Rethinking Routines in Multiple Sclerosis Management:

What the Future Holds for DMTs and Cognitive Assessment Strategies

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Learning Objective 1

Apply clinical data on efficacy and safety of recently approved therapies to individualized treatment decisions for patients with MS.

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Learning Objective 2

Incorporate cognitive assessment into routine monitoring for patients with MS.

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Learning Objective 3

Evaluate emerging data on the effects of MS therapies on cognition.

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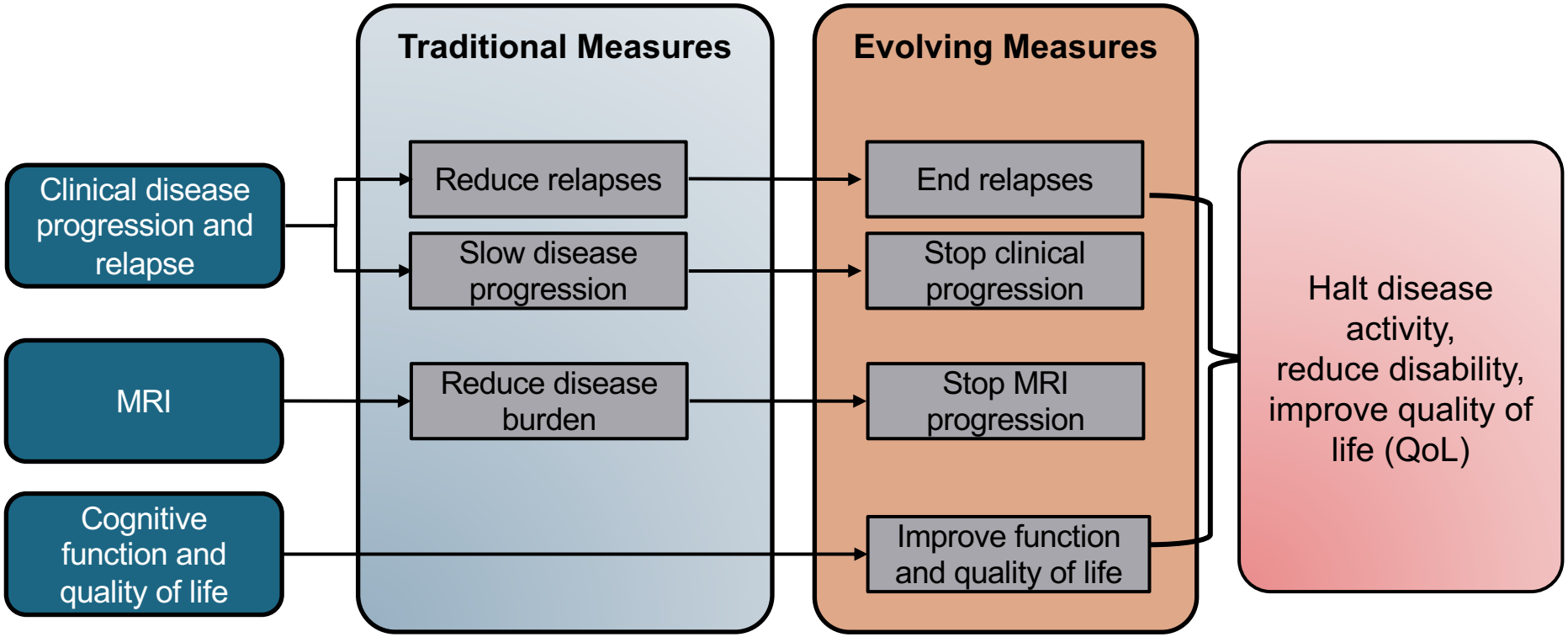
Treatment Goals in MS



Smith AL, et al. *Neurotherapeutics.* 2017;14:952-960. Rotstein DL, et al. *JAMA Neurol.* 2015;72(2):152-158. Lazibat I, et al. *Acta Clin Croat.* 2016;55(1):125-133.

Predictors of Poor Prognosis in MS

Demographic and Environmental Factors

- Older age at onset
- Male sex
- Not of European descent
- Low vitamin D levels
- Smoking (recently questioned)
- Comorbid conditions

Clinical Factors

- Primary progressive disease subtype
- High relapse rate
- Shorter interval between the 1st and 2nd relapses
- Brainstem, cerebellar, or spinal cord onset
- Poor recovery from the first relapse
- Higher EDSS score at diagnosis
- Polysymptomatic onset
- Early cognitive deficits

MRI Observations

- High number of T2 lesions
- High T2 lesion volume
- Presence of Gd-enhancing lesions
- Presence of infratentorial lesions
- Presence of spinal cord lesions
- Whole brain atrophy
- Grey matter atrophy

Biomarkers

- High number of T2 lesions
- Presence of IgG and IgM oligoclonal bands in CSF
- High serum or CSF levels of neurofilament light chain
  High levels of chitinase in the CSF
- Retinal nerve fiber layer thinning detected with OCT

CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; IgG = immunoglobulin G; IgM = immunoglobulin M; MRI = magnetic resonance imaging; OCT = optic coherence tomography

Rotstein D, Montalban X. *Nat Rev Neurol*. 2019;15(5):287-300.

MS Treatment Landscape Continues to Expand

1993 IFN-β-1b

1996 glatiramer acetate

2002 IFN-β-1a sc

2012 teriflunomide

2014 pegIFN-β-1a

2015 glatiramer acetate (generic)

2019 cladribine

2019 siponimod

2020 ofatumumab

Injectables

Infusions

Orals

1996 IFN-β-1a IM

2000 mitoxantrone

2004 natalizumab

2010 fingolimod

2013 dimethyl fumarate

2014 alemtuzumab

2017 ocrelizumab

2019 diroximel fumarate

2020 ozanimod

Thompson AJ, et al. *Lancet.* 2018;391(10130):1622-1636. Pinion K, Crispino A. The Evolving Landscape in the Management & Treatment of Multiple Sclerosis: Payer Considerations for Providing Support to People with MS and Their Care Partners. MSAA. 2020. https://mymsaa.org/PDFs/evolving_landscape.pdf.

Disease Modifying Medications: Categories

Immunomodulators

Interferon-beta
Glatiramer Acetate
Dimethyl Fumarate
Diroximel Fumarate
Teriflunomide

Pros
- Safety
- Long term experience

Cons
- Modest efficacy
- Many injectable

Cell-Trafficking Inhibition Agents

Natalizumab
Fingolimod
Siponimod
Ozanimod

Pros
- Greater efficacy
- Onset of action quick
- Well tolerated

Cons
- Opportunistic infections (PML)
- Cells still in body
- Rebound disease
- Long term safety unclear

Cell-Depleting Therapies

Alemtuzumab
Cladribine
Ocrelizumab
Rituximab*
Ofatumumab
AHSCT (BMT)

Pros
- Definitive in depleting disease-causing cells
- Some are IRT
- No rebound disease

Cons
- Opportunistic infections
- Secondary autoimmunity (alemtuzumab)
- Most cumbersome

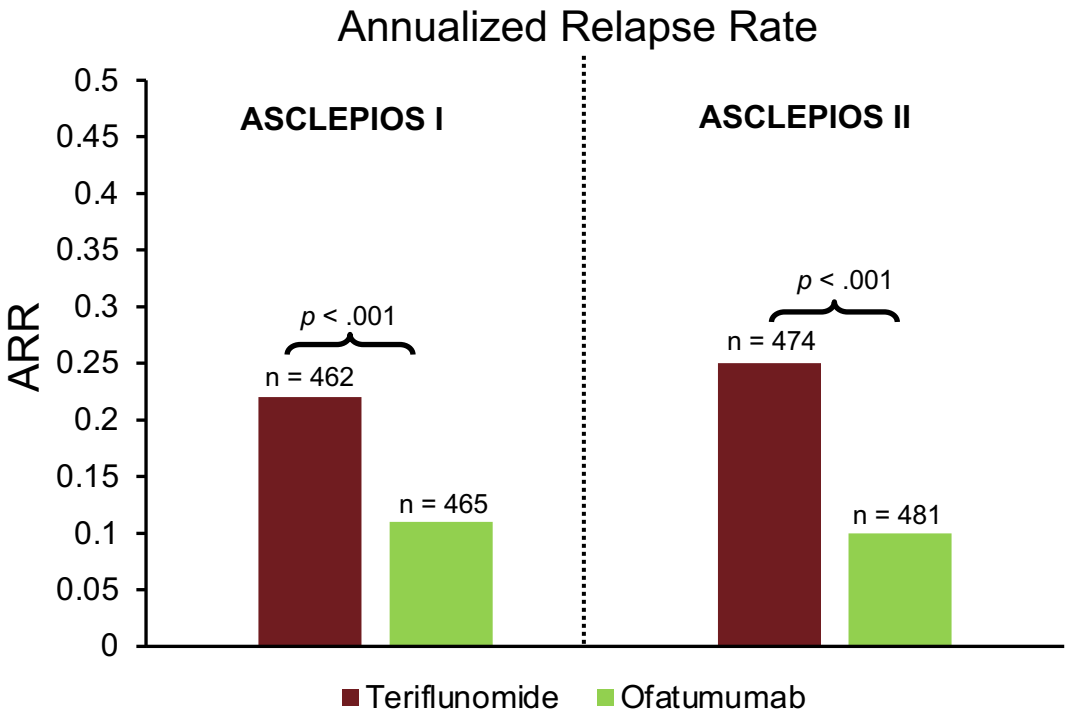
* Not approved by the FDA for treatment of MS

AHSCT = autologous hematopoietic stem cell transplantation; BMT = bone marrow transplant; IRT = immune reconstitution therapy; PML = progressive multifocal leukoencephalopathy

Rizvi SA, et al. *Clinical Neuroimmunology*. 2nd ed. 2020.

