How Comorbidities Complicate Treatment Options and Increase Disease Burden

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Disclosure

ADVISORY BOARDS OR SPEAKER HONORARIA/CONSULTING

Amicus Therapeutics, AstraZeneca, Bayer, Biogen, Hemofarm, Janssen, Medis Therapeutics, Medtronic, Merck, Novartis, Roche, Sanofi-Genzyme, Swiss Pharma, Teva Pharmaceuticals, Zentiva

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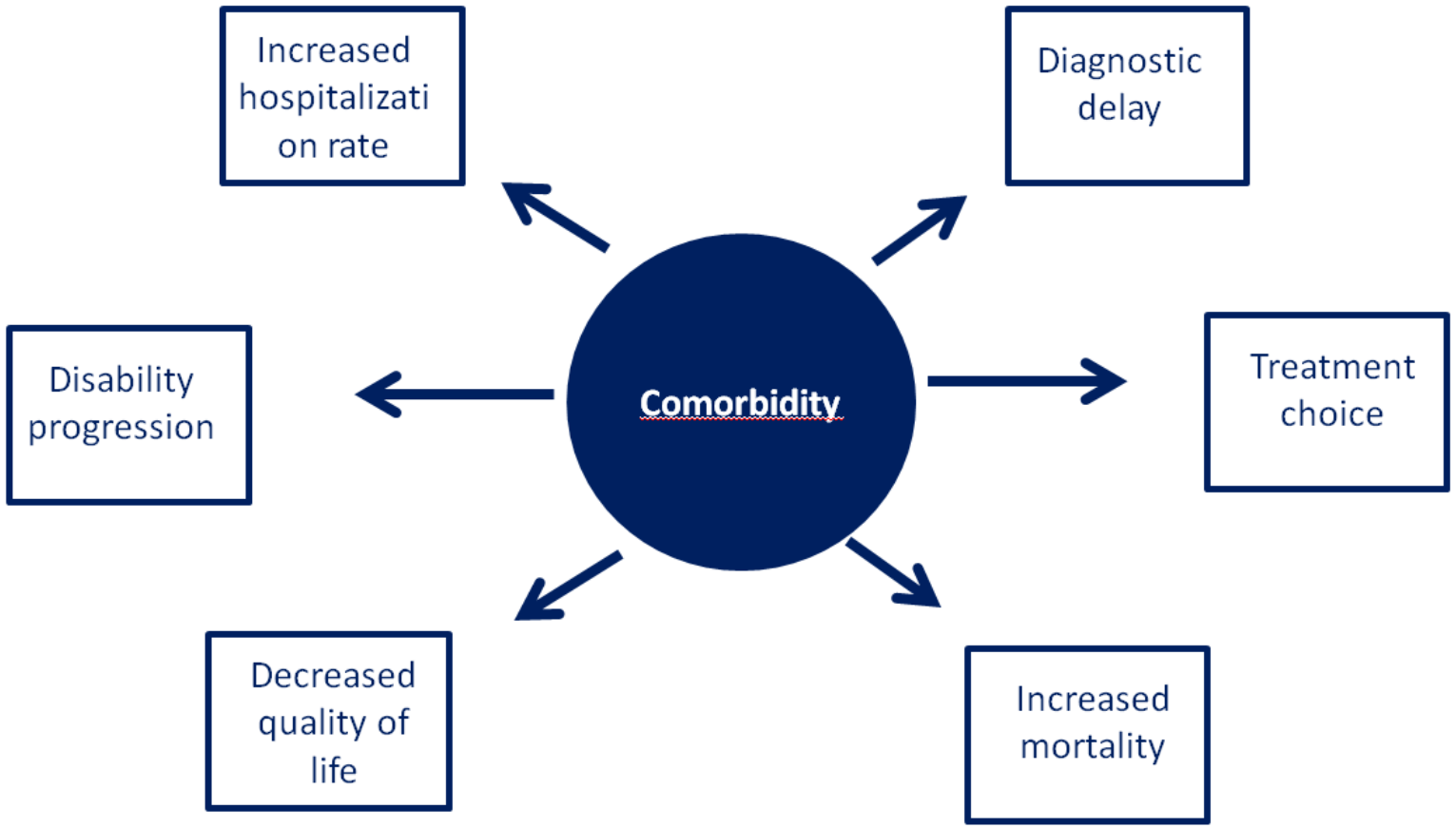
Comorbidity in multiple sclerosis



