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

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Abstract

The last Association of British Neurologists (ABN) Disease Modifying Treatment (DMT) guidelines were published in 2015. Since then, additional DMTs have been licensed and approved for prescribing within the National Health Service (NHS) for Relapsing Remitting (RR) Multiple Sclerosis (MS), early Primary Progressive (PP) MS and active Secondary Progressive (SP) MS. This updated guidance provides a consensus-based approach to DMT use. We provide recommendations for eligibility, initiation, monitoring, switching, and discontinuation 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 ABN first published its guidelines for the use of DMTs for MS in 1999; these have subsequently been periodically updated.[1] They were historically used to determine prescribing practice in the United Kingdom (UK). From 2013, NHS 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 devolved nations.[2] In 2018 and then updated in 2023, NHSE published its Treatment Algorithm for MS DMT to provide a framework for clinical decision making.[3] Table 1 provides a summary of 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 NICE Technology Appraisals (TAs), which also inform prescribing policies from the devolved nations within the UK. A key requirement is that complex cases or those in which higher efficacy DMT are proposed should be discussed within a multi-disciplinary team (MDT), consisting of at least two MS specialist consultant neurologists, a specialist MS nurse and access to neuro-radiology expertise.

As the NHSE treatment algorithm adheres to NICE TA 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 the needs of an individual to be met, for instance around pregnancy planning. A further challenge is that the algorithm is hampered by inconsistent and outdated definitions of disease activity, which are largely based on pivotal study inclusion criteria used in historical NICE TAs.

The ABN guidance presented here aims to articulate some of the key challenges and make recommendations for DMT prescribing based on best available evidence and expert opinion, some of which differ from the NHSE treatment algorithm. However, it must be noted that prescribing in the NHS remains subject to current national commissioning policies. This guidance is not intended to provide a complete description of the possible complications and monitoring of DMT in MS; for this we refer prescribers to the relevant summaries of product characteristics (SmPC).

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. Subsequent to this meeting, and following further discussion, a consensus was endorsed by

all advisory group members. The guidance was then reviewed by relevant stakeholders (for full list see Appendix 1) and further revised, with the final version endorsed by the ABN council.

ABN Guidance

DMT eligibility

Licensing and NICE approval of DMTs to date has focused on the conventional subtyping of MS into RR MS, SP MS and PP 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 RR 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 out-dated definitions of active disease.
- For clinically isolated syndrome where McDonald criteria for RR MS are fulfilled, patients should be offered all available treatments as per RR MS.
- All DMTs should be available to eligible patients according to licence.

DMT initiation

Trial and real-world data increasingly illustrates the impact of early DMT use in reducing 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 (commencing on a moderate efficacy therapy to minimise potential risk and escalation to 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 which 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 high efficacy therapy initiation within two years of disease onset.[6,7] Early intensive versus escalation treatment strategies are currently being directly compared in two randomised controlled trials in RR MS.[8,9] Epidemiological studies, which predominantly pre-date widespread use of higher efficacy DMT, suggest that higher

relapse frequency,[10] Magnetic Resonance Imaging (MRI) activity,[11] early involvement of pyramidal tracts or spinal cord,[12] and acquiring significant early disability are poor prognostic markers.

Currently no DMTs are licensed for Radiologically Isolated Syndrome (RIS) but recent clinical trials suggest DMT efficacy in this cohort.[13,14]

ABN Recommendations: DMT Initiation Principles

- 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 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.
- When high efficacy therapies are being contemplated, there should be discussion in an MDT meeting.

ABN Recommendations: Shared Decision Making in DMT Initiation

- DMT choice should be a patient-centric decision, balancing clinical activity, prognostic factors, co-morbidity, 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 options available with an MS specialist healthcare professional, potentially supported by decision aids.
- A risk-benefit discussion should take place regarding adverse effects, infection risk and co-morbidity. Any potential modifiable factors which may increase the risk of complications should be mitigated, and patients encouraged to complete relevant vaccinations prior to starting DMT.
- Proactive support should be offered to patients on commencing DMT to minimise risk of poor adherence and ensure safe monitoring.
- We support the use of generics and biosimilars when they offer significant cost savings to the NHS and no disadvantage to the patient. Where services enabling safe initiation and delivery have been supplied alongside the innovator DMT, it is imperative that equivalent services are provided at no detriment to prescribing centres.

