001
Hyperlipidemia	1.03	0.99

Comparison of 23,382 incident MS cases and 116,638 age-, sex-, and geographically matched controls.

Marrie RA, Patten SB, Tremlett H, et al. *Neurology*. 2016;1-8.

Factors Affecting Treatment Adherence

- Patient motivation and readiness for treatment is key to adherence
- Factors that negatively affect readiness include:
  - Lack of knowledge about MS
  - Denial of illness
  - Unrealistic expectations of treatment outcomes
  - Cost of medical care/treatment
  - Side effects
  - Cultural factors
  - Lack of support (medical team, family, caregivers)
  - Distrust of medical community and/or prescription medications

Remington G, Rodriguez Y, Logan D, Williamson C, Treadaway K. *Int J MS Care*. 2013;15(1):36-45.

Interventions That May Optimize Adherence

Factors Affecting Adherence	Possible Interventions
Forgetting medication doses	• Assess patient response to specialized requirements associated with medication • Perform cognitive assessment, including assessment for memory impairment • Evaluate/facilitate adjustment of frequency and complexity of regimen • Arrange for telephone and/or text messaging support/reminders • Incorporate family (eg, spouse and older children) into treatment plan • Consider switching to a DMT with less frequent dosing
Injection site reactions	Prevention • Rotate injection site • Warm medication to room temperature • Evaluate formulation and regimen • Pretreat with ice for 1 minute Treatment • Apply ice or cold compress to reduce swelling • Use hydrocortisone cream for swelling/rash relief
Fear or anxiety related to injections	• Assess patient self-efficacy • Enlist support of patient family, significant others • Consider thinner gauge, shorter needle, or autoinjector
Fatigue/tiring of injections	• Evaluate/facilitate adjustment of frequency and complexity of regimen • Consider switch to a DMT with less frequent dosing
Economic/financial challenges	• Enlist support of social worker for help navigating system/finances • Facilitate contact with medication assistance programs for DMTs

Remington G, Rodriguez Y, Logan D, Williamson C, Treadaway K. *Int J MS Care*. 2013;15(1):36-45.

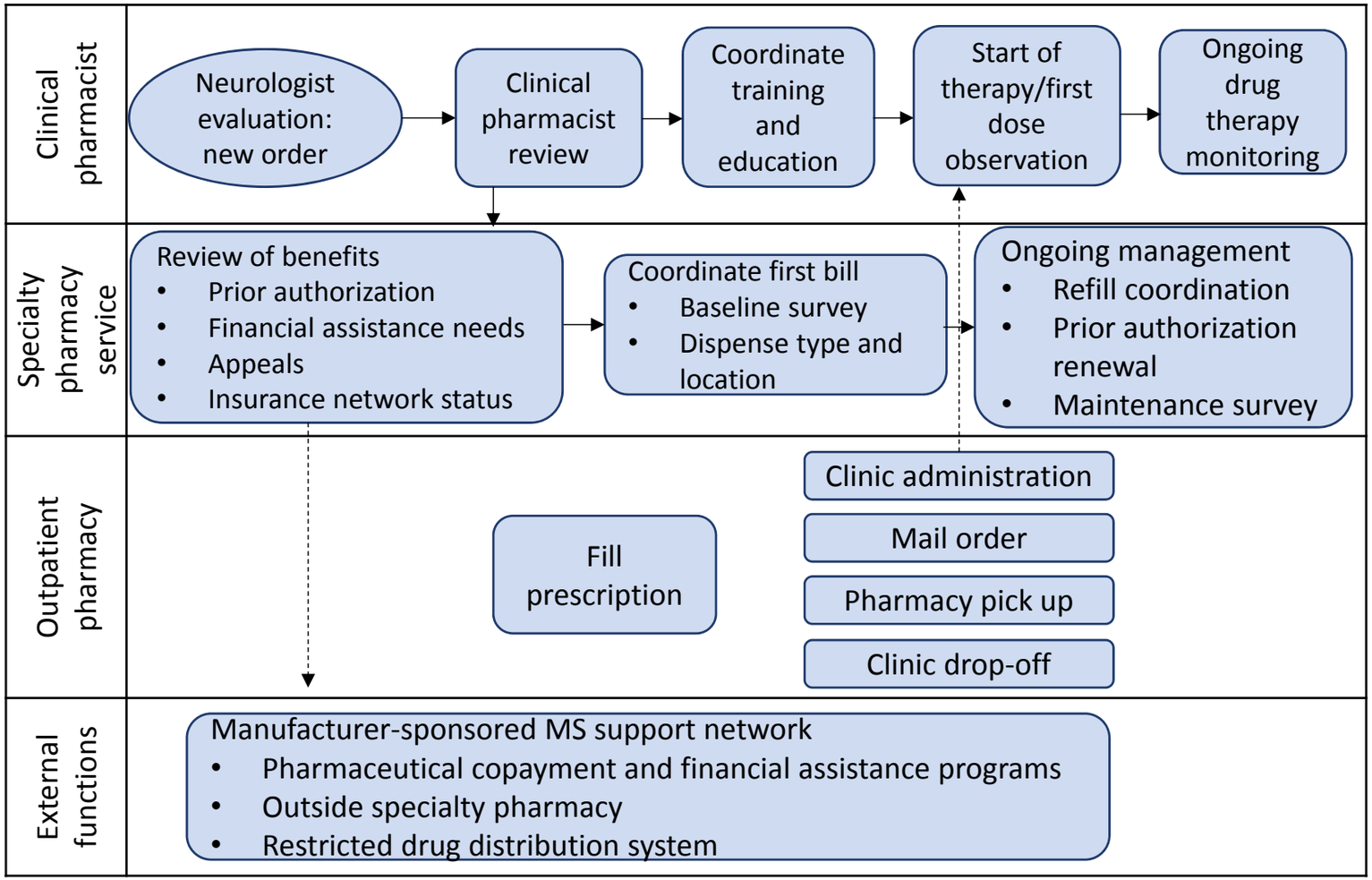
Patient-Clinical Relationship and Adherence

