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CONy and Teva Neuroscience MS Matters live webinar series

MS Matters: Exploring the bi-directional relationship between MS and comorbidities

This webinar was organised and funded by Teva Pharmaceuticals Europe B.V.
Date of preparation: November 2019 | HQ/MS/19/0028

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Welcome and introduction

Prof. Sven Schippling

Faculty

Prof. Sven Schippling, Moderator

Deputy Head of the Department of Neuroimmunology and Clinical Multiple Sclerosis Research (nims) at the University Hospital Zürich, Switzerland

Dr Marja-Liisa Sumelahti, Presenter

Associate Professor of Neurology at the Neuroimmunology Unit, Faculty of Medicine and Life Science, University of Tampere, Finland

Agenda

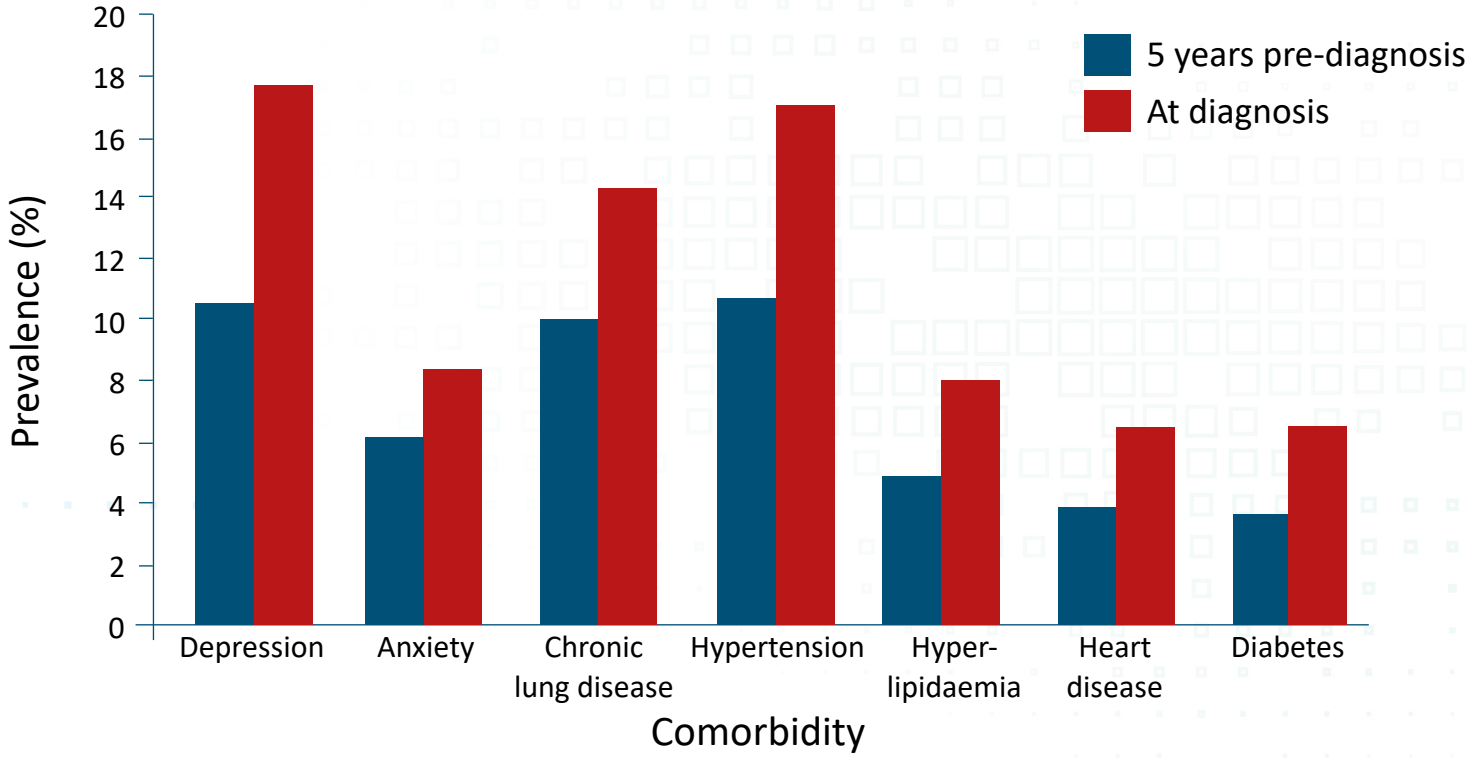
Time (CEST)	Title	Speaker
13:30	**Welcome and introduction**	Sven Schippling
13:35	**A two-way street for MS and its comorbidities**	Marja-Liisa Sumelahti
13:45	**Audience Q&A**	All
13:50	**Comorbidities and MS progression**	Marja-Liisa Sumelahti
14:00	**Audience Q&A**	All
14:05	**Managing patients with MS and their comorbidities**	Both
14:20	**Audience Q&A**	All
14:25	**Closing remarks**	Sven Schippling

Conflicts of interest

- Sven Schippling is supported by the Swiss National Science Foundation (SNF), the Swiss Multiple Sclerosis Society, the Betty and David Koetser Foundation for Brain Research and the Myelin Repair Foundation (USA)
- He is Co-Director of the Clinical Research Priority Program for Multiple Sclerosis (CRPPMS) supported by the University of Zürich, Switzerland
- He is a member of the International Clinical Consortium of the Guthy-Jackson NMO Charitable Foundation (California, USA)
- He sits on the steering committees of the OCTIMS, PASSOS, BENEFIT, REFINE, EMPIRE, ENSEMBLE and CLARIFY-MS trials, the MS in the 21st Century and the ParadigMS initiatives
- He is a founding member of the Neuromyelitis Optica Study Group (NEMOS) in Germany, and the Drug Development Network (DDNZ) in Zürich, Switzerland
- He has received travel support as well as speaker fees from Actelion, Almirall, Bayer Healthcare, Biogen, Sanofi Genzyme, Merck, Novartis, Roche, Santen, Teva

