The Aging MS Patient: Management and Updates

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Disclosures

- I serve as an unpaid member of the The MOG Project medical advisory board
- I have done paid CME work for NeurologyLive
- Served as site Principal investigator for clinical trial sponsored by Sanofi
- Served as site Principal investigator for clinical trial sponsored by Novartis
- I have participated in paid advisory board work for EMD serono.
- CanDoMS paid panel member

Outline

MS overview

MS over the life span

The aging immune system

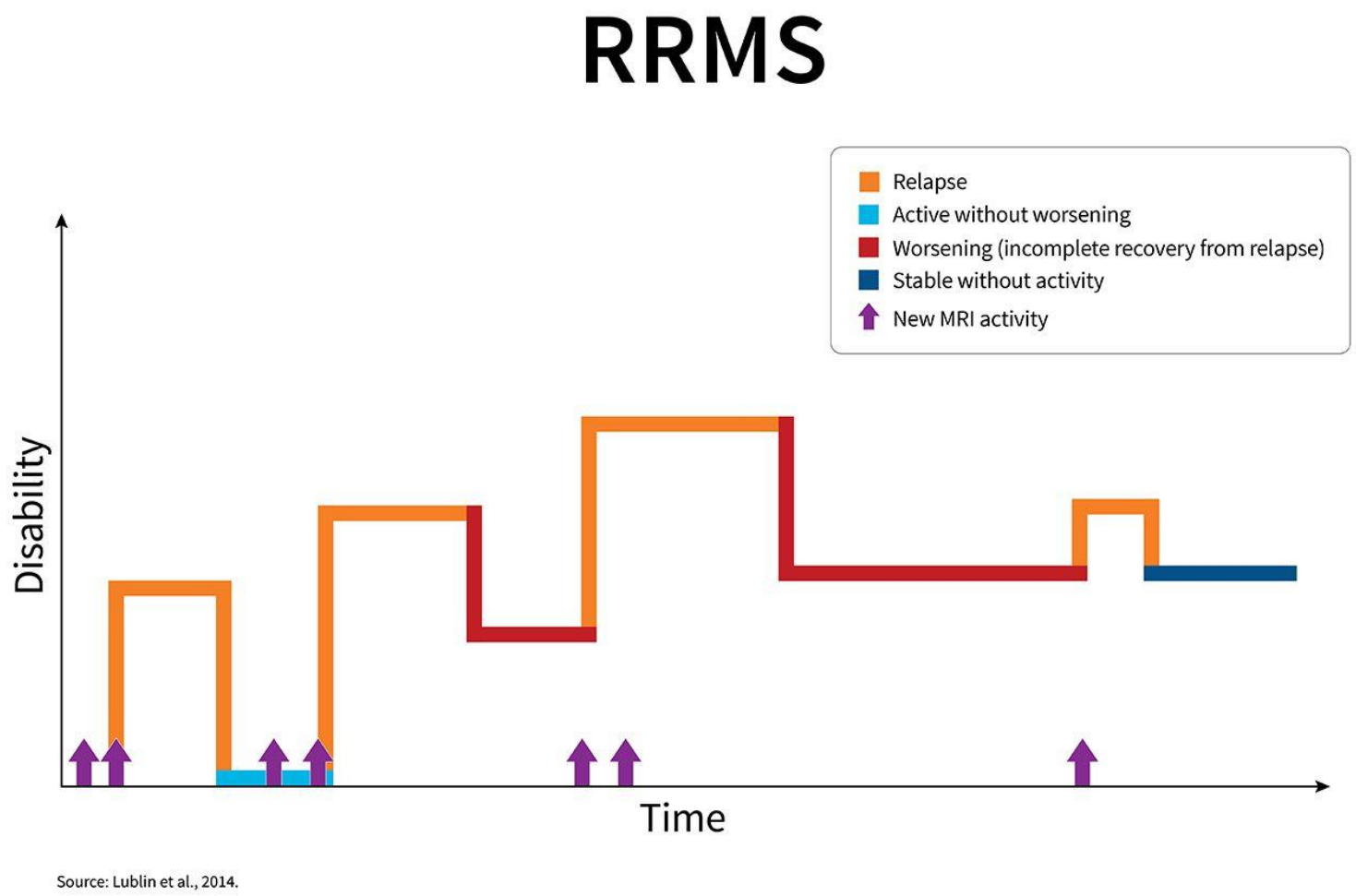
Disease modifying therapy use

Special considerations

MS Overview

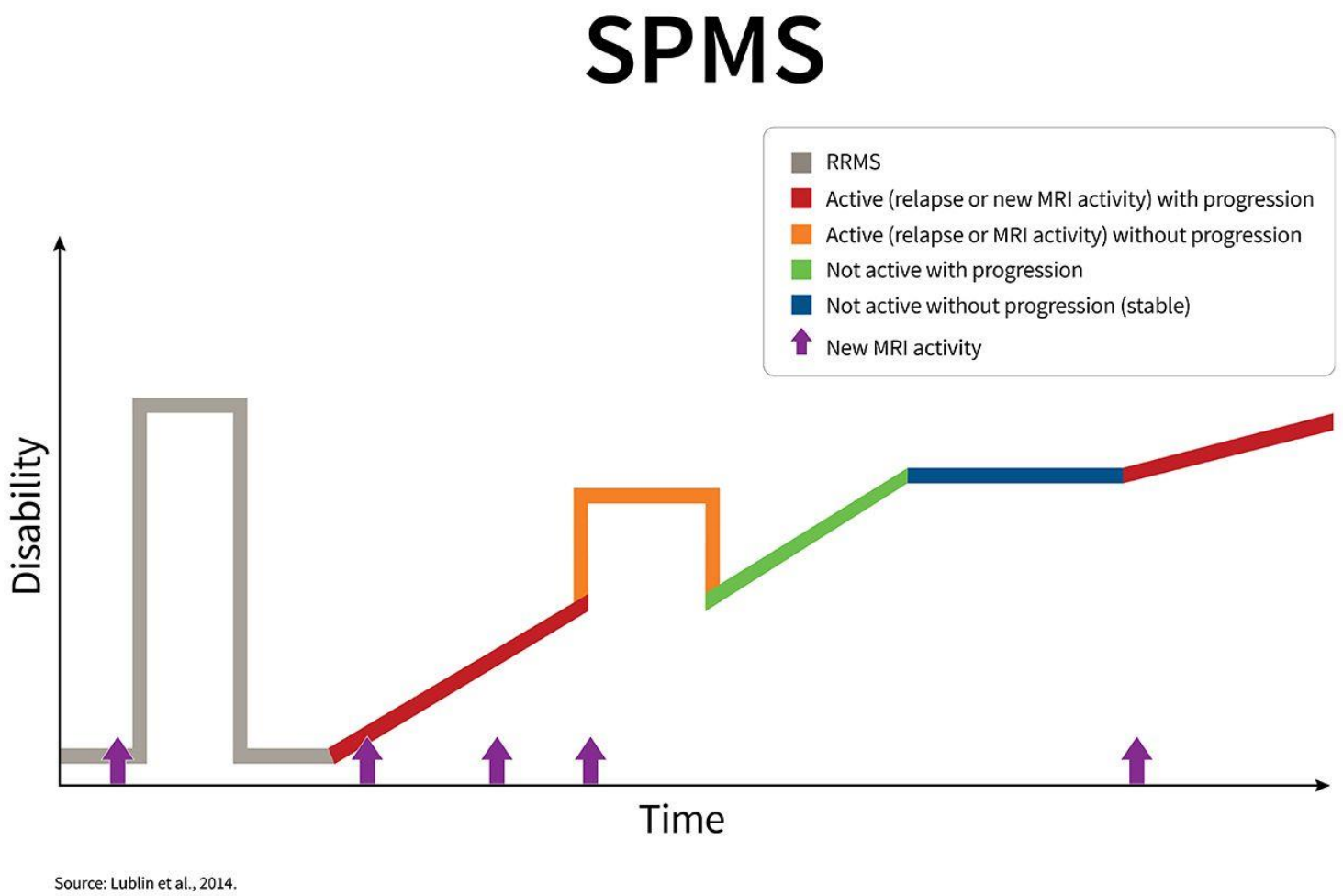
- Age of onset 20-40s
  - Late onset MS (LOMS)
- 2.8 million people worldwide
- The MS population is aging
  - US – peak prevalence 55-64 years
- Normal life expectancy

