Disease-modifying therapies in multiple sclerosis: Current perspectives on the latest data

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How are new and emerging data changing the way we think about the management of multiple sclerosis?

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What do long-term data with older agents tell us about symptom progression and secondary progressive multiple sclerosis?

Long-term data from platform therapies in MS

Glatiramer acetate[1]

US Glatiramer Acetate Trial
SC dosing, 20 µg QD
15-year (n=100) and
20-year (n=74) open-label
extension study data

ARR: 0.25 (15 y) and 0.2 (20 y)

SPMS: 35% (15 y) and 47% (20 y)

EDSS ≥6
(patient not ambulatory)
18% (15 y) and 20.5% (20 y)

IFN β-1b[2]

IFN β-1b Trial, SC dosing EOD
Placebo (n=79)
50 µg (n=85)
250 µg (n=96)

EDSS ≥6 (median time to EDSS ≥6)
Placebo: 46% (14.5 y)
50 µg: 39% (12.8 y)
250 µg: 46% (16.1 y)

EDSS ≥6 or SPMS
Placebo: 56%
Any dose: 53%
250 µg: 57%

ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; EOD, every other day; INF, interferon; MS, multiple sclerosis; QD, every day; SC, subcutaneous; SPMS, secondary progressive MS; y, year.

1. Wynn DR. *Mult Scler Int.* 2019:7151685; 2. Ebers GC, et al. *J Neurol Neurosurg Psychiatry.* 2010;81:907–12.

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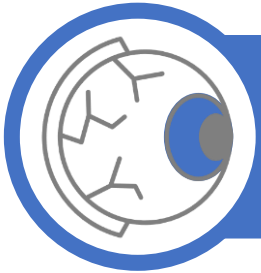
Does current patient monitoring catch disease progression early enough?

Disease progression monitoring in MS

- Current recommendations are symptomatic, without robust MRI monitoring guidance[1]
  - Diagnostic MRI lacks sensitivity to grey matter neurodegeneration, and is not easily quantitative[2]
- Early lesion progression detection could allow therapy adjustment to prevent symptoms

Specialist neuroradiology input to MDTs for complex neurological conditions is essential for optimal patient management[3]

- Reduced thalamic volume[4] and thalamic atrophy[5] via T1-weighted MRI are endpoints for disease progression in clinical trials of neuroprotective agents
  - In pediatric patients, complete baseline MRI assessment and accurate clinical and MRI monitoring during the first 2 years of disease are predictive of long-term prognosis[6]



Structural and functional changes in retinal ganglion cell layer and retinal nerve fiber layer predict long-term visual outcomes in MS[7]

MDT, multidisciplinary team; MRI, magnetic resonance imaging; MS, multiple sclerosis.

1. Rae-Grant A, et al. *Neurology*. 2018;90:777–88; 2. Ontaneda D, Fox RJ. *Neurotherapeutics.* 2017;14:24–34; 3. Ramsay S, et al. AAN 2021 Virtual Annual Meeting. Abstr. S2.002; 4. Petracca M, et al. *Neurol Ther.* 2018;7:265–85; 5. Azevedo CJ, et al. *Ann Neurol*. 2018;83:223–34; 6. De Meo E, et al. AAN 2021 Virtual Annual Meeting. Abstr. S28.005; 7. Galetta SL, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.096.

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How effective are newer disease-modifying therapies for long-term treatment?

Long-term experience with highly effective DMTs

Alemtuzumab[1]

CARE-MS II (RRMS)
Other DMTs permitted in OLE
9-year follow-up

- 41% of ALE-treated pts did not receive DMTs after Y2
- ARR 0.19 years 3–9
- 68% stable/ improved EDSS
- 69% free of disease activity on MRI

Ocrelizumab[2]

OPERA OLE (RMS)
OLE following 2-year study
6-year follow-up

- ARR 0.13–0.05 during years 3–6 (OLE years 1–4)
- 19.2% with 24-week CDP at year 6 (OLE year 4)

Ofatumumab[3]

APOLITOS (RRMS)
48-week follow-up to 24-week phase II study

- ARR 0.081
- Mean 0.027 Gd+ T1 lesions

Reduced ARR and lesions in patients who switched to OFA from placebo in initial study

Ublituximab[4]

ULTIMATE I and II (RMS)
96-week phase III study

- ARR 0.076 and 0.091
- Mean 0.016 and 0.009 Gd+ T1 lesions

Significantly reduced ARR and lesions with ublituximab vs teriflunomide

Sustained responses and low rates of progression/disability after multiple years' therapy with highly effective DMTs

ALE, alemtuzumab; ARR, annualized relapse rate; CDP, confirmed disability progression; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; OFA, ofatumumab; OLE, open-label extension; MRI, magnetic resonance imaging; MS, multiple sclerosis; RMS, relapsing MS; RRMS, relapsing-remitting MS.

