Using disease-modifying treatments in multiple sclerosis: Association of British Neurologists (ABN) 2024 guidance

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ABSTRACT

The Association of British Neurologists last published guidelines on disease-modifying treatment (DMT) in multiple sclerosis (MS) in 2015. Since then, additional DMTs have been licensed and approved for prescribing within the National Health Service for relapsing-remitting MS, early primary progressive MS and active secondary progressive MS. This updated guidance provides a consensus-based approach to using DMTs. We provide recommendations for eligibility, starting, monitoring, switching and stopping of DMTs; pregnancy; equitable access to DMT; autologous haemopoietic stem-cell transplantation; and use of generics. We highlight best practice where it exists and discuss future priorities.

INTRODUCTION

The Association of British Neurologists (ABN) first published its guidelines for the use of disease-modifying treatments (DMTs) for multiple sclerosis (MS) in 1999; these have subsequently been periodically updated.[1] They were historically used to determine prescribing practice in the UK. From 2013, National Health Service England (NHSE) published a clinical commissioning policy to provide guidance on the use of DMTs and to confirm arrangements for funding in England. Similar mechanisms are in place for the UK devolved nations.[2] In 2018 and then updated in 2023, NHSE published its treatment algorithm for MS DMTs to provide a framework for clinical decision-making.[3] Table 1 summarises the currently available DMTs within the UK grouped by efficacy based on reductions in relapse rate.

DMT eligibility within the NHSE treatment algorithm was informed by National Institute of Health and Care Excellence (NICE) technology appraisals, which also inform prescribing policies in the UK devolved nations. A key requirement is that complex cases or those proposing higher efficacy DMTs should be discussed within a multi-disciplinary team (MDT), comprising at least two MS specialist consultant neurologists, a specialist MS nurse and have access to neuro-radiology expertise.

As the NHSE treatment algorithm adheres to NICE technology appraisal recommendations, many of which were written a decade or more ago, it does not necessarily reflect current perceptions of best clinical practice. Thus, the algorithm does not always allow individual needs to be met, for instance, around pregnancy planning. The algorithm is also hampered by inconsistent and outdated definitions of disease activity, which are largely based on pivotal study inclusion criteria used in historical NICE technology appraisals.

The ABN guidance presented here aims to articulate some of the key challenges and make recommendations for DMT prescribing based on the best available evidence and expert opinion, some of which differ from the NHSE treatment algorithm. However, prescribing in the National Health Service (NHS) remains subject to current national commissioning policies. This guidance is not intended to provide a complete description of the

Table 1 DMTs currently licensed within the UK

ABN classification of disease modifying therapies	Therapies (in chronological order of commissioning)
Moderate efficacy therapies for relapsing-remitting multiple sclerosis	β-interferons Glatiramer acetate Fingolimod (may in some circumstances be used as an escalation therapy) Teriflunomide Dimethyl fumarate Ozanimod (Scotland only) Ponesimod (may in some circumstances be used as an escalation therapy) Diroximel fumarate
Higher efficacy therapies for relapsing-remitting multiple sclerosis†	Natalizumab* Alemtuzumab* Ocrelizumab* Cladribine* Ofatumumab*
Therapies for early primary progressive multiple sclerosis	Ocrelizumab
Therapies for active secondary progressive multiple sclerosis	Interferon-β1b Siponimod

*Also eligible for use in rapidly evolving severe relapsing-remitting multiple sclerosis.
†Higher efficacy therapies are considered as those with >50% reduction (or otherwise significant reduction) in relapse rate compared to placebo/comparator. Note that there is variation in whether DMTs were compared to active comparator or placebo and so studies are not directly comparable.
ABN, Association of British Neurologists; DMTs, disease-modifying treatments.

possible complications and monitoring of DMT in MS; for this prescribers should look at the relevant summaries of product characteristics.

METHODS

Members of the ABN Advisory Group in MS and Neuroinflammation convened in London, UK in September 2023. The panel discussed and agreed on new or modified recommendations on the use of DMTs. Subsequently, and following further discussion, all advisory group members endorsed a consensus. The guidance was then reviewed by relevant stakeholders (for full list see Author note) and further revised, with the final version endorsed by the ABN council.