Marrie RA, et al. Front Immunol. 2023;14:1197195.

Comorbidity in multiple sclerosis

A 2015 systematic review suggested that the most prevalent comorbidities among people with MS were depression (23.7%), anxiety (21.9%), hypertension (18.6%), hyperlipidemia (10.9%) and chronic lung disease (10.0%).

(Marrie RA et al. Mult Scler J 2015)

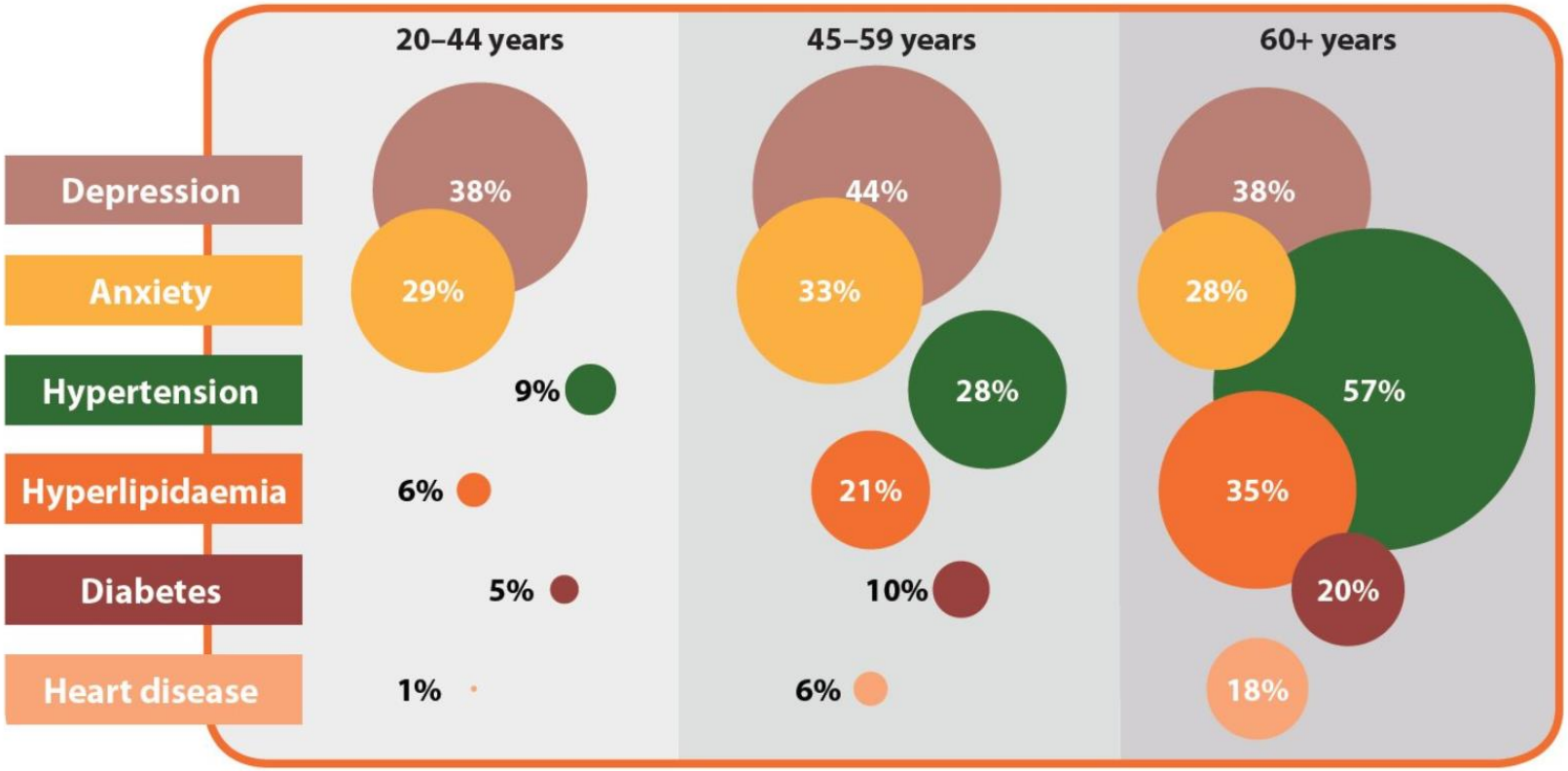


Figure 1. Lifetime prevalence of common comorbidities in people with MS, by age group.[1]

Adapted from: Nat Rev Neurol 2017 ;13(6):375-382

Comorbidity and clinical outcomes in multiple sclerosis: disability

- While some small studies have not observed associations between comorbidity and physical impairments-disability, well-powered studies from Canada and Europe have consistently reported associations.

- The presence of cardiovascular comorbidities in PwMS seems to be related to certain worse clinical outcomes:
    - higher admission risk,
    - accelerated disease and disability progression,
    - higher economic and psychological burden,
    - increased mortality rates.

Shangraw K, et al. Int J MS Care 2022; 24:169–74.; Zhang T, et al. Neurology 2018; 90:e419–e27.; Maric G, et al. Acta Neurol Scand 2022;145:24–9; Frank HA et al. Mult Scler Relat Disord. 2024 ;92:105943.

Cardiovascular comorbidities and multiple sclerosis

Frequent co-occurrence of MS and cardiovascular disorders (CVD) is due at least partially to the higher prevalence of CVD risk factors in persons with MS including:

- the presence of smoking,
- hypertension,
- hyperlipidemia,
- increased body mass index.

In a retrospective cohort of 2,725 individuals from Serbia, hypertension was associated with a shorter time to reaching EDSS scores of 4, 6 and 7. The presence of any of the investigated CVD comorbidities and type 2 diabetes significantly contributed to faster reaching EDSS 4 and EDSS 6.