- The clinician-patient relationship is a crucial factor affecting adherence, especially as treatment continues over the long term
- Clinicians can work with each patient to set expectations regarding
  - Disease diagnosis and prognosis
  - Benefits expected from treatment interventions
  - Strategies to overcome barriers to achieving a specific health outcome (including adherence)

Bubalo J, Clark RK, Jiing SS, et al. *J Am Pharm Assoc* (2003). 2010;50(3):394-406.

Integrated MS Pharmacy Practice Model

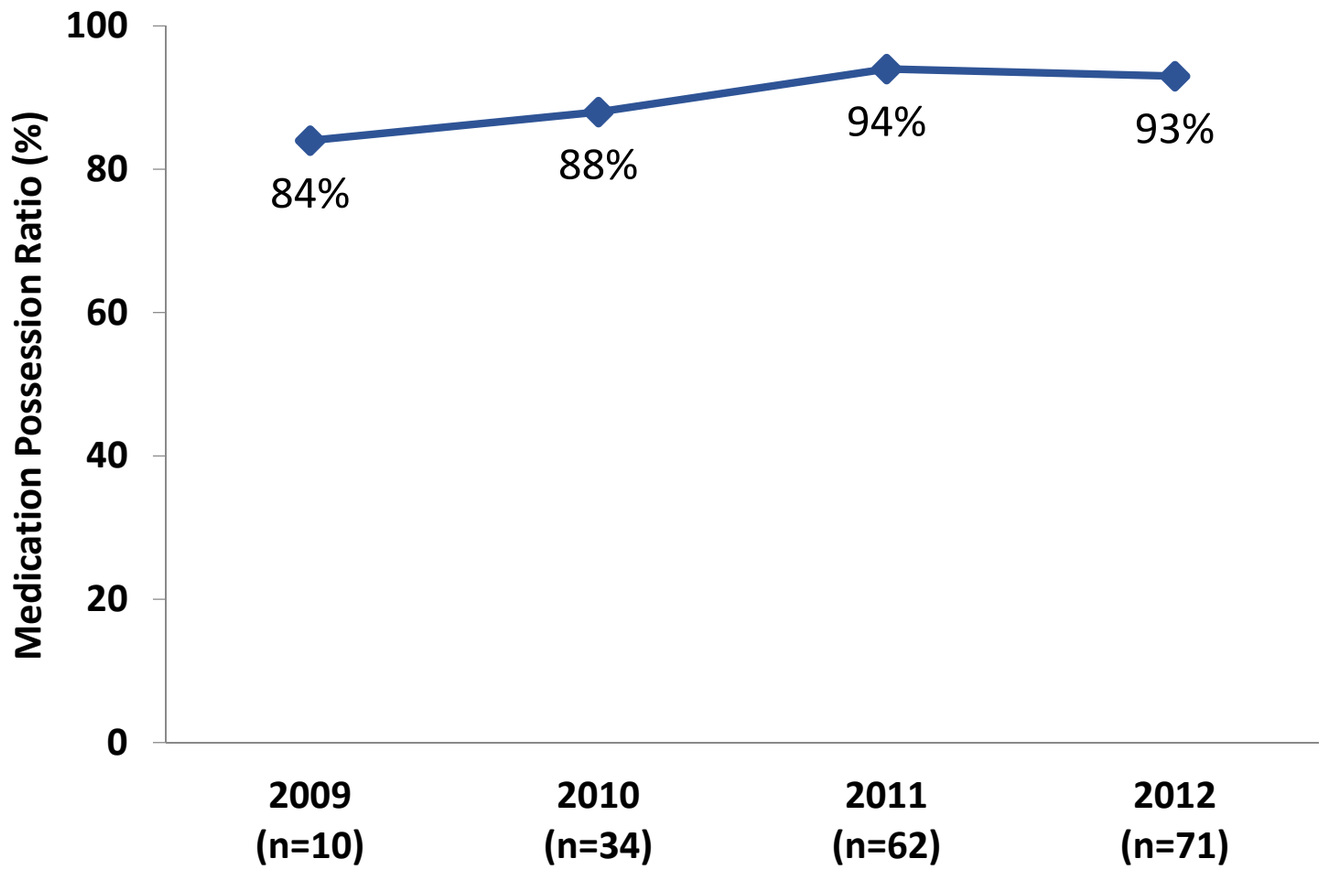
- University of Illinois Hospital and Health Sciences System
- Features include
  - Interdisciplinary team of physicians, nurses, and pharmacists
  - Dedicated clinical pharmacist on the MS specialty team
  - Integrated specialty pharmacy service
  - Direct access to the electronic medical record
  - Face-to-face interaction with patients
  - Refill coordination



Hanson RL, Habibi M, Khamo N, Abdou S, Stubbings J. *Am J Health Syst Pharm*. 2014;71(6):463-9.

Integrated Pharmacy Practice Model Increased Patient Compliance With MS Therapies

- Since the inception of the collaborative model, the Medication Possession Ratio (MPR) for disease modifying therapies (DMTs) has increased and now exceeds the 90% goal



