THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

Alabama Academy of Neurology Annual Conference
August 21, 2021
Grand Bohemian Hotel, Mountain Brook

Complexity of Multiple Sclerosis Disease Modifying Therapy in the Current Era

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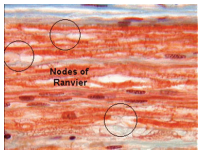
MS – How Far Have We Come…

- 1421 – Saint Lidwina van Schiedam
- 1838-1868 – First sightings
- 1868-1870 – Jean-Martin Charcot
- 1978 - Description of Myelin Structure
- 1870s – Official recognition
  - Walter Moxen and Edward Seguin



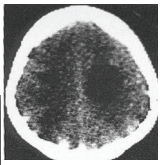
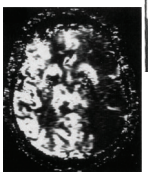


Conflict of Interest

- Research Grants
  - NIH, NMSS, Biogen-Idec, Novart Genzyme, Roche, Actelion, Teva Neuroscience, PCORI, Abbvie, Alexion, GW Pharma

MS – How Far Have We Come…

- 1930s – Thomas Rivers (EAE)
- 1950-1960s – MS diagnostic criteria
- 1960s – Role of the immune system
- 1980s – MRI for MS
- 1990s – First MS disease modifying therapies
- 2000-2021 – Drug Treatment Explosion

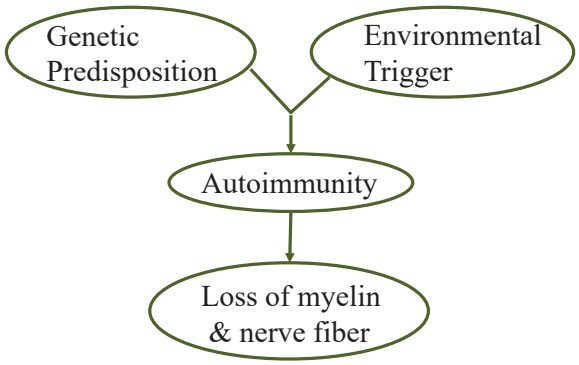





MS drug shortage prompts patient 'lottery'
10 September 1993
By Susan Katz Miller

Objectives

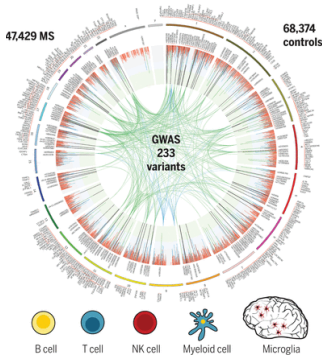
- At the end of this presentation, the audience will be able to:
  - Discuss changing landscape of MS disease modifying therapies
  - Discuss strategies for choosing the "right MS patient" for the "right treatment"
  - Discuss optimizing immunumodulatory treatment for MS patients

What Causes MS?



Genes Associated with the Development of MS

International MS Genetics Consortium Confirms 233 MS-Related Gene Variations in Largest Study to Date



Beecham et al., Nature Genetics 2013

Evolution of MS Diagnostic Criteria

- 1800's-1960's
  - Clinical diagnosis alone
    - 1868 Charcot – (Triad of nystagmus, intention tremor, and scanning speech)
    - 1936 Marburg – (Uhthoff's sign, absent abdominal reflexes, pyramidal tract involvement)
    - 1954 Allison-Millar Criteria
    - 1965 – Schumacher Criteria
- 1970's
  - CSF and EP as supportive evidence
- 1980's-1990's
  - Introduction of MRI into diagnostic criteria
- 2000 – 2021
  - Increasing reliance on MRI for earlier diagnosis

Multiple Sclerosis: An Immuno-genetic Disease

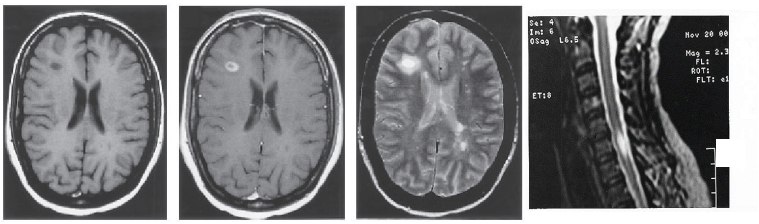
Genetic Predisposition
-Twins studies
-HLA-DR2 (DRß1*1501) (antigen presentation)
-IL-2Ra (regulatory T-cells)
-IL-7Ra (memory T-cells)
GWAS (>200 alleles)
-OAS1 polymorphism, AA genotype
-CBLB in Sardinia
-KIF 1B
-GPC5
-CLEC16A
-IRF8
-TNFRSF1A
-HLA C*05, HLA DRB1*01
-HLA G5
-CD58

