Multiple Sclerosis: Continuity in Care From Diagnosis Through Disability

Gavin Giovannoni, MBBCh, PhD

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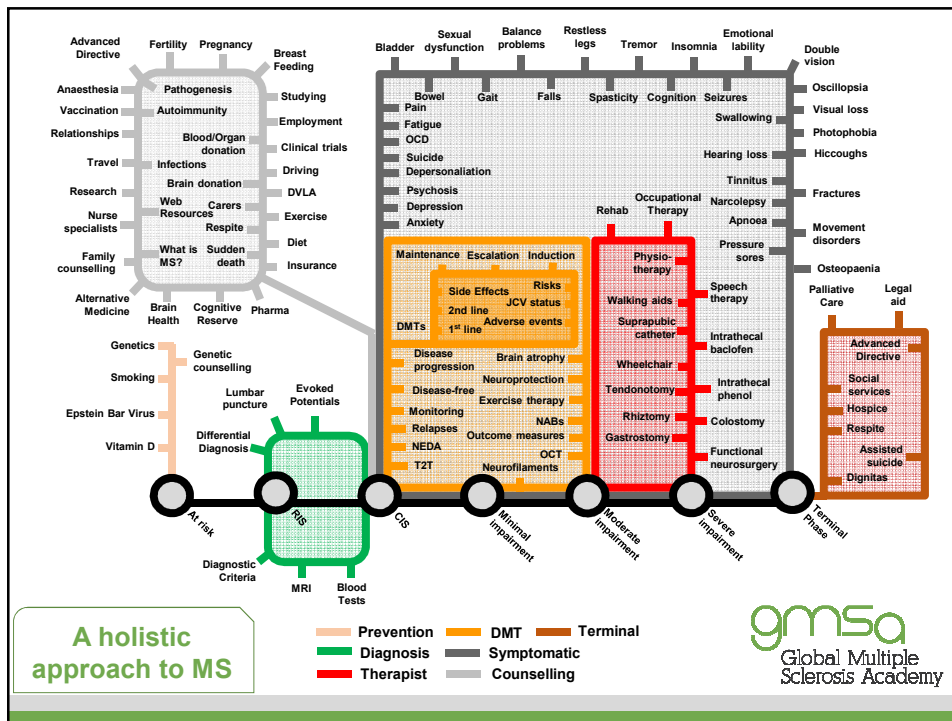## Section 1

Overview of Multiple Sclerosis

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Section 1: Learning Objectives

By the end of this section, you will be able to:

- Recognise the natural history of MS.

- Recognise the socioeconomic and personal disability associated with MS.

- Recognise how to use the Expanded Disability Status Scale (EDSS) as a method to quantify disability in MS.

A holistic approach to MS

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The Emotional Responses to a Diagnosis of MS

1. Denial
2. Anger
3. Bargaining
4. Depression
5. Acceptance
6. Anxiety

These emotional responses are based on Elisabeth Kübler-Ross's model, the five stages of grief. The sixth stage, anxiety, has been added to reflect the uncertainty that comes with a diagnosis of a chronic disease with an uncertain prognosis.

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Kübler-Ross E. *On Death and Dying.* London, UK: Routledge; 1969.

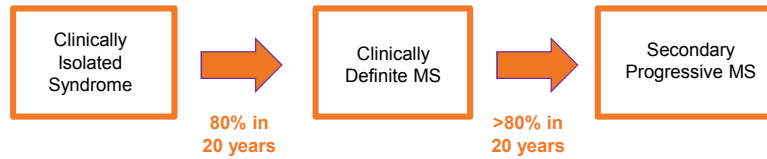---

Clinical Subtypes of Multiple Sclerosis
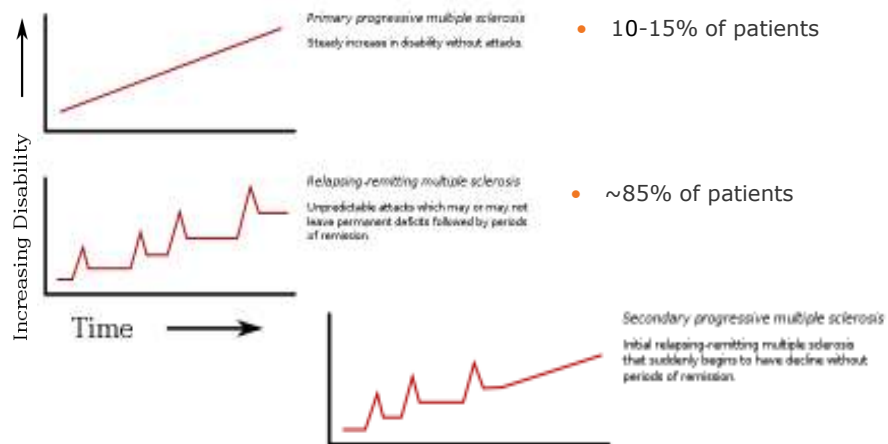
- 10-15% of patients

- ~85% of patients

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Natural History of Relapsing Remitting MS

Clinically Isolated Syndrome	→	Clinically Definite MS	→	Secondary Progressive MS

80% in 20 years   **>80% in 20 years**

1. Median time to EDSS 6 (walking aid) from onset is ~20 years
2. Median time to EDSS 7 (wheelchair) from onset is ~30 years
3. Average life expectancy reduced by 5-14 years

Ebers GC. Natural history of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2001;71 Suppl 2:ii16-ii19.; Compston A, McDonald I, Noseworthy J, Lassmann H, Miller D, Smith K, Wekerle H, Confavreux C, eds. *McAlpine's Multiple Sclerosis*. London, UK: 2005.

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Population-based MS Mortality Studies

First Author	Population & time period	Size of cohort	Standardised mortality ratio (SMR)	Additional survival measures
Grytten Torkildsen[1]	Western Norway 1953-2003	878	2.66 (95% confidence interval [CI]: 2.31-3.06)	• Median survival time from onset: 41 years MS vs 49 years general population ▪ 8 years life lost in MS
Smestad[2]	Oslo 1940-1980	368	2.47 (95% CI: 2.09-2.90)	• Reduction of median life expectancy vs. general population ▪ Female: 11.2 years ▪ Male: 7.4 years
Brønnum-Hansen[3]	Danish MS Registry 1949-1996	9881	2.89 (95% CI: 2.81 ± 2.98)	• Median survival time (from disease onset) vs. general population: ▪ ~10 years life lost in MS
Hirst[4]	South Wales 1985-2006	373	2.79 (95% CI: 2.44 to 3.18)	• Median age of death: 63.1 years MS vs 70.6 years general population ▪ 7.5 years life lost in MS
Sumelahti[5]	Finland 1964-1993	1595	2.8 (95% CI: 2.6-3.1)	• Survival decreases with disease progression ▪ SMR, 2-9.9 years after diagnosis: 2.4 ▪ SMR, ≥10 years after diagnosis: 3.1
Wallin[6]	USA 1956-1996	2489	2.18 (Not specified)	• Healthy soldier effect speculated to have a favourable effect on survival
Leray[7]	West France 1976-2004	1879	1.3 (95% CI: 1.01-1.7)	• Mean follow-up duration of 12.7 years from clinical onset; may be basing estimate on relatively immature dataset

1. Grytten Torkildsen N, Lie SA, Aarseth JH, Nyland H, Myhr KM. Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway. *Mult Scler*. 2008;14:1191-1198.; 2. Smestad C, Sandvik L, Celius EG. Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. *Mult Scler*. 2009;15(11):1263-70.; 3. Brønnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain*. 2004;127:844-850. 4. Hirst C, Ingram G, Swingler R, Compston DA, Pickersgill T, Robertson NP. Change in disability in patients with multiple sclerosis: a 20-year prospective population-based analysis. *J Neurol Neurosurg Psychiatry*. 2008 Oct;79:1137-1143.; 5. Sumelahti ML, Hakama M, Elovaara I, Pukkala E. Causes of death among patients with multiple sclerosis. *Mult Scler*. 2010;16:1437-1442. 6. Wallin MT, Page WF, Kurtzke JF. Epidemiology of multiple sclerosis in US veterans. VIII. Long-term survival after onset of multiple sclerosis. *Brain*. 2000;123:1677-1687.; 7. Leray E, Morrissey S, Yaouanq J, et al. Long-term survival of patients with multiple sclerosis in West France. *Mult Scler*. 2007;13:865-874.