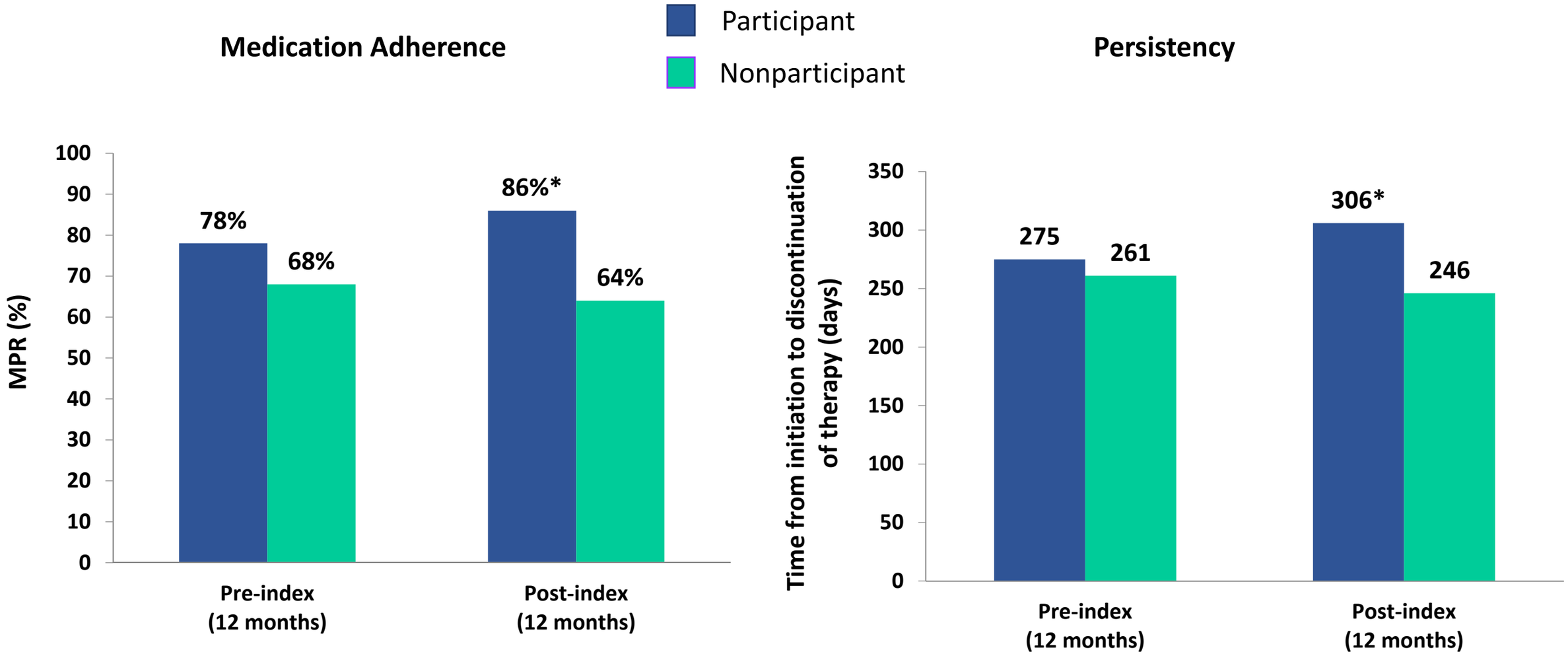
Hanson RL, Habibi M, Khamo N, Abdou S, Stubbings J. *Am J Health Syst Pharm*. 2014;71(6):463-9.

Impact of a Specialty Care Management Program on Adherence, Persistency, and Cost of Care

- Retrospective cohort analysis of MS patients ≥18 years (n=3993) using administrative claims data from the HealthCore Integrated Research Database
  - Patients had ≥2 claims for MS diagnosis and ≥1 MS medications
  - Time frame: January 2004-April 2008
- Interventions
  - Mailing of medication and disease-specific patient education directly to the patient
  - Assessment phone calls by nurses at the beginning and follow-up assessments at months 3, 6, and 12, and every 12 months thereafter to provide a liaison to the pharmacy, a source of medical information, adherence support, AE management, and refill reminders
- Outcomes assessed
  - Medication adherence and persistence
  - MS-related hospitalization
  - Total MS-related cost of care during the 12 months post-index period

Tan H, Yu J, Tabby D, Devries A, Singer J. *Mult Scler*. 2010;16(8):956-63.