Ofatumumab Efficacy and Safety

- ASCLEPIOS I and II
  - N = 927, N = 954, respectively
- 97% and 93% reduction in Gd+ lesions in ofatumumab group vs. teriflunomide
- 51% and 59% reduction in ARR in ofatumumab group compared to teriflunomide
- Demonstrated safety and tolerability profile with infection rates similar to teriflunomide

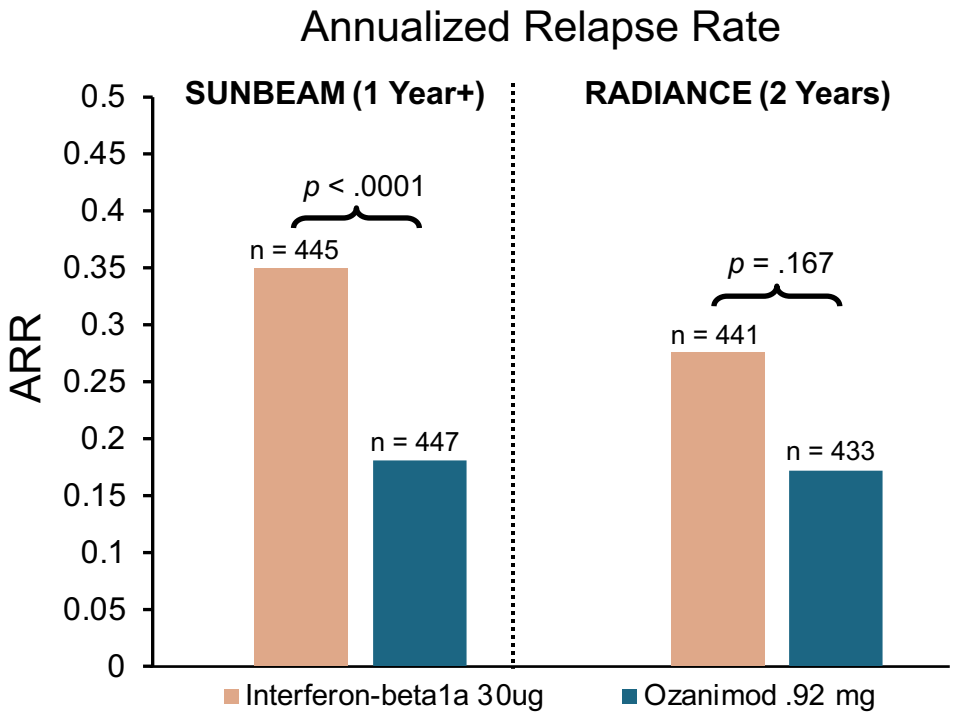


FDA-approved in August 2020 for the treatment of relapsing forms of MS in adults.

Hauser SL, et al. *N Engl J Med*. 2020;383(6):546-557.

Ozanimod Efficacy and Safety

- SUNBEAM and RADIANCE trials
  - N = 1346, N = 1313, respectively[1,2]
- 63% and 53% reduction in Gd+ lesions in ozanimod group versus interferon-beta 1a[1,2]
- 48% and 38% reduction in ARR in patients receiving ozanimod vs. interferon-beta 1a[1,2]
- No clinically significant cardiac adverse effects, lymphopenia and macular edema in patients receiving ozanimod[1,2]



FDA-approved in March 2020 for the treatment of relapsing forms of MS in adults.

1. Cohen JA, et al. *Lancet Neurol.* 2019;18(11):1021-1033. 2. Comi G, et al. *Lancet Neurol.* 2019;18(11):1009-1020.

Individualizing Treatment Decisions for Patients with MS to Optimize Adherence and Outcomes

Disease Activity

- Inactive
- Active
- Highly active
- Rapidly evolving
- Severe

Drug-related Issues

- Tolerability
- Safety profile
  - Immunosuppression
  - PML risk
- Monitoring frequency
- Drug effects
  - Drug-drug interactions

Patient Profile

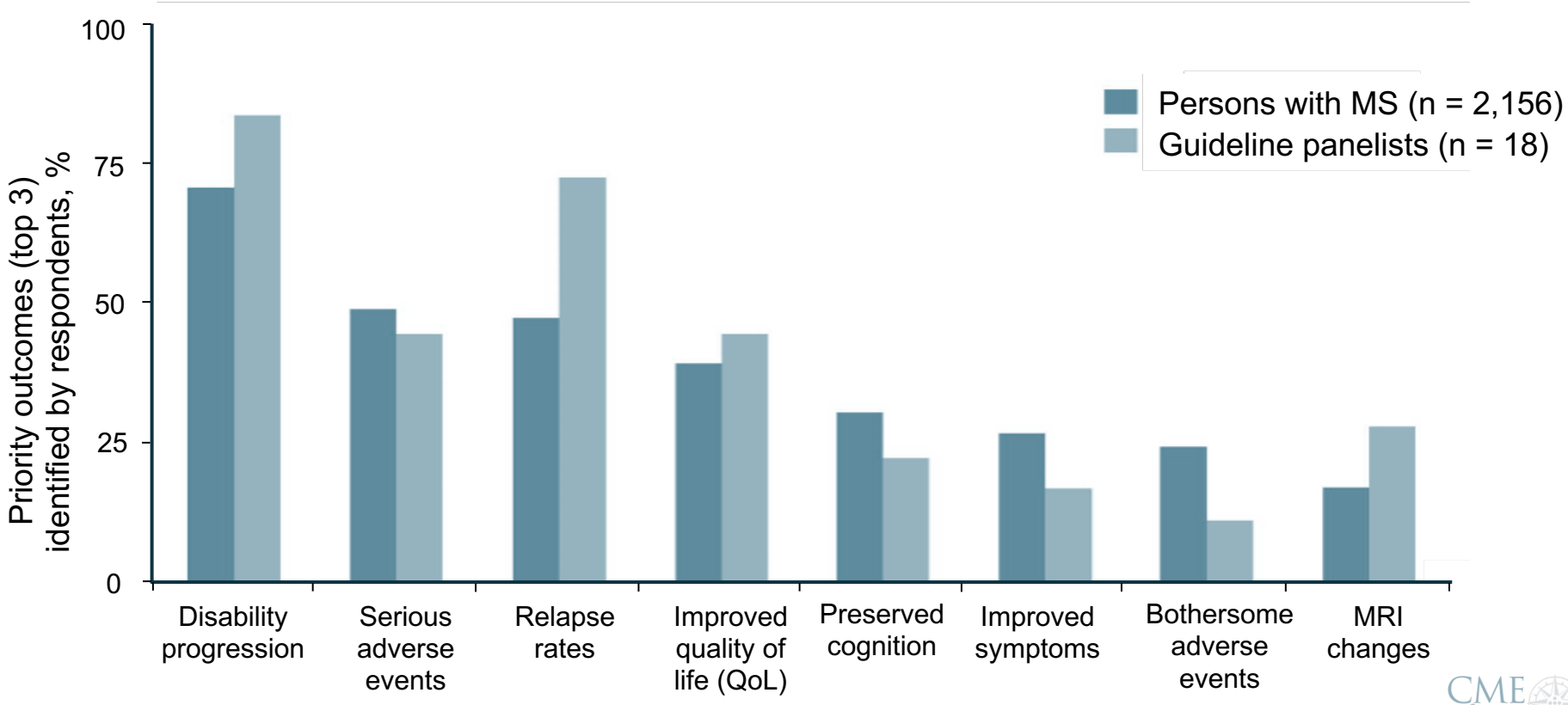
- Adherence
- Comorbidities
- Personal factors
  - Pregnancy
  - Travel
  - Work
  - Treatment expectations

Shared Decision Making

PML = progressive multifocal leukoencephalopathy

Wingerchuk DM, Weinshenker BG. *BMJ.* 2016;354:i3518. Colligan E, et al. *Mult Scler.* 2017;23(2):185-190.

Identifying Priority Outcomes that Influence DMT Selection In MS



Day GS, et al. *Neurol Clin Pract.* 2018;8(3):179-185.