Disease – Relapsing Remitting



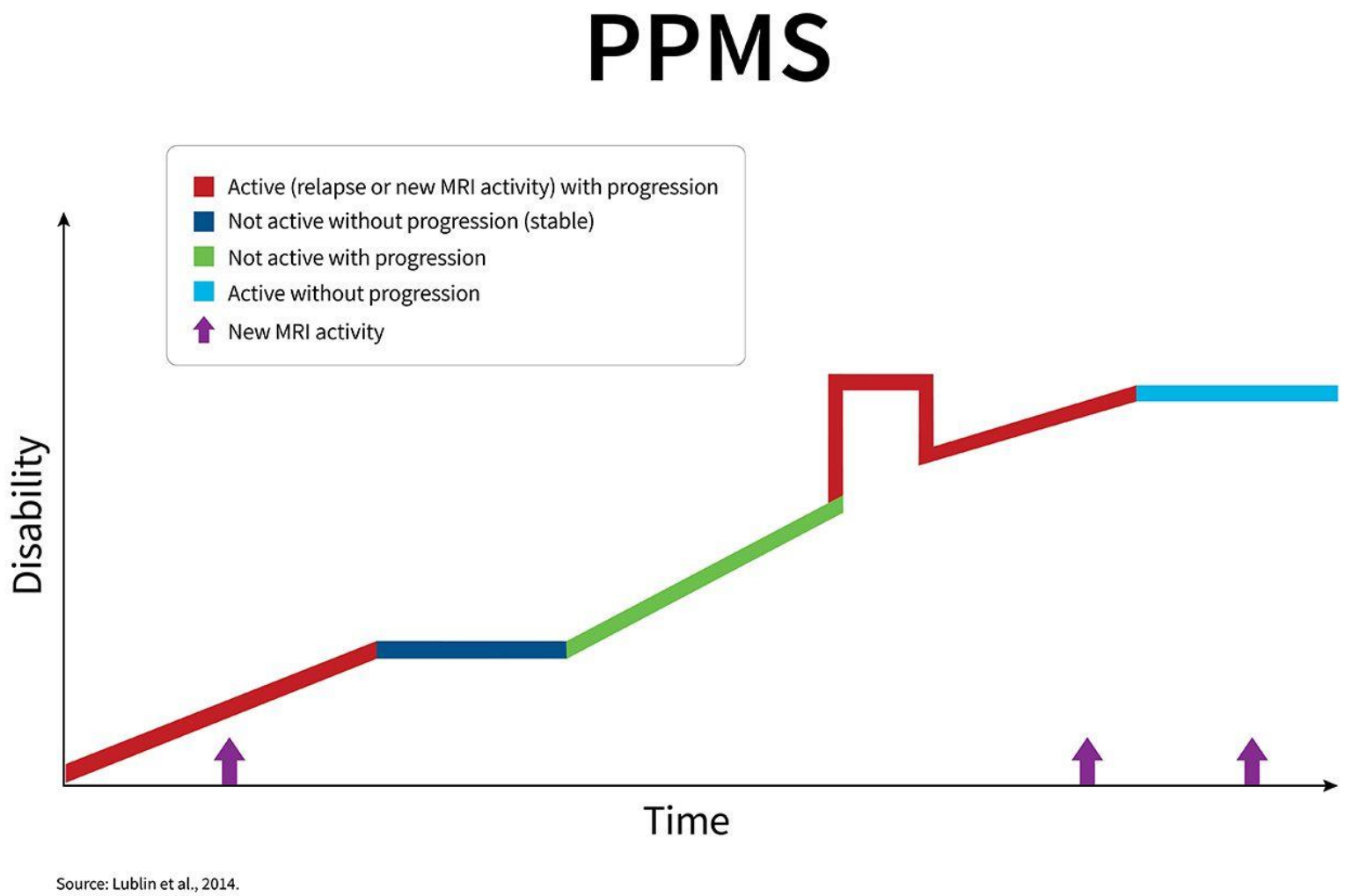
Source: Lublin et al., 2014.

Disease – Secondary Progressive



Source: Lublin et al., 2014.

Disease – Primary Progressive



Source: Lublin et al., 2014.

Expanded Disability Status Score (EDSS)

