



# New Guidelines for MS Treatment

Will new guidelines address variability in the care of patients with MS?

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There is an excess of variability in health care, from treating a child's ear infection with antibiotics versus watchful waiting to how to choose a disease-modifying therapy (DMT) for a patient with multiple sclerosis (MS). The last time the American Academy of Neurology (AAN), the largest organization of neurologists in the US, published a guideline on the use of DMTs in MS was in 2002. As this article goes to press, we eagerly await the updated guideline, which is to be released at the AAN annual meeting April 21st-27th, 2018.

The AAN guideline provides an extensive review of each of the DMTs rather than a guideline with pathways of treatment as seen in some other areas (eg, oncology). This means that even after publication of the updated AAN guideline, clinicians, patients, and payors will have little guidance in terms of choosing which DMTs to try in what order.

## Hope From Abroad?

In the meantime, the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) recently published their guideline on the pharmacological treatment of MS with the aim of enabling "homogeneity of treatment decisions across Europe."<sup>1</sup>

Although the guideline steering committee did an excellent job of formulating questions and making recommendations, do not expect the guideline to outline the exact treatment of individual patients with MS. While this is often termed the *Art of Medicine*, it does leave treating clinicians, patients, and payors with unanswered questions about how individual patients should be treated. The published guidelines provide more guidance on which questions should be considered in the shared decision making between clinicians and individual patients.

## Topics Focused on by Guideline Task Force

The guideline task force, made up of European MS experts, focused their discussion on:

1. Early treatment in patients with clinically isolated syndrome (CIS).

2. Treatment in patients with established disease, both relapsing and progressive.
3. Monitoring of treatment response.
4. Treatment strategies in case of inadequate response.
5. Treatment discontinuation and/or switch.
6. Treatment in special situations (pregnancy).

## Questions Asked by Guideline Task Force

In order to address the topics of discussion, the guideline task force posed 3 therapeutic intervention questions and 7 clinical management questions as follows:

1. What is the benefit of starting DMT compared to no treatment for patients with CIS?
2. What is the benefit of a DMT versus another or no treatment for patients with relapsing-remitting multiple sclerosis (RRMS) and secondary-progressive MS?
3. What is the benefit of DMT compared to no treatment for patients with primary-progressive MS?
4. Does the presence of early disease activity (relapses and/or disability progression and/or MRI activity at 6 months and 12 months) predict an increased risk of future disability for patients with relapsing MS treated with DMT?
5. Should a follow-up MRI be performed within a pre-specified time frame to monitor treatment response and safety for MS patients treated with DMT?
6. What is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs for patients with relapsing MS treated with interferon or glatiramer acetate and with evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6 and 12 months)?
7. Is there a risk of return and/or rebound disease activity (increased risk of relapses, disability progression and/or MRI activity) for patients with relapsing MS who stop taking a highly efficacious drug?
8. What is the benefit of further treatment for patients with relapsing MS who stop taking a highly efficacious drug?



9. What is the benefit of continuing treatment versus stopping treatment for patients with relapsing MS treated with DMT who remain stable over a long time period?
10. What should the therapeutic approach be for women with MS treated with DMT who wish to become pregnant or who have an unplanned pregnancy?

### Guideline Recommendations

This guideline was developed using careful methodology including electronic database searches, reading of individual published articles, and assessment of potential bias in the studies referenced. The guideline task force used a 3-round consensus process to arrive at 21 recommendations that were graded as consensus, strong, and weak recommendations.

**Consensus Statements.** There are 9 recommendations that achieved full consensus agreement from the task force members.