Treatment Initiation Choices

Induction (Higher Risk)

- Start with a higher efficacy agent
  - Obtain a treatment response for a given period
- Monitor for safety

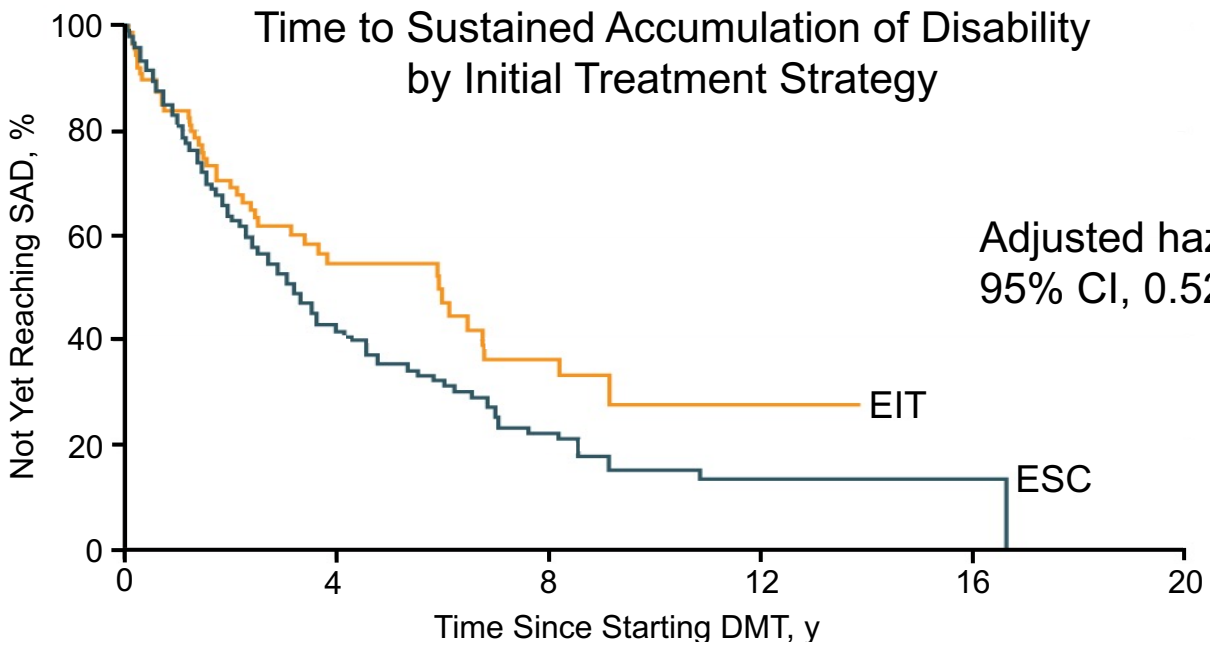
vs.

Escalation (Lower Risk)

- Start with a 1st line agent (“platform therapy”)
- Monitor treatment response
- If sub-optimal response, move to a higher efficacy agent
- Monitor treatment response

Lazibat I, et al. *Coll Antropol*. 2014;38(1):385-393.

Early Intensive vs Escalation Treatment Leads to Improved Long-term Outcomes



Adjusted hazard ratio, 0.74;
95% CI, 0.52-1.06; *P* = .10.

No. at risk

ESC	316	75	21	6	1
EIT	89	29	12	1	0

EIT = early intensive treatment; ESC = escalation approach; SAD = sustained accumulation of disability

Harding K, et al. *JAMA Neurol.* 2019;76(5):536-541. Merkel B, et al. *Autoimmun Rev*. 2017;16(6):658-665.

Learning Objective 2

Incorporate cognitive assessment into routine monitoring for patients with MS.

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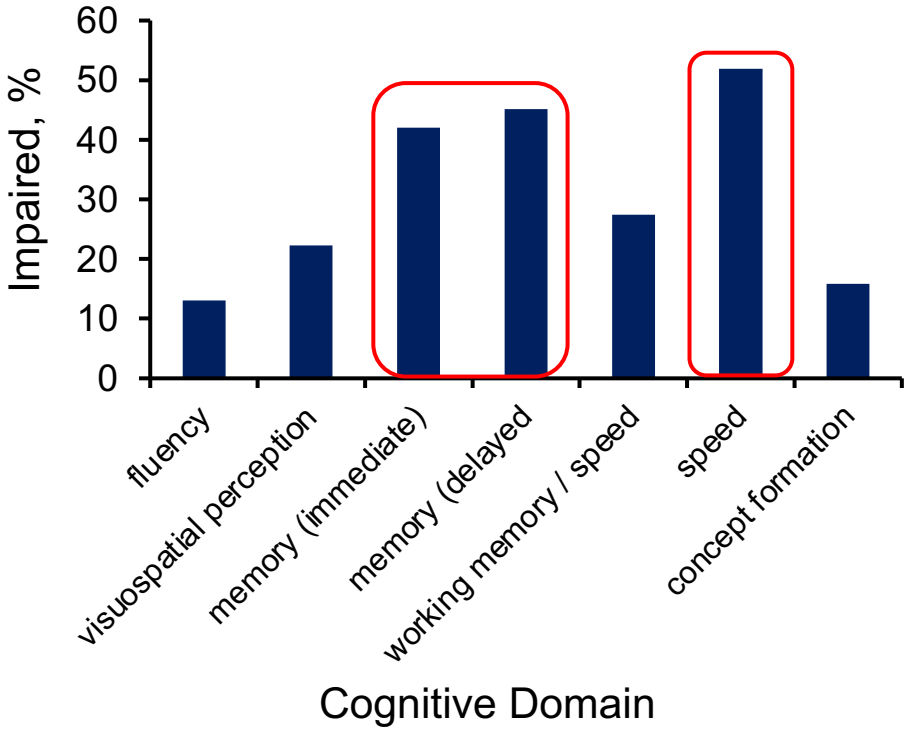
Cognitive Problems and Everyday Life Functioning

- Cognitive deficits in MS have been shown to negatively affect daily life including:
  - Employment
  - Driving
  - Social and vocational activities
  - Household activities
  - Sexual functioning
  - Family activities
  - Overall QoL
  - Increased psychiatric illness
- Beyond physical disability alone

Rao SM, et al. *Neurology.* 1991;41(5):685-691. Schultheis MT, et al. *Neurology.* 2001;56(8):1089-1094.

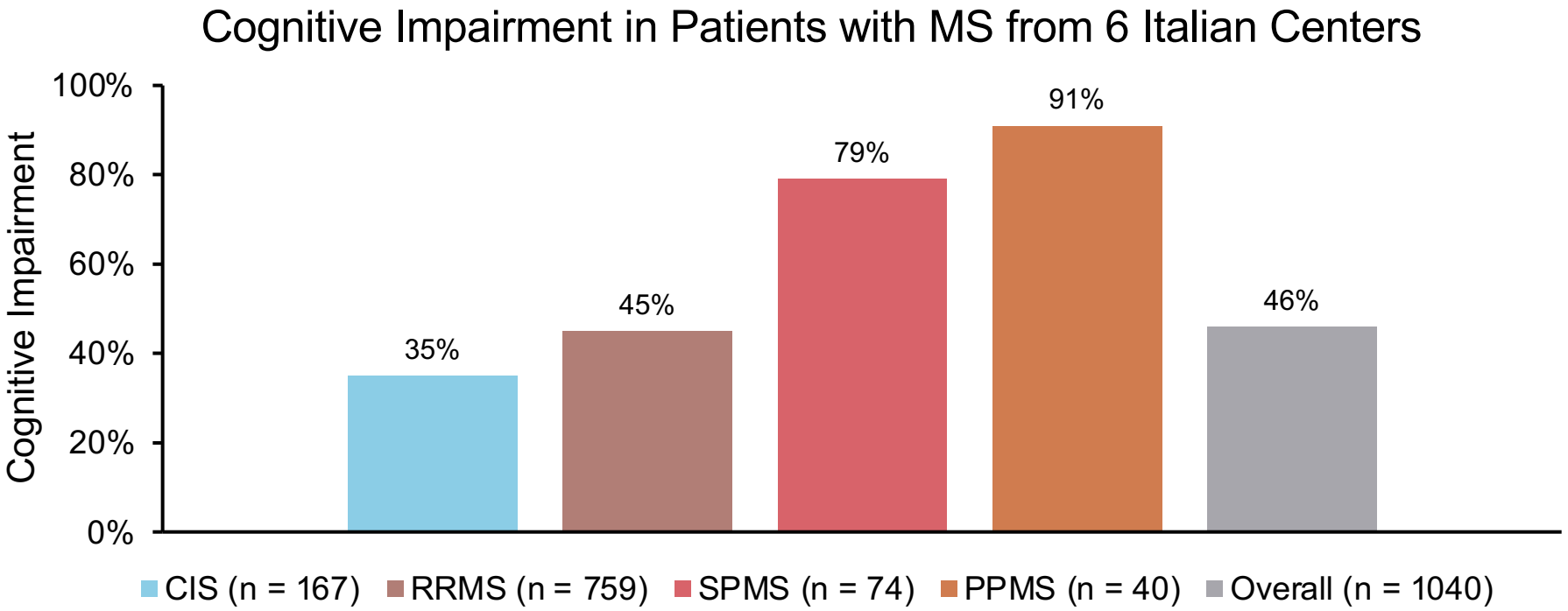
Cognitive Impairment (CI) in MS

- Information processing speed/ efficiency
- Learning and Memory
  - Acquisition vs. retrieval
- Executive functions
  - Planning, organization, initiation
- Perceptual processing



Chiaravalloti ND, DeLuca J. *Lancet Neurol*. 2008;7(12):1139-1151.