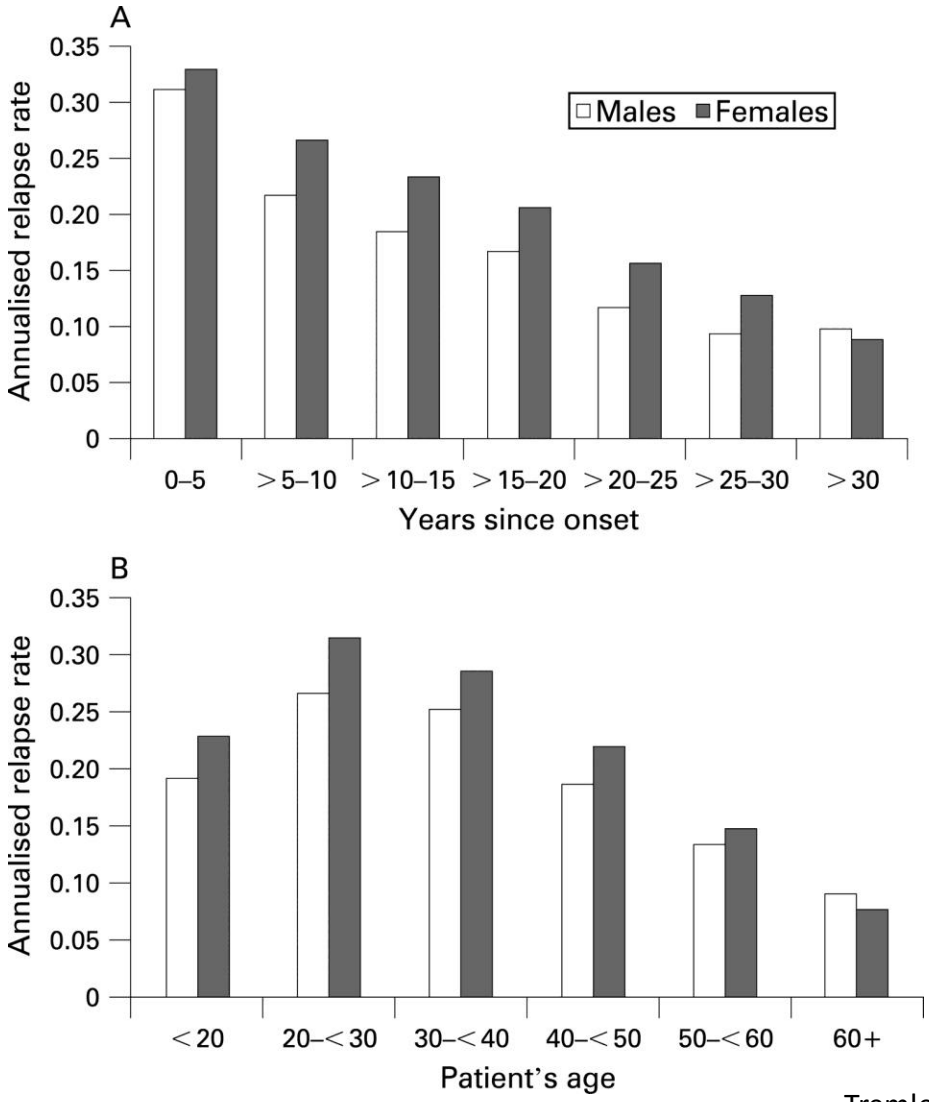
MSTrust.UK.org

Clinical Impact of Aging on MS

- Chronological age most associated with the various features of MS
- Children more likely to relapse
- Young adults experience more relapses than adults
- Chronological age linked to rate of disability accrual
- Atrophy expedites with aging

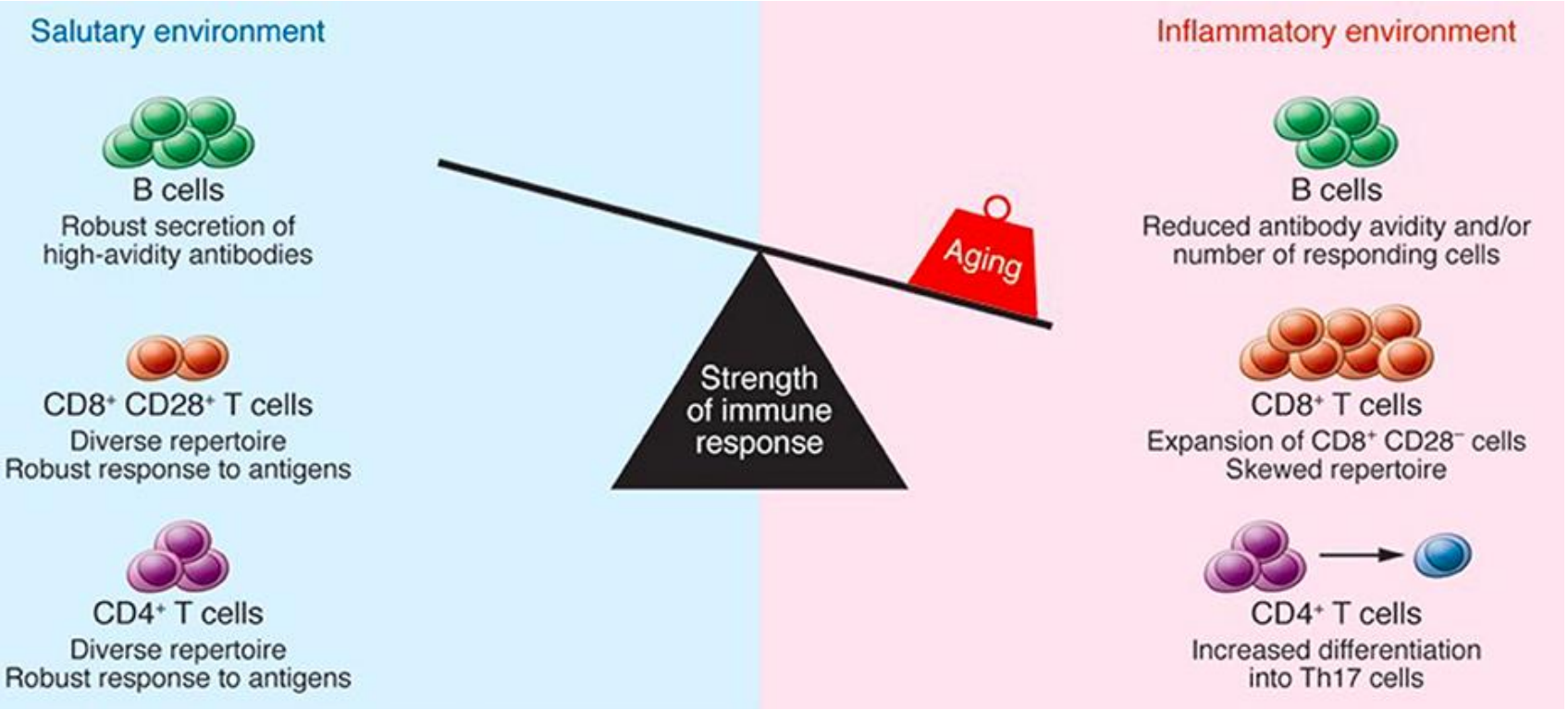
Graves JS, Krysko KM, Hua LH, Absinta M, Franklin RJM, Segal BM. Ageing and multiple sclerosis. Lancet Neurol. 2023 Jan;22(1):66-77. doi: 10.1016/S1474-4422(22)00184-3. Epub 2022 Oct 7. PMID: 36216015.