Environmental Factors
Demographics/Epidemics
Microbial Agents
EBV
Vit. D
Smoking
Weight
Sodium
Microbiome
Comorbidities

Immune Dysregulation

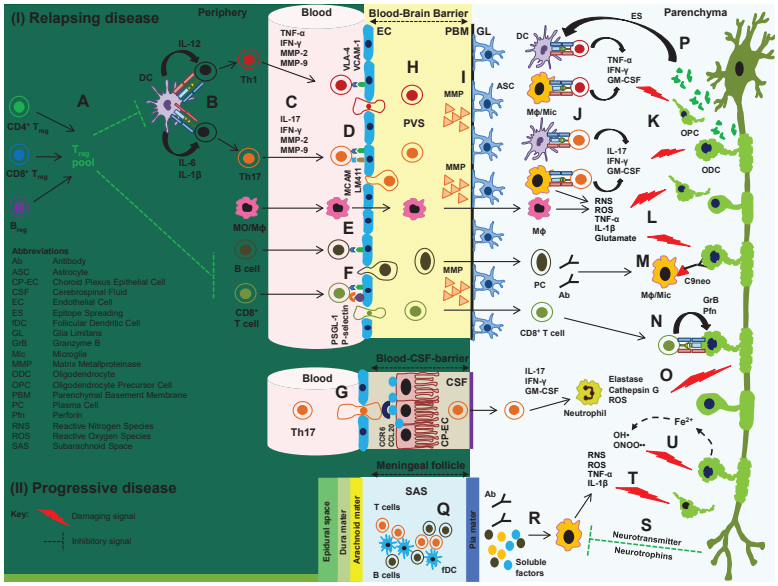
MS

MRI in Multiple Sclerosis



But what to do after a patient has been diagnosed….

Barkhof F, van Walderveen M. *Phil Trans R Soc Lond B.* 1999;354:1678 (fig. 2)



Current State of MS

- Early identification
- More confident diagnosis
- Better monitoring tools
- Effective therapeutic options

The Changing Landscape of MS

Prior to 1993, the MS landscape looked fairly barren

- There were no FDA-approved treatments for MS
- Limited approach to treating symptoms and managing the disease
- No consistent use of rehabilitation services

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

MS has a negative impact on…

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

Mortality
Mortality ratio of patients with MS exceeds CV disease,[1,10] stroke,[1,11] 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%)[1,14]

Relationships
Compared with general population, patients with MS have a higher probability of separating/divorcing and doing so sooner[15]

*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; QOL=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. *Neurology*. 1992;42:991-994; 4. Ebers GC. *J Neurol Neurosurg Psychiatry*. 2001;71:16-19; 5. Torkildsen G et al. *Mult Scler*. 2008;14:1191-1198; 6. Smestad C et al. *Mult Scler*. 2009;15:1263-1270; 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;22:756-761; 11. Petty DW 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. Beg J et al. *Eur J Health Econ*. 2006;7(suppl 2):S75-S85.

The Changing Landscape of MS

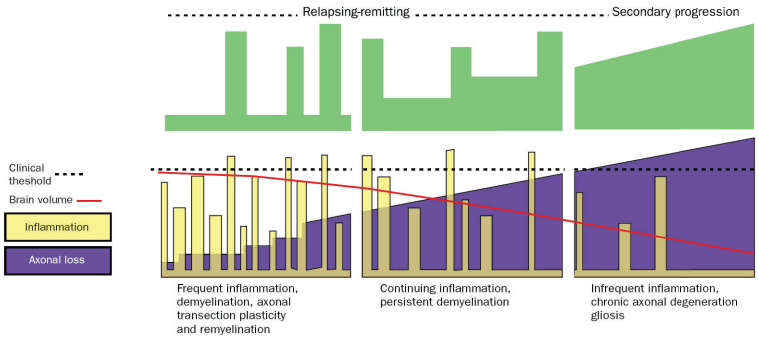
Because of such limited options at the time, advice to many MS patients included statements such as . . .