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The Survival Disadvantage in MS Is Greater Than in Other Chronic Diseases

SMRs in chronic diseases

Disease	SMR (range)
Cardiovascular disease[1*]	1.34 (1.23-1.44)
Ischaemic stroke[2†]	1.75(1.38-2.19)
Early breast cancer[3]	2.0 (1.6-2.7)
Crohn's disease[4]	2.8
MS[5]	2.8 (2.6-3.1)
MS (2-9.9 years after diagnosis)[5]	2.4 (1.9-2.9)
MS (≥10 years after diagnosis)[5]	3.1 (2.8-3.4)
Parkinson's disease[6]	3.66 (3.37-3.95)
Type 2 diabetes[1]	4.47 (3.91-5.10)

*In patients with type 2 diabetes †In patients with valvular heart disease in Olmsted County, Minnesota,
1. de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes Care*. 1999;22(5):756-761; 2. Petty GW, Khandheria BK, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Outcomes among valvular heart disease patients experiencing ischemic stroke or transient ischemic attack in Olmsted County, Minnesota. *Mayo Clin Proc*. 2005;80:1001-1008.; 3. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *Int J Radiat Oncol Biol Phys*. 2006;64:1081-1091.; 4. South East England Public Health Observatory. Mortality trends. 2006. Available at: http://www.inisphoedata.org/phis/indicators/tables.php?resID=378.; 5. Sumelahti ML, Hakama M, Elovaara I, Pukkala E. Causes of death among patients with multiple sclerosis. *Mult Scler*. 2010;16:1437-1442.; 6. Hristova DR. Standardized mortality ratio and seasonal fluctuations of mortality in Parkinson's disease. *Folia Med (Plovdiv)*. 2009;51:40-45.
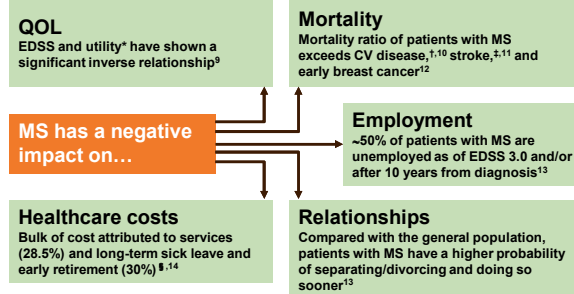
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Untreated MS Is a Devastating Disease

Cognitive dysfunction
- Prevalence: 43% to 65%[1,2]
- Affects employment, activities of daily living, and social functioning[2]

Life shortening
- 5- to 14-year decrease in life expectancy[3-7]
- 2- to 7-fold increase in suicide risk[5,8]
- ~50% of patients with MS die of disease-related causes[5,6,8]

QOL
EDSS and utility* have shown a significant inverse relationship[9]

MS has a negative impact on…

Mortality
Mortality ratio of patients with MS exceeds CV disease,[†,10] stroke,[‡,11] and early breast cancer[12]

Employment
~50% of patients with MS are unemployed as of EDSS 3.0 and/or after 10 years from diagnosis[13]

Healthcare costs
Bulk of cost attributed to services (28.5%) and long-term sick leave and early retirement (30%)[§,14]

Relationships
Compared with the general population, patients with MS have a higher probability of separating/divorcing and doing so sooner[13]

*In this study, utility measures were derived from EQ-5D using the EuroQoL instrument; †In patients with type 2 diabetes; ‡In patients with valvular heart disease in Olmsted County, Minnesota; §MS patients with EDSS ≥6
EDSS = Expanded Disability Status Scale; QO = quality of life; CV = cardiovascular; EQ-5D = European Quality of Life-5 Dimensions.

1. Rao SM, et al. *Neurology*. 1991;41:685-691.; 2. Rao SM, et al. *Neurology*. 1991;41:692-696.; 3. Sadovnick AD, et al. *J Neurol Neurosurg Psychiatry*. 2001;71 Suppl 2:ii16-ii19.; 5. Grytten Torkildsen N, et al. *Mult Scler*. 2008;14:1191-1198.; 6. Smestad C, et al. *Mult Scler*. 2009;15(11):1263-70.; 7. Kingwell E, et al. *J Neurol Neurosurg Psychiatry*. 2012;83:61-66.; 8. Sadovnick AD, et al. *Neurology*. 1991;41:1193-1196.; 9. Orme M, et al. *Value Health*. 2007;10:54-60.; 10. de Marco R, et al. *Diabetes Care*. 1999;22(5):756-761.; 11. Petty GW, et al. *Mayo Clin Proc*. 2005;80:1001-1008.; 12. Hooning MJ, et al. *Int J Radiat Oncol Biol Phys*. 2006;64:1081-1091.; 13. Pfleger CC, et al. *Mult Scler*. 2010;16:121-126.; 14. Berg J, et al. *Eur J Health Econ*. 2006;7 Suppl 2:S75-S85.
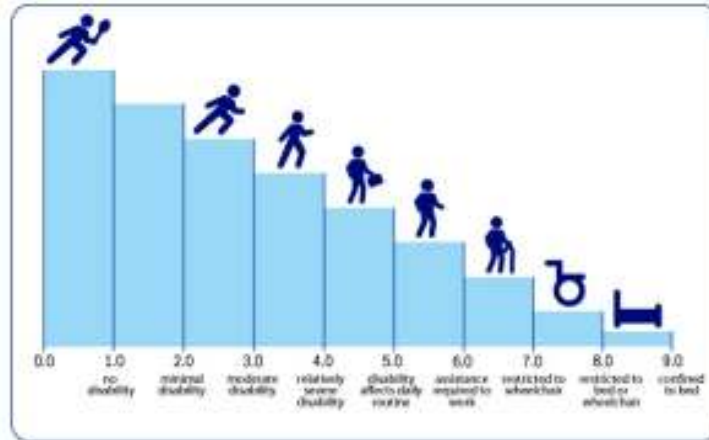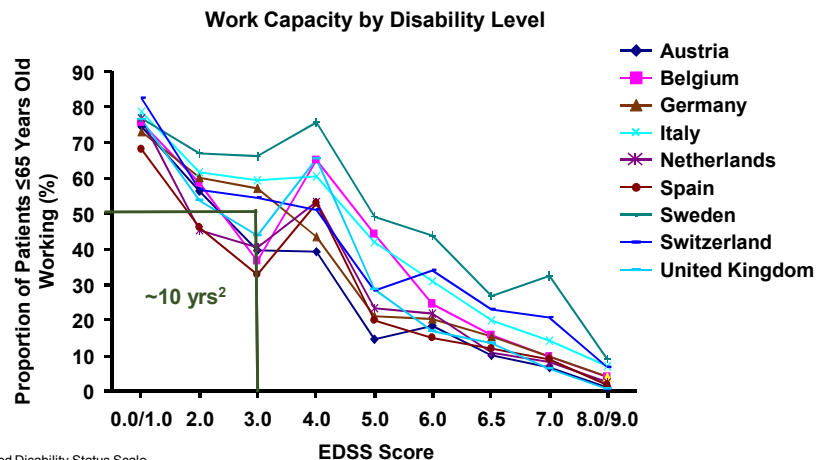
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Expanded Disability Status Scale (EDSS)

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.; Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain*. 1989;112:133-146.