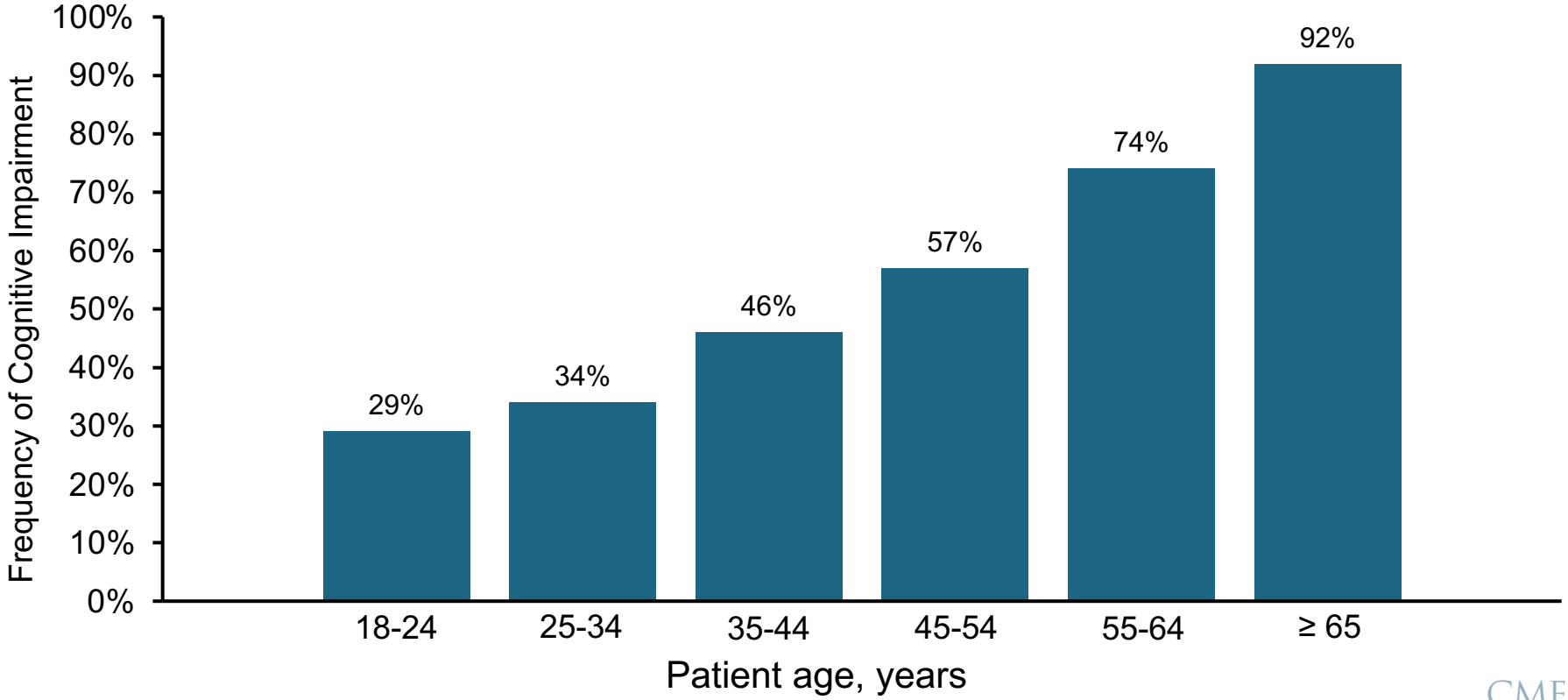
Cognitive Impairment Frequency Varies According to MS Subtype



CIS = clinically isolated syndrome; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Ruano L, et al. *Mult Scler.* 2017;23(9):1258-1267. Potages C, et al. *J Neurol Sci.* 2008;267(1-2):100-106.

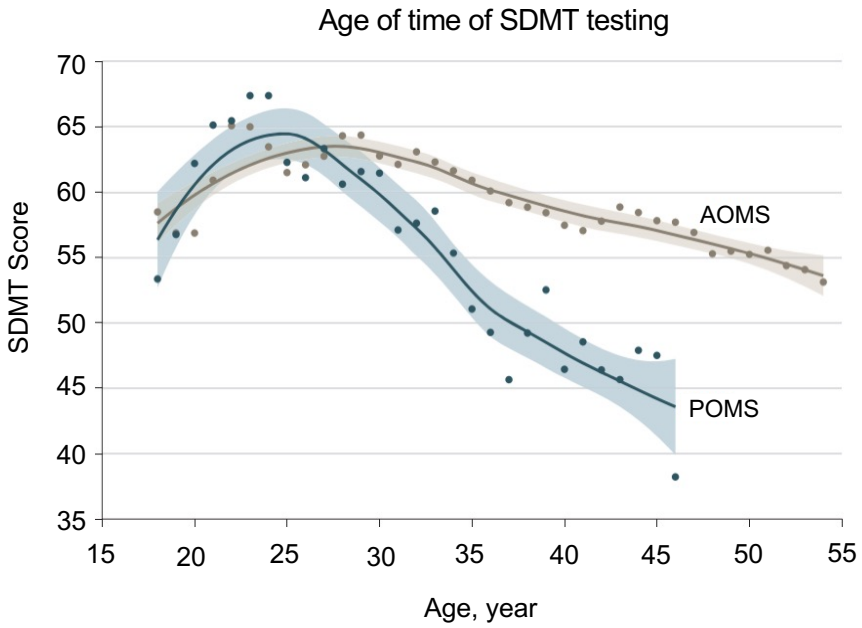
Frequency of Cognitive Impairment in MS by Age

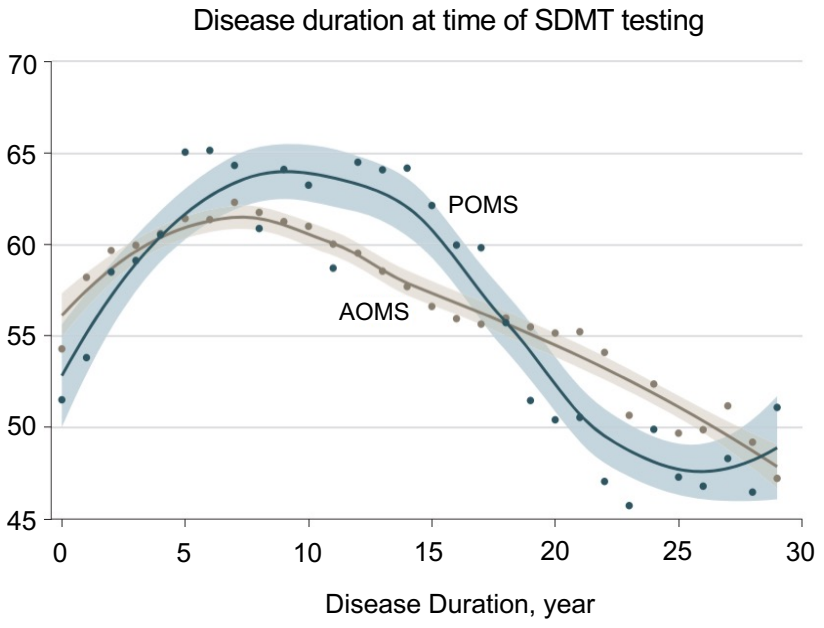


Branco M, et al. *Neurol Sci.* 2019;40(8):1651-1657.

Cognitive Processing Speed Over Time in Pediatric- and Adult-Onset MS

Mean Symbol Digit Modalities Test (SDMT) Scores for Patients with Pediatric-Onset (POMS) and Adult-Onset (AOMS) Multiple Sclerosis





McKay KA, et al. *JAMA Neurol.* 2019;76(9):1028-1034.

Baseline CI Predicts Clinical and Cognitive Deterioration

- 42 MS patients and 30 HC underwent MRI and NP evaluation at 1, 2 and 6 years
- 62.2% deteriorated over 6 years: mostly PS and memory
- # impaired domains at baseline was the strongest predictor of 6 year deterioration
- Baseline thalamic volume was associated with cognitive deterioration
- Striatal atrophy during the 6-year period associated with cognitive decline

Emphasizes the importance of cognitive assessment at time of diagnosis and follow-up

Percentage of RRMS patients with impairment per cognitive domain at each study time point

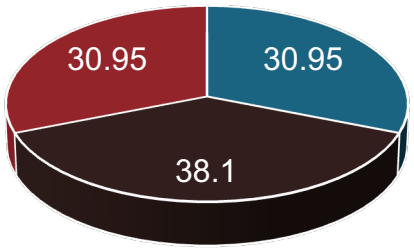
		Baseline	2 years	6 years
Cognitive domain: % (z score)	Verbal memory	19.0 (0.03)	45.0 (–0.59)	59.5 (–1.15)
	Visual memory	47.6 (–0.90)	55.0 (–1.55)	64.9 (–1.13)
	Information processing speed	31.0 (–0.88)	27.5 (–0.68)	64.9 (–1.50)
	Verbal fluency	7.1 (–0.14)	5.0 (–0.06)	2.7 (–0.05)
FSS index		3.55 ± 1.70	3.35 ± 1.71	3.75 ± 1.66
Zung Depression Score		36.29 ± 8.61	34.20 ± 8.55	35.60 ± 8.62

FSS = Functional Systems Score; HC = healthy control; NP = neuropsychological; PS = processing speed

Damasceno A, et al. *Mult Scler.* 2020;26(13):1740-1751.