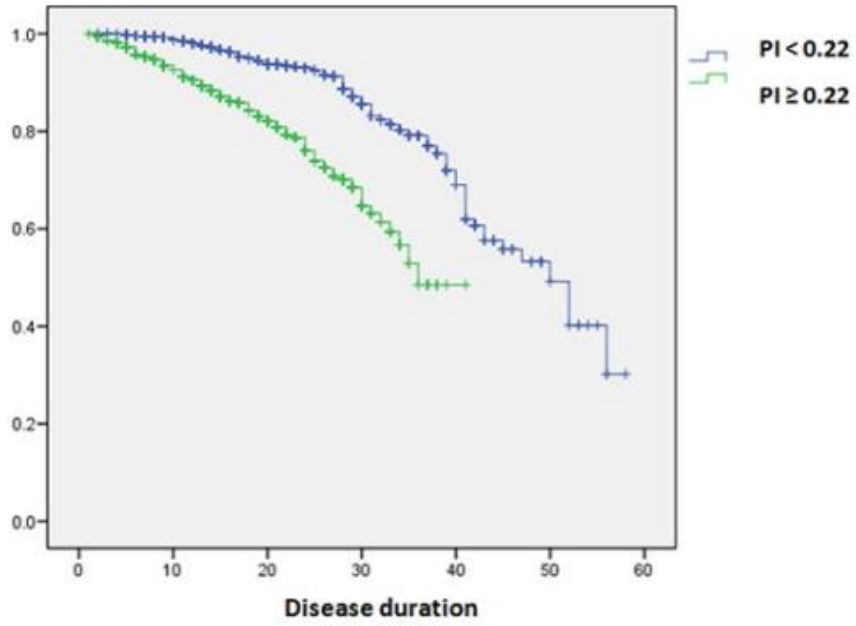


FIGURE 1 The figure presents Kaplan-Meier curves for the occurrence of cardiovascular comorbidities in the total Belgrade MS cohort (2725 PwMS) divided into two groups, according to the median PI value (0.22), MS patients with PI ≥0.22 and MS patients with PI <0.22

Maric G, et al. Acta Neurol Scand 2022;145:24–9; Giannopapas V et al. J Clin Med 2023; 12:4948: Maric et al. PLOS ONE 2024

Insulin resistance

- **Insulin resistance** is when cells in your muscles, fat, and liver don’t respond well to insulin, a hormone made by your pancreas that helps manage your blood glucose (blood sugar).
- Once glucose enters your bloodstream, insulin helps it get into your cells, where it's either used or stored for later.
- If you have insulin resistence, this process doesn't work well. Your cells aren't letting glucose in when insulin "asks" them to. As a result, more and more blood glucose piles up in your bloodstream. And your pancreas keeps making insulin.
- **Prediabetes** usually happens to people who have some insulin resistance. Your blood sugar is higher than normal, but still not high enough for diabetes.
- **Insulin resistance and prediabetes can both lead to type 2 diabetes.** So, much glucose stays in your bloodstream, you will need medication to treat it.

Goldstein BJ. Am J Cardiol. 2002;90:3G-10G

Insulin resistance in multiple sclerosis

- Physical disability, measured by the EDSS score
- Cognitive impairement
- Secondary progressive MS

Ruiz-Argüelles et al. Mult. Scler. Relat. Disord. 2018;25, 316–321.; J Neuroendocrinol 2023;35:e13288; Oliveira et al. Nutrition 2014;268-273

Insulin resistance in multiple sclerosis

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Could the performance of oral glucose tolerance test contribute to the brain health-focused care in multiple sclerosis?