# Consequences of Increasing EDSS* Scores: Loss of Employment in the European Union

*EDSS; Expanded Disability Status Scale

The proportion of patients employed or on long-term sick leave is calculated as a percentage of patients aged 65 or younger Kobelt G, Berg J, Lindgren P, Fredrikson S, Jönsson B. Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry*. 2006;77:918-926. 2. Pfleger CC, Flachs EM, Koch-Henriksen N. Social consequences of multiple sclerosis (1): early pension and temporary unemployment--a historical prospective cohort study. *Mult Scler*. 2010;16:121-126.

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The Effect of MS on Quality-of-Life (QoL)

EDSS and utility[a] show a significant inverse relationship[b]
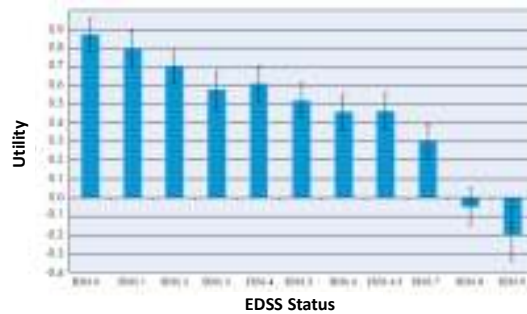
- MS is one of the most common causes of neurological disability in young adults
- Natural history studies indicate that it takes a median time of 8, 20, and 30 years to reach the irreversible disability levels of EDSS 4, 6, and 7, respectively

[a]Utility measures are derived from EQ-5D using the EuroQoL instrument
[b]Error bars depict 95% confidence intervals. Half points on EDSS are not shown on graph axis, except at EDSS 6.5.

Adapted from Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health*. 2007;10:54-60.; WHO and MSIF. Available at: http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1 &codcol=15&codcch=747. Accessed October 6, 2010.; Compston A, McDonald I, Noseworthy J, Lassmann H, Miller D, Smith K, Wekerle H, Confavreux C, eds. *McAlpine's Multiple Sclerosis*. London, UK: 2005.; 4. Compston A, Coles A. Multiple sclerosis. *Lancet*. 2008;372:1502-1517.
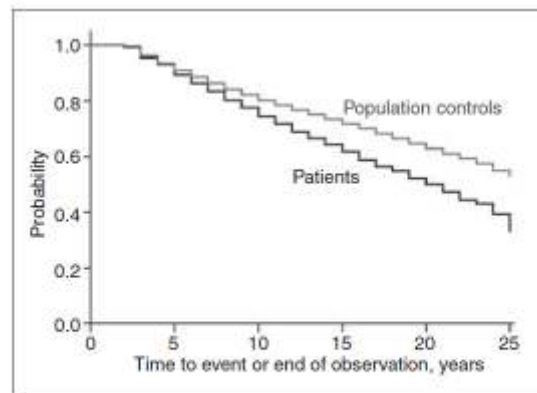

Divorce and Separation

Figure 1. Crude probability of remaining in a relationship after onset of MS (life table method).

Pfleger CC, Flachs EM, Koch-Henriksen N. Social consequences of multiple sclerosis (1): early pension and temporary unemployment--a historical prospective cohort study. *Mult Scler*. 2010;16:121-126.

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Baseline Prognostic Factors in MS and their Impact on Disease Progression and Disability

Good prognosis	Poor prognosis
▪ Young	▪ Older age of onset
▪ Female sex	▪ Male sex
▪ Optic neuritis	▪ "Multifocal" onset
▪ Isolated sensory symptom	▪ Efferent system affected (motor or cerebellar)
▪ Full recovery from attack	▪ High relapse rate in the first two to five years
▪ Long interval to second relapse	▪ Substantial disability after five years
▪ No disability after five years	▪ Abnormal MRI with large lesion load
▪ Normal MRI/low lesion load	

Adapted from Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol.* 2005;4(5):281-288.

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Section 1: Summary

Here is a quick recap of what we covered so far:

- The most inclusive way to view MS, and its impact on patients and families affected, is to view it holistically.

- The SMR is a quotient derived from the observed to the expected number of deaths and is used to compare mortality rates for patients with MS and the general population.

- The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time.

- Employment is adversely affected for half of MS patients within 10 years of their diagnosis, and interpersonal relationships are frequently destroyed. As MS-associated disability progresses, quality-of-life dramatically worsens.

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Section 2

Getting the Diagnosis Correct and Predictors of Long-term Outcome

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Section 2: Learning Objectives

By the end of this section, you will be able to:

- Recognise the evolving definition of MS.
- Recognise the MS timeline from asymptomatic disease to death.
- Relate the link between various MS disease parameters and prognosis.
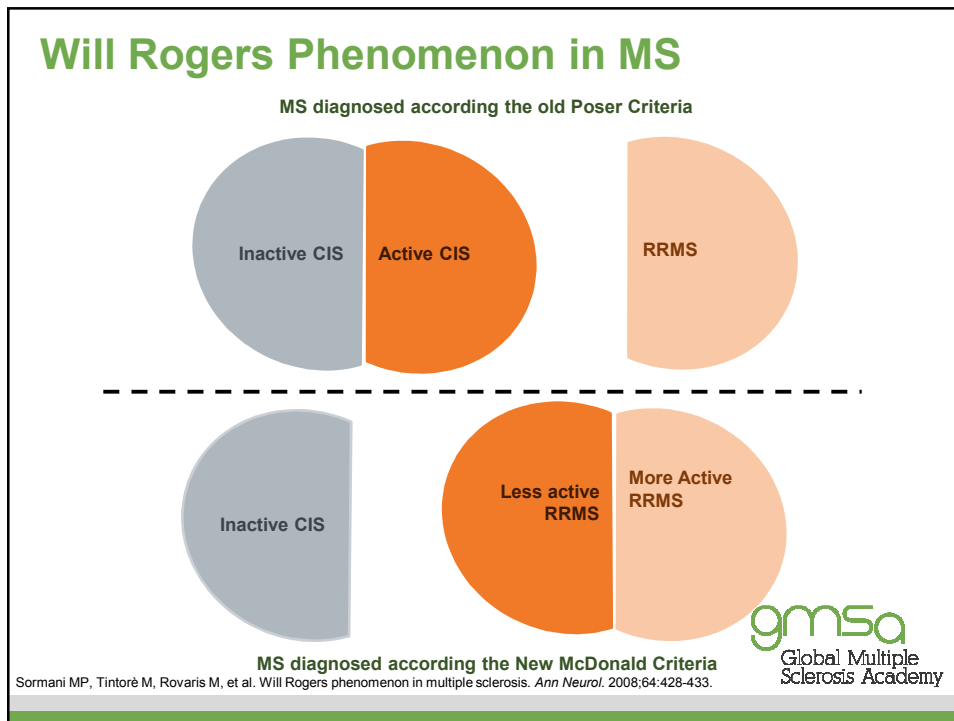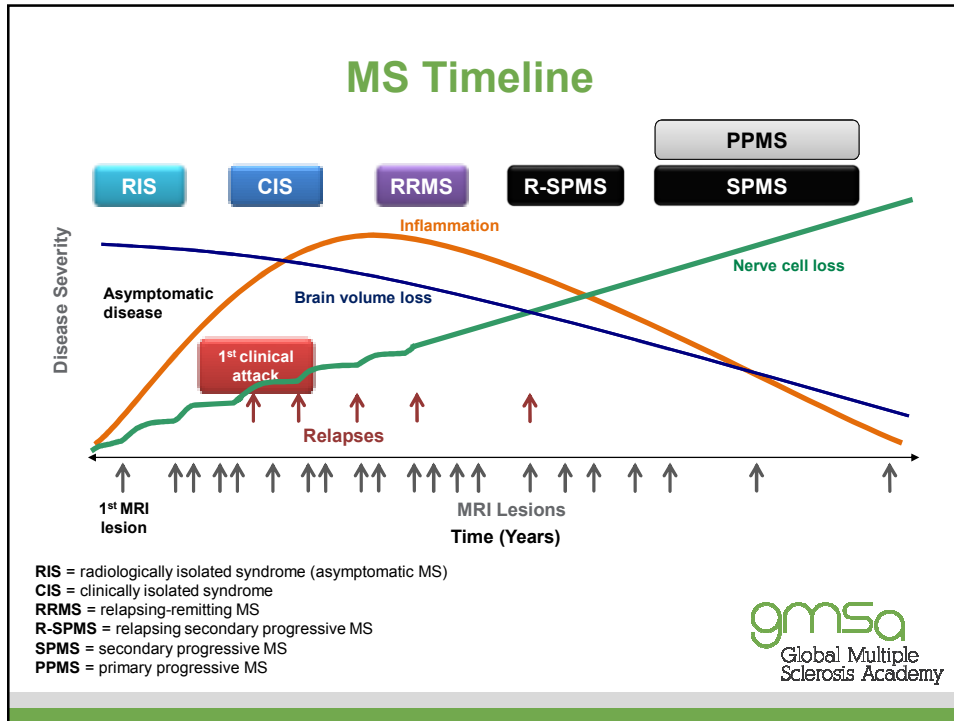
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Definition of Multiple Sclerosis