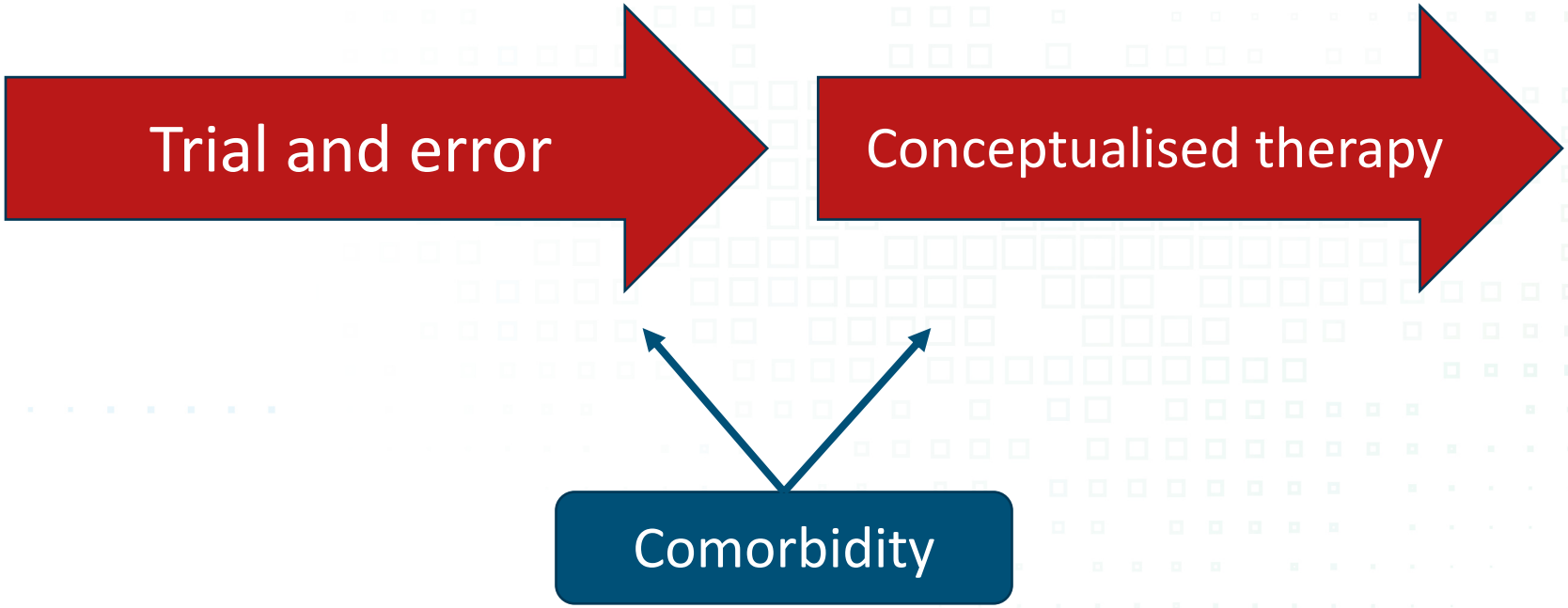
NMO, neuromyelitis optica

Prevalence of comorbidity at MS diagnosis and 5 years earlier (n=23,382)



Marrie RA, et al. Nat Rev Neurol. 2017;13(6):375–82

Trial and error and conceptualised therapy in MS



A changing MS patient profile

More **younger** patients with MS due to shorter times to diagnosis:

- 1996: 5.3 ± 4.2 years
- 2016: 1.16 ± 2.6 years
  - p<0.001

+

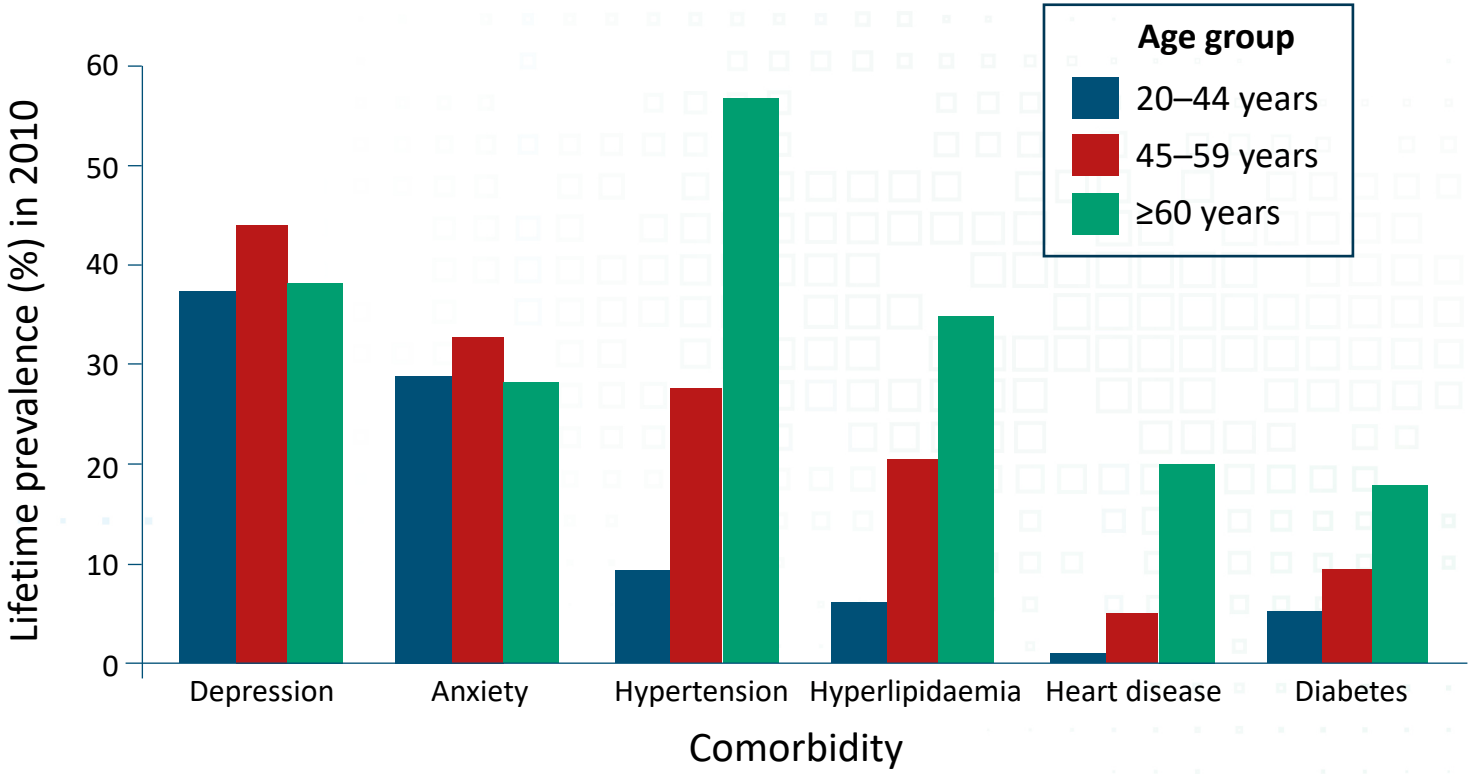
More **elderly** patients with MS due better treatment and general increased life expectancy