- "Go home and rest – try not to do too much"
- "Never go out in the heat"
- "You may want to consider not having children"
- "You need to get your finances in order since you will likely be divorced and unemployed"

Treatment of MS in Early 1800's

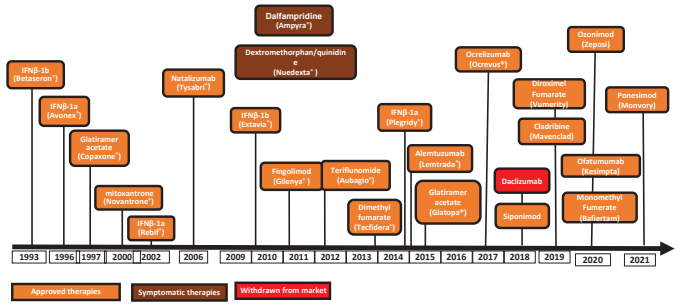
- Beef steaks
- Alcoholic drinks
- Leg brushes
- Horseback riding
- Blood letting
- "Open-hand slaps to the back"
- Counterirritant plaster
- Hot flannel bandages
- Herbs and Flowers
- Sea bathing
- Electricity / Galvanism
- Heavy metals
- Application of wet sheets and friction

A Model of MS Disease Course

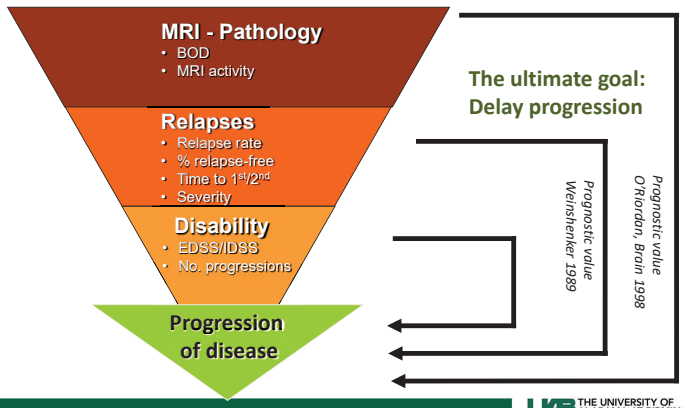


From Compston A and Coles A. Lancet 2002; 359:1221-1231.

Existing MS Therapies: 2021



Treatment Goal



What strategies are available for choosing the right treatment for MS

- Type of MS – Relapsing vs Progressive
- Risk stratification of patients – Risk of disability
- Risk stratification of DMT – Risk vs Benefit of a given DMT
- Therapeutic philosophy – Sequential monotherapy vs Escalation therapy vs Induction strategy
- Cost of DMT
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Treatment Selection

- Typical MS patients
- MS patients with little to no disability
- Patient preference

- Patients with significant disability
- Patients at risk for aggressive disease

Disease Modifying Therapies (FDA approved)

Relapsing MS

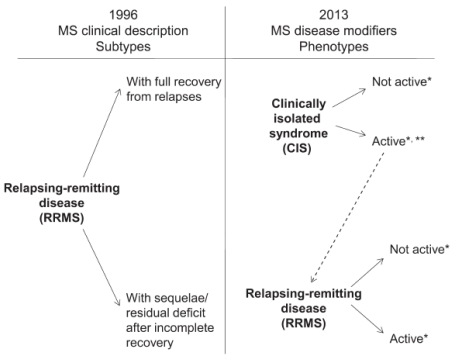
- IFN β
- Glatiramer Acetate
- Fingolimod
- Teriflunomide
- Fumaric Acid Derivatives
- Natalizumab
- Alemtuzumab
- Anti-B cell

Progressive MS

- IFN β (IFN β-1b SC in Europe)
- Mitoxantrone
- Ocrelizumab

MS Clinical Subtypes
(Lublin, Reingold, et al., 2013)

Figure 1 The 1996 vs 2013 multiple sclerosis phenotype descriptions for relapsing disease



*Activity determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually); if assessments are not available, activity is "indeterminate." **CIS, if subsequently clinically active and fulfilling current multiple sclerosis (MS) diagnostic criteria, becomes relapsing-remitting MS (RRMS).