Cognitive Trajectories in MS Patients According to Baseline CI

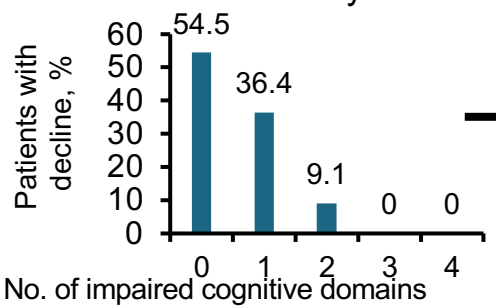
Cognitive impairment at baseline (%, of patients)

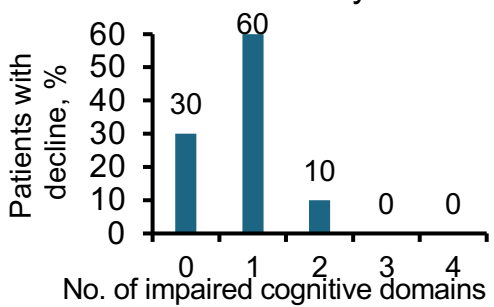


After two years

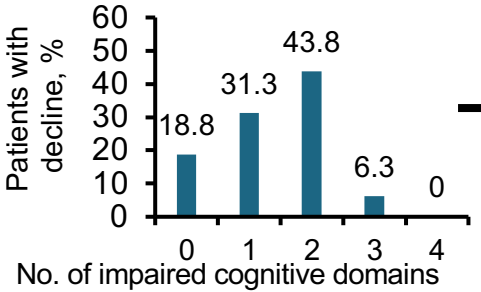
After six years

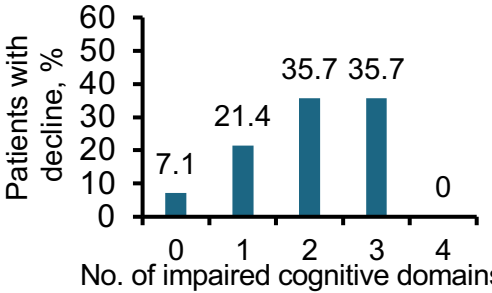
- Not impaired



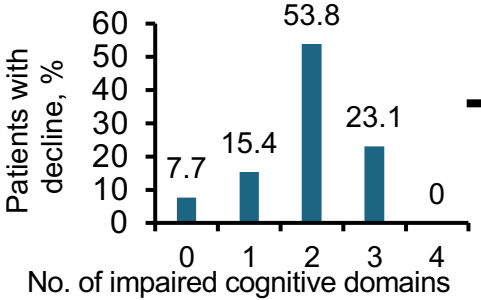


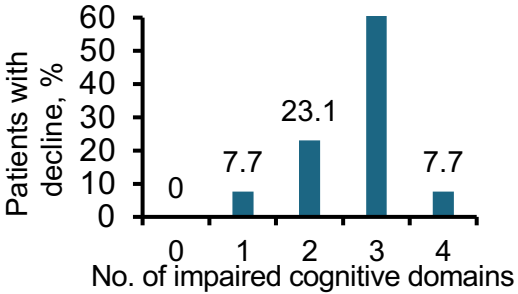
- Isolated domains





- Combined domains





Damasceno A, et al. *Mult Scler.* 2020;26(13):1740-1751.

Cognitive Screening Tools Validated in MS Populations

- The Symbol Digit Modalities Test (SDMT; 5 min)
- Brief International Cognitive Assessment for MS (BICAMS; 15 min)
  - SDMT
  - CVLT: verbal learning / verbal memory
  - BVMT-R: visual learning / visual memory
- Processing Speed Test (PST; 5 min)
- Computerized Speed Cognitive Test (CSCT; 5 min)
- Minimal Assessment of Cognitive Function in MS (MACFIMS; 90 min)

CVLT = California Verbal Learning Test – Second Edition; BVMT-R = Brief Visuospatial Memory Test – Revised

Kalb R, et al. *Mult Scler.* 2018;24(13):1665-1680. Langdon DW, et al. *Mult Scler.* 2012;18(6):891-898.

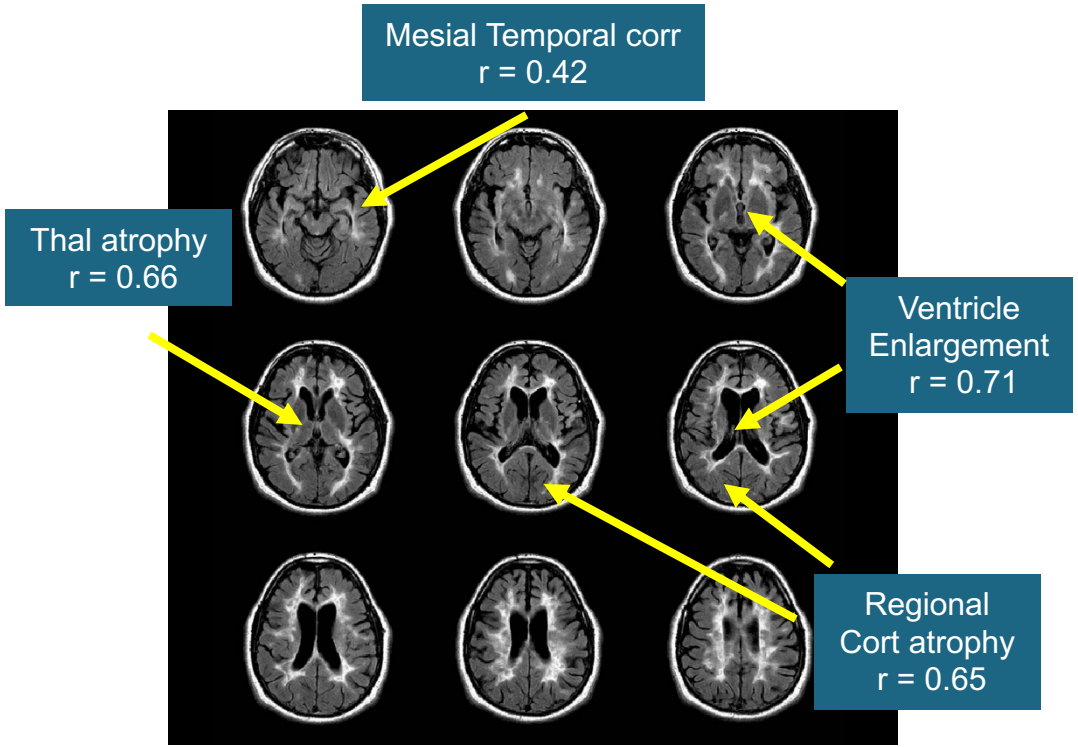
Recommendations for Cognitive Screening in MS Care

The National MS Society, Consortium of MS Centers, and International MS Cognition Society Recommend:

- For adults and children (8+ years of age) with MS, when stable:
  - As a minimum, early baseline screening with the Symbol Digit Modalities Test (SDMT) or similarly validated test
  - Annual re-assessment with the same instrument, or more often as needed
- For adults (18+ years): more comprehensive assessment for anyone who tests positive on initial cognitive screening or is experiencing consequences from significant cognitive decline
- For children (< 18 years): more comprehensive assessment for unexplained change in school functioning (academic or behavioral)

Kalb R, et al. *Mult Scler.* 2018;24(13):1665-1680.

SDMT Performance Correlates with Multiple Brain Regions



Courtesy of Ralph Benedict, PhD.

Nonpharmacologic Treatment Options for CI in MS

- Aerobic training
- “Mind Diet” (slows cognitive decline in the elderly)
- Cognitive exercises
- Neuropsychological rehabilitation
- Computer-based training programs
- Remedial interventions/accommodations for adults and children to improve functioning at home, work, or school

Kalb R, et al. *Mult Scler.* 2018;24(13):1665-1680. Miller E, et al. *Curr Neuropharmacol.* 2018;16(4):475-483.