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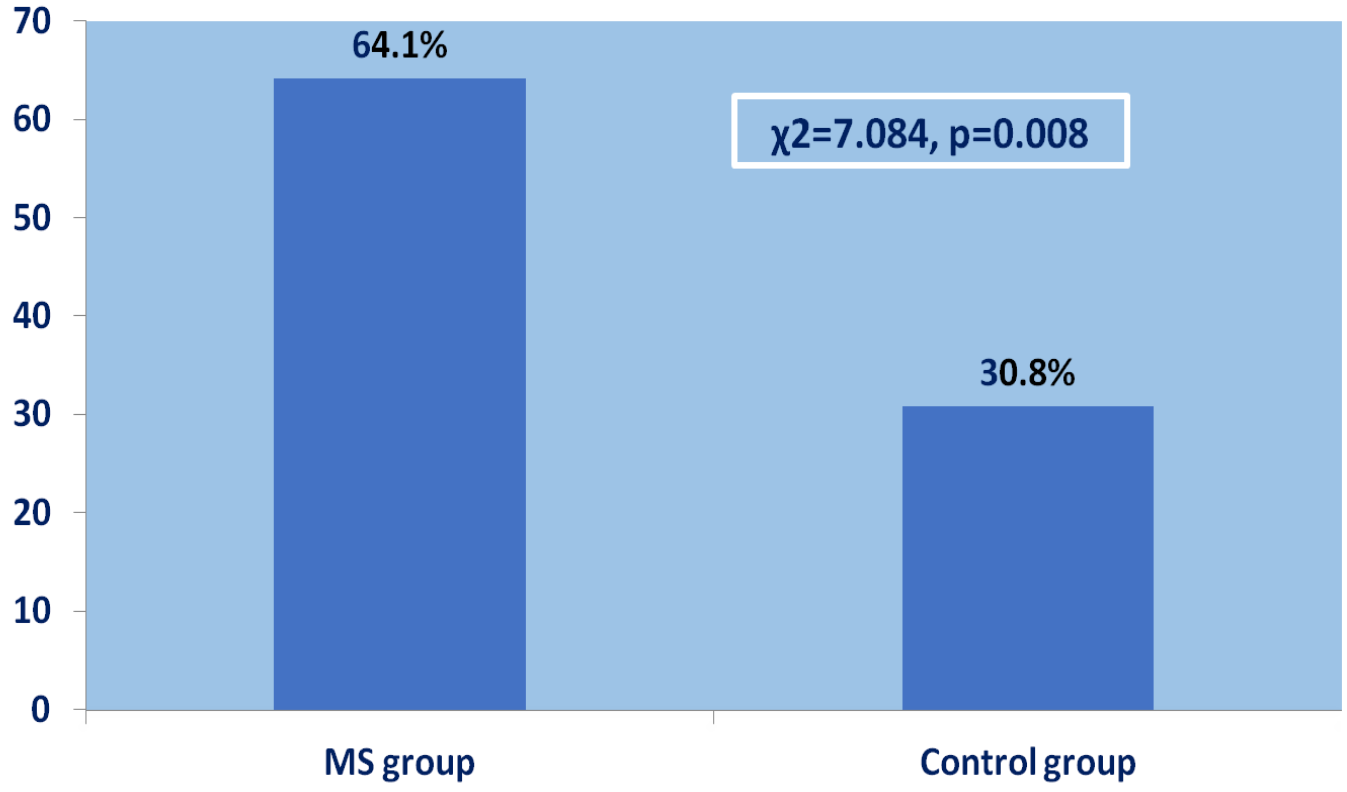
ABSTRACT

Background: It has not been clarified yet if persons with multiple sclerosis (MS) are at increased risk to develop glucose metabolism dysregulation. The aims of the present study were to evaluate glucose metabolism characteristics in persons with MS and to compare it to the healthy individuals; to examine the association of glucose metabolism with the level of disability and its progression.

- MS patients have almost four times higher risk of impaired glucose metabolism in comparison with healthy individuals
- Having in mind correlation with physical disability (EDSS, PI), should the performance of OGTT, HbA1c, be included in the brain health-focused care in MS ?