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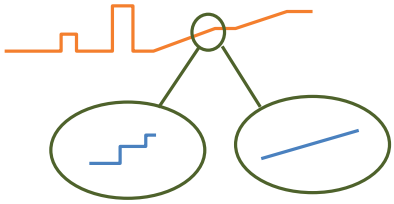
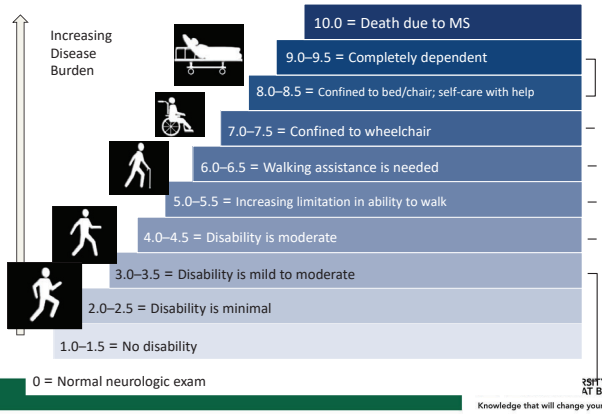
Mechanisms of Worsening of MS

- Clinical
  - Incomplete recovery from exacerbations in relapsing forms (step-wise worsening)
  - Gradual, progressive worsening independent of relapses-progressive forms
- Pathological
  - Inflammatory Disease
  - Degeneration

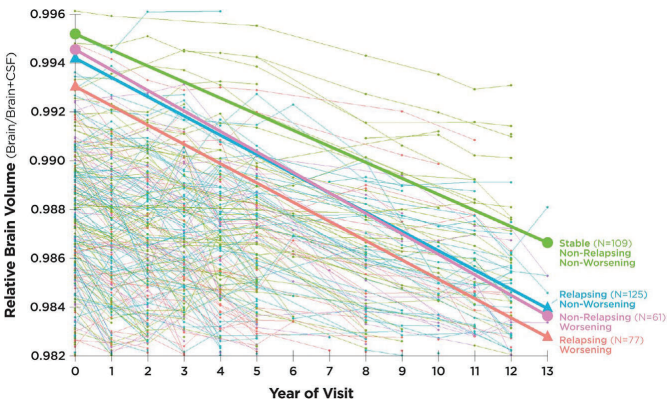


Risk Stratification of Patients

- Some patients have very active disease from onset
- Some patients have very mild disease for long periods of time



Silent Progression



MS EPIC. Ann Neurol. 2019

Risk Stratification of Patients

- Age at onset ≥ 40
- Male gender
- African American
- Motor, sphincter, cerebellar symptoms
- MRI lesions in brainstem or spinal cord at onset
- Spinal cord or cerebellar symptoms
- ≥ 2 attacks in first 2 years of onset
- Incomplete recovery from relapse

Risk Stratification of Patients

- Risk of Active Disease
  - Time to EDSS 3
  - EDSS 4 within five years of onset
  - Confirmed EDSS ≥6 within five years of MS onset
  - Confirmed EDSS ≥6 by age 40
  - Higher early relapse frequencies
  - Shorter first inter-attack intervals
  - Increase in T2 lesion burden within the first five years
  - Secondary progressive MS within three years of a relapsing-onset course
  - New or enlarging T2 lesions or gd-enhancing lesions despite treatment
  - No response to therapy with one or more DMTs for up to one year

Risk stratification of DMT – Benefit vs Risk

- Short and long term safety are critical factors in the selection of DMTs for MS
- The injectable therapies for MS (IFNβ-1a, IFNβ-1b, and GA) have established long term safety profiles over more than 20 years of continuous use
- Oral immunomodulatory agents and monoclonal antibodies for MS are welcome additions to the selection of DMTs. The long term safety profiles of these drugs in MS have yet to be elucidated.
- Safety concerns associated with some therapies and added requirements for safety monitoring may increase the complexity of a therapeutic selection.