Relapses are age and time dependent



Tremlett H, et al. *Journal of Neurology, Neurosurgery & Psychiatry* 2008

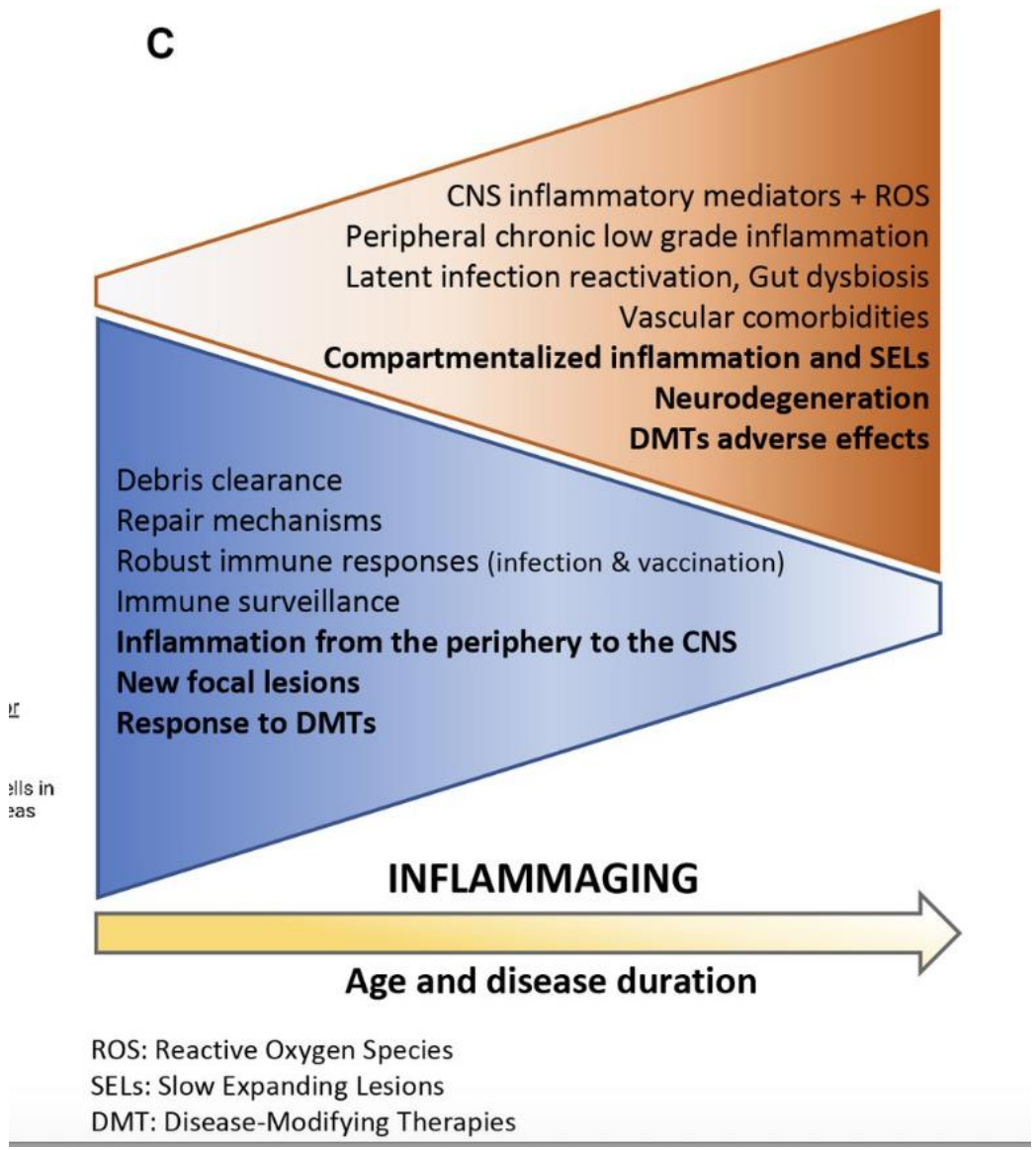
The Aging Immune System



Montecino-Rodriguez E, et al. J Clinical Invest