- **Pathological Definition**: Inflammatory disease of the CNS characterised by demyelination and variable degrees of axonal loss and gliosis

- **Clinical Definition**: Objective CNS dysfunction (involvement of two or more white matter structures separated by time) with no other etiology
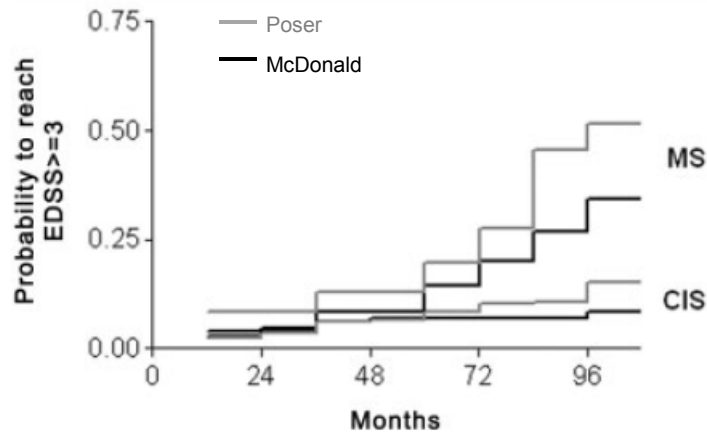
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The Evolving Clinical Definition of MS

1. Schumacker GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci*. 1965;122:552-568.

2. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol. 1983;13:227-231.

3. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121-127.

4. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58:840-846.

5. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292-302.

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MS Timeline

Disease Severity

RIS | CIS | RRMS | R-SPMS | SPMS | PPMS

Inflammation

Nerve cell loss

Asymptomatic disease

Brain volume loss

1st clinical attack

Relapses

1st MRI lesion

MRI Lesions

Time (Years)

RIS = radiologically isolated syndrome (asymptomatic MS)
CIS = clinically isolated syndrome
RRMS = relapsing-remitting MS
R-SPMS = relapsing secondary progressive MS
SPMS = secondary progressive MS
PPMS = primary progressive MS

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Will Rogers Phenomenon in MS

MS diagnosed according the old Poser Criteria

Inactive CIS | Active CIS | RRMS

Inactive CIS | Less active RRMS | More Active RRMS

MS diagnosed according the New McDonald Criteria

Sormani MP, Tintorè M, Rovaris M, et al. Will Rogers phenomenon in multiple sclerosis. *Ann Neurol.* 2008;64:428-433.

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Will Rogers Phenomenon in MS

Sormani MP, Tintorè M, Rovaris M, et al. Will Rogers phenomenon in multiple sclerosis. *Ann Neurol.* 2008;64:428-433.

Baseline Number of Brain Lesions Predicts Progression to EDSS Score ≥3.0
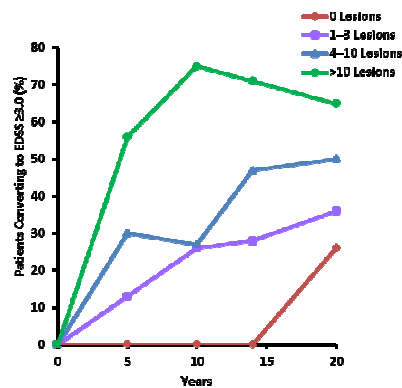
The data presented for years 5, 10, 14, and 20 were obtained from different publications based on the same longitudinal study. The exact relationship between MRI findings and the clinical status of the patient is unknown.

Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain.* 2008;131:808-817.; Morrissey SP, Miller DH, Kendall BE, et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. *Brain.* 1993;116:135-146.; O'Riordan JI, Thompson AJ, Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. *Brain.* 1998;121:495-503.; Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med.* 2002;346:158-164.

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Impact of MS: Cognitive Functioning in the CIS Stage
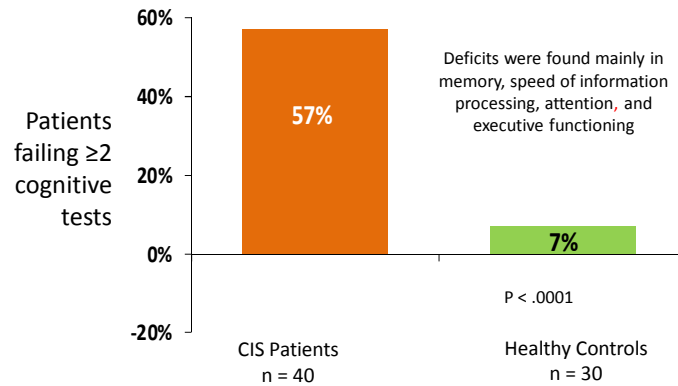
Patients failing ≥2 cognitive tests

- 60%
- 40%
- 20%
- 0%
- -20%

57% — CIS Patients n = 40

7% — Healthy Controls n = 30

Deficits were found mainly in memory, speed of information processing, attention, and executive functioning

P < .0001

Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler*. 2007;13:124-127.

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What Constitutes a Useful Diagnostic Test or Set of Criteria?

Pathological Diagnosis

Diagnostic Criteria

		TARGET DISORDER		
		PRESENT	ABSENT	
DIAGNOSTIC TEST RESULT	+	a	b	a + b
	-	c	d	c + d
		a + c	b + d	a + b + c + d

From these we determine the sensitivity and specificity as follows:

SENSITIVITY = a/(a+c) >80%
SPECIFICITY = d/(b+d) >80%

The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association, The National Institute on Aging Working Group. Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease". *Neurobiol Aging*. 1998;19:109-116.