Prevalence of insulin resistance in MS patients in Serbia



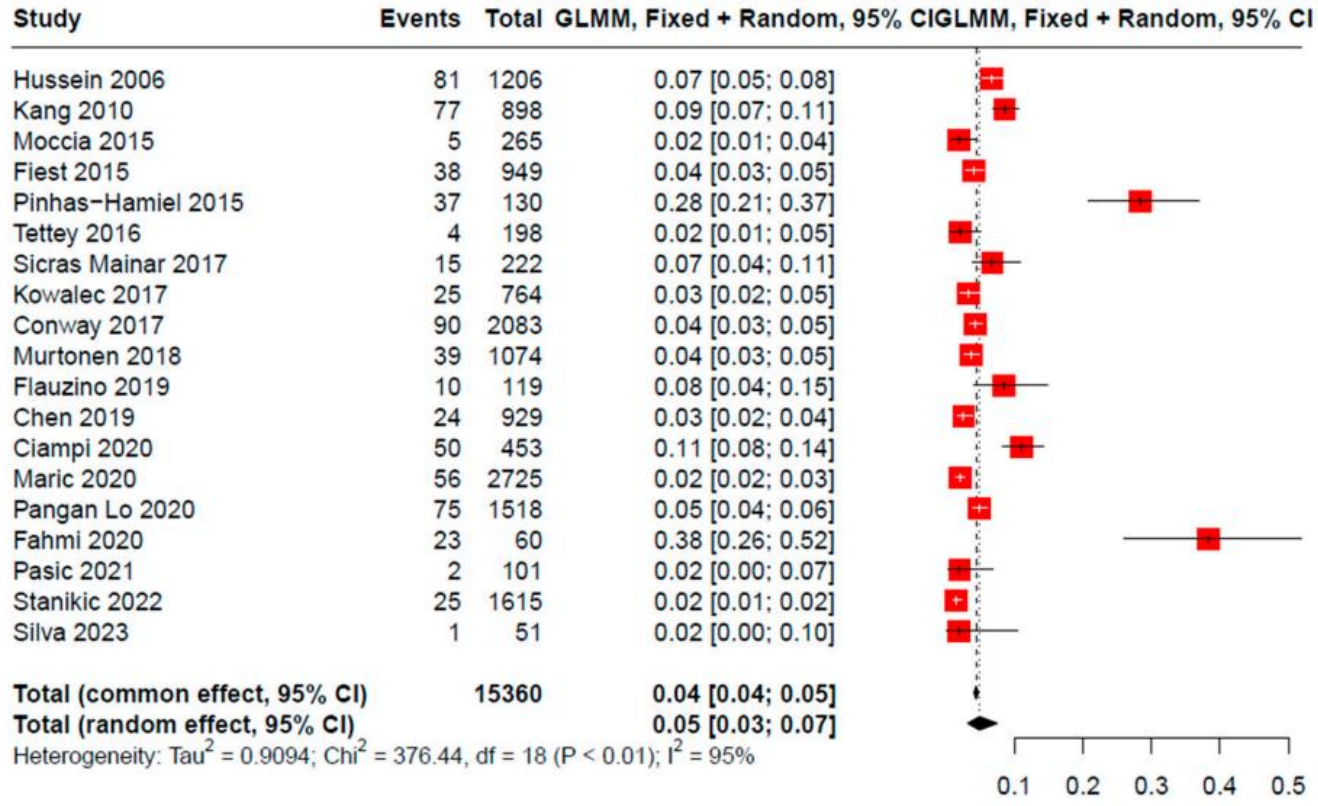
Maric G, et al. Mult Scler Relat Disord 2020;46:102536

Multiple sclerosis and type 2 diabetes

MS patients with type 2 diabetes:

- appear to have **higher levels of fatigue,**
- appear to have **faster cognitive decline and disability progression**,
- are more likely to adopt **a sedentary lifestyle,**
- **have a higher body mass index,**
- **have a higher prevalence of depressive symptoms,**
- **have, a lower quality of life**.

Pooled prevalence of DMII cases among PwMS



Singh, R et al. PLoS ONE 2016, 11, e0165652.; Wong, E. et al. Lancet Diabetes Endocrinol. 2013, 1, 106–114.; Maric G, et al. Acta Neurol Scand 2022;145:24–9; Giannopapas V, et al. J Clin Med. 2023;12:4948.; Giannopapas, V et al. J. Clin. Neurosci. 2023, 112, 20–24.

Multiple sclerosis and comorbid type 2 diabetes

This may

- accelerate the disability progression of patients with MS,
- reduce their functional capacity,
- further increase their psychological and economic burden.

Even though the prevalence of DMII in the MS population is lower than 10%, the interactions between the two conditions create significant challenges for patients, caregivers, and physicians.

Type 2 diabetes should be systematically recorded in MS !!!

Singh, R et al. PLoS ONE 2016, 11, e0165652.; Wong, E. et al. Lancet Diabetes Endocrinol. 2013, 1, 106–114.; Maric G, et al. Acta Neurol Scand 2022;145:24–9; Giannopapas V, et al. J Clin Med. 2023;12:4948.;Giannopapas, V et al. J. Clin. Neurosci. 2023, 112, 20–24.