Simon AK, et al. Proc Biol Sci. 2015

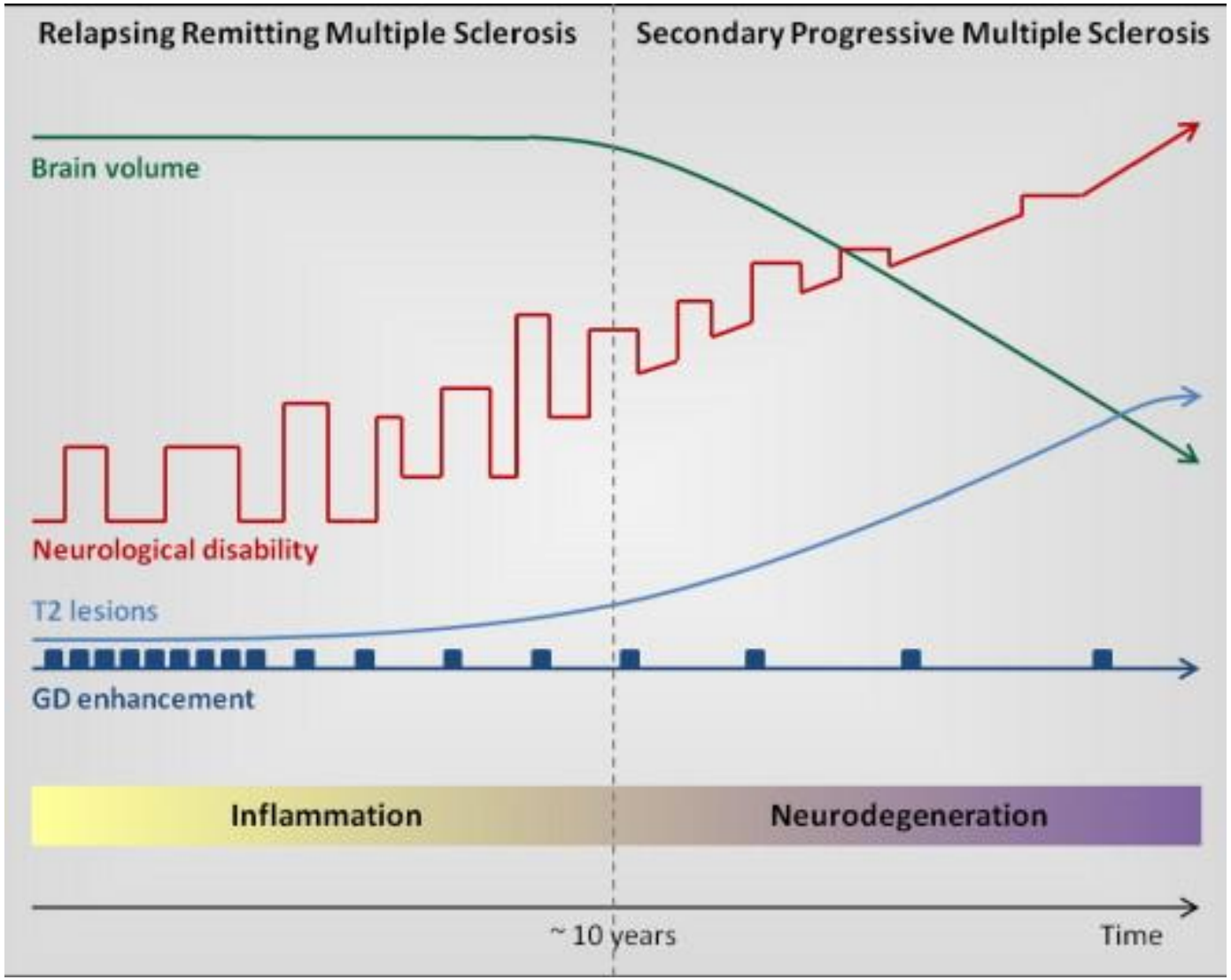
Immunosenescence

- “Age related weakening of adaptive and innate immune responses” (Nikolich-Žugich, 2018)