ABN GUIDANCE

Consensus recommendations are outlined in the boxes, and further discussion is included under the corresponding sub-headings.

DMT eligibility

Licensing and NICE approval of DMTs to date has focused on the conventional subtyping of MS into relapsing-remitting MS, secondary progressive MS and primary progressive MS. However, these subtypes do not necessarily reflect current understanding of the underlying mechanisms of nervous system injury, and it has recently been proposed to redefine MS accordingly.[4] This shift in understanding challenges current assumptions within DMT algorithms of linear progression through MS subtypes.

ABN recommendations: DMT eligibility

- MS should be considered a single disease with relapsing and progressive components, with the relative extent of each process dictating the dominant clinical expression at that time. This balance may change over time. If progression has been the dominant issue, this should not preclude the future use of DMT for relapsing-remitting MS if clear inflammatory disease returns.
- Active disease should be defined as clinical (relapse) and/or radiological (new or enhancing lesion on MRI) evidence of disease activity. This should replace outdated definitions of active disease.
- For clinically isolated syndrome where McDonald criteria for relapsing-remitting MS are fulfilled, patients should be offered all available treatments as per relapsing-remitting MS.
- All DMTs should be available to eligible patients according to licence.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; MS, multiple sclerosis.

Starting DMTs

Trial and real-world data increasingly support early DMT use to reduce longer-term disability and risk of secondary progression.[5] However, DMT selection and approach can be complex. The current main treatment strategies are either an escalation approach (starting on a moderate-efficacy therapy to minimise potential risk and escalating to a higher efficacy DMT if there is disease breakthrough) or an early intensive approach (using a higher efficacy DMT from outset to maximise early disease control with possible increased risk that may be minimised by later de-escalation). Induction therapies, with an immune reconstitution mechanism of action, may be used as part of either an early intensive or escalation strategy.

Emerging evidence suggests improved long-term disability with starting high-efficacy therapy within 2 years of disease onset.[6 7] Early intensive versus

ABN recommendations: principles of starting DMTs

- Patients with active disease should be offered and have access to all DMTs for which they are eligible as early as possible.
- High efficacy therapy should be considered as the first option in eligible patients.
- People with progressive MS who meet the prescribing criteria for eligible DMTs (currently ocrelizumab or siponimod) should be identified and considered for treatment.
- Patients being considered for high-efficacy therapies should be discussed in an MDT meeting.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; MDT, multi-disciplinary team; MS, multiple sclerosis.

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escalation treatment strategies are currently being directly compared in two randomised controlled trials in relapsing-remitting MS.[8 9] Epidemiological studies, which predominantly predate widespread use of higher efficacy DMT, suggest that higher relapse frequency,[10] MRI activity,[11] early involvement of pyramidal tracts or spinal cord,[12] and acquiring significant early disability are poor prognostic markers. Previous guidance[2 3] have included timeframes regarding disease activity, but these may be a barrier to early treatment. We would expect people to be assessed in a timely manner and for treatment decisions generally to be based on disease activity within the last 1–2 years, but decisions should always be made in an individual's best interests and with MDT input as appropriate.

Currently, there are no DMTs licensed for radiologically isolated syndrome but recent clinical trials suggest DMTs are effective in this condition.[13 14]

ABN recommendations: shared decision-making when starting DMTs

- DMT choice should be a patient-centric decision, balancing clinical activity, prognostic factors, comorbidity, social determinants of health, safety, risk and other important considerations to that person, including potential pregnancy plans and individual risk and benefit perception.
- Patients should be able to discuss all available options with an MS specialist healthcare professional, potentially supported by decision aids.
- There should be a risk–benefit discussion regarding adverse effects, infection risk and comorbidity. Any potential modifiable factors that might increase the risk of complications should be mitigated, and patients encouraged to complete relevant vaccinations before starting DMT.
- Patients starting DMTs should be offered proactive support to minimise the risk of poor adherence and to ensure safe monitoring.
- We support using generics and biosimilars when they offer significant cost savings to the NHS and do not disadvantage the patient. Where services enabling safe starting and delivery have been supplied to support the initial DMT prescription, it is imperative to provide equivalent services to prescribing centres without detriment.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; MS, multiple sclerosis; NHS, National Health Service.