1. Centers with adequate infrastructure to provide proper patient monitoring, comprehensive assessment, and the ability to detect and address side effects should be the only places where DMT is given.
2. For active RRMS, choosing among the wide range of available drugs that range from modestly effective to the highly efficacious depends upon patient characteristics and comorbidities, disease severity and activity, drug safety profile, and the accessibility of the drug.
3. The Summary of Product Characteristics should always be consulted for dosage, special warnings, precautions for use, contraindications, and monitoring of side effects and potential harms.
4. To monitor response to treatment, standardized reference brain MRI should be done approximately 6 months and 12 months after treatment begins. Timing of both MRIs may be adjusted, taking into account the drug's mechanism and speed of action and the patient's disease activity (including clinical and MRI measures).
5. Measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method for monitoring response to DMT, supplemented by GAD-enhancing lesions. Evaluation of these parameters requires high-quality, standardized MRI scans and interpretation by highly qualified readers with experience in MS.
6. Use standardized reference brain MRI to monitor treatment safety as follows:
  - a. yearly for low-risk progressive multifocal leukoencephalopathy (PML) patients
  - b. every 3 to 6 months for high-risk PML patients (John Cunningham virus positive, natalizumab treatment duration over 18 months)
  - c. At the start or discontinuation of any treatments for patients with high risk of PML who switch treatments.

7. Consider patient characteristics and comorbidities, drug safety profiles, and disease activity and severity when deciding changes to treatment in consultation with the patient.
8. Consider starting another highly efficacious drug when treatment with a highly efficacious drug is stopped because of inefficacy or safety concerns. When starting the new drug, take into account:
  - a. disease activity (clinical and MRI), the greater the activity, the higher the urgency to start new treatment;
  - b. half-life and biological activity of the previous drug;
  - c. the potential for resumed disease activity or even rebound (particularly with natalizumab).
9. Advise all women of childbearing potential that with the exception of glatiramer acetate 20 mg/mL, no DMT is approved for use during pregnancy.

**Strong Recommendations.** There are 3 additional recommendations that received enough approval to be considered strong.

1. Offer interferon or glatiramer acetate to patients with CIS and an abnormal MRI image with lesions suggestive of MS who do not fulfil criteria for MS.
2. Offer early treatment to patients with active RRMS as defined by clinical relapses and/or MRI activity (active lesion, contrast-enhancing lesions, and new or unequivocally enlarging T2 lesions assessed at least annually). This includes CIS fulfilling current diagnostic criteria for MS.
3. Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity assessed as recommended in this guideline.

**Weak Recommendations.** An additional 9 recommendations received enough support to be included as weak recommendations.

1. Consider treatment with interferon-1a (sc) or -1b for patients with active secondary-progressive MS taking into account, in discussion with patient, the dubious efficacy, and the safety and tolerability profile of these drugs.
2. Consider treatment with mitoxantrone for patients with active secondary-progressive MS taking into account, in discussion with the patient, the efficacy, and specifically the safety and tolerability profile of this agent.
3. Consider treatment with ocrelizumab or cladribine (not approved in the US) for patients with active secondary-progressive MS.
4. Consider treatment with ocrelizumab for patients with primary-progressive MS.
5. Consider combining MRI with clinical measures when evaluating disease evolution in treated patients.
6. In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab.

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7. Consider continuing a DMT if a patient is stable (clinically and on MRI) and shows no safety or tolerability issues.
8. For women planning a pregnancy, if there is a high risk of disease reactivation, consider using interferon or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered.
9. For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who, despite this advice, still decide to become pregnant or have an unplanned pregnancy:
  - a. treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications.
  - b. treatment with alemtuzumab could be an alternative therapeutic option for planned pregnancy in very active cases, provided that a 4-month interval is strictly observed from the latest infusion until conception.

### What the European Guideline Does Not Do

The jointECTRIMS/EAN guideline does not dictate the use of specific DMT for individual patients, but rather offers broad guidance on the appropriate use of DMT. Additionally, the guideline does not address the current fundamental underlying question in MS treatment: whether patients should be started on lower efficacy (but potentially safer DMTs) and escalated as needed or whether all patients should be started on the DMTs with the highest efficacy first.

### Looking to the Future

In order to address the question of escalation therapy versus initiating higher-efficacy DMT from the onset, ongoing and planned clinical trials, as well as real-world registry data will help in moving the MS community toward greater consensus. It is important that as we continue these discussions, researchers and clinicians actively engage the patient community.

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1. Notice of copublication: Montalban X, Gold R, Thompson AJ, et al.ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Multi Scler*. 2018;24(2):96-120. *Eur J Neurol*. 2018 Feb;25(2):215-237.

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