1. Bass AD, et al. *Neurology.* 2020;94(15 Suppl.):151; 2. Hauser SL, et al. *Mult Scler J.* 2020;26(1 Suppl.):45; 3. Saida T, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.103; 4. Steinman L, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.074.

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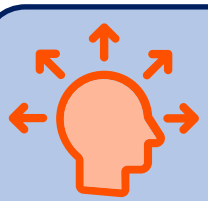
What do we know about switching to highly effective disease-modifying therapies, and when should patients switch?

Switching to highly effective DMTs



- The decision to switch to a highly effective DMT should be discussed with patients
- Additional or more intensive patient monitoring may prompt discussions should pre-symptomatic lesions be detected

Alemtuzumab[1]

- 282 pts in CARE-MS I/II OLE switched to ALE from IFN β-1a
- 230 pts completed 7 years' ALE:
  ARR was 0.11
  68% had stable/improved EDSS

Ocrelizumab[2]

- Pts with sub-optimal response to prior DMT switched to OCR in the CHORDS study
- 555 pts completed 2 years' OLE:
  ARR was 0.046
  62% had stable EDSS
  23% had improved EDSS

Natalizumab[3]

- Pts who switched from NAT to high- or moderate-efficacy DMT (n=130 and n=270, respectively)
- At 2 years post-switch:
  No difference in ARR
  Moderate-efficacy group had greater risk of new T2 and Gd+ lesions, and lower risk of absence of disease activity (all $p<0.05$)

Switching from platform therapies to highly effective DMTs is associated with improved outcomes and few additional safety concerns

ALE, alemtuzumab; ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; INF, interferon; NAT, natalizumab; OCR, ocrelizumab; OLE, open-label extension; pts, patients.

1. Pelletier D, et al. *Mult Scl J.* 2020;26(Suppl. 1):43; 2. Weinstock-Guttman B, et al. *Eur J Neurol.* 2020;27(Suppl. 1)43; 3. Hersh C, et al. *Neurology.* 2020;94(Suppl. 15):683.

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Highly effective disease-modifying therapies in multiple sclerosis: What is the role of early treatment?

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Does real-world evidence support clinical trial data for highly effective disease-modifying therapies?

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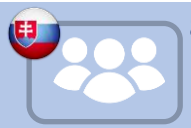
Real-world data for DMTs in MS

Alemtuzumab



84 Slovakian patients with RRMS, ≥2 doses[1]
Mean age 37.5 years old

- EDSS score unchanged (3.5 ± 1.47 vs 3.23 ± 1.58)
- **Mean ARR reduced from 0.58 ± 0.96 to 0.04 ± 0.21**
- MRI progression reduced from 0.56 to 0.16

49 Croatian patients with RRMS, ≥2 doses[2]
Mean age 33.2 years old

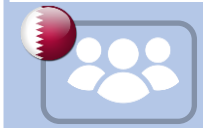
- ARR 1.86 in year before treatment
- ARR 0.08, 0.07, and 0.24 after 1, 2, and 3 years, respectively; all p<0.001
- **ARR reductions of 87–96%**

Natalizumab

Long-term multinational real-world observational study in patients with RRMS who received natalizumab[3]

- 1,649 patients continued treatment and 1,309 discontinued after ≥1 year
- 5 years' follow-up: conversion to non-active SPMS lower with continued natalizumab than discontinuation (0.14 vs 0.2; p<0.0001)
- Patients mostly discontinued natalizumab due to anti-JCV Ab positivity (38%) or patient decision (24%)
- **Natalizumab has long-term real-world effectiveness and slows RRMS disease progression**

Ocrelizumab



65 patients with MS in Qatar (52 with RRMS)[4]
Mean age 38.7 years old

- Mean 3.2 infusions
- **Mean number of lesions on MRI reduced from 1.27 to 0.07**
- Patients older than those in the OPERA I/II studies, but with longer disease duration