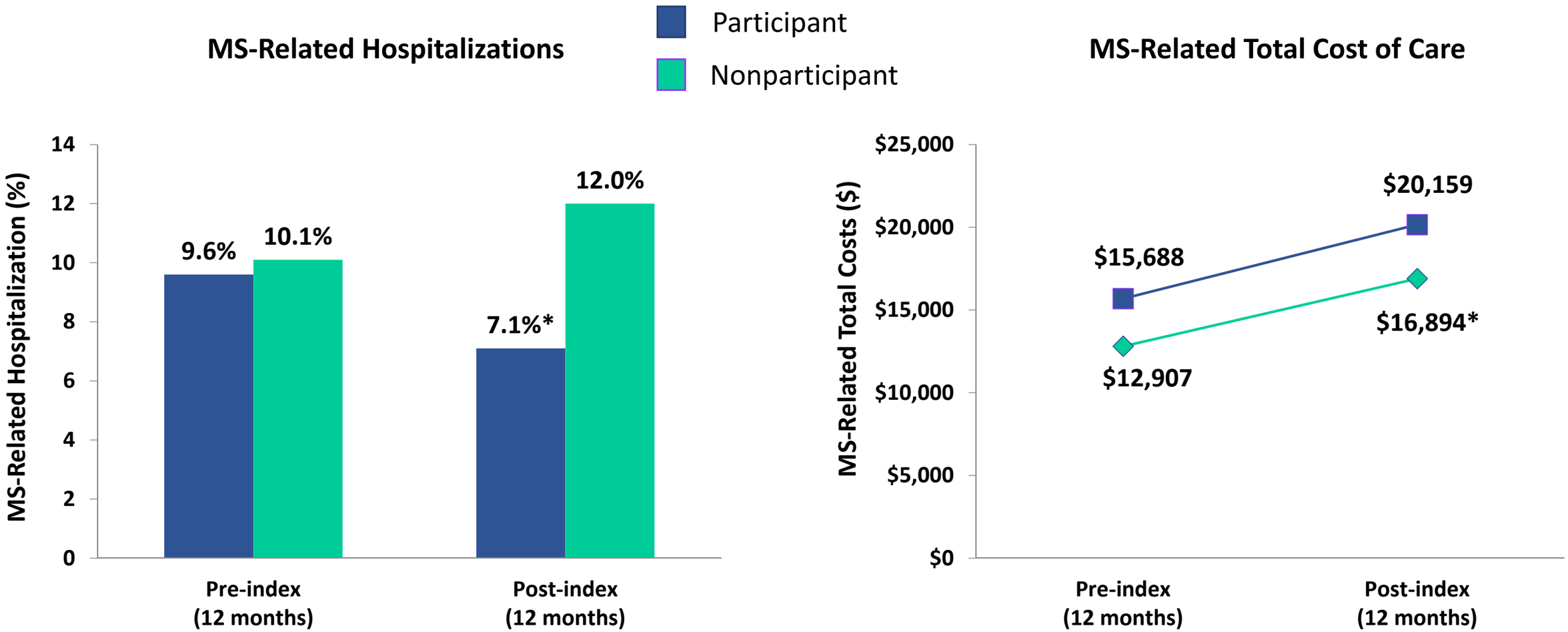
Participation in a Specialty Care Management Program Improved Adherence and Persistency



*P<0.001 vs nonparticipant

Tan H, Yu J, Tabby D, Devries A, Singer J. *Mult Scler*. 2010;16(8):956-63.