Proposed Prognostic score

1.	Age of onset (<40 vs. >40 years)	(1)
2.	Sex (F vs. M)	(1)
3.	Sites: unifocal vs. multifocal onset	(1)
4.	System:	
a.	Motor: no vs. yes	(1)
b.	Cerebellar: no vs. yes	(1)
c.	Bladder: no vs. yes	(1)
d.	Cognition	
i.	Impairment: no vs. yes	(1)
ii.	Learner: yes vs. no	(1)
5.	Recovery: complete vs. partial or no recovery from initial relapses	(1)
6.	Relapse rate: low/ ≤ 2 vs. high / >2 in the first 2 year	(1)
7.	Early disability: EDSS < 3.0 vs. EDSS ≥ 3.0 within 5 years	(1)
8.	MRI	
a.	Baseline lesion load: low / <9 T2 vs. ≥ 9 T2 lesions	(1)
b.	Active: no Gd-enhancing vs. Gd-enhancing lesions	(1)
c.	Posterior fossa lesions: no vs. yes	(1)
d.	Spinal cord lesions: no vs. yes	(1)
e.	Brain atrophy: no vs. yes	(1)
9.	CSF	
a.	OCBs (oligoclonal IgG bands): no vs. yes	(1)
b.	Raised neurofilament levels: no vs. yes	(1)
10.	Vitamin D levels: low vs. normal	(1)
11.	Smoker: no vs. yes	(1)
12.	Comorbidities (diabetes/prediabetes, hypertension, hypercholesterolaemia, obesity): no vs. yes	(4)
Adapted from Miller et al., Lancet Neurology 2005: 4; 281-288		(24)

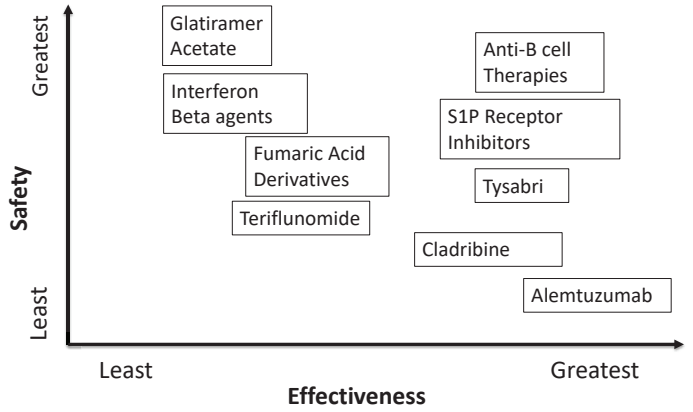
>70% poor prognosis

30-50% intermediate prognosis

<30% good prognosis

Courtesy Gavin Giovannoni

Risk stratification of DMT – Benefit vs Risk



Courtesy: John Rinker, MD

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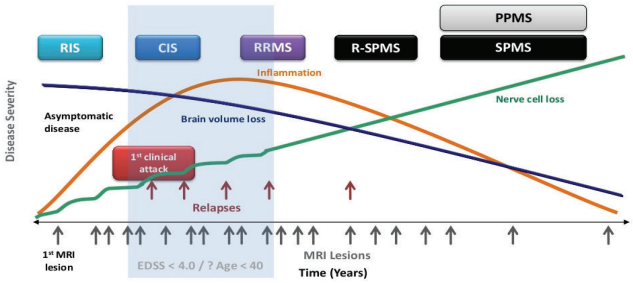
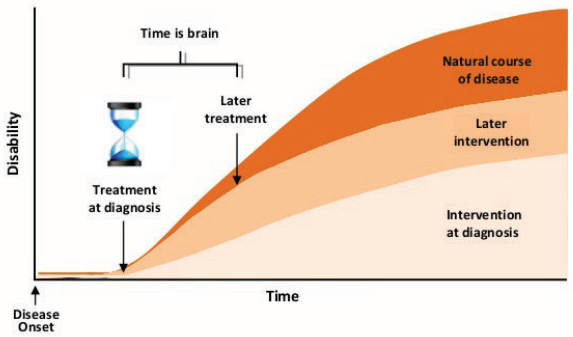
The therapeutic window for recovery