100 patients with MS in Colorado (82% RRMS)[5]
Mean age 44.3 years old

- Over 2 years, 2% experienced clinical relapse, 1% an enhancing lesion, and 6% a new T2 lesion
- 20% discontinued treatment by 24 months
- **Ocrelizumab safe and effective for MS treatment in the real-world setting**

Ab, antibody; ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

1. Kantorová E, et al. *Mult Scler J.* 2020;26(1 Suppl.):28; 2. Habek M, et al. *Eur J Neurol.* 2020;27(Suppl. 1):671; 3. Kappos L, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.078; 4. Yousuf W, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.070; 5. Vollmer B, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.217.

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What are the risks and benefits of earlier use of highly effective disease-modifying therapies?

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Benefits and risks of early treatment with highly effective DMTs

AAN guidelines for DMTs allow for their use up front in RRMS, instead of escalating from less effective therapies[1]

Highly effective DMTs are associated with lower levels of brain atrophy and brain volume change than IFN-β1a[2]

Further data are needed to support this strategy from prospectively randomized studies[3]

- Limited prognostic markers available to identify suitable patients
- Longer-term efficacy and safety data needed for newer therapies

AAN, American Academy of Neurology; DMT, disease-modifying therapy; IFN, interferon; RRMS, relapsing-remitting multiple sclerosis.

1. Rae-Grant A, et al. *Neurology*. 2018;90:777–88; 2. Andravizou A, et al. *Autoimmun Highlights.* 2019;10:7; 3. Corboy JR, et al. *Neurology.* 2018;90:1106–12 .

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What do we know about early use of highly effective disease-modifying therapies in relapsing-remitting multiple sclerosis?

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Early DMT use in RRMS

Retrospective cohort study[1]

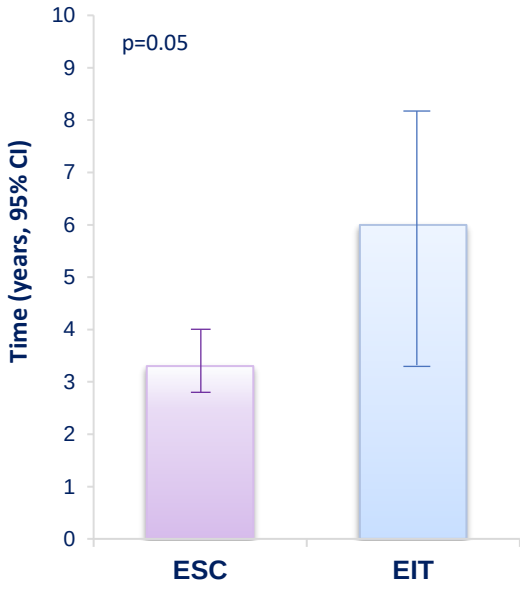
592 pts who received DMTs for MS

- **104 pts EIT** (alemtuzumab/ natalizumab)
- **488 pts ESC** (from moderate-efficacy DMTs)

Significantly lower EDSS increase after 5 years with EIT vs ESC (mean 0.3 vs 1.2; p<0.001)

- Better long-term outcomes with EIT, in a cohort of patients with poorer prognostic factors
- 58 patients on ESC stepped up to DMT after a median 2.4 years
- Relapse reduction rate with DMTs similar first-line or as escalation therapy

Median time to sustained accumulation of disability by initial treatment strategy



OPERA extension study[2]

2 years → 3 years

623 pts IFN

702 pts ocrelizumab

→ **Ocrelizumab**

Significantly lower CDP at year 5 in continuous ocrelizumab group vs switch (16% vs 21.3%; p=0.014)

- All pts had near complete and sustained suppression of new brain MRI lesion activity from years 3–5
- Continuous ocrelizumab associated with lower whole brain volume loss (-1.87% vs -2.15% at year 5; p<0.01)

CI, confidence interval; DMT, disease-modifying therapy; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; EIT, early intensive therapy; ESC, escalating therapy strategy; LIT, late intensive therapy; MRI, magnetic resonance imaging; pts, patients; RRMS, relapsing-remitting multiple sclerosis.