Adaptive Cognitive Remediation Can Improve Cognitive Functioning in MS

RESEARCH ARTICLE

Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial

Leight E. Charvet[1], Jie Yang[2], Michael T. Shaw[1], Kathleen Sherman[1], Lamia Haider[3], Jianjin Xu[4], Lauren B. Krupp[1]

1 Department of Neurology, NYU School of Medicine, New York, New York, United States of America, **2** Department of Family, Population, and Preventive Medicine, Stony Brook Medicine, New York, New York, United States of America, **3** Taub Institute, Columbia University Medical Center, New York, New York, United States of America, **4** Department of Applied Mathematics and Statistics, Stony Brook Medicine, Stony Brook, New York, United States of America

Charvet LE, et al. *PLoS One.* 2017;12(5):e0177177.

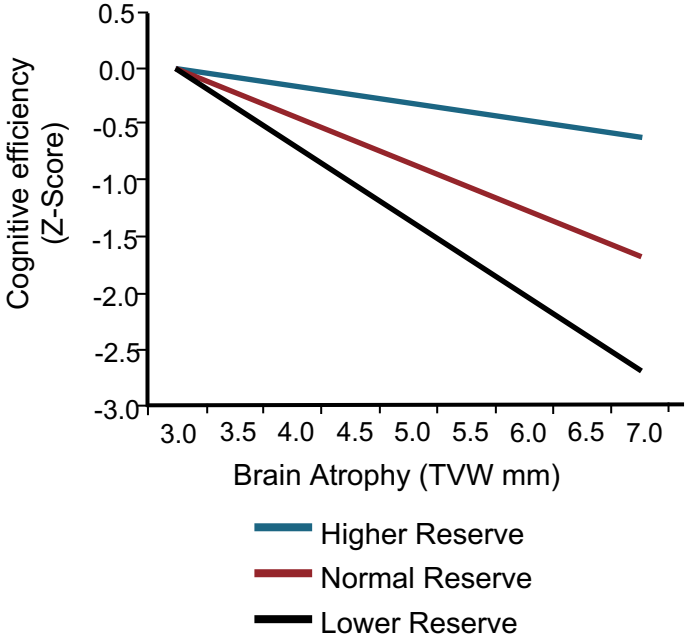
Systematic Review of Cognitive Rehabilitation Treatments in MS

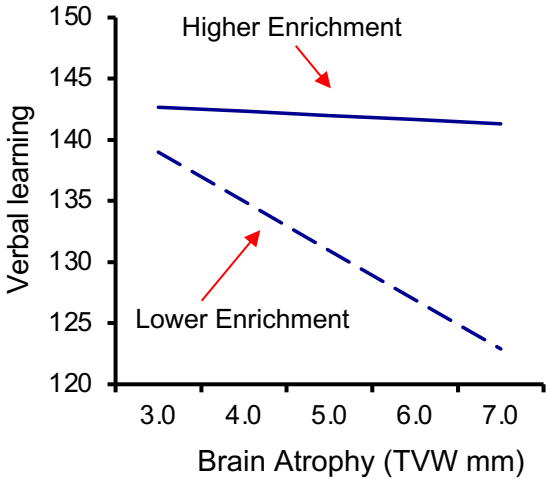
- Classified studies on level of evidence based on AAN criteria for therapy trials
- Yielded **40** studies (2007-2016) in contrast with **16** studies (ALL prior years)

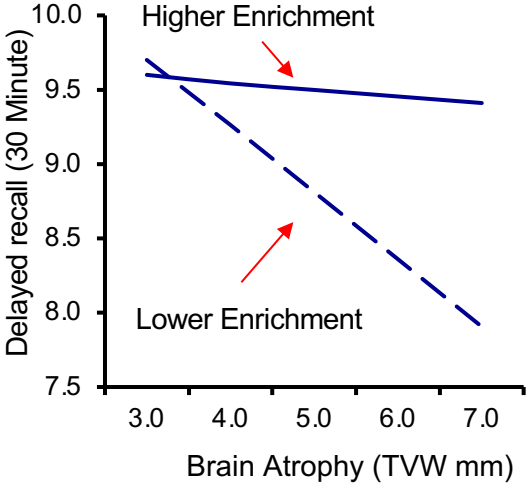
Recommendations Based on Evidence			
Cognitive domain	**Practice Standards**	**Practice Guidelines**	**Practice Options**
Attention	ND	• Attention Process Training (APT)	• RehaCom
Learning and memory	• modified Story Memory Technique (mSMT)	ND	• Music • Self-generation • Spaced trials • Visual imagery
Working memory and PS	ND	None	ND
Executive function	ND	None	ND
Metacognition	ND	None	ND
Nonspecific/multicognitive domains	ND	• RehaCom	ND

AAN =American Academy of Neurology; ND = no data
Goverover Y, et al. *Arch Phys Med Rehabil.* 2018;99(2):390-407.

Cognitive Reserve in MS





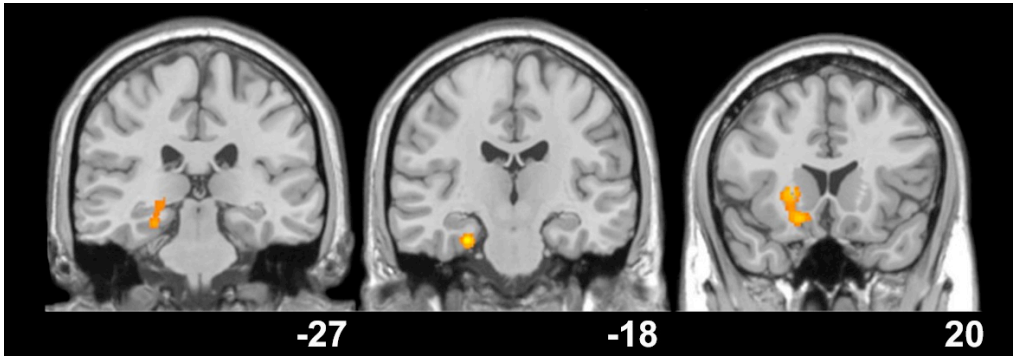


TVW = third ventricle width

Sumowski JF, et al. *J Clin Exp Neuropsychol.* 2009;31(8):913-926. Sumowski JF, et al. *J Int Neuropsychol Soc.* 2009;15(4):606-612.

Cognitive Interventions can Increase Gray Matter Volume

- In patients with RRMS (n = 11) and HC (n = 12) enrolled in an 8-week second language learning program:
  - Gray matter volume (GMV) significantly increased in language-related brain regions
  - GMV increases in right hippocampus and parahippocampus significantly correlated with vocabulary knowledge gain and improvements in HRQoL



HRQoL = health-related quality of life

Ehling R, et al. *PLoS One.* 2019;14(12):e0226525.

Learning Objective 3

Evaluate emerging data on the effects of MS therapies on cognition.

CME Outfitters

Systematic Reviews of Pharmacologic Treatment for CI in MS

Pharmacological treatment for memory disorder in multiple sclerosis (Review)

He D, Zhang Y, Dong S, Wang D, Gao X, Zhou H

Cochrane Library

Cochrane Database of Systematic Reviews

"We found no convincing evidence to support the efficacy of pharmacological symptomatic treatment for MS-associated memory disorder … "

REVIEW ARTICLE

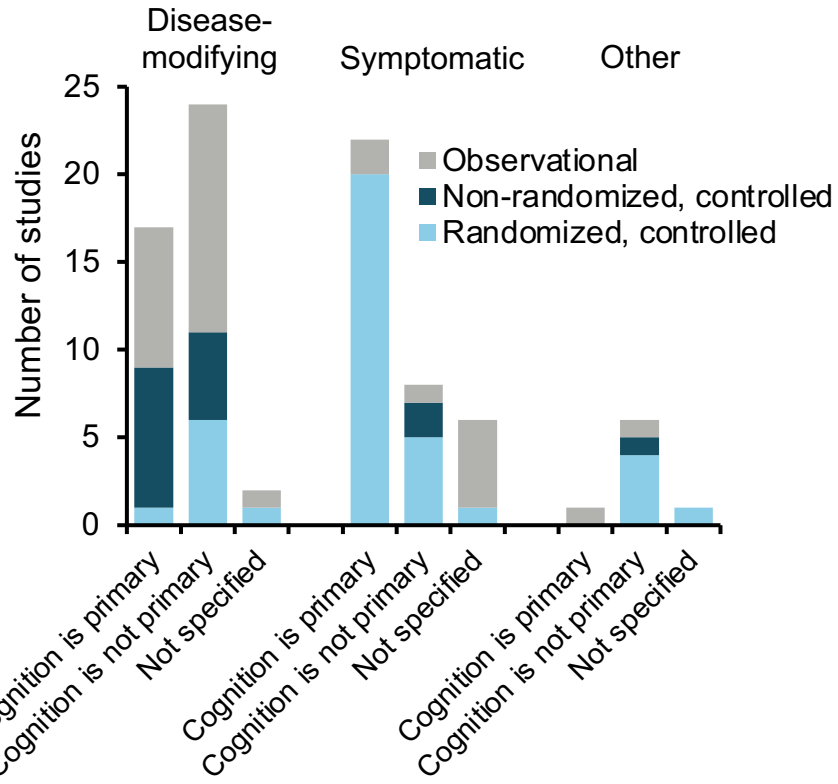
Pharmacological and non-pharmacological therapies of cognitive impairment in multiple sclerosis