=

A challenge to treat younger patients (psychiatric comorbidities) and elderly patients (CV disease and cancer)

Ozakbas, S et al. Mult Scler Relat Disord. 2019;33:1-4

Age-specific prevalence of common comorbidities in a prevalent MS cohort



Marrie RA, et al. Nat Rev Neurol. 2017;13(6):375–82

A two-way street for MS and its comorbidities

Dr Marja-Liisa Sumelahti

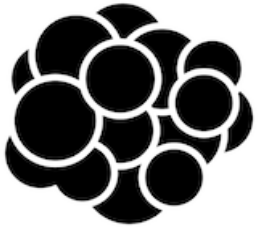
Conflicts of interest

- Grant/Research Support/Advisory Board:
  - Novartis, Merck
- Lectures, workshops, conferences:
  - Roche, Biogen, Novartis, Allergan, Teva, Merck

Autoimmune, vascular and cancer comorbidities – their association with MS

- Increased risk of inflammatory bowel disease
- Possible increased risk of pemphigoid[1]
- An impact of smoking on this shared risk?[2]

- Association of **vascular** comorbidity with rapid disability progression in MS[3]
- Significantly higher risk for **ischaemic** (odds ratio [OR] 1.49) and **haemorrhagic** (OR 2.5) strokes in MS vs controls[4]



- Only association between **cancer** and MS is through previous immunosuppression exposure[5]
- Non-significant OR of 0.80 (p=0.092) for cancer risk in MS vs controls[6]

1. Marrie RA, et al. Mult Scler. 2015;21(3):282–93; 2. Marrie RA, et al. Neuroepidemiology. 2011;36(2):85–90; 3. Marrie RA, et al. Neurology. 2010;74(13):1041–7; 4. Murtonen A, et al. Mult Scler Relat Disord. 2018;19:109–14; 5. Ragonese P, et al. BMC Neurol. 2017;17(1):155; 6. Hongell K, et al. Mult Scler Relat Disord. 2019;35:221–7

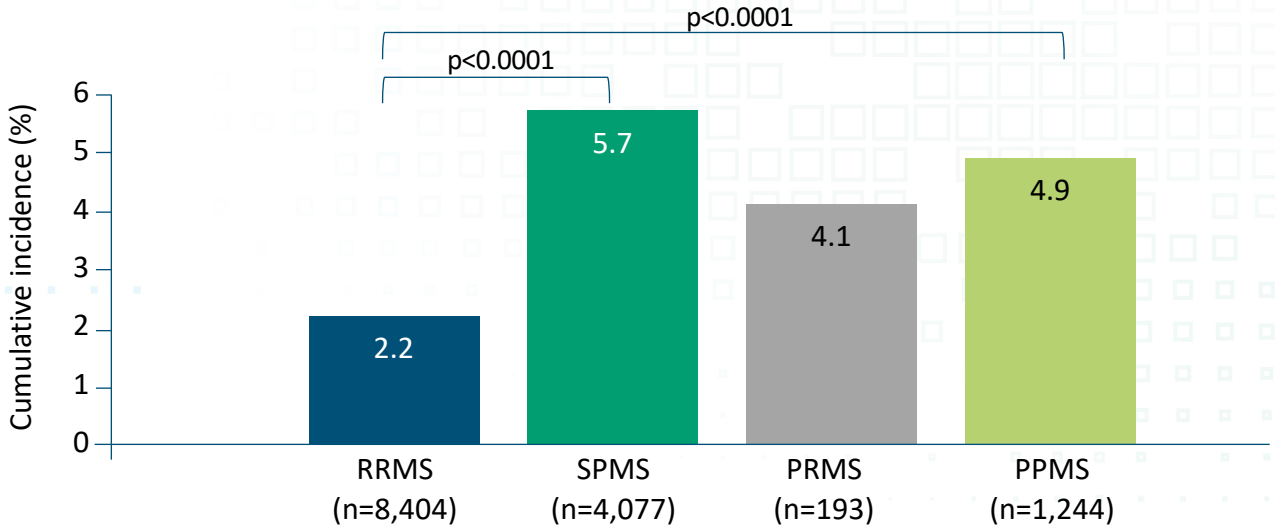
Epilepsy and MS

There is a direct link between MS severity and epilepsy[1]

A meta-analysis of 11 studies showed an increased epilepsy risk in patients with MS of 3.09 (95% CI: 2.01–4.16)[2]

MS lesions in grey matter may increase susceptibility to epilepsy[1]

Cumulative incidence of epilepsy in patients with MS[1]



PPMS, primary progressive MS; PRMS, progressive–relapsing MS; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS

1. Burman J & Zelano J. Neurology. 2017;89(24):2462–68; 2. Marrie RA, et al. Mult Scler. 2015;21(3):282–93

Depression and MS

50% of patients with MS also have depression; generally 2- to 3-times higher than in general population[1]

- **Biological mechanisms** (e.g. hippocampal microglial activation, lesion burden, regional atrophy)[1]
  - Grey matter atrophy, white matter abnormalities and corpus callosum involvement in psychiatric diseases have common features with MS[2]
- **Stressors**, **threats** and **losses** that accompany living with an unpredictable and often disabling disease[1]

Prominent risk factors such as younger age, female sex and family history of depression are less consistently associated with depression in MS than they are in the general population[1]

1. Patten SB, et al. Int Rev Psychiatry. 2017;29(5):463–72; 2. Sparaco M, et al. J Neurol. 2019 [Epub ahead of print]

Fatigue: A complex relationship with MS

Is fatigue a symptom of MS or a MS-related comorbidity?