1. Harding K, et al. *JAMA Neurol.* 2019;76:536–41; 2. Hauser SL, et al. *Neurology.* 2020;95:e1854–67.

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Early DMT use in RRMS

Retrospective matched cohort study[1]

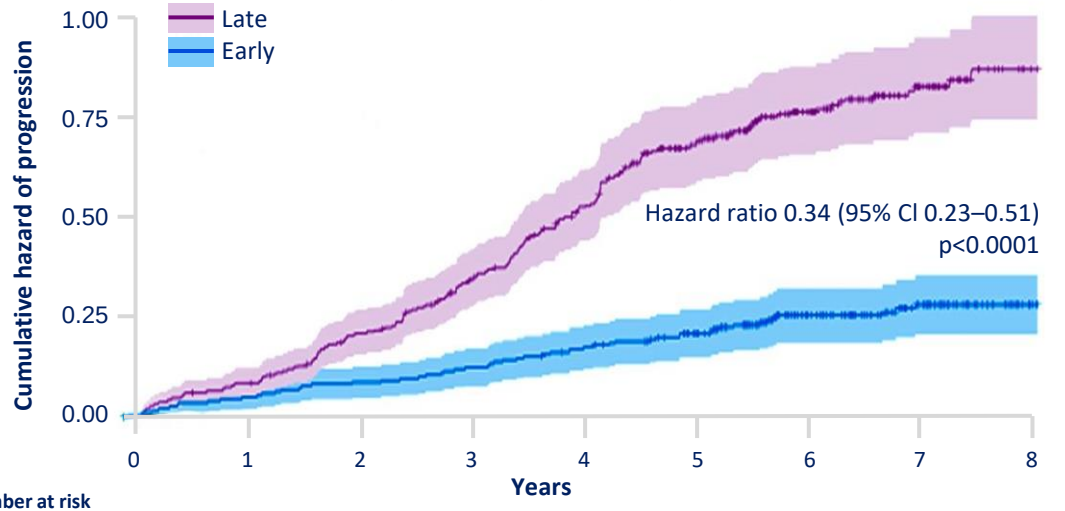
544 pts from Swedish MS Registry

- **213 pts EIT** (≤2 years after disease onset)
- **253 pts LIT** (4–6 years after disease onset)

Median follow-up 7.8 years (matched cohort)

- 6 years after onset, significantly lower EDSS in EIT vs LIT (2.2 vs 2.9; p<0.0001)
- Difference in mean EDSS still apparent 10 years after onset (2.3 vs 3.5; p<0.0001)
- Time-adjusted EDSS difference of -0.98 between EIT and LIT groups across 6- to 10-year follow-up period

Risk of disease progression after commencement of high-efficacy therapy



Number at risk (censored)									
Late group	253 (0)	251 (2)	248 (5)	242 (11)	233 (20)	209 (44)	145 (108)	90 (163)	48 (205)
Early group	213 (0)	213 (0)	213 (0)	213 (0)	211 (2)	198 (15)	141 (72)	101 (112)	48 (165)

CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EIT, early intensive therapy; LIT, late intensive therapy; MS, multiple sclerosis; MRI, magnetic resonance imaging; pts, patients; RRMS, relapsing-remitting multiple sclerosis.

1. He A, et al. *Lancet Neurol.* 2020;19:307–16.

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What do we know about long-term safety with highly effective disease-modifying therapies?

Safety profile and monitoring with highly-effective DMTs[1]

	Major AE profile features (clinical trials)	Further experience (extension studies/case reports)	Routine monitoring
Alemtuzumab anti-CD52 mAb	• IRRs (headache, rash, pyrexia, hypotension) • Infections (URTI, UTI, viral/fungal/bacterial) • Secondary autoimmune conditions and malignancies (including thyroid)	• Similar profile after 5 years; fewer infections and thyroid conditions after 3 years	• TSH, CBC, LFT, creatinine and urine analysis • Anti-viral prophylaxis • Skin and gynecologic exam
Natalizumab anti-α4 integrin mAb	• IRRs, fatigue, headache, arthralgia, flu-like symptoms, hypersensitivity reactions • Infections (URTI, UTI, viral/fungal/bacterial) • PML, raised liver enzymes	• Malignancies (melanoma, CNS and T-cell lymphomas) • Infections (including herpes, VZV, encephalitis and meningitis)	• Anti-JCV Ab testing • CBC and LFT • Brain MRI • Neutralizing Abs
Ocrelizumab anti-CD20 mAb	• IRRs, headache, nasopharyngitis • Infections (URTI, UTI, pneumonia, viral/fungal/bacterial, hep B reactivation) • Secondary carcinomas and melanoma	• Late-onset neutropenia, hypogammaglobulinemia, viral infections, hep B reactivation, fulminant hepatitis, PML	• CBC, LFT • Immunoglobulin levels if severe/recurrent infections