Participation in a Specialty Care Management Program Reduced Hospitalizations and MS-Related Costs



*$P<0.001$ vs nonparticipant

Tan H, Yu J, Tabby D, Devries A, Singer J. *Mult Scler*. 2010;16(8):956-63.

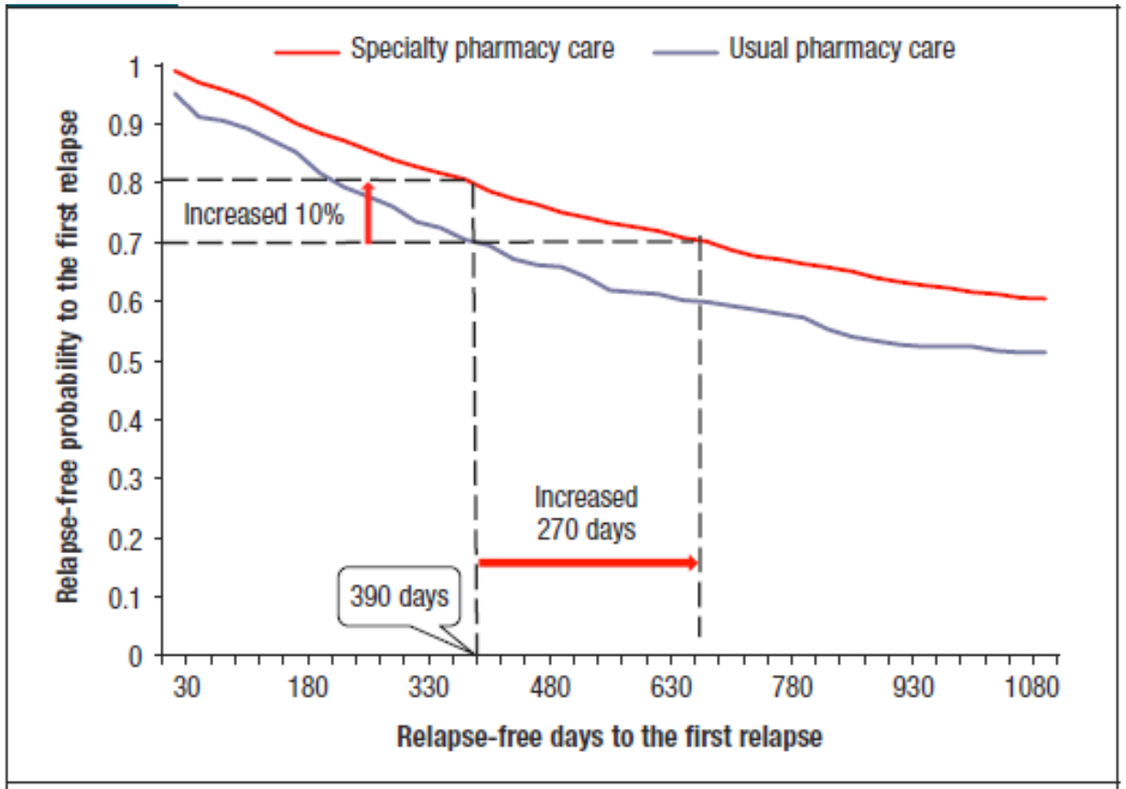
Impact of a Specialty Care Management Program on Health Outcomes