DMT monitoring

International guidelines have been developed to recommend the use of MRI for monitoring treatment effectiveness and disease activity.[15] However, it is not clearly established what are the optimal clinical measures that should be used to assess efficacy or what is considered evidence of treatment failure.

The *No Evidence of Disease Activity* (NEDA)-3 paradigm[16] is the best-known endpoint to assess treatment response. This consists of no progression of disability (usually defined as no change in Expanded Disability Status Scale (EDSS) score), clinical stability (no new relapse) and radiological stability on MRI. Achieving NEDA-3 at 1–2 years is associated with a two-times higher odds of no longer-term disability progression at 6 years.[17] However, in clinical practice, NEDA may not be achievable in all, as no DMT reduces the risk of disease activity by 100%. It may be more realistic to have some tolerance of minimal disease activity, such as a new MR lesion without contrast enhancement and no relapses, but noting that further investigation is required.[18] There is strengthening evidence that the isolated finding of two or more new T2 lesions while on a moderate-efficacy DMT for at least 12 months is associated with a significantly increased risk of subsequent clinical relapse and therefore provides a rationale to consider DMT escalation.[19]

ABN recommendations: DMT monitoring

- All patients on DMT should be actively monitored for disease activity and safety.
- All patients (including those not on DMT) should be able to report new disease activity in a timely manner and be reviewed promptly.
- We support the 2021 Magnetic Resonance Imaging in Multiple Sclerosis study group, Consortium of Multiple Sclerosis Centres and North American Imaging in Multiple Sclerosis Cooperative (MAGNIMS CMSC NAIMS) consensus recommendations on the use of MRI in monitoring MS.
- A re-baseline MR scan should be undertaken usually 3–6 months after starting DMTs to account for therapeutic lag.
- MR brain imaging should be performed annually for surveillance of disease activity, although it may be appropriate to reduce the frequency of surveillance after 5 years, with spinal cord MRI recommended for special clinical conditions, in line with international guidelines. Additional frequency of MRI may be required for safety monitoring.
- Safety monitoring requirements should follow the recommendation in the summary of product characteristics for each DMT.
- It is essential that a prescribing centre has sufficient capacity and protocols in place to ensure compliance with robust safety monitoring requirements, including a process for managing the risk of progressive multifocal leucoencephalopathy.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; MS, multiple sclerosis.

The value of adding further metrics to monitoring assessments, such as patient reported outcome measures, volumetric MRI, cognitive measures and fluid biomarkers in unselected clinical populations is unclear and requires further evaluation.

DMT switching

ABN recommendations: DMT switching due to disease activity

- It should be made clear at DMT initiation that most therapies take several months to reach full clinical efficacy (therapeutic lag). Therefore, if tolerated, the medication should be given sufficient time (usually a minimum of 6 months) before consideration is given to switching on the grounds of efficacy.
- Although aiming for clinical stability as expressed in the NEDA-3 construct may be the ideal goal, this may not be feasible. Decisions about switching due to efficacy should be individualised.
- DMT escalation to a higher efficacy therapy should be considered following a clinical relapse. For MRI activity, two or more new T2 brain lesions, or one new spinal cord lesion, should trigger consideration of DMT escalation.
- Patients on DMT for progressive disease should be considered for switching to DMT for relapsing disease if the current phenotype is predominantly relapsing.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; NEDA-3, No Evidence of Disease Activity-3.

DMT switching is increasingly common[20] for a range of reasons, including disease activity, tolerance or safety concerns (eg, de-risking for patients on natalizumab at high risk of progressive multifocal leucoencephalopathy). However, there is currently no consensus as to the safest or most effective sequencing of therapies.