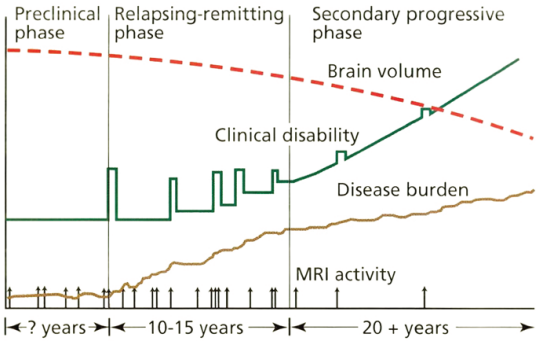


RIS = radiologically isolated syndrome (asymptomatic MS)
CIS = clinically isolated syndrome
RRMS = relapsing-remitting MS
R-SPMS = relapsing secondary progressive MS
SPMS = secondary progressive MS
PPMS = primary progressive MS

Theoretical model: treat early and effectively



Disease Stages



Fox, Cohen. Cleve Clin J of Med. 2001

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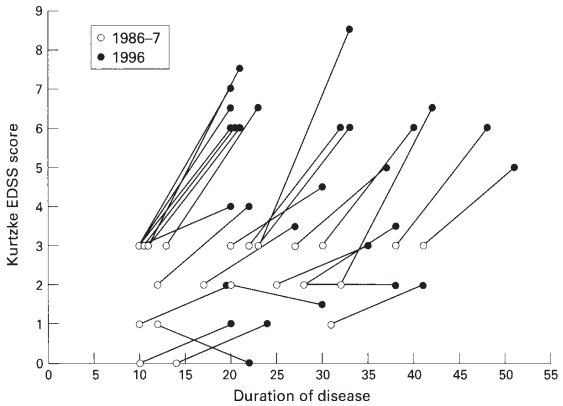
Change in Disability in "Benign Multiple Sclerosis" Between 1986-7 and 1996



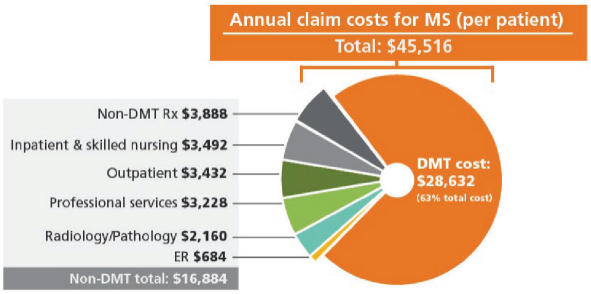
Hawkins and McDonnell. J Neurol Neurosurg Psychiatry 1999; 67:148-152

Cost of MS DMT

- The top 3 most expensive diagnoses for health care payers:
  - Cancer
  - Multiple sclerosis
  - Rheumatoid arthritis
- How did this come to be?
  - MS pharmacotherapy consumes $1 of every $40 pharmacy benefit dollars
  - Total medication expenditures increased 13.6% each year between 2010 and 2013, driven primarily by drug price increases

Healthcare Cost of MS Patients (2016)

MS ranked eighth by drug invoice spending among the top therapeutic classes in the U.S. in 2016, representing nearly $19 billion in drug spending alone.



Report by the QuintilesIMS Institute. May 2017.

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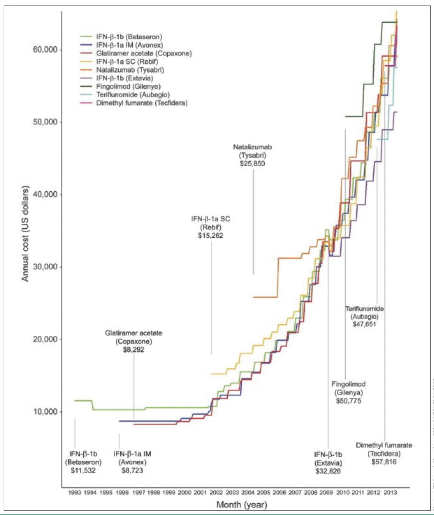
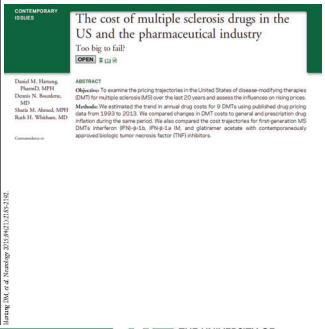
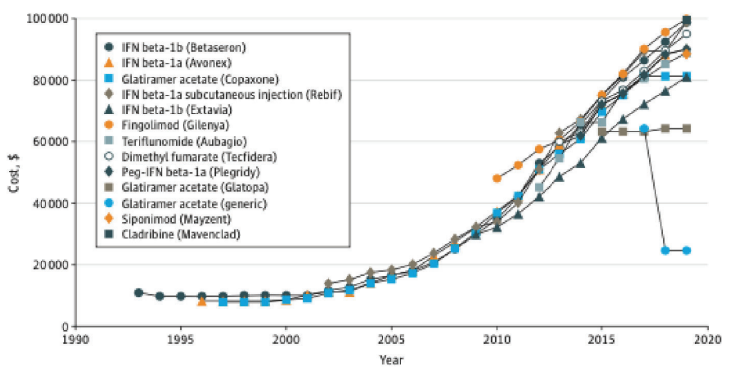