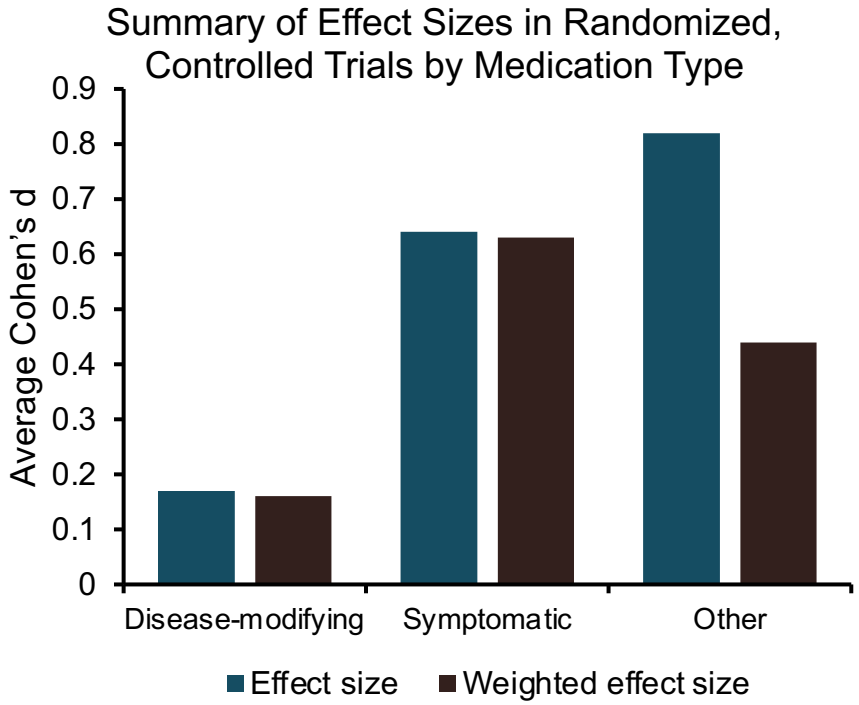
Miller E, Morel A, Redlicka J, Miller I, Saluk J

"While pharmacological therapies for reducing disease activity in MS significantly expanded … no effective treatment has been established in the case of cognitive problems"

He D, et al. *Cochrane Database Syst Rev.* 2013;(12):CD008876. Miller E, et al. *Curr Neuropharmacol.* 2018;16(4):475-483.

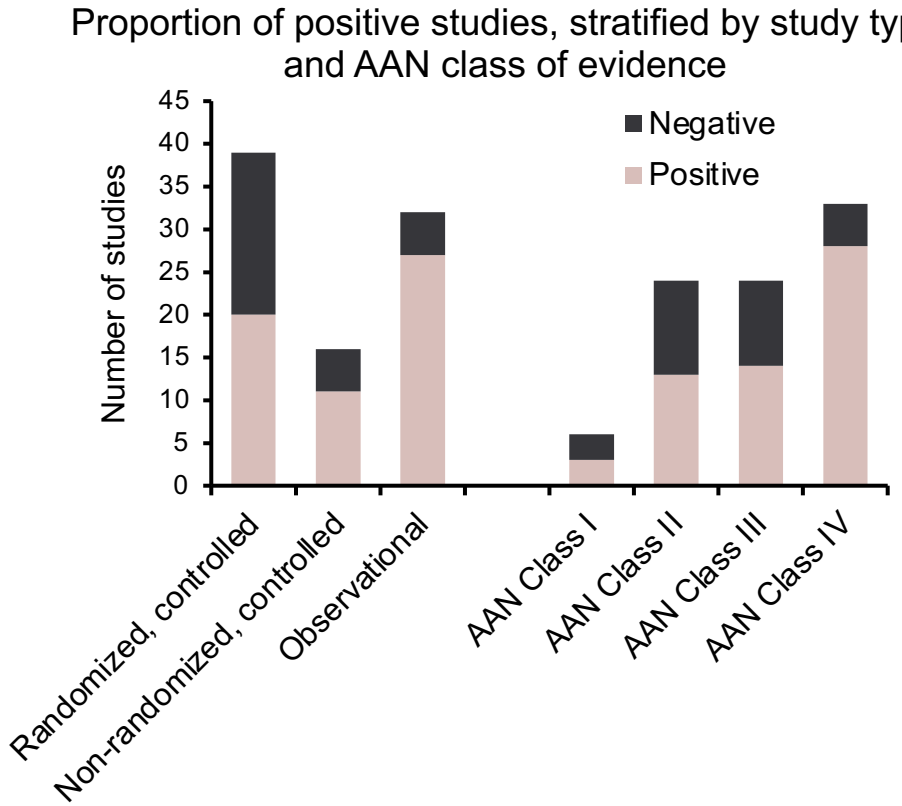
Systematic Review of Cognitive Efficacy of Pharmacologic Treatments in MS





Chen MH, et al. *CNS Drugs.* 2020;34(6):599-628.

Proportion of Positive Studies Increased as Quality of Evidence Decreased

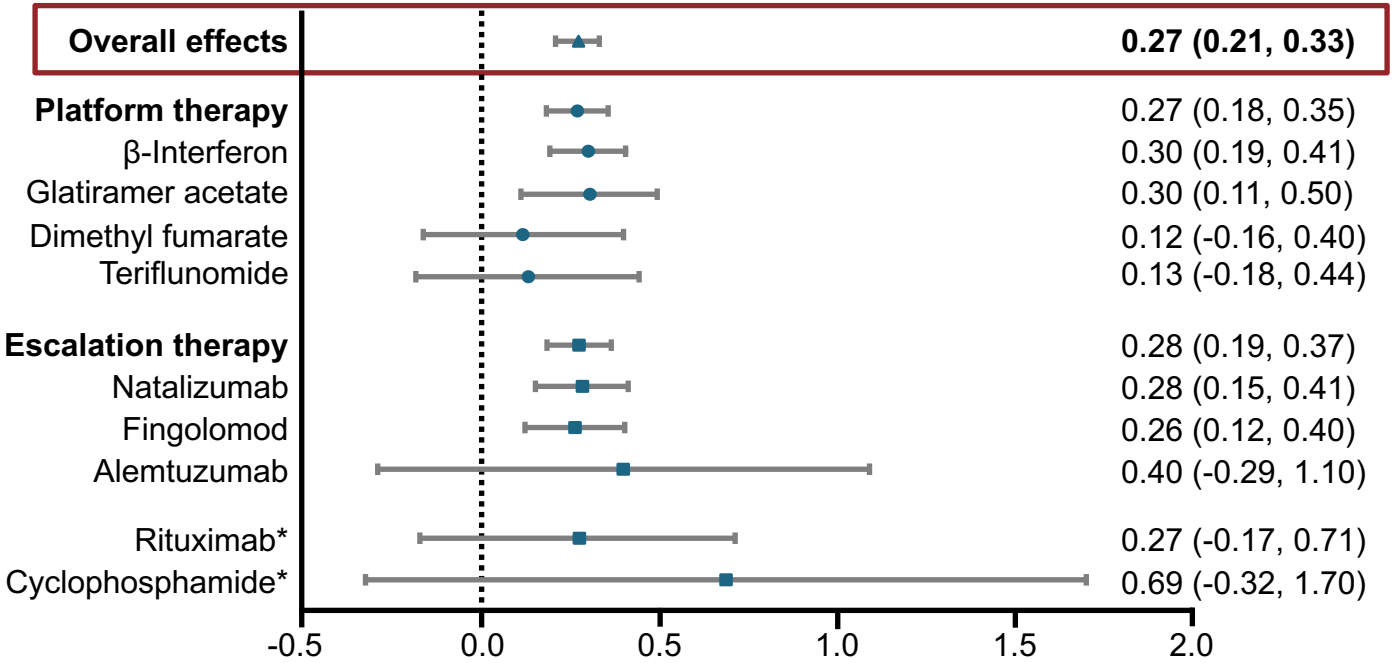


- Over-reliance on *p*-values crossing the arbitrary 0.05 threshold is one reason for the reproducibility crisis
- Statisticians recommend using *effect sizes* and *confidence intervals* around the effect sizes to denote significance of a result

Chen MH, et al. *CNS Drugs.* 2020;34(6):599-628.