ABN recommendations: other DMT switching considerations

- Switching DMT due to intolerance or safety concerns should be to a DMT of at least similar efficacy, and patients should have the option of any DMT for which they were eligible at the time of initiation.
- Where patients are switching for family planning, they should have the option of switching to a similar or higher efficacy DMT regardless of disease activity.
- DMT switching should be planned carefully especially when stopping immune sequestering drugs (natalizumab, fingolimod, and other sphingosine-1-phosphate (S1P) receptor modulators), due to the potential for a 'rebound' of disease activity. In general, treatment gaps after therapies that are known to be associated with the risk of rebound (natalizumab, fingolimod) should be kept to a minimum, no more than 4–6 weeks. Switching from low-risk DMTs, for example, interferons and glatiramer acetate, does not necessitate a wash-out period. Similarly, switching within the same class of drugs (eg, from ocrelizumab to ofatumumab or from fingolimod to siponimod) may not require a wash-out period.
- If there is a temporary contraindication to switching to the chosen DMT, such as prolonged lymphopenia, patients may require bridging with an alternative DMT.

ABN, Association of British Neurologists; DMT, disease-modifying treatment.

Stopping and de-escalating DMTs

Natural history studies suggest that inflammatory MS disease activity diminishes over time and with increasing age in most people, partly through immunosenescence.[21] Thus, the benefits from immunomodulatory DMT may reduce over time, providing a rationale to consider a de-escalation strategy in some patients. A further key concern with continuous use immunosuppressive therapies is cumulative risk in the longer-term, particularly related to infection and low-grade malignancy.[22]

ABN recommendations: DMT discontinuation and de-escalation

- We do not advocate any arbitrary time limitation on the use of a DMT. Disease duration, phenotype, age and disability should not be used to restrict prescribing where evidence supports benefit.
- We recommend regular discussion with the patient about long-term treatment approaches and a potential 'exit-strategy' from continuous use medications if it is felt the risk of recurrence of inflammatory activity is low.
- Any patient stopping or de-escalating DMT should be monitored for a recurrence of disease activity.
- We support clinical trials investigating the efficacy of DMT in people with high levels of disability.

ABN, Association of British Neurologists; DMT, disease-modifying treatment.

Studies suggest that the risk of disease recurrence on stopping DMT is higher in those who are younger, those with more relapses and/or contrast enhancing lesions before starting DMT, and those with shorter duration of therapy.[23] There remains considerable uncertainty regarding the timing and overall risk: benefit balance of de-escalating patients from higher to moderate efficacy DMT or stopping in the context of a sustained period of clinical stability, and similarly in the context of increasing age and advancing disability. A recent study suggested that in people aged over 55 years, who have been stable with no relapse within the past 5 years or new MR lesion in the past 3 years while continuously taking an approved DMT, stopping the DMT might be a reasonable option, but may be associated with a small increased risk of new MRI activity.[23] Non-ambulatory patients can still be at risk of losing neurological function through disease activity; automatically stopping DMT at a defined level of disability without taking other factors into account may not be in the patient's best interest.

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Pregnancy

While pregnancy does not appear to influence long-term outcomes, DMT withdrawal, particularly of natalizumab and fingolimod, can lead to relapses resulting in long-term disability.[24 25] More recent data support using some DMTs at least to conception, and an increasing proportion of women now continue treatment during pregnancy.[26] Advance planning is key to optimal management, but current treatment algorithms do not always facilitate this.

Over half of women may show radiological disease activity post-partum or following pregnancy loss.[27 28] Pre-pregnancy disease activity, higher EDSS, withdrawal of high efficacy therapies and relapses during pregnancy are all associated with postpartum disease activity.[29] Modern cohorts do not show an elevated relapse rate following assisted reproduction technique cycles.[30 31]

There is still uncertainty around the optimal timing of resuming DMT to minimise postpartum inflammatory activity. Breastfeeding is associated with a mild reduction in relapse rate; however, this appears to be time limited to 4–6 months.[32] Some DMTs are safe to use while breastfeeding, and women should be supported to resume appropriate DMT while breastfeeding where this is indicated.