DMT monitoring

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

The *No Evidence of Disease Activity* (NEDA)-3 paradigm[16] is the most well-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 has been reported to be associated with a two-times higher odds of no longer-term disability progression at six years.[17] However, in clinical practice NEDA may not be achievable in all, as no DMT reduces the risk of disease activity by 100%. Some tolerance of minimal disease activity, such as a new MRI lesion without contrast enhancement and no relapses, may represent a more realistic goal but further investigation is required.[18] There is strengthening evidence that the isolated finding of two or more new T2 lesions on a moderate efficacy DMT for at least 12 months is associated with a significant increased subsequent risk of clinical relapse and therefore provides a rationale to consider DMT escalation.[19]

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.

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 MAGNIMS CMSC NAIMS consensus recommendations on the use of MRI in monitoring MS.
- A re-baseline MRI scan should be undertaken usually 3-6 months after DMT initiation to account for therapeutic lag.
- MRI brain 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 MRI frequency may be required for safety monitoring.
- Safety monitoring requirements should follow the recommendation in the SmPC for each DMT.
- It is vital that a prescribing centre has sufficient capacity and protocols in place to ensure that robust safety monitoring requirements are complied with, including a process for managing the risk of PML.

DMT switching

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

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. The timeframe to assess this would be generally within the last year but can be extended up to two years especially for DMT initiation due to the possibility of service capacity limitations.
- Patients on DMT for progressive disease should be considered for switching to DMT for relapsing disease if the current phenotype is predominantly relapsing.

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 S1P modulators), due to the potential for a 'rebound' of disease activity. In general, treatment gaps after therapies which 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, e.g., interferons and glatiramer acetate, does not necessitate a wash out period. Similarly, switching within the same class of drugs (e.g., 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, bridging with an alternative DMT may be required.

DMT discontinuation and de-escalation

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]

Studies suggest that risk of disease recurrence on discontinuing DMT is higher in those who are younger, those with more relapses and/or contrast enhancing lesions prior to DMT, and 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 above the age of 55, who have been stable with no relapse within the past 5 years or new MRI lesion in the past 3 years while continuously taking an approved DMT, discontinuation of 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 best interest of the patient.

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.

Pregnancy

Whilst pregnancy does not appear to influence long term outcomes, DMT withdrawal, particularly natalizumab and fingolimod, can lead to relapses resulting in long term disability.[24,25] More recent data supports use of 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 post-partum disease activity.[29] Modern cohorts do not show an elevated relapse rate following assisted reproduction technique cycles.[30,31]

Uncertainty remains around the optimal timing of DMT resumption to minimise postpartum inflammatory activity. Breast feeding 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 whilst breastfeeding, and women should be supported to resume appropriate DMT whilst breastfeeding where this is indicated.

Consideration around individual DMT whilst trying to conceive, during pregnancy and in the postpartum period, including whilst breastfeeding, are discussed in more details in dedicated guidelines.[26,33]

ABN Recommendations: Pregnancy

- Family planning should be discussed regularly with patients as appropriate and taken into explicit 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 IVF should be treated with a pregnancy compatible DMT, ideally to at least the time of embryo transfer.
- Where infants are potentially exposed to immunosuppressive DMT, they should avoid live infant vaccinations in the first six months of life.

Equitable access to DMT

Whilst specialist commissioning has enabled a more equitable prescribing structure there remain challenges, and the current move from national to local commissioning in England carries potential risk to 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 six weeks.[34] However, 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 initiation of DMTs and describes the structure required to deliver a comprehensive MS service.

Autologous haematopoietic stem cell transplantation (AHSCT)

The availability of AHSCT 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 (EBMT).[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]

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.

Future priorities

Whilst 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 which need further analysis. Key amongst 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, the development of biomarkers to detect worsening MS pathology more sensitively, especially for patients who experience disability worsening in the absence of new radiological activity, is crucial.[39]

Current treatment paradigms continue to be overly dependent on ambulatory function, and studies focusing on other potentially disabling features including upper limb function, cognition and fatigue are needed. 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 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.

Appendix 1

This guidance has been authored by the MS and Neuroinflammation Advisory Group to the ABN and reviewed by the following stakeholders:

ABN Quality Committee

ABN MS and Neuroinflammation Specialist Interest Group

Clinical representative for MS Services in Northern Ireland

Clinical representative for MS Services in Scotland

Clinical representative for MS Services in Wales

MS Society UK

MS Specialist Nurse Association (MSSNA)

MS Trust

Neurology Academy

NHS England

Representative of the UKCPA Neurosciences group and London MS Pharmacist network

Table One: 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. It must be noted that there is variation in whether DMTs were compared to active comparator or placebo and so studies are not directly comparable.

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