Meta-analysis of Disease Modifying Therapies and Cognition in RRMS

Mean effect sizes of longitudinal improvement of cognitive processing speed under different DMTs

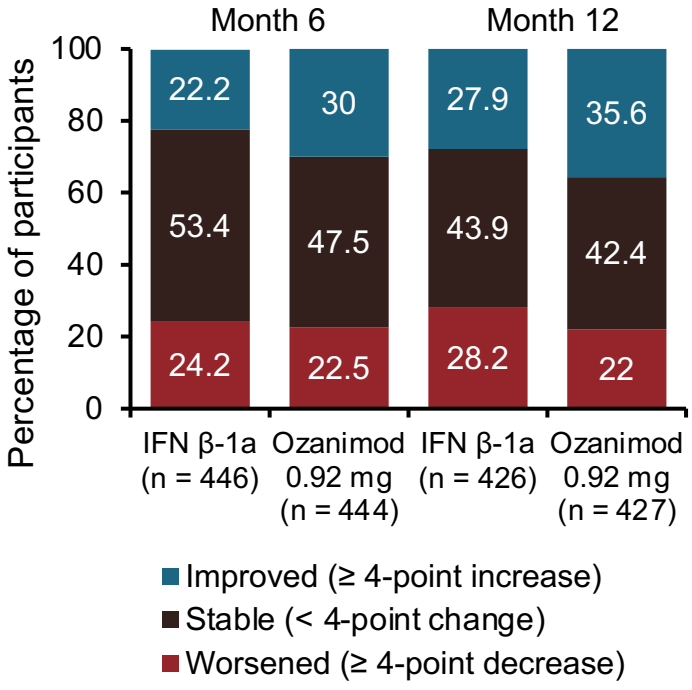


*third-line or unapproved therapy in some countries

Landmeyer NC, et al. *Neurology.* 2020;94(22):e2373-e2383.

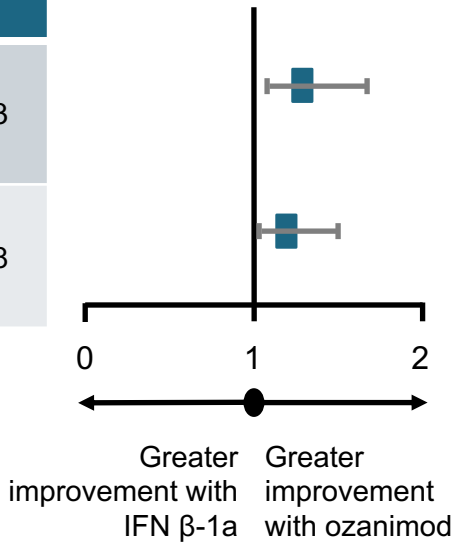
SDMT Improvement with Ozanimod vs. IFN β-1a in SUNBEAM

Categorical analysis of clinically meaningful change in SDMT



Rate ratios (ozanimod vs interferon β-1a) for clinically meaningful SDMT improvement (≥ 4-point increase) from baseline

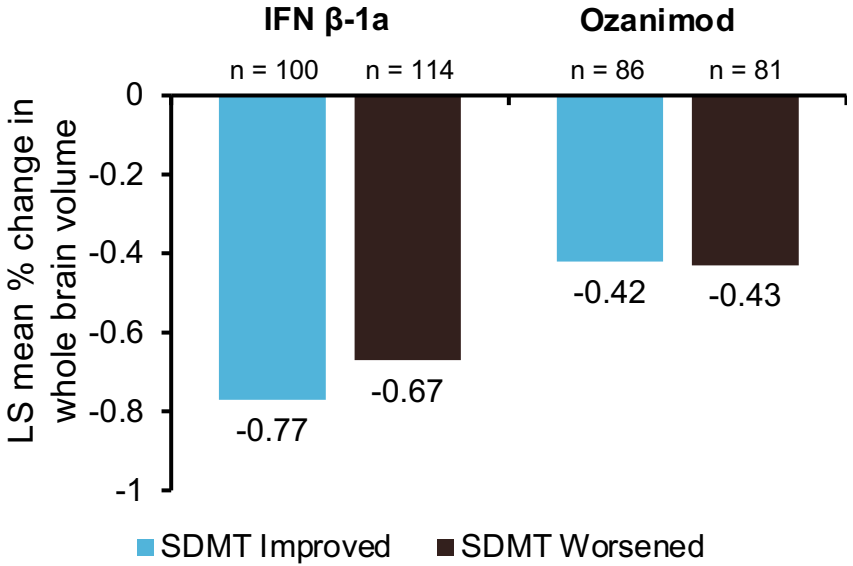
Time	Rate Ratio	95% CI	*p* value	Cohen's *d*
Month 6	1.3	1.08 to 1.68	0.0082	0.23
Month 12	1.2	1.02 to 1.50	0.0302	0.18



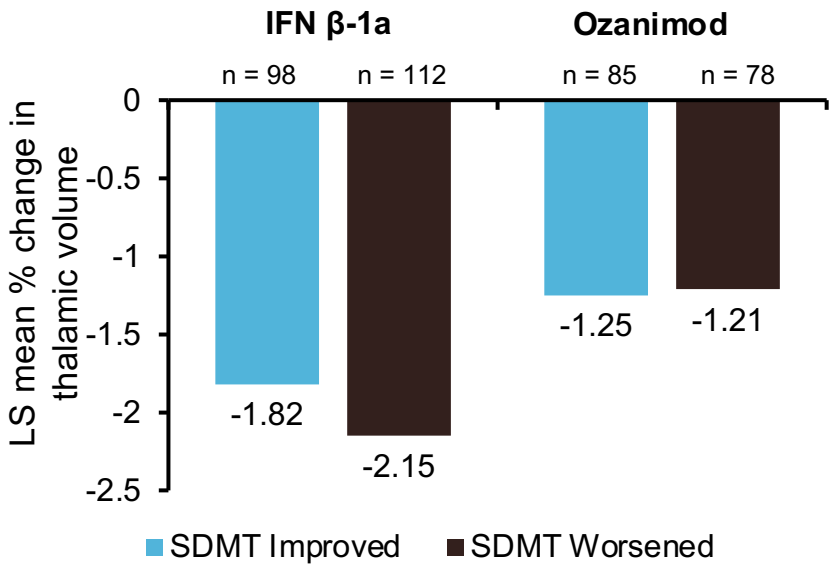
DeLuca J, et al. *Mult Scler Relat Disord.* 2020;48:102673.

Brain Volume Changes with Ozanimod vs. IFN β-1a by SDMT Response

Change in Whole Brain Volume by Treatment Arm and SDMT Response at Month 12



Change in Thalamic Volume by Treatment Arm and SDMT Response at Month 12



DeLuca J, et al. *Mult Scler Relat Disord.* 2020;48:102673.

DAYBREAK Extension Study

- Patients completing SUNBEAM could roll over into the DAYBREAK long-term open-label extension study
- Exploratory analysis at month 24:

SUNBEAM Months 0-12	DAYBREAK Months 12-24	SDMT Improvement at Month 24 vs. baseline	SDMT Worsening at Month 24 vs. baseline
Ozanimod	Ozanimod	41.2% (113/274)	21.9% (60/274)
IFN β-1a	Ozanimod	34.5% (91/264)	25.4% (67/264)

DeLuca, J et al. 2020 Virtual Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC). 2020. Abstract no. DXT38.

Ongoing: ENLIGHTEN Study Design

- **Primary** endpoint: clinically meaningful changes in SDMT (≥ 4-point or 10% change from baseline) over **3 years** in patients with early RMS treated with ozanimod
- Secondary endpoints:
  - Changes from baseline in whole brain and substructure volume;
  - MRI measures of disease activity
  - Patient-reported outcomes (PROs) and QoL
  - Disability status based on Timed 25-Foot Walk, 9-Hole Peg Test, and Expanded Disability Status Scale (EDSS)
  - Safety of ozanimod

Riolo JV, et al. 2020 Virtual Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC). 2020. Abstract no. DXT40.
Clinicaltrials.gov Website. NCT04140305.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Individualize MS management balancing treatment efficacy, safety, and patient-specific factors
- Educate patients regarding strategies to enhance their cognitive function
- Implement routine monitoring of cognitive changes using SDMT or other validated tools
- Refer patients for neuropsychiatric assessment and treatment as needed

Please submit your questions for the live Q&A to follow this presentation

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To receive CME/CE credit, click on ***Supporting Materials*** to complete the post-test and evaluation online.

Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation so we can submit your credit to ABIM.

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- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation
- Complete the follow-up survey from CME Outfitters in approximately 3 months

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CME for MIPS
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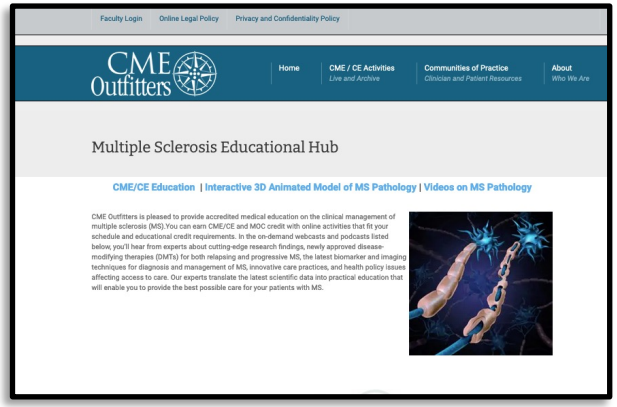

Visit the **Multiple Sclerosis Hub**

Free resources for health care providers and patients

- CME activities
- Videos on MS pathology
- 3D animated models of MS

CME Outfitters

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Don’t forget to collect your credit.

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