The cost of multiple sclerosis drugs in the US and the pharmaceutical industry
Too big to fail?

Realistic Expectations of DMTs

- ***Should***
  - Reduce or eliminate relapses
  - Be well tolerated
  - Prevent or reduce disability over time
  - Reduce MRI disease activity
  - Improve quality of life
  - Be acquirable
- **Do Not**
  - Control pre-existing symptoms
  - Heal old damage from MS
  - Cost nothing
  - Come without side effects
  - Continue without surveillance

Figure. Annual Prices of Disease-Modifying Therapies for Multiple Sclerosis



JAMA 2019

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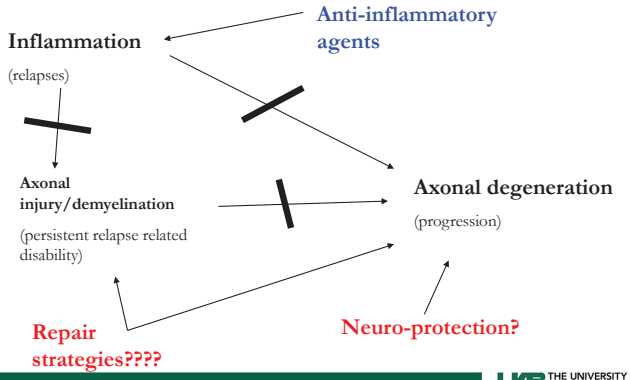
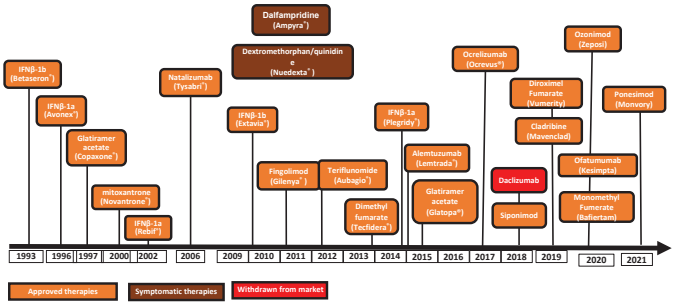
UAB MULTIPLE SCLEROSIS CENTER
Knowledge that will change your world

Disease evolution and treatment strategies in MS



Existing MS Therapies: 2021

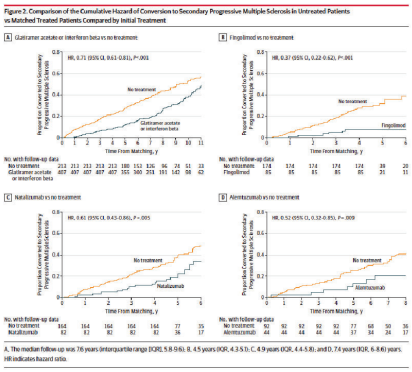


Altering the course

DMTs reduce development of SPMS

Natural history studies

- SPMS rates of 54% at 19 years
- MS EPIC cohort
  - 517 MS Patients
  - 91% retention at 10 years
  - SPMS rate of 11.3% at 16.8 years



MS Base. JAMA. 2019

Approved and Emerging Therapies for MS

Immunomodulation	Cell Migration Inhibition/ Lymphocyte-Sequestering	Lymphocyte-Depleting	Remyelination