- Retrospective cohort analysis of MS patients ≥18 years (n=1731) using administrative claims data from an integrated database of pharmacy and medical claims of a major national pharmacy benefit management company
  - Conducted between 2006-2009
  - Enrollees with continuous medical and pharmacy benefits were followed for 3 years
- Outcomes assessed
  - MS relapse status was compared in patients who had specialty pharmacy care vs those with usual community pharmacy care including time to the first and second disease relapses and the number of relapses

Tang J, Bailey J, Chang C, et al. *Am Health Drug Benefits*. 2016;9(8):420-429.

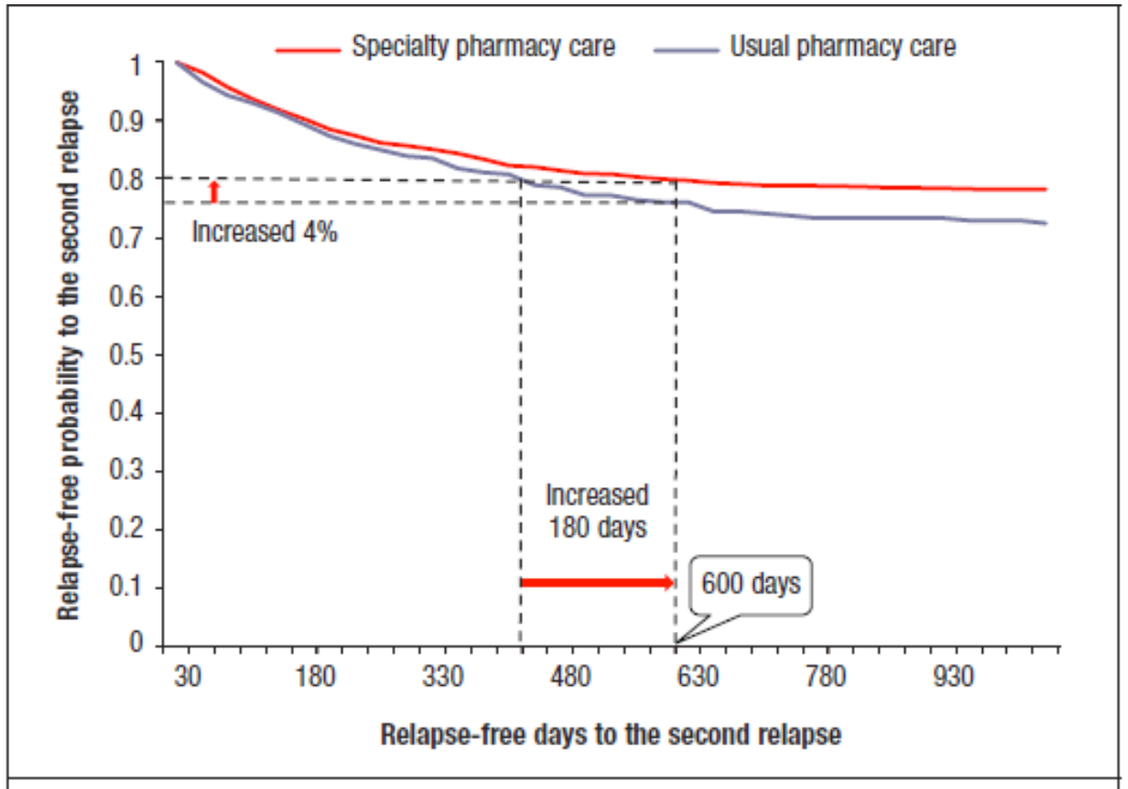
Specialty Pharmacy Care Was Associated with Lower Risk for Disease Relapse