Prevalence of fatigue among 949 patients with MS: 38.8%

Prevalence was higher in the following groups:

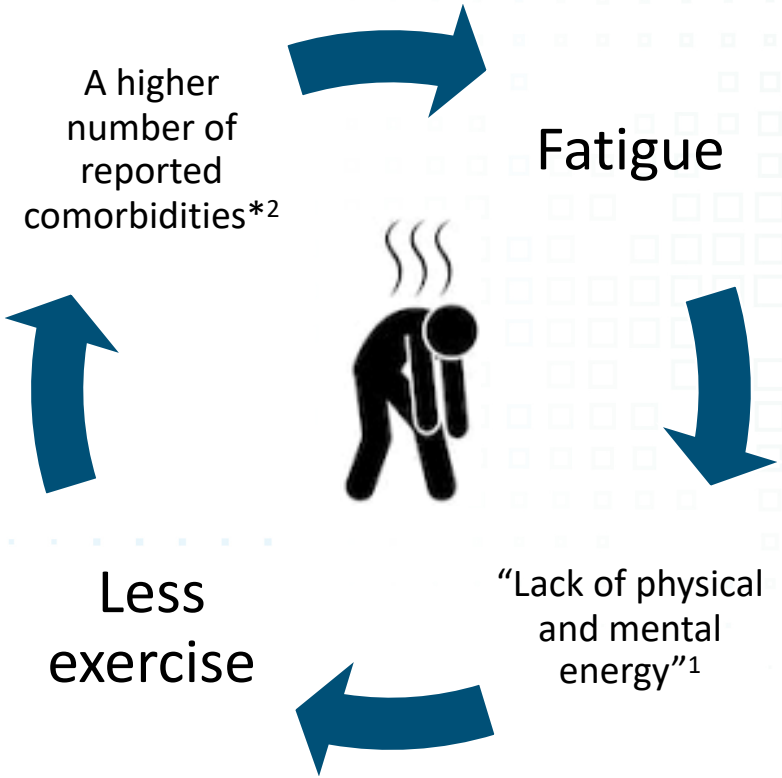
- Older age (p=0.0004)
- Longer time since symptom onset (p=0.005)
- Greater disability (p<0.0001)

Comorbidities that were independently associated with fatigue

- Migraine
- Anxiety
- Depression
- Irritable bowel syndrome

Fiest KM, et al. Int J MS Care. 2016;18(2):96–104

A proposed fatigue cycle



*Those not meeting the physical activity guidelines **reported a higher number of comorbidities** than those meeting physical activity guidelines ($p<0.01$)[2]

1. Fiest KM, et al. Int J MS Care. 2016;18(2):96–104; 2. Balto JM, et al. Am J Health Behav. 2017;41(1):76–83

Comorbidities and MS progression

Dr Marja-Liisa Sumelahti

Why it is important to consider comorbidities for the quality of life in patients with MS

The consequence of the interaction with MS symptoms

Detrimental effects on many health outcomes

Comorbidity considerations in MS

Distinguishing between comorbidity and MS complication

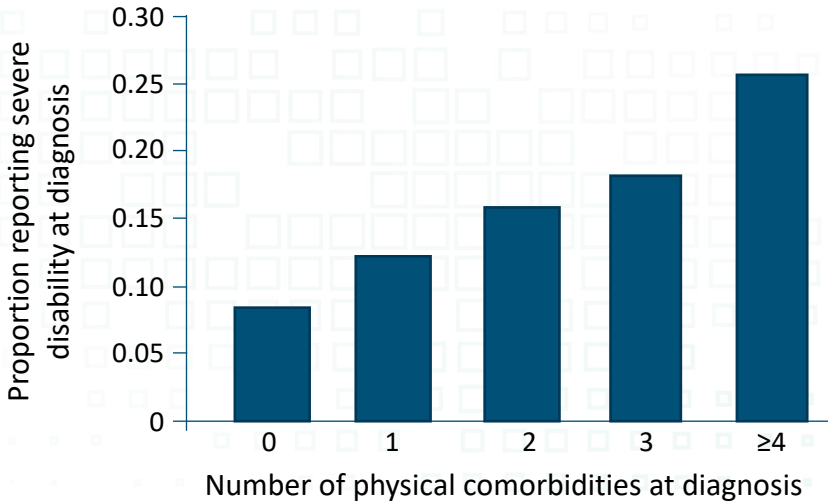
Different underlying mechanisms: different management approaches

Clinical opinion of speaker

Comorbidities and diagnosis

Comorbidity is associated with diagnostic delays and the severity of disability at diagnosis[1]

NARCOMS Study:
Severe disability at diagnosis VS number of physical comorbidities present[2]



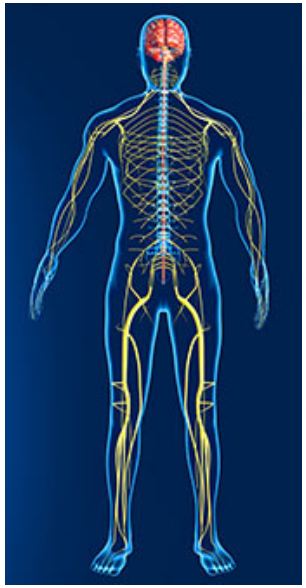
Comorbidities mask symptoms?

Untreated MS or comorbidity: greater disability at diagnosis?