• Dimethyl fumarate
• Diroximel Fumarate
• Monomethyl Fumarate
• Glatiramer acetate
• Interferon β
• Teriflunomide
	• Natalizumab
	• Fingolimod
	• Siponimod
	• Ozanimod
	• Ponesimod
		• B and T cells:
		  • Alemtuzumab
		  • Cladribine
		• B cells:
		  • Ocrelizumab
		  • Ofatumumab
			• MD1003 (High dose biotin)*
			• Opicinumab*

*Investigational
MOA = mechanism of action
Gohil K. *PT.* 2015;40(9). Retrieved from www.ptcommunity.com/journal/article/full/2015/9/604/multiple-sclerosis-progress-no-cure. Accessed 4/10/18; ClinicalTrials.gov. Accessed 10/18/2018.

Current DMTs

Approved and Emerging Therapies for MS

Injectable
- Interferon β
- Glatiramer acetate
- Ofatumumab

Oral
- Fumaric Acid Derivatives
- Teriflunomide
- S1P Receptor Inhibitors
- Cladribine

Infusions
- Natalizumab
- Mitoxantrone
- Alemtuzumab
- Ocrelizumab

Future Opportunities

- Combination Therapies
- Personalized/Precision Medicine

Discontinuation/Switching of MS Therapy

- 17–41% patients ultimately discontinue therapy, most in first 2 years
- 30–50% discontinue therapy due to lack of efficacy
- 22–70% due to adverse effects
- 75% switch to another DMT - at least 1 time
- 11% switch - 2 times
- 14% switch - 3 or more times

Treatment Monitoring

- An annual assessment of disability using a validated MS disability scale The Kurtzke EDSS is the most commonly used scale
- Determination of relapse rate, severity and recovery
- MRI surveillance (at time of diagnosis, initiation of DMT, switching DMT, “periodically” thereafter)

Issues to consider when switching MS therapies

- How long has patient been on the current DMT?
- How well has this agent controlled the disease?
- Are there safety or tolerability issues that may guide selection of the new DMT?
- How often is it safe to change DMT?
- Will the patient really have better adherence with the new DMT?
- What monitoring is involved?
- Age/gender/race issues
- Comorbid conditions
- Will the insurance cover a different DMT?

Treatment Monitoring

- Fall risk screening
- Bladder evaluation
- Exercise and appropriate physical activity counseling
- Fatigue outcome measurement on a validated fatigue rating instrument
- Cognitive impairment testing
- Clinical depression screening using an age-appropriate standardized depression screening tool
- Quality of Life measurement using an age-appropriate quality of life tool

Therapeutic Failure in MS

- Not all MS patients respond optimally to DMT
  - 20-50% may not respond well
- This is likely magnified by:
  - Delaying therapy
  - Not matching patients and initial DMT choice well
  - Not identifying poor response quickly
- New concepts emphasize:
  - Early treatment
  - Close follow up clinically and by MRI (esp. in the first 2 years)
  - Optimizing compliance
- Ideal treatment goal is “Treat-to-Target”

When NOT to Treat

- Hotly debated!
- Benign MS – 10-24% of MS patients
- SPMS – treatment withdrawal can lead to increased disability but low risk of relapse
- Non-ambulatory patients *may* consider stopping therapy

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Summary

- The treatment of multiple sclerosis has become complex as a result of success in clinical research and drug development
- There is no single consensus approach to prescribing disease modifying drugs; *there is no cookbook*
- The drugs for MS are exceedingly expensive and engender high intensity, rapid response marketing campaigns from pharmaceutical industry
- Data needed for true evidence-based best practices is lacking and existing drugs cannot be targeted to the patients most likely to benefit

Summary

- First 6-24 months and DMT is important to identify poor responders; patient should be followed clinically and with serial MRI
- Patients who are not doing well should be assessed for
  - Adherence/compliance
  - Optimized management of side effects
  - Unacceptable breakthrough disease activity
- Unacceptable breakthrough disease activity should result in switch to a different MOA DMT
- Minimize washout period
- Consider efficacy
- Data from IFN β studies indicates ≥ 1 contrast-enhancing or ≥ 2 T2 lesions is an acceptable reason to switch DMT (not clear that this applies to other DMT)
- NEDA goal is probably too stringent to use clinically at this time
- For MRI criteria alone (except for IFN β), it may be reasonable to require more than one MRI studies