ABN recommendations: pregnancy

- Family planning should be discussed regularly with patients as appropriate and explicitly taken into consideration when discussing risks and benefits associated with DMT.
- Greater flexibility should be afforded, in particular with switching DMT, to enable women to access similar or higher efficacy therapies associated with superior safety in pregnancy.
- Women should not be denied or discouraged treatment on the basis of pregnancy plans.
- Where oral treatment is preferred, there is no evidence of harm with use of dimethyl fumarate to the time of conception.
- In general, monoclonal antibodies used in the treatment of MS are not associated with increased risk of congenital malformations and are not contraindicated during breastfeeding.
- Induction therapies may be an attractive choice for those planning future pregnancies.
- People with MS undergoing in vitro fertilisation should be treated with a DMT that is compatible with pregnancy, ideally to at least the time of embryo transfer.
- Where infants have been potentially exposed to immunosuppressive DMT, they should avoid live infant vaccinations in the first 6 months of life.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; MS, multiple sclerosis.

Considerations around using particular DMTs while trying to conceive, during pregnancy and in the post-partum period, including while breastfeeding, are discussed in more detail in dedicated guidelies.[26 33]

Equitable access to DMT

While specialist commissioning has enabled a more equitable prescribing structure there remain challenges. In England, the current move from national to local commissioning potentially risks equitable access. Most people with MS are diagnosed in general neurology clinics. NICE guidelines recommend that everyone with a new diagnosis of MS should be offered an appointment with a healthcare professional with expertise in MS within 6 weeks.[34] However, in practice, access to specialist services is often limited by inadequate staffing and resources.

ABN recommendations: equitable access to DMT

- It is imperative that MS services are funded sufficiently to provide safe and timely access to DMT.
- Access to DMTs may be facilitated by an integrated pathway. The Optimum MS pathway, due for publication in 2024, includes quality standards for the diagnostic process and the starting of DMTs and describes the structure required to deliver a comprehensive MS service.

ABN, Association of British Neurologists; DMT, disease-modifying treatment; MS, multiple sclerosis.

Autologous haematopoietic stem cell transplantation

ABN recommendation: AHSCT

- We support the appropriate use of AHSCT and advocate for the widening of its availability in the UK when agreed criteria for site qualification are met.

ABN, Association of British Neurologists; AHSCT, autologous haematopoietic stem cell transplantation.

The availability of autologous haematopoietic stem cell transplantation on the NHS is restricted to people with treatment-resistant inflammatory-active MS based on guidelines from the European Group for Blood and Marrow Transplantation.[35] Candidate patients need to be discussed at a specialist stem cell transplantation MDT meeting. There is increasing experience informing optimal protocols and patient selection, with promising real-world results.[36] There are ongoing clinical trials including comparative studies with high efficacy DMT investigating these important questions.[37 38]

Future priorities

While increasing DMT choice offers opportunity for both clinicians and patients, it inevitably makes the treatment landscape more complex. DMT eligibility criteria need to be simplified in commissioning policy,

as recommended in this guidance, and there remain several areas of uncertainty that need further analysis. Key among these is the need to determine longer-term DMT risk–benefit balance and treatment strategies, particularly when patients have been clinically stable for several years. Additionally, it is crucial to develop biomarkers for more sensitive detection of worsening MS pathology, especially for patients who experience disability worsening without new radiological activity.[39]

Current treatment paradigms continue to be overly dependent on ambulatory function, and we need studies focusing on other potentially disabling features including upper limb function, cognition and fatigue. We encourage further investigation into these, and other questions highlighted in this guidance.

We support the MS International Federation's call to improve MS awareness and to promote early diagnosis and treatment availability across all health systems to address unequal access around the world.[40] Within the UK, it is crucial to ensure people from all backgrounds have prompt investigation and diagnosis of MS and can access all DMT in a timely manner. We plan to update these revisions again in a few years and seek to address these questions further.

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