Macaron G, et al. *Front. Neurol.*, 06 July 2023

Neurodegeneration in MS



Schaeffer J, et al. Neurobiology of Brain Disorders. 2015

Disease Modifying Therapy

- The DMT landscape has rapidly expanded

Disease Modifying Therapy

Varying pharmacokinetics in older patients

Efficacy in age 55 and up less known (Weidman)

- More likely to be progressive
- Do our meds impact degeneration?

Higher risk for adverse events

DISCO-MS

Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial

*John R Corboy, Robert J Fox, Ilya Kister, Gary R Cutter, Charity J Morgan, Rebecca Seale, Eric Engebretson, Tarah Gustafson, Aaron E Miller, on behalf of the DISCOMS investigators**

Can we discontinue DMT in the older patient?

DISCO-MS

- METHODS
  - Randomized, non-inferiority trial
  - Determine risk of disease activity in stable MS* patients age 55 and up who discontinue DMT vs those who stay on DMT

	Continue disease-modifying therapy group (n=128)	Discontinue disease-modifying therapy group (n=131)
Median age (IQR), years	62 (59–68)	63 (59–67)
Sex		
Female	107 (84%)	109 (83%)
Male	21 (16%)	22 (17%)
Race or ethnicity		
Black or African American	12 (9%)	11 (8%)
Hispanic	1 (<1%)	1 (<1%)
White	112 (88%)	119 (91%)
Other	3 (2%)	0 (0%)
Time since symptom onset, years	20·9 (10·4)	23·4 (11)
Time since last documented relapse, years*	13·2 (6·2)	14·5 (7)
Expanded Disability Status Scale score†	3·3 (1·8)	3·4 (1·8)
Multiple sclerosis subtype		
Primary progressive	2 (2%)	6 (5%)
Secondary progressive	18 (14%)	17 (13%)
Relapsing-remitting	108 (84%)	108 (82%)
Disease modifying therapy at randomisation		
Interferon beta-1a	47 (37%)	46 (35%)
Interferon beta-1b	5 (4%)	12 (9%)
Glatiramer acetate	44 (34%)	35 (27%)
Teriflunomide	4 (3%)	4 (3%)
Dimethyl fumarate	15 (12%)	23 (18%)
Fingolimod	12 (9%)	6 (5%)
Natalizumab	1 (0·8%)	3 (2%)
Ocrelizumab	0 (0%)	2 (2%)

Data are n (%) or mean (SD), unless otherwise specified. *Only for participants with relapsing multiple sclerosis and secondary progressive multiple sclerosis. †Baseline Expanded Disability Status Scale score was missing for three participants (continue n=1, discontinue n=2).

DISCO-MS

	Continue disease-modifying therapy group (n/N)	Discontinue disease-modifying therapy group (n/N)	Absolute difference, percentage points (95% CI)	p value
Primary outcome event (relapse or new or enlarging T2 lesion)	6/128 (4·7%)	16/131 (12·2%)	7·5 (0·6 to 15·0)	0·52*
Relapse (post-hoc)	1/128 (0·8%)	3/131 (2·3%)	1·5 (–2·3 to 6·0)	0·0051*
New T2 lesion (post-hoc subanalysis of primary outcome)	5/128 (3·9%)	14/131 (10·7%)	6·8 (0·3 to 13·8)	0·42*
Confirmed Expanded Disability Status Scale progression (rater-blinded secondary outcome)	14/126 (11·1%)	16/130 (12·3%)	1·2 (–7·2 to 9·6)	0·77†

*p value from exact test for inferiority with a non-inferiority margin of 8%. A statistically significant p value indicates that discontinuing disease-modifying therapy was shown to be non-inferior to continuing for that endpoint. A non-significant p value indicates that non-inferiority was not shown. †p value from χ^2 test.

Table 2: **Proportions of participants with a disease event and confirmed Expanded Disability Status Scale progression (intention-to-treat population)**

Corboy JR, Fox RJ, Kister I, Cutter GR, Morgan CJ, Seale R, Engebretson E, Gustafson T, Miller AE; DISCOMS investigators. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial. Lancet Neurol. 2023 Jul;22(7):568-577. doi: 10.1016/S1474-4422(23)00154-0. PMID: 37353277.

Special Considerations for the Aging MS Patient

Drug-Drug interactions

Comorbidities

Vascular comorbidities

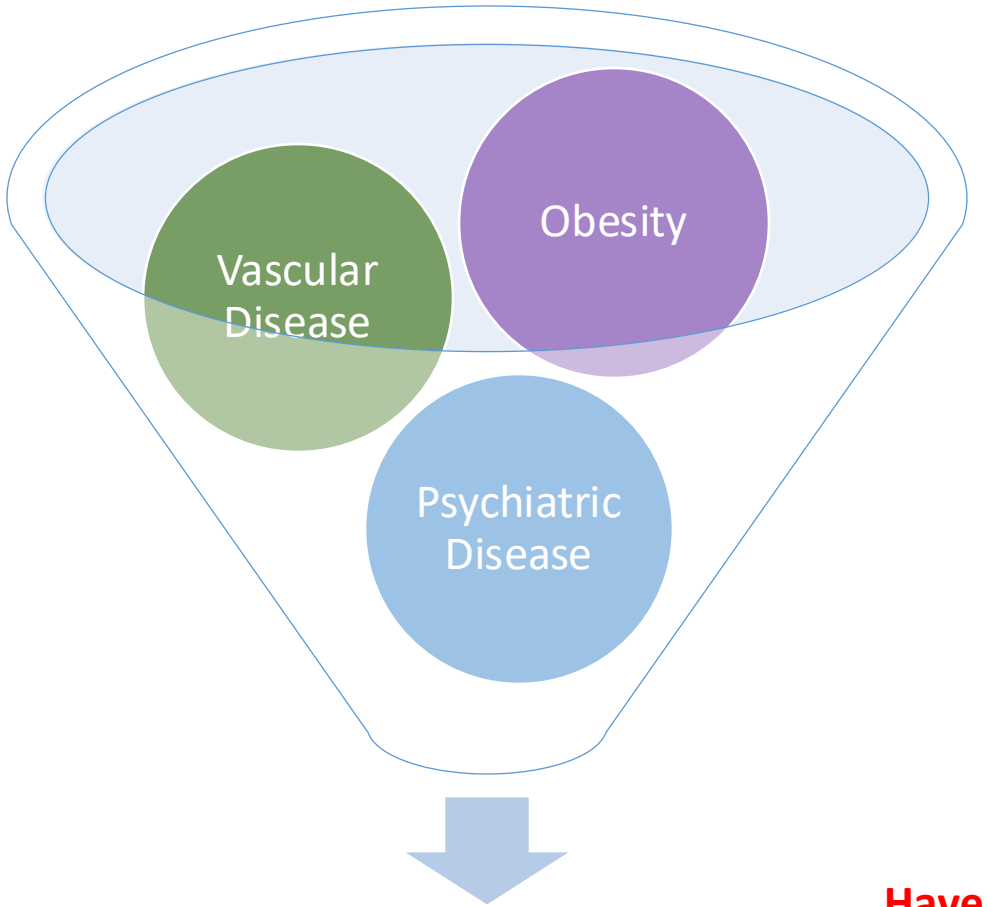
Metabolic comorbidities

Other autoimmune diseases

Psychiatric disorders

Obesity

Comorbid Disease



DISABILITY

Have to also consider the additive impact

Graves JS, Krysko KM, Hua LH, Absinta M, Franklin RJM, Segal BM. Ageing and multiple sclerosis. Lancet Neurol. 2023 Jan;22(1):66-77. doi: 10.1016/S1474-4422(22)00184-3. Epub 2022 Oct 7. PMID: 36216015.
Marck CH, Neate SL, Taylor KL, Weiland TJ, Jelinek GA. Prevalence of comorbidities, overweight and obesity in an international sample of people with multiple sclerosis and associations with modifiable lifestyle factors. PloS One (2016) 11(2):e0148573. doi: 10.1371/journal.pone.0148573
Kowalec K, McKay KA, Patten SB, Fisk JD, Evans C, Tremlett H, et al.. Comorbidity increases the risk of relapse in multiple sclerosis: a prospective study. Neurology (2017) 89(24):2455–61. doi: 10.1212/wnl.0000000000004716
Salter A, Kowalec K, Fitzgerald KC, Cutter G, Marrie RA. Comorbidity is associated with disease activity in Ms: findings from the combirx trial. Neurology (2020) 95(5):e446–e56. doi: 10.1212/WNL.0000000000010024

Practical Considerations

- Have an honest conversation about the role of DMTs
- Shift the focus
  - Don’t forget about therapy services!
- Don’t blame MS for everything
- Control what we can control
  - Separate symptom management from DMTs
- Better studies focused on degeneration are needed

Questions?

References

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