NARCOMS, North American Research Committee on Multiple Sclerosis

1. Marrie RA. Nat Rev Neurol. 2017;13(6):375–382; 2. Marrie RA, et al. Neurology. 2009;72(2):117–24

Comorbidity adversely influences MS throughout the disease course



Comorbidities in MS

Diagnosis, disease activity and progression

Delays in diagnosis:
- Obesity, physical or mental comorbidity

Disability progression:
- Vascular comorbidity
- Mood changes

Relapse rate:
- Number of comorbidities
- Migraine, hyperlipidaemia

HRQoL

- Depression
- Social support

Treatment

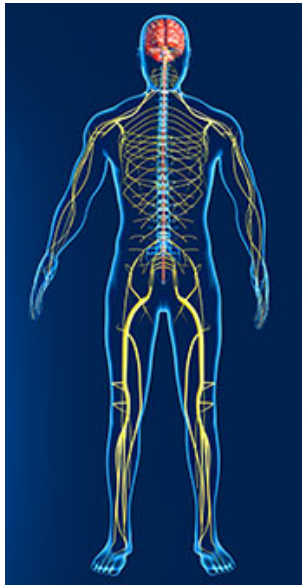
- DMTs
- Symptomatic treatment

DMT, disease-modifying therapy; HRQoL, health-related quality of life

Marrie RA. Clin Invest Med. 2019;42(1):E5–12

Comorbidity adversely influences MS throughout the disease course

Obesity, smoking, inactivity, treatment adherence



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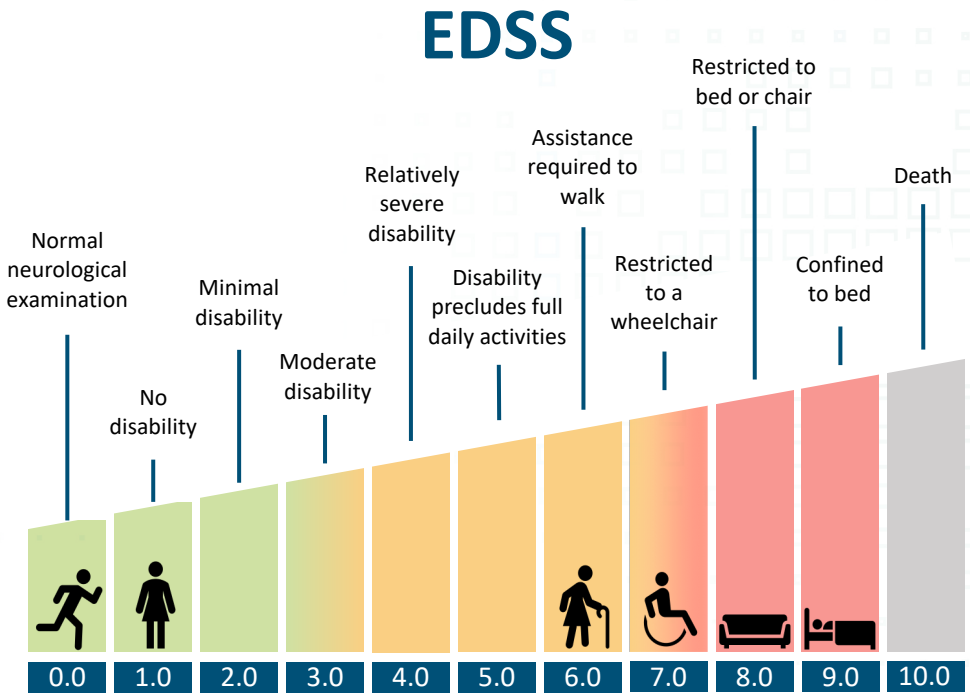
Marrie RA. Clin Invest Med. 2019;42(1):E5–12

Comorbidities and disability progression



Adapted from Kurtzke JF. Neurology. 1983;33:1444–52

- Any mood or anxiety disorder was associated with **a mean increase in the EDSS score (β coefficient: 0.28 [0.13–0.44])**[1]
- Physical comorbidities are associated with an apparent increase in MS disability progression[2]
- The combination of MS and psychiatric comorbidity synergistically increased the risk of receiving a disability pension[3]

EDSS, Expanded Disability Status Scale

1. McKay KA, et al. Neurology. 2018;90:e1316–23; 2. Zhang T, et al. Neurology. 2018;90(5):e419–27; 3. Tinghog P, et al. BMC Neurol. 2014;14:117

Managing patients with MS and their comorbidities

Prof. Sven Schippling and Dr Marja-Liisa Sumelahti

Do comorbidities impact DMT use?

Physician's perspective

Choice of treatment: DMT and symptomatic

When to start treatment

E.g. a Canadian study (n=10,698) showed that more comorbidities, decreased the likelihood of initiating a DMT

Comorbidity and DMT

Patient's perspective

Adherence

Challenges with managing other medication

Marrie RA. Nat Rev Neurol. 2017;13(6):375–382

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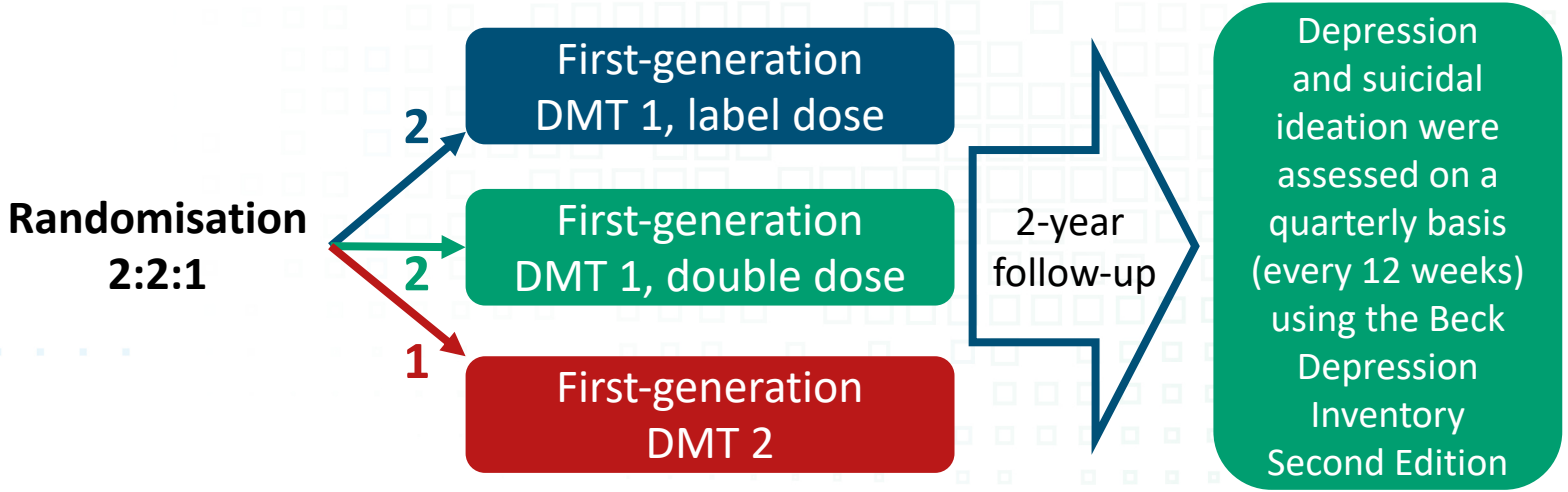
The contemporary view on first-generation DMTs links with psychiatric comorbidities: The BEYOND study