Time to First MS-Relapse



P value of log-rank test = .001.

Time to Second MS Relapse



P value of log-rank test = .05.

Tang J, Bailey J, Chang C, et al. *Am Health Drug Benefits*. 2016;9(8):420-429.

Summary

- MS disease and symptom control as well as treatment of comorbid conditions requires lifelong care management
- MS patients benefit from care delivered by a coordinated multidisciplinary care team
- Effective symptom management involves medication, rehabilitation strategies, emotional support—and coordinated, multidisciplinary care
- Clinicians need to be aware of any comorbidities when prescribing MS medication due to the potential for unwanted interactions between therapies
- Specialty pharmacy care is associated with greater adherence, decreased risk for disease relapse, and lower cost of care
- The clinician-patient relationship is a crucial factor affecting adherence, especially as treatment continues over the long term

Case Studies: Multidisciplinary Care Coordination, Symptom Management; and Patient Counseling

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Learning Objectives

- Review MS symptom management strategies
- Review the impact of effective patient counseling interventions on MS treatment outcomes

Patient Case 1: Multidisciplinary Care

- **Patient:** 35-year old female seen in the Neurology Clinic
- **Imaging:** MRI scan revealed a multifocal white matter disease; areas of increased T2 signal in both cerebral hemispheres
- **Laboratory results**: Oligoclonal bands in CSF; visual evoked response testing was abnormal with slowed conduction in optic nerves
- **Diagnosis:** Multiple sclerosis
- **Family history:** Mother died following a diagnosis of breast cancer; father had an MI at 59
- **Comorbidities:** Diabetes (controlled on medication)
- **Current complaints**: Stumbling gait, diminishing visual acuity, tremors, fatigue, tendency to aspirate liquids and also solids, continuous tinnitus, decreased finger dexterity, bilateral weakness of the hands, impaired short-term memory and irritability

Patient Case 1: Discussion

- How would you approach the care of this patient?
- In addition to MS care from a neurologist, what other medical providers might help this patient manage her MS?
- Where should this patient turn to help manage her diabetes and address her family history of cardiac disease and malignancy?

Patient Case 2: Symptom Management

- **Patient:** 51-year old male diagnosed with MS in 2003
  - Treated with a DMT since diagnosis
  - No relapses in the last 4 years
  - Recent MRI indicates no new activity or active lesions
- **Current complaints**: increasing fatigue, heat sensitivity, ambulation problems, spasticity, cognitive impairment, and mood changes

Patient Case 2: Discussion

- How would you approach the management of this patient's symptoms?
  - What are his short- and long-term symptom management goals?
  - Where would you find the resources necessary to effectively manage his symptoms and improve his quality of life?

Patient Case 3: Patient Counseling

- **Patient:** 40-year-old female diagnosed 7 years ago after experiencing numbness in her legs and an MRI revealed characteristic brain lesions of demyelinating disease
- **Current treatment**: DMT; struggles with adherence
- **Social history**: single mother of 2 boys
- **Current complaint**: MS now affects every aspect of her life and she worries she may no longer be able to work and support her kids

Patient Case 3: Discussion

- What are your biggest concerns with this patient?
- What steps would you take to help improve the overall care of this patient?
- Where can this patient find the support she needs to develop additional self-management skills?