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A Clinico-Pathoanatomical Study of the MS Diagnosis

SENSITIVITY AND SPECIFICITY

- Neuropathological examination of 518 consecutive patients with clinically definite MS revealed a correct diagnosis in 485 cases (94%)…appropriate sensitivity
  - Clinical diagnosis had been established by a neurologist in all cases
  - Erroneous diagnosis included a variety of other neurological disorders
- In this example, 33 patients had a false-positive diagnosis
- Similar deficiency with false negatives or specificity

Engell T. A clinico-pathoanatomical study of multiple sclerosis diagnosis. *Acta Neurol Scand.* 1988;78:39-44.

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What Is Benign MS?

Benign multiple sclerosis

Cognitive, psychological and social aspects in a clinical cohort

Maria Pia Amato
Valentina Zipoli
Benedetta Goretti
Emilio Portaccio
Maria Fara De Caro
Laura Ricchiuti
Gianfranco Siracusa
Medena Masini
Sandro Sorbi
Maria Trojano

163 patients with benign MS

(disease duration >15 years and EDSS <3.5):

45% cognitive impairment

49% fatigue

54% depression

Amato MP, Zipoli V, Goretti B, et al. Benign multiple sclerosis: cognitive, psychological and social aspects in a clinical cohort. *J Neurol.* 2006;253:1054-1059.

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No Evident Disease Activity (NEDA)

Treat-2-target
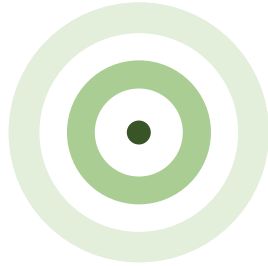
No evidence of disease activity defined as:

× No relapses

× No sustained disability progression

× No MRI activity

× No new or enlarging T2 lesions

× No gadolinium (Gd)-enhancing lesions

Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol*. 2009;8:254-260.; Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol*. 2011;10:329-337.

Brain (1989), 112, 1419–1428

THE NATURAL HISTORY OF MULTIPLE
SCLEROSIS: A GEOGRAPHICALLY BASED STUDY

2. PREDICTIVE VALUE OF THE EARLY CLINICAL COURSE

by B. G. WEINSHENKER, B. BASS, G. P. A. RICE, J. NOSEWORTHY,
W. CARRIERE, J. BASKERVILLE *and* G. C. EBERS

(*From the Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada*)
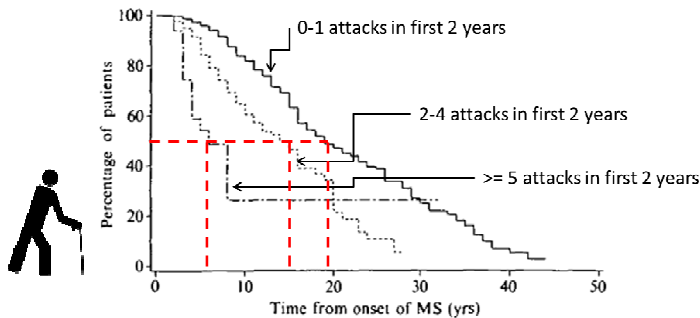
0-1 attacks in first 2 years

2-4 attacks in first 2 years

>= 5 attacks in first 2 years

Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain*. 1989;112:1419-1428.

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Predictors of Long-Term Outcome in Patients With MS Treated With Interferon Beta-1a
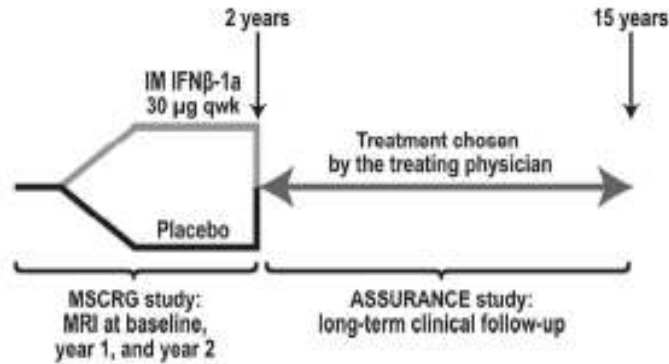
*MSCRG, Multiple Sclerosis Collaborative Research Group

Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon β. *Ann Neurol.* 2013;73:95-103.

Predictors of Long-Term Outcome in Patients With MS Treated With Interferon Beta-1a (con't.)
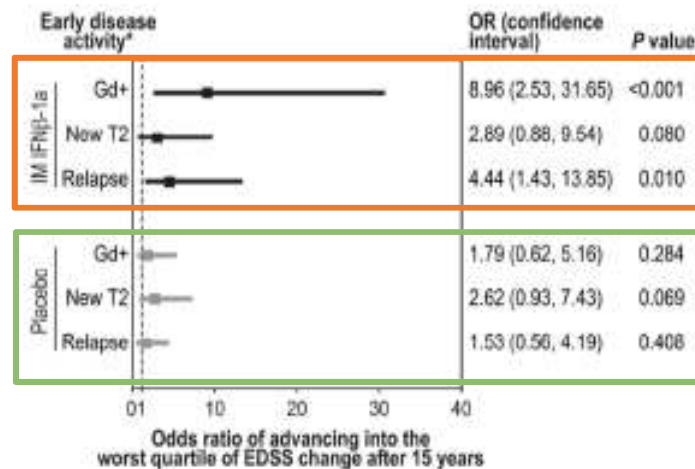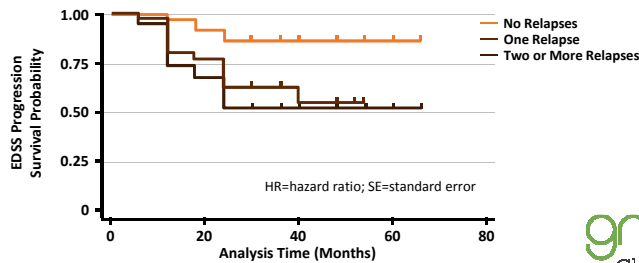
Treatment vs. Natural History

Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon β. *Ann Neurol.* 2013;73:95-103.

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Relapse on Interferon β Therapy Increases Risk of Sustained Disability Progression

HR of EDSS Increase in Patients During the First Two Years of Interferon Treatment

	HR	SE	*P* Value	95% CI
No relapses (reference = 1)	1			
One relapse	3.41	1.47	.005	1.46-7.98
Two or more relapses	4.37	1.74	.000	1.90-9.57

HR=hazard ratio; SE=standard error

Bosca I, Coret F, Valero C, et al. Effect of relapses over early progression of disability in multiple sclerosis patients treated with beta-interferon. *Mult Scler*. 2008;14:636-639.

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Relapses and Residual Deficits
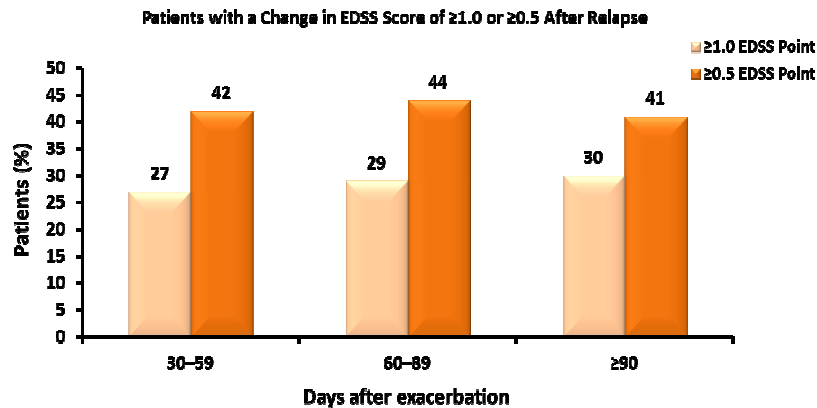
Patients with a Change in EDSS Score of ≥1.0 or ≥0.5 After Relapse

Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology*. 2003;61:1528-1532.