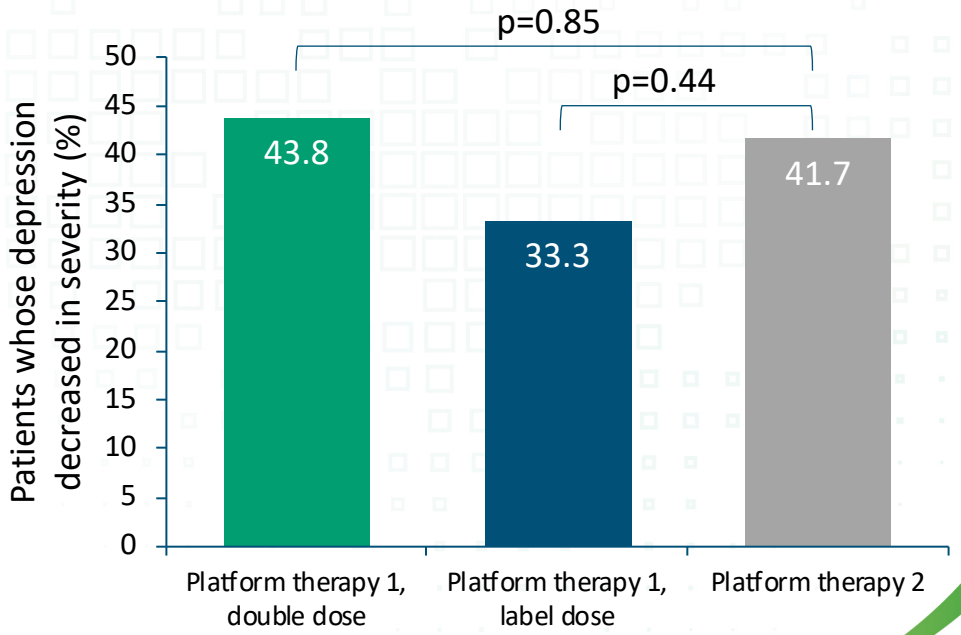


DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; RRMS, relapsing–remitting MS
Schippling S, et al. J Neurol. 2016;263(7):1418–26

The available dataset show no increased risk of depression associated with first-line DMTs

- There were initial concerns that a first-line therapy might provoke onset[1]
- Recent trials looked into the psychiatric effects of first-generation DMTs[1,2]

BEYOND trial: Proportion of patients who received a first-generation DMT and had reduced depression scores (n=794)



DMT, disease-modifying therapy

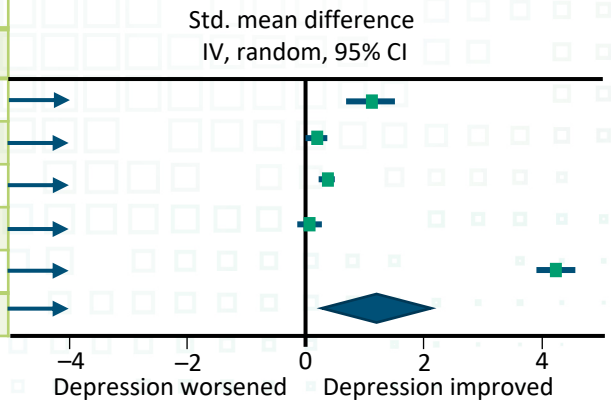
1. Schippling S, et al. J Neurol. 2016;263(7):1418–26; 2. Zecca C, et al. BMC Neurol. 2019;19:159

More recent DMTs are not associated with an increased risk of psychiatric comorbidities

- The meta-analysis showed that five second-generation DMTs were **not associated with an increased risk of adverse psychiatric effects** in MS, and some may **reduce the incidence of depressive symptoms**. An example of one second-generation DMT can be seen here:

	Baseline			End of study				Std. mean difference
Study or subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight (%)**	**IV, random, 95% CI**
Bayas (2016)	19.8	5.47	52	13.7	5.47	52	19.6	1.11 (0.69, 1.52)
Hersch (2017)	6.35	5.7	264	5.26	4.85	264	20.2	0.21 (0.03, 0.38)
Hunter (2016)	11.7	9.13	768	8.4	9.13	768	20.2	0.36 (0.26, 0.46)
Moreau (2017)	5.4	3.9	198	5.2	3.9	198	20.1	0.05 (–0.15, 0.25)
Popova (2017)	11.66	0.77	230	8.78	0.58	230	19.9	4.22 (3.89, 4.55)
Total (95% CI)			**1512**			**1512**	**100.0**	**1.18 (0.17, 2.19)**

Heterogeneity. $Tau^2 = 1.30$; $Chi^2 = 536.88$, df = 4 ($p<0.00001$); $I^2 = 99\%$. Test for overall effect: Z = 2.29 (p=0.002)



Does this reflect either a positive direct effect (e.g. immune modulation) or is it an indirect effect arising due to a positive impact on disease activity or course?

DMT, disease-modifying therapy; IV, intravenous. Gasim M, et al. Mult Scler Relat Disord. 2018;26:124–56

Some of the main concerns around MS treatment compounding common MS comorbidities...