- Real-world evidence supports the safety and efficacy profiles of highly effective DMTs[2–6]

Ab, antibody; AE, adverse event; CBC, complete blood count; CNS, central nervous system; DMT, disease-modifying therapy; hep B, hepatitis B; IRR, infusion-related reaction; JCV, John Cunningham virus; LFT, liver function test; mAb, monoclonal antibody; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; TSH, thyroid stimulating hormone; URTI, upper respiratory tract infection; UTI, urinary tract infection; VZV varicella zoster virus.

1. Jalkh G, et al. *Vaccines.* 2021;9:12; 2. Kantorová E, et al. *Mult Scler J.* 2020;26(1 Suppl.):28; 3. Habek M, et al. *Eur J Neurol.* 2020;27(Suppl. 1):671; 4. Kappos L, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.078; 5. Yousuf W, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.070; 6. Vollmer B, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.217.

How does immunotherapy for multiple sclerosis impact COVID-19 vaccination?

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COVID-19 in patients receiving DMTs for MS

6-month single-center retrospective chart review: rates of COVID-19 varied by DMT type[1]

- Natalizumab: 4%
- Rituximab: 21%
- Ocrelizumab: 10%
- Fingolimod/siponimod: 10%

Italian retrospective observational study:[2] increased frequency of ICU admission or death with anti-CD20 therapies (8%) compared with IFN (0%) or other therapies (5%)

- Risk factors for severe COVID-19 were: age, EDSS, male sex, and anti-CD20 treatment (vs other drugs), recent high dose steroids

How to protect pts on anti-CD20 therapy:

- Use antibodies against spike protein (bamlanivimab etc.) in the first days of SARS-CoV-2 positivity
- Recommend vaccination to all pts with MS (with proper timing in those on anti-CD20 therapy and cell-depleting therapies)[3,4]

Recommend to all patients with MS to adhere to all antiepidemic preventative measures[3]

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; ICU, intensive care unit; IFN, interferon; MS, multiple sclerosis; MSIS, MS Impact Scale; pts, patients.

1. Smith T, et al. AAN 2021 Virtual Annual Meeting. Abstr. P15.014; 2. Sormani MP, et al. AAN 2021 Virtual Annual Meeting. Abstr. S28.002; 3. CNMSC COVID-19 Recommendations. Available at: https://cnmsc.ca/Covid19VaccineGuidance (accessed May 2021); 4. Achiron A, et al. *Mult Scler.* 2021;27:864–70.

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Centering the patient: Considering the needs and preferences of patients at each treatment decision-making moment

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How important is treatment adherence in patients with multiple sclerosis?

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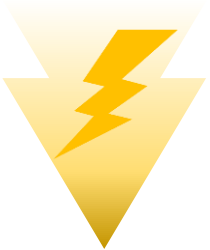
Adherence to DMTs

Adherence to DMTs varies (40–90%), but has significant clinical benefits compared with non-adherence[1–4]



42–46% decrease in relapses[3,5]

50–52% decrease in hospitalizations[3,4]

Reduced healthcare utilization
↓ in emergency visits (38%)[3]
↓ in physician visits (20%)[4]
↓ in ambulatory care visits (20%)[4]
↓ in outpatient visits (0.7/year)[3]

Adherence and outcomes with DMTs are not affected by route of administration[3,5]

DMT, disease-modifying therapy.

1. Bowen J, et al. *Adv Ther.* 2020;37:3163–77; 2. Lahdenperä S, et al. *Acta Neurol Scand.* 2020;142:605–12; 3. Burks J, et al. *Clinicoecon Outcomes Res.* 2017;9:251–60; 4. Gerber B, et al. *Mult Scler Relat Disord.* 2017;18:218–24; 5. Freeman L, et al. *Clinicoecon Outcomes Res.* 2021;13:65–75.

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Which treatment-related and non-treatment-related factors influence adherence to disease-modifying therapies in patients with multiple sclerosis?