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Predictors of Long-Term Outcome in MS Patients Treated with Interferon Beta-1a
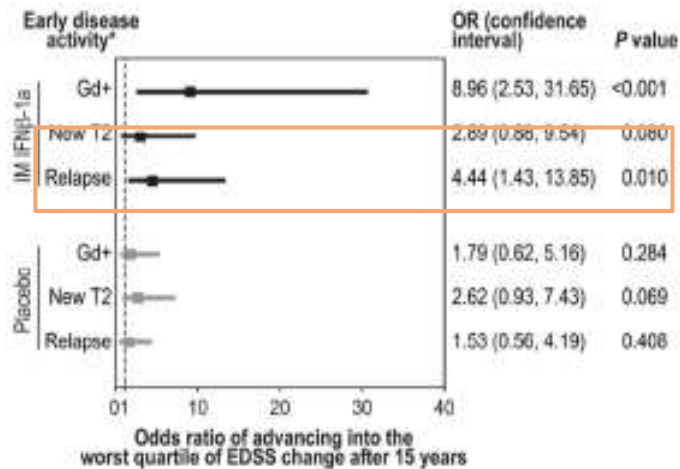
Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon β. *Ann Neurol.* 2013;73:95-103.

MRI to Monitor Treatment Response to Interferon β: a Meta-analysis
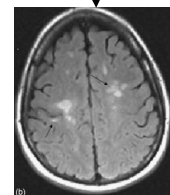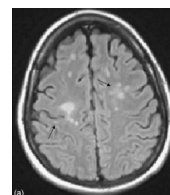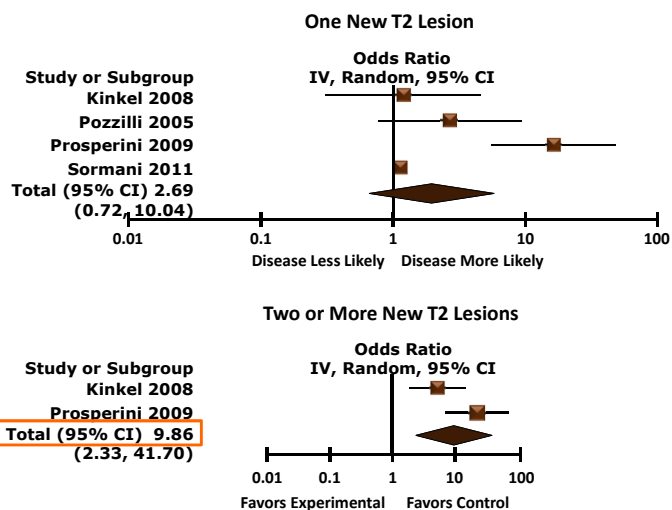
Dobson R, Rudick RA, Turner B, Schmierer K, Giovannoni G. Assessing treatment response to interferon-β: is there a role for MRI? *Neurology*. 2014;82:248-254.

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MRI to Monitor Treatment Response to Interferon β: a Meta-analysis (con't.)

One New Gd+ Lesion

Study or Subgroup	Odds Ratio IV, Random, 95% CI
Kinkel 2008	
Pozzilli 2005	
Tomassini 2006	
Total (95% CI) 3.34 (1.36, 8.22)	

0.01 0.1 1 10 100
Disease Less Likely   Disease More Likely

Two or More New Gd+ Lesions

Study or Subgroup	Odds Ratio IV, Random, 95% CI
Kinkel 2008	
Rio 2008	
Total (95% CI) 5.46 (2.48, 12.04)	

0.01 0.1 1 10 100
Disease Less Likely   Disease More Likely

Dobson R, Rudick RA, Turner B, Schmierer K, Giovannoni G. Assessing treatment response to interferon-β: is there a role for MRI? *Neurology*. 2014;82:248-254.

Section 2: Summary

Here is a quick recap of what we covered so far:

- Multiple sclerosis is defined as a disease based on a clinicopathological correlate. However, this definition is evolving as new innovations are emerging and getting incorporated into the diagnostic criteria.

- Early in the disease neuronal reserve allows patients with MS to adapt to the damage; once the reserve capacity is exhausted, they enter the progressive phase of the disease.

- Cognitive function is affected in CIS.

- A larger number of lesions present at the first demyelinating event is associated with a greater risk of progressing to an EDSS score ≥3.

- NEDA is defined by the absence of clinical attacks and disease progression and being free of pathologic MRI activity.

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Section 3

Disease and Disability
Progression in Clinical
Practice

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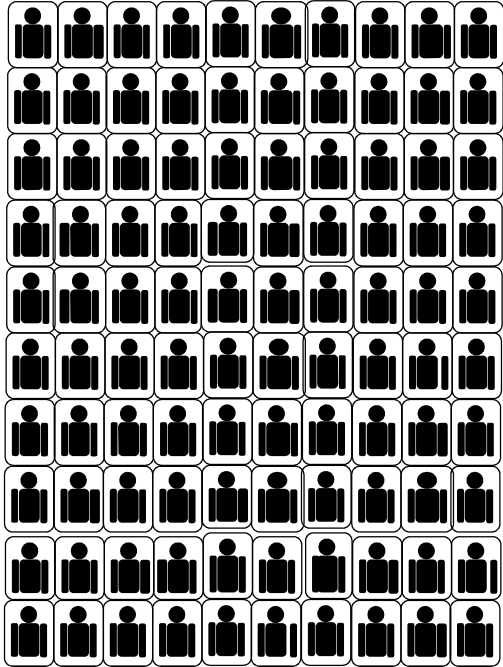
Section 3: Learning Objectives

By the end of this section, you will be able to:

- Recognise the relationships between disease activity and disability progression in therapy.

- Identify brain atrophy as a major cause of disability.

- Identify the paradigm shift in managing MS related to reducing end organ damage.

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100 Patients With MS

Who Are the Responders?

Strongest Predictor of Disability Progression on Interferon β Therapy Is Progression Itself

Disease activity during two years of treatment and prediction of disability progression* at six years

Group	Sensitivity (%) (CI)	Specificity (%) (CI)
A. An increase of at least one EDSS step confirmed at six months	**85 (64-95)**	**93 (86-97)**
B. Occurrence of any relapse	80 (58-92)	51 (41-61)
C. Occurrence of two or more relapses	45 (26-66)	81 (72-82)
D. A decrease in relapse rate less than 30% compared to two years before therapy	40 (22-61)	86 (77-91)
E. A decrease in relapse rate less than 50% compared to two years before therapy	40 (-61)	81 (72-88)
F. No decrease or identical relapse rate compared to two years before therapy	35 (18-57)	88 (79-93)
G. Definition A or B	90 (70-97)	48 (38-58)
H. Definition A or E	85 (64-95)	76 (66-83)
I. Definition A and B	75 (53-89)	97 (91-99)
J. Definition A and E	40 (22-61)	99 (94-99)

*EDSS score ≥6.0 or increase in at least three EDSS steps

Río J, Nos C, Tintoré M, et al. Defining the response to interferon-beta in relapsing-remitting multiple sclerosis patients. *Ann Neurol.* 2006;59:344-352.