Treatment-emergent autoimmune diseases are a well-recognised complication of alemtuzumab, with up to 1 in 5 treated patients with MS developing thyroid disease, and 1 in 100 treated patients developing idiopathic thrombocytopenic purpura[1]

Specific DMTs have been shown to impact CV risk factors in a variety of ways:[2] Consider the DMT choice

There is a higher cancer risk in patients with MS switching from more than two DMTs[3]

Will this DMT potentially worsen this patient's comorbidity?

Will this patient's comorbidity increase the risk of AEs with this DMT?

AE, adverse event; CV, cardiovascular; DMT, disease-modifying therapy

1. Marrie RA. Nat Rev Neurol. 2017;13(6):375–82; 2. Sternberg Z, et al. Cardiovasc Ther. 2014;32:33–9; 3. D'Amico E, et al. Front Neurol. 2019;10:337

The nurse's role in MS-related comorbidity care

- Adherence to DMTs is an important issue in patients with psychiatric comorbidities[1]
- The nurse's role becomes particularly imperative for patients suffering from MS-related comorbidities

Ensuring patients understand treatment side effects and monitoring requirements

Promoting patient adherence

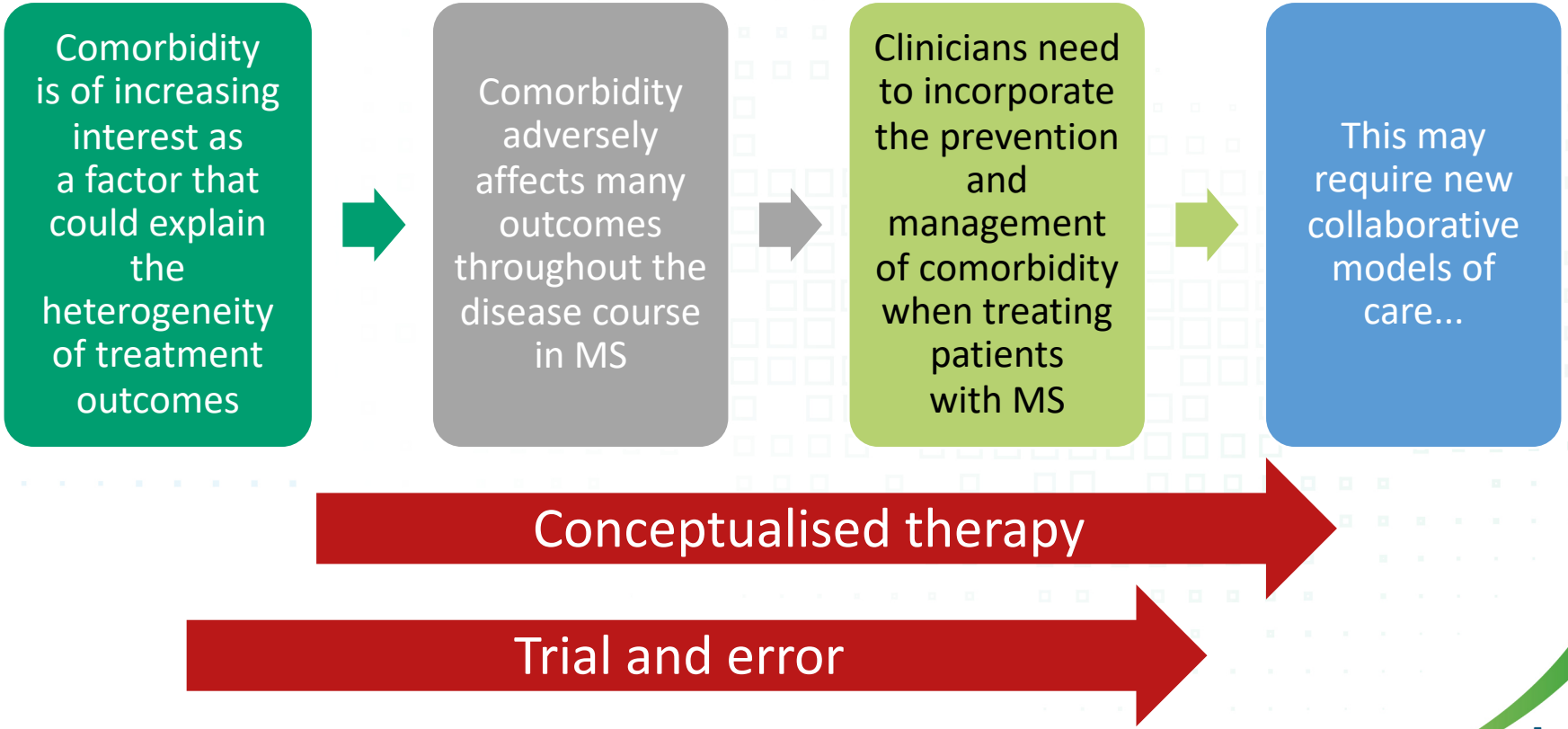
The nurse's role in MS care

Consider sequencing and reversibility implications of DMTs when making clinical decisions