Factors affecting adherence to DMTs in MS

Female gender, comorbidities[1,2]

Patient clinical factors[1,3,4]
- Negative perception of efficacy and illness
- Acceptance of illness
- Physical limitations
- Cognitive deficit
- Mental illness
- Support

Treatment related
- Side effects[3]
- Practical issues relating to administration[1]
- Relapses and symptom progression[2,3]

Disability[2]

Insurance coverage, out-of-pocket costs, income[1,2]

DMT, disease-modifying therapy; MS, multiple sclerosis.

1. Ben-Zacharia A, et al. *Int J MS Care.* 2018;20:287–97; 2. Li P, et al. *Value Health.* 2020;23:328–34; 3. Pust GEA, et al. *Int J MS Care.* 2020;22:219–25; 4. Kołtuniuk A, Rosińczuk *J. Int J Med Sci.* 2021;18:216–25.

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How much do comorbidities contribute to adherence in multiple sclerosis?

Comorbidities and adherence in MS

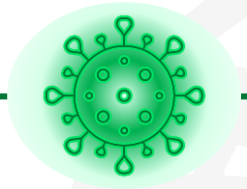
Comorbidities **increase treatment costs**

- In patients with MS, mental illness comorbidities have the highest cost-of-illness and high loss of productivity[1]

Patients with MS have a **high burden of depressive symptoms, low sleep quality** and **increased perception of fatigue** (one of the most disabling MS symptoms)[2,3]

Anxiety and depression adversely impact **adherence**

- Acceptance of MS increases treatment adherence and is associated with fewer treatment side-effects[4]



COVID-19 pandemic and lockdown increased the burden of mental illness comorbidities and fatigue in people with MS[2]

MS, multiple sclerosis.

1. Bütepage G, et al. *Mult Scler J Exp Transl Clin.* 2020;6:2055217320968597; 2. Motolese F, et al. *Front Neurol.* 2020;11:580507;
3. Davis BE, et al. *Neurol Ther.* 2021;1–21. doi: 10.1007/s40120-021-00240-9; 4. Kołtuniuk A, Rosińczuk *J. Int J Med Sci.* 2021;18:216–25.

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How can therapy adherence be supported in patients with multiple sclerosis?

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Strategies to support DMT adherence in MS

Patient support programs
DMT manufacturer-led[1,2]
Social support[3]

Computerization
Electronic autoinjectors, web tools, reminders, tracking apps[4]

Home monitoring
Telephone or pharmacist one-on-one counseling[4]

Web-based patient programs
Actively engage patients (MSmonitor, MSInvigor8)[4]

↑ QoL
↑ Autonomy

DMT, disease-modifying therapy; MS, multiple sclerosis; QoL, quality of life.

1. Lenz F, Harms L. *Adv Ther.* 2020;37:2999–3009; 2. Evans C, et al. *BMJ Open.* 2021;11:e043930; 3. Eizaguirre MB, et al. AAN 2021 Virtual Annual Meeting. Abstract P15.059; 4. Ben-Zacharia A, et al. *Int J MS Care.* 2018;20:287–97.

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How can clinicians involve patients in treatment decisions?

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Shared decision-making improves adherence

Information and interpretation
MRI scans, QoL, progression, prognosis, treatment goals, relapse prevention[1–6]

Address misconceptions
About disease and treatment (internet/social media)[4]

Manage expectations
Regarding prognosis and treatment[4]

Understanding of disease
Shared understanding of disease progression and other terms with HCP,[1] access to MRI scans[5,6]

Treatment options
Rationale, benefits and risks of different DMTs[4]

Preferences and situation
Route of administration, tolerance, work environment, lifestyle[1–4,6]

Agreed treatment strategy

DMT, disease-modifying therapy; HCP, healthcare professional; MRI, magnetic resonance imaging; QoL, quality of life.

1. Celius EG, et al. *Patient Pref Adherence.* 2021;15:15–27; 2. Rahn AC, et al. *Int J MS.* 2020;22:285–93; 3. Eskyte I, et al. *Mult Scler Relat Disord.* 2019;27:370–7;
4. Ben-Zacharia A, et al. *Int J MS Care.* 2018;20:287–97; 5. Kennedy F, et al. AAN 2021 Virtual Annual Meeting. Abstract P15.231;
6. Shirani A, et al. AAN 2021 Virtual Annual Meeting. Abstract P15.232.

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