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Relationship Between Early Clinical Characteristics and Long-term Disability Outcomes: 16-year Cohort Study of the Pivotal Interferon Beta-1b Trial

Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon β-1b trial in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2012;83:282-287.

Pros and Cons of Maintenance vs. Induction Therapies

Maintenance therapies

- Continuous treatment
- Low to very high efficacy
- Reversible
- Perceived to be lower risk
- Examples
  - Laquinimod, GA, IFN-beta, teriflunomide, BG12, fingolimod, natalizumab, daclizumab
- Breakthrough disease
  - Suboptimal or failure to respond
  - NEDA reliable metric for efficacy
- Rebound activity
  - Highly likely
  - Can be life threatening
- Pregnancy
  - Contra-indicated
- No potential for a cure
  - Rebound
  - SPMS & progressive brain atrophy

Induction therapies

- Short-courses or pulsed therapy
- Very high efficacy
- Irreversible
- Perceived to be higher risk
- Examples
  - Cladribine, alemtuzumab, anti-CD20*, BMT
- Breakthrough disease
  - Marker for retreatment
  - NEDA unreliable to assess efficacy
- Rebound activity
  - Less likely
  - Unlikely to be life-threatening
- Pregnancy
  - Strategy of choice
- Potentially curative
  - 15-20 year experiment
  - BMT, alemtuzumab, cladribine

*Anti-CD20, a B-cell depleting therapy, is included as a possible induction therapy; it is currently in phase 3 development

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Different Treatment Philosophies Maintenance-Escalation vs. Induction

Survival analysis

"Start safe and smooth"

"Hard and early"

MS is a neurodegenerative disease hypothesis

MS is an autoimmune disease hypothesis

15-20 year experiment

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No evident disease activity — NEDA

END-ORGAN DAMAGE

Relapses

Unreported relapses

Clinical disease worsening

Subclinical relapses: focal MRI activity

Focal grey and white matter lesions not detected by MRI

Brain atrophy

Biomarkers

Spinal fluid neurofilament levels

Clinical activity

Focal MRI activity

Hidden focal and diffuse MRI activity

Microscopic or biochemical pathology

MS Iceberg

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End-Organ Damage
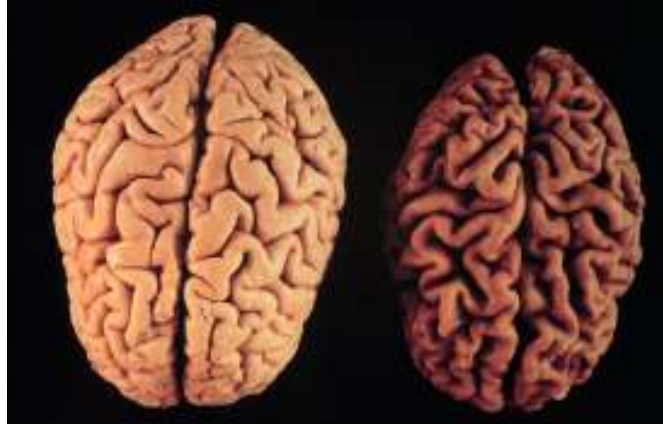
Control   **Multiple sclerosis**

Brain Atrophy Occurs Across All Stages of the Disease

n= 963 patients with MS
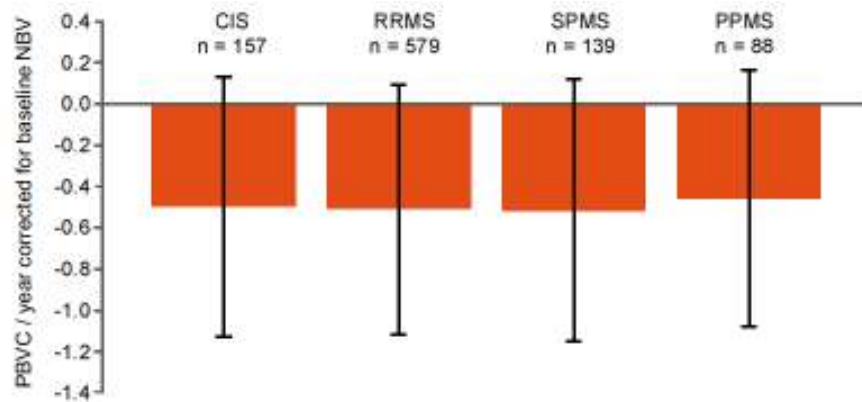
De Stefano N, Giorgio A, Battaglini M, et al. Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. *Neurology*. 2010;74:1868-1876.

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Treatment-Effect on Atrophy Correlates With Treatment-Effect on Disability

Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. *Ann Neurol.* 2014;75:43-49.

Treatment Effect on Disability Predicted by Effect on T2-Lesion Load and Brain Atrophy
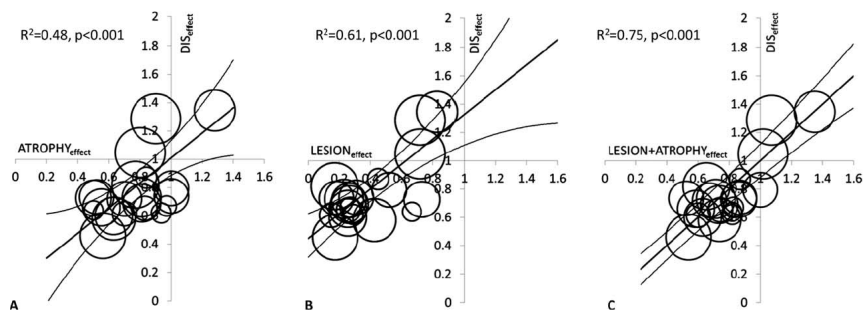
Meta-analysis of treatment effect on EDSS worsening (y) vs. effects on MRI lesions and brain atrophy, individually or combined, in 13 placebo-controlled RRMS trials (13,500 patients)

Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. *Ann Neurol.* 2014;75:43-49.

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AFFIRM Study: Natalizumab and Brain Atrophy
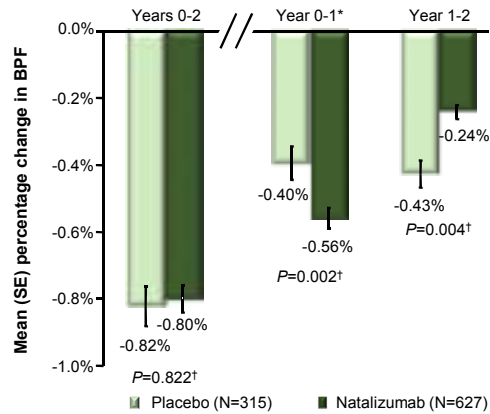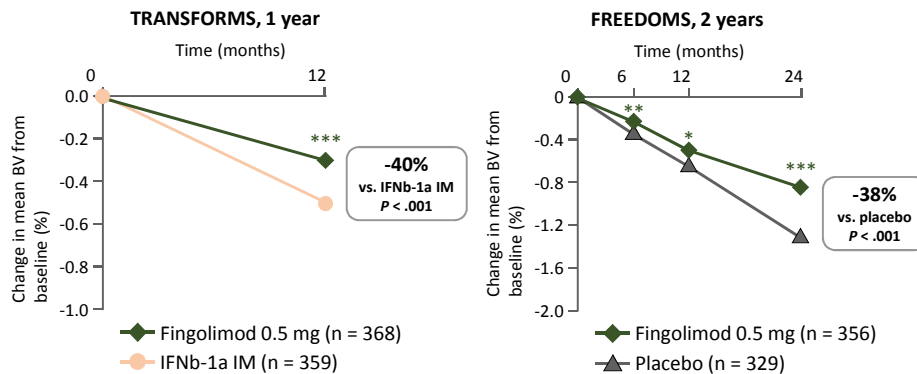
†Difference between treatments; ‡Change from baseline
Miller DH, Soon D, Fernando KT, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology.* 2007;68:1390-1401.