DMT, disease-modifying therapy

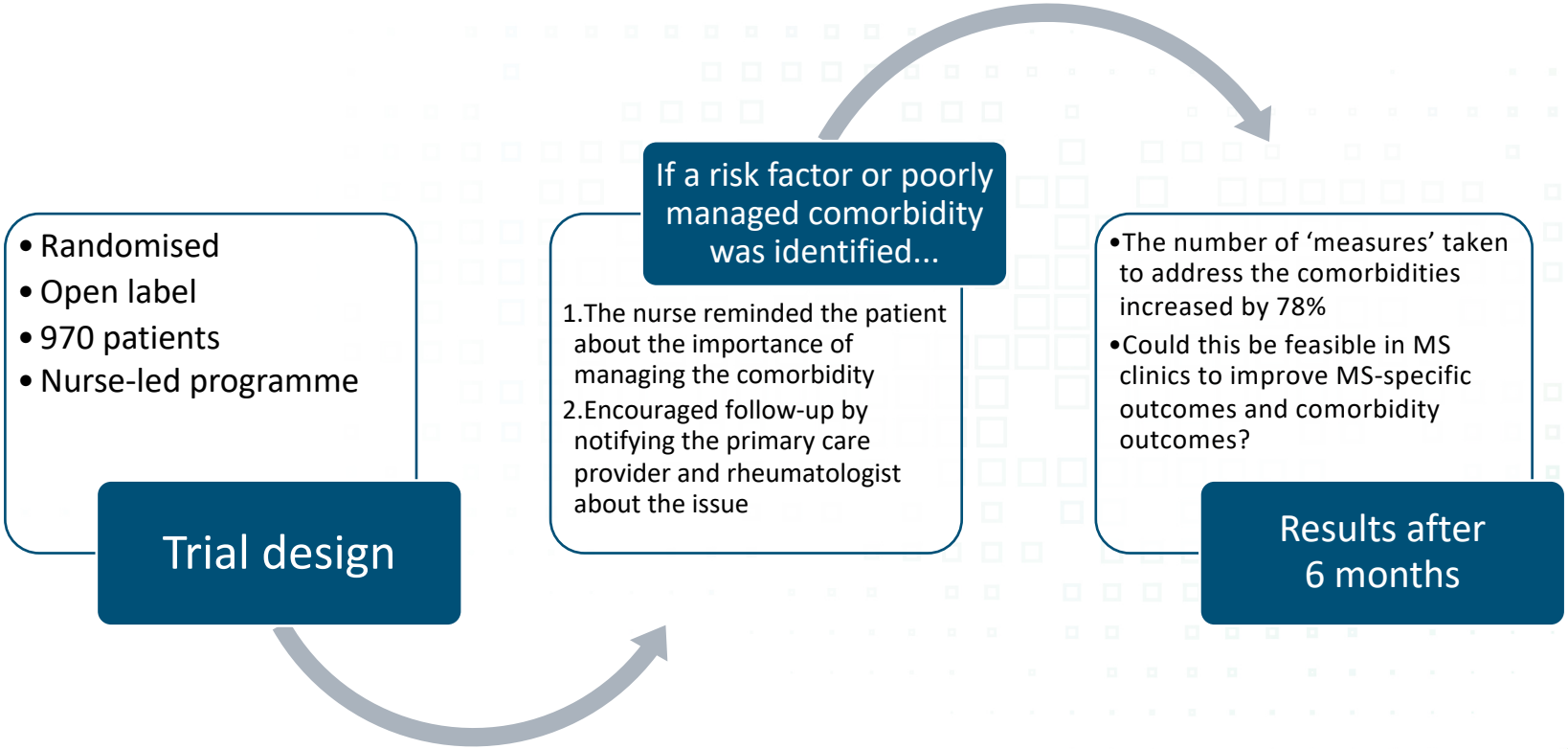
Roman C & Menning K. J Am Assoc Nurse Pract. 2017;29(10):629–38

The implications of comorbidities in patient care



Marrie RA. Nat Rev Neurol. 2017;13(6):375–82

Rheumatoid arthritis: A potential management approach for comorbidities



Marrie RA. Nat Rev Neurol. 2017;13(6):375–82

Examples of collaborative models of mental healthcare

Community model	Setting	Providers/type of care
Communication between practices	Separate practices	• Primary care provider • Psychiatric consultant
Medical-provided mental healthcare	Separate practices	• Consultation–liaison • Physician-provided care with specialised support
Co-location	Shared space	• Space is shared but primary care and mental health services are separate; care is collaborative • Education and self-management training are provided • Treatment plans are independent
Shared care	Shared space	• Services are provided at the primary care site; a care manager provides support and follow-up regarding treatment response and adherence • Education and self-management training are provided • Mental health service provides outreach to the primary care provider • The treatment plan is a primary care plan of which mental healthcare is a component
Reverse shared care	Shared space	• Services are provided at the mental health site • The primary care provider is in the mental health setting • The treatment plan is mental health oriented, of which primary care is a component
Unified care	Shared space	• Full service primary care and mental healthcare in one place • All clinical services, medical records and treatment plans are integrated across the organisation

Marrie RA. Nat Rev Neurol. 2017;13(6):375–82

Strategies to effectively manage comorbidities in MS

1

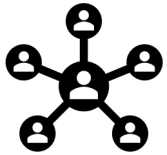
- Empower patients with MS to adopt positive health behaviours
- Smoking, obesity and physical inactivity are associated with increased risks of several of the comorbidities

2

- Better identify and treat the most prevalent comorbidities
- Depression remains underdiagnosed and undertreated in MS
- Screening tools, such as the Hospital Anxiety and Depression Scale can be used

3

- Emphasise vascular comorbidities given their rising incidence and rising prevalence with age, widespread effects on outcome and the existence of effective treatments for them



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- Identify the best models of care to achieve these goals
- Several collaborative models of care have been proposed for improving mental healthcare; these could guide comorbidity management approaches

Marrie RA. Nat Rev Neurol. 2017;13(6):375–82

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Comorbidity and treatment in MS summary

- First- and second-generation DMTs are not associated with worsening psychiatric comorbidities[1,2]
- Adverse events associated with the DMTs need to be considered[3]
- Collaboration and nurses can be especially important in patients with MS who also have comorbidities[4]
- Conceptualised therapy

1. Schippling S, et al. J Neurol. 2016;263(7):1418–26; 2. Gasim M, et al. Mult Scler Relat Disord. 2018;26:124–56; 3. Marrie RA. Nat Rev Neurol. 2017;13(6):375–82; 4. Roman C & Menning K. J Am Assoc Nurse Pract. 2017;29(10):629–38

Closing remarks

Prof. Sven Schippling

Closing remarks

- There are some common underlying pathologies for psychiatric comorbidities and MS – which comes first?[1,2]
- Comorbidities worsen/quicken most of the disease progression measures[3]
- Patient management strategies that take into account patient comorbidities are essential[4]
- Collaboration and nurse involvement becomes even more important for patients with MS who have comorbidities[4,5]

1. Burman J & Zelano J. Neurology. 2017;89(24):2462–68; 2. Sparaco M, et al. J Neurol. 2019 [Epub ahead of print]; 3. Marrie RA. Clin Invest Med. 2019;42(1):E5–12;
4. Marrie RA, et al. Nat Rev Neurol. 2017;13(6):375–82; 5. Roman C & Menning K. J Am Assoc Nurse Pract. 2017;29(10):629–38

Thank you!