Relationship between comorbidities and the disease-modifying therapies used to treat multiple sclerosis

Direction and summary of effect	Observed effect of the comorbidity	Specific examples from the literature	Examples of key outstanding issues and/or directions for future work
Comorbidity → DMTs			
Comorbidity may affect DMT use	Delay or prevent initiation of a DMT	• ≥3 vs. no comorbidities present at MS diagnosis associated with a 25% lower risk (hazard) of starting a DMT (83) • specific comorbidities present at diagnosis - anxiety or ischemic heart disease - associated with a 22-28% lower risk (hazard) of starting a DMT (83) • only the injectable DMTs were studied (IFNB, GA)	Information is limited: • for the more recently approved DMTs (including orals and infusions) • across many world regions and healthcare settings (most cited studies are from Canada/N. Europe & universal health care settings)
	Lower DMT adherence	• Alcohol dependence associated with two-fold higher odds of poor adherence (<80% expected doses in last 30 days) to DMTs over 2-year study period (87) • only the injectable DMTs were studied (IFNB, GA)	
	Earlier DMT discontinuation	• Mental health disorders or antidepressant use associated with a 47-51% higher risk (hazard) for earlier DMT discontinuation (84)	
	Earlier DMT switch or escalation	• Presence of any comorbidity associated with a 42% higher risk of earlier safety or tolerability-related switch from first DMT used; findings differed by DMT (86) • Higher cardiovascular risk score associated with earlier escalation of DMT (36)	

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Relationship between comorbidities and the disease-modifying therapies used to treat multiple sclerosis

Direction and summary of effect	Observed effect of the comorbidity	Specific examples from the literature	Examples of key outstanding issues and/or directions for future work
DMTs → comorbidity			
DMTs may affect subsequent comorbidity burden	DMT triggers/causes onset of new disease‡	• alemtuzumab-associated autoimmune disease (affects 1 in 3 users) (88, 89) • mitoxantrone-associated cardiotoxicity and acute myeloid leukemia • several DMTs associated with severe hepatoxicity • several DMTs associated with risk of hypertension	DMT use and cancer risk largely unknown; long-term follow-up in large cohorts needed
	DMT worsens/re-activates an existing comorbidity or underlying comorbidity increases risk of another comorbidity‡	• Ofatumumab may reactivate hepatitis B virus • Macular oedema associated with several DMTs; presence of diabetes may increase risk	
	DMT improves an existing comorbidity	• Emerging work suggests that some DMTs (e.g., fingolimod) may improve underlying depression (unclear if direct or indirect effect) (90)	Limited work in this area. Inclusion of persons with comorbidities in clinical trials offers opportunity to provide further insights

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Comorbidity management in multiple sclerosis

Needs to be integrated into MS care, and this would be facilitated by determining optimal models of care !

Management Concern	Optimal Approach	Specific MS Considerations
Single-disease focus adopted by healthcare systems & providers (result: fragmented, inefficient & sometimes discordant care and adverse health/quality of life consequences for person with MS and their family caregivers)	Reconfigure and technologically enhance healthcare systems – including improved balance & integration of, and communication between, specialists, generalists, and primary care providers Develop & implement healthcare policies that account for comorbidity and facilitate integration/continuity of care and person/family centered approaches Modify existing curricula to better educate new clinicians about comorbidity and its prevention & management	Include persons with MS and their family caregivers in discussions of what changes are most needed and how best to implement them Focus first on changes to healthcare systems/policies that prioritize complex comorbidity (e.g., affect multiple body systems), prevalent disease clusters (e.g., MS with depression), and/or comorbidity deemed most important to persons with MS/family caregivers Expand MS-focused interdisciplinary care teams that address identified priorities, collaborative (health & social) care needs, and support self-management, medicines management, and healthy behaviours including those relevant to comorbidity Conduct research on implementation efforts and include outcomes important to persons with MS/family

Adapted from: Marrie RA, et al. Front Immunol. 2023;14:1197195

Thank you for your attention!

University Clinical Center of Serbia

Multiple Sclerosis Association of Serbia