Fingolimod Has an Early and Sustained Effect on the Rate of Brain Atrophy Compared With Placebo and Interferon beta-1a Intramuscular Injection

ITT population with evaluable MRI images. Note: n numbers for FREEDOMS data reflect the number of patients with available data at 24 months. *P < .05; **P < .01; ***P < .001 vs. comparator; P-values are for comparisons over months 0-6, months 0-12, months 0-24 BV, brain volume; ITT, intent-to-treat. GILENYA (fingolimod) capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2014. Reproduced with permission. Doggrell SA. Oral fingolimod for relapsing-remitting multiple sclerosis Evaluation of: Kappos L, Radue E-M, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387-401; and Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402-15. *Expert Opin Pharmacother.* 2010;11:1777-1781. Copyright © 2011 Massachusetts Medical Society. All rights reserved.

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Reduction in Brain Atrophy on Alemtuzumab
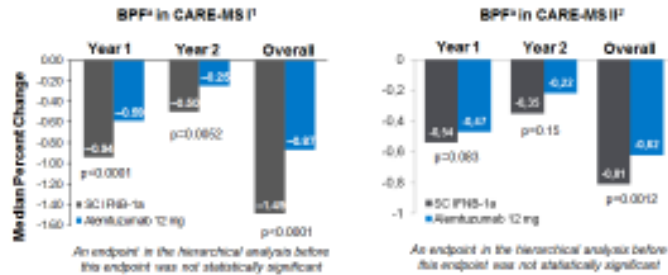
- Brain parenchymal fraction (BPF), as a measure of brain atrophy, was reduced by 42% and 23% in alemtuzumab patients vs. SC IFNB-1a patients over 2 years in CARE-MS I and CARE-MS II, respectively[1,2]
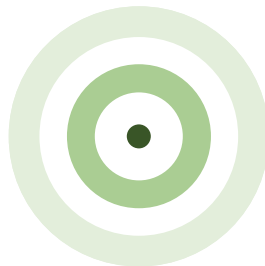- BPF is considered to be a marker of neurodegeneration in MS[3]

Method of calculation: (white matter + gray matter + lesion mask volumes) / total intracranial volume. 1. Arnold DL, et al. AAN 2012, S11.006. 2. Arnold DL, et al. ECTRIMS 2012, P577. 3. Shiee N et al. PLoS One 2012;7(5):e37049.

No Evident Disease Activity (NEDA)

Treat-2-target

No evidence of disease activity defined as:

× No relapses

× No sustained disability progression

× No MRI activity

  × No new or enlarging T2 lesions
  × No Gd-enhancing lesions

Normalisation of brain volume loss needs to be included in future definitions of NEDA

Gd, gadolinium.

Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol.* 2009;8:254-260.; Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol.* 2011;10:329-337.

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Treatment Objectives in Relapsing MS (con't.)

Treat early

NEDA	Functional improvement

Reduced ongoing damage	Maintain reserve capacity
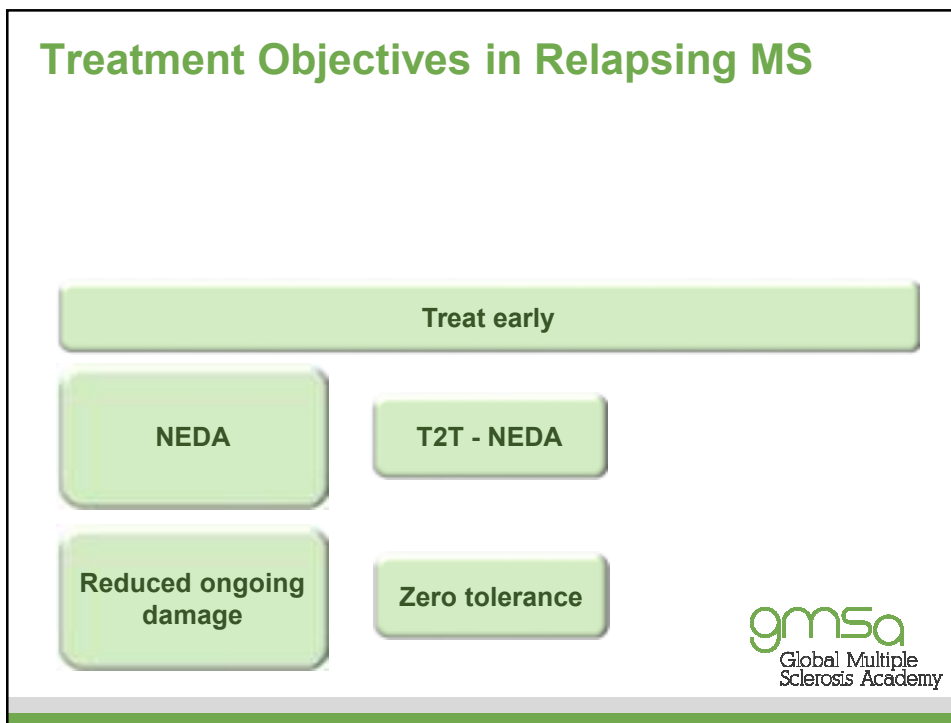
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Treatment Objectives in Relapsing MS (con't.)

Treat early		

NEDA	Functional improvement	CNS repair

Reduced ongoing damage	Maintain reserve capacity	Healthy ageing

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Treatment Objectives in Relapsing MS (con't.)

Improved quality of life/brain health

Treat early

| NEDA | Functional improvement | CNS repair |

| Reduced ongoing damage | Maintain reserve capacity | Healthy ageing |

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Section 3: Summary

Here is a quick recap of what we covered so far:

- MS disease-modifying treatments can be classified as either maintenance therapies or induction therapies.

- Patients with MS are at a higher risk of brain atrophy. The new findings suggest that a treatment focus on brain atrophy might markedly change the meaning of continuity in care.

- The emerging treatment objective in multiple sclerosis is to treat early with the target being no evident disease activity.

- Suppressing all evidence of disease activity should improve the quality of life of patients with MS.

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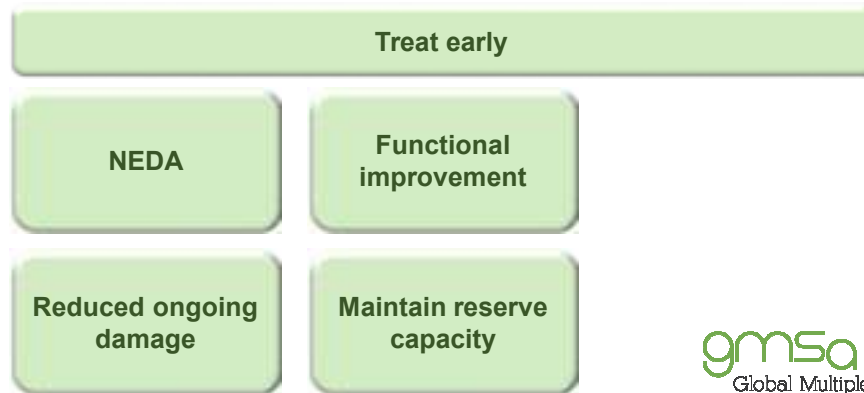- Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon β-1b trial